ABSTRACT BOOK

CONTENT

20th ESID Biennial Meeting Anniversary

PARALLEL SESSION

PS001

AUTOIMMUNE CYTOPENIAS AND INTERSTITIAL LUNG DISEASE ARE ASSOCIATED WITH EXPANDED TH1 CELLS IN LOCID AND CVID PATIENTS

PARALLEL SESSION 01: IMMUNE DYSREGULATION IN CVID

Martin Perez-Andres[1], Alba Torres Valle[2], Sonia De Arriba[3], Larraitz Aragon[4], Cristina Serrano[5], Susana Silva[6], Dolores Subira[7], Marta Ruiz Mercado[8], Miguel Marcos[9], Sandra Ines[9], Catarina Martins[10], Beatriz Albarran[11], Abelardo Barez[12], Guillermina Hurtado[13], Jana Neirinck[14], Carlos Cervero[15], Pedro Pablo Arenas Cabo[4], Ignacio Madruga[9], Maria Jara[1], Carlos Prieto[16], Carolien Bonroy[17], Ana E. Sousa[6], Alvaro Prada[4], Jacques J.M. Van Dongen[1,18], Alberto Orfao[1]
[1]University of Salamanca (USAL), Cancer Research Centre (ibmcc, Usal-csic; Ciberonc Cb16/12/00400), Institute For Biomedical Research of Salamanca (ibsal), Department of Medicine And Cytometry Service (nucleus Research Support Platform), Salamanca, Spain, [2]Cancer Research Centre (IBMCC, USAL-CSIC), Cytometry Service (NUCLEUS), University of Salamanca (USAL), Institute of Biomedical Research of Salamanca (IBSAL), Salamanca, Spain, Medicine, Salamanca, Spain, [3]Hospital Clin Univ Salamanca, Servicio De Pediatria, Salamanca, Spain, [4]Donostia University Hospital, Immunology Department, San Sebastian, Spain, [5]Fundacion Jimenez Diaz, Servicio De Inmunologia, Madrid, Spain, [6]Universidade de Lisboa, Instituto De Medicina Molecular João Lobo Antunes, Lisboa, Portugal, [7]Hospital Univ Guadalajara, Flow Cytometry Unit, Department of Hematology, Guadalajara, Spain, [8]Hospital Costa del Sol, Hematologia Y Hemoterapia, Marbella, Spain, [9]Hospital Clin Univ Salamanca, Servicio De Medicina Interna, Salamanca, Spain, [10]Faculdade de Ciências Médicas Universidade Nova de Lisboa, Nova Medical School, Lisboa, Portugal, [11]CAU Palencia, Hematology, Palencia, Spain, [12]Complejo Asistencial Avila, Servicio Hematologia, Avila, Spain, [13]Complejo Hospitalario de Navarra,, Servicio Hematologia, Pamplona, Spain, [14]Ghent University, Diagnostic Sciences, Ghent, Belgium, [15]Hospital Virgen de la Luz, Servicio Hematologia, Cuenca, Spain, [16]University of Salamanca, Bioinformatics Service (nucleus), Salamanca, Spain, [17]Ghent University, Department of Diagnostic Sciences, Ghent, Belgium, [18]Leiden University Medical Cente, Department of Immunology, Leiden, Netherlands

Background and Aims: Several alterations of CD4T subsets have been reported in CVID patients, although most studies did not discriminate patients with an underlying defect in CD4T cell production fulfilling late onset combined immunodeficiency criteria (LOCID).

Methods: CD4T subsets were analyzed in 49 CVID and 20 LOCID patients, in parallel with 155 healthy donors (4-88 years) using EuroFlow-based flow cytometry methods

Results: Higher percentage of patients with decreased T-cell subset counts were observed in LOCID vs. CVID, including Treg (85% vs. 61% of patients), Th2 (95% vs. 47%), Th17 (90% vs. 47%), and Th1/Th2 (65% vs. 29%), as compared to age-reference values. In contrast, few LOCID and CVID patients showed decreased TFH (5% and 2%), Th1 (25% and 18%), and Th1/Th17 counts (15% and 12%). Multivariate analysis showed two clearly distinct subgroups of LOCID, those with higher Th1 counts presenting with a higher frequency of autoimmune cytopenia (89% vs 19%, p=0.003) and interstitial lung disease (78% vs. 9%, p=0.003), together with lower frequency of non-respiratory infections (57% vs. 100%, p=0.03). In addition, three CVID subgroups were identified based on Th1 and TFH cells (CVID1, CVID2, and CVID3) with a significantly higher frequency of autoimmune cytopenias in CVID cases with higher Th1 cells (63% vs. 8% vs. 22%, p=0.005).

Conclusions: LOCID patients presented with a deeper T-cell defect than CVID patients. Interestingly, increased Th1 counts strongly associates with the presence of autoimmune cytopenia in LOCID and CVID; this coincides with interstitial lung disease in LOCID patients, but not in CVID.

Disclosure: No.

PS002

MAP KINASE ACTIVATING DEATH DOMAIN (MADD) DEFICIENCY IS A NOVEL CAUSE of IMPAIRED LYMPHOCYTE CYTOTOXICITY

PARALLEL SESSION 01: IMMUNE DYSREGULATION IN CVID

Kerstin Schütze[1], Miriam Gross[2], Kerstin Cornils[1], Katharina Wustrau[1], Sonja Schneppenheim[3], Henning Lenhartz[4], Georg-Christopf Korenke[5], Gritta Janka[1], Svea Ledig[1], Ingo Müller[6], Stephan Ehl[2], Kai Lehmberg[6]
[1]University Medical Center Eppendorf, Department of Pediatric Hematology And Oncology, Hamburg, Germany, [2]University of Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency, Medical Center, Freiburg, Germany, [3]Medilys Laborgesellschaft mbH, ., Hamburg, Germany, [4]Catholic Children's Hospital Wilhelmstift, ., Hamburg, Germany, [5]University Children's Hospital Klinikum Oldenburg, Department of Neuropediatrics, Oldenburg, Germany, [6]University Medical Center Eppendorf, Division of Pediatric Stem Cell Transplantation, Hamburg, Germany

Background and Aims: Most hereditary forms of hemophagocytic lymphohistiocytosis (HLH) are caused by defects of cytotoxicity, including the vesicle trafficking disorder Griscelli syndrome 2 (GS2, RAB27A deficiency). Deficiency of the mitogen activated protein (MAP) kinase activating death domain protein (MADD) results in a protean syndrome with neurological and endocrinological involvement. MADD acts as a guanine-nucleotide exchange factor for small GTPases, including RAB27A.

Methods: A female infant with syndromal features, secretory diarrhea, and features of HLH underwent routine exome sequencing. Degranulation and cytotoxicity of cytotoxic cells and platelet secretion were analyzed. To prove the relationship between the detected MADD defect and the detected functional impairment, we performed the assays in an NK-92mi cell line, in which we had introduced a CRISPR/Cas9 based MADD knock-out. A second MADD deficient patient was analyzed for confirmation.

Results: A homozygous splice site mutation in MADD was identified. Aberrant splicing caused by this mutation leads to an in-frame deletion of 30 bp and favors other aberrant variants. Patient NK cells and cytotoxic T cells showed a severe degranulation defect leading to absent perforin-mediated cytotoxicity. Platelets displayed defective ATP secretion, comparable to GS2. MADD deficient NK-92mi cells showed a degranulation defect and impaired cytotoxicity similar to that of the patient. The defect of cytotoxicity was confirmed in another the second MADD deficient patient.

Conclusions: In conclusion, RAB27A-interacting MADD is involved in vesicle release by cytotoxic cells and platelets. MADD deficiency causes a degranulation defect, most likely due to impaired RAB27a activation, and represents a novel disease predisposing to an HLH phenotype.

Disclosure: No.

Keywords: macrophage activation, vesicle trafficking, Hemophagocytic Lymphohistiocytosis, cytotoxicity, platelet secretion

PS003

IS THE PRESENCE of CYTOKINE-AUTOANTIBODIES IN PATIENTS WITH ENDOCRINE AUTOIMMUNE DISORDERS POINTING TO AN UNDERLYING MONOGENIC ETIOLOGY?

PARALLEL SESSION 02: IEI PHENOCOPIES

Thea Sjogren[1,2], Eirik Bratland[1,3], Bergithe Oftedal[1,2], Ellen Royrvik[1], Marianne Grytaas[2], Per Knappskog[1,3], Eystein Husebye[1,2], Anette Wolff[1,2]
[1]University of Bergen, Department of Clinical Science, Bergen, Norway, [2]Haukeland University hospital, Medicine, Bergen, Norway, [3]Haukeland University hosp, Department of Medical Genetics, Bergen, Norway

Background and Aims: Monogenic causes of several different disorders with simultaneous autoimmune and immune deficiency features have been identified. Apt examples are patients with mutations in AIRE, RAG1 or 2, FOXP3, CTLA-4 and IKZF2. Curiously, all these conditions are hallmarked by presence of neutralizing autoantibodies against type I Interferons and IL-22-antibodies. We here wanted to utilize screening of antibodies against IFN-ω and IL-22 in patients with endocrine autoimmune disorders to identify individuals with monogenic etiology.

Methods: Patients in the Norwegian registry for organ-specific autoimmune disorders were screened for antibodies against IFN-ω (N ~1700) and IL-22 (N=675) using radioimmunoassay and ELISA, respectively. Sequencing of the AIRE-gene and NGS with an in house immune panel (N=312 genes) was done to identify rare genetic aberrations (MAF<0.5%) in cytokine antibody-positive individuals.

Results: Screening patients with endocrine autoimmune disorders for IFN-ω antibodies have the last years identified at least 8 patients with AIRE-mutations, i.e. autoimmune polyendocrine syndrome type I in our cohort. In addition, we have identified 24 patients with antibodies against IFN-ω and/or IL22 but without AIRE-mutations in this project. Two patients were found to harbor disease-causing mutations in CTLA4 and NFKB2, respectively, while nine rare variants in genes encoding checkpoints within the T cell pathway in six other patients were also found. The functional consequences of the identified variants need to be explored further to draw conclusion about their disease-causing potential.

Conclusions: Screening of cytokine autoantibodies in patient cohorts with autoimmune endocrine diseases could be a valuable tool to identify the molecular cause of their disease.

Disclosure: No.

Keywords: il22, type I interferons, AIRE, autoimmune, autoantibodies, immune deficiencies

PS004

A HIGH-THROUGHPUT AMPLICON SCREEN FOR SOMATIC UBA1 VARIANTS IN CYTOPENIC AND GIANT CELL ARTERITIS COHORTS

PARALLEL SESSION 02: IEI PHENOCOPIES

James Poulter[1], Alesia Khan[2], Bosko Andjelic[3], Mark Grey[4], Emma Nga[5], Diana Triantafyllopoulou[3], Sarah Mackie[1], Ann Morgan[1], Catherine Cargo[2], Sinisa Savic[1]
[1]University of Leeds, School of Medicine, Leeds, United Kingdom, [2]St James's University Hospital, Haematology, Leeds, United Kingdom, [3]Royal Blackburn Teaching Hospital, Department of Haematology, Blackburn, United Kingdom, [4]Blackpool and Lancashire Teaching Hospitals, Lancashire Haematology Centre, Blackpool, United Kingdom, [5]Airedale NHS Foundation Trust, Haematology, BD TD, United Kingdom

Background and Aims: Somatic mutations in UBA1 exon 3 are a known cause of VEXAS syndrome, a late-onset acquired auto-inflammatory syndrome. Differential diagnoses for patients subsequently found to have VEXAS include, relapsing polychondritis (most frequent diagnosis), Sweet's syndrome, myelodysplastic syndrome (MDS), giant cell arteritis (GCA) and undifferentiated systemic autoinflammatory disease (uS **Background and Aims:** AID). We sought to investigate the frequency of VEXAS associated mutations in patients with confirmed GCA and those with unexplained cytopenia.

Methods: A one-step, PCR-based amplicon sequencing assay was developed to screen UBA1 exon 3 in high-throughput. Using the amplicon sequencing assay, 612 males diagnosed with GCA, and 1,055 cases with an undiagnosed cytopenia were sequenced by massively paralleled sequencing.

Results: No GCA cases were found to have UBA1 mutations, however 4 different mutations in the cytopenic cohort were identified in 7 individuals (1.0% of males of males screened). We identified a female with VEXAS due to a UBA1 mutation who was subsequently found not to have Monosomy X.

Conclusions: We identified 1.0% of males with a non-diagnostic cytopenia had VEXAS syndrome. The finding of a female case adds further evidence that VEXAS should not be ruled out as a differential diagnosis in females.

Disclosure: No.

Keywords: VEXAS, UBA1, Giant cell arteritis, cytopenia

PS005

CIS JUNIOR: ALTERED STAT1 SIGNALLING YIELDS CD8+ T CELL DYSFUNCTION IN INBORN ERRORS of IMMUNITY

PARALLEL SESSION 03: IEI IN THE WORLD (IAPIDS SESSION)

Andrea Mauracher[1], Peyton Conrey[1], Samir Sayed[1], Jose Campos[1], Ceire Hay[1], Robert Lindell[1], Jenna Bergerson[2], Maureen Degragne[2], Elena Gonzalez[1], Isabel Cardi[1], Asako Takanohashi[3], Alexander Vargas-Hernandez[4], Adeleine Vanderver[3], Jennifer Leiding[5], Lisa Forbes Satter[4], Steven Holland[2], Alexandra Freeman[2], Sarah Henrickson[1]
[1]Children's Hospital of Philadelphia, Division of Allergy And Immunology, Department of Pediatrics, Philadelphia, United States of America, [2]NIH, Laboratory of Clinical Immunology And Microbiology (lcim), Niaid, Bethesda, United States of America, [3]Children's Hospital of Philadelphia, Division of Neurology, Department of Pediatrics, Philadelphia, United States of America, [4]Baylor College of Medicine, William T. Shearer Center for Human Immunobiology, Department of Pediatrics, Houston, United States of America, [5]Johns Hopkins All Children's Hospital, Immunology, St. Petersburg, United States of America

Background and Aims: Interferons are a group of cytokines known to play a pivotal role in mediating antiviral and inflammatory responses. STAT1 has a central role within this signaling axis, relaying inflammatory signals, and orchestrating the antiviral immune response, including a key role in CD8 T-cells (CD8T). There is currently limited understanding of how alterations in STAT1 signaling affect CD8T function in vivo in human cells. Here, we evaluate how modulating STAT1 signaling can affect CD8T function by studying patients with STAT1 loss of function (LOF) and gain of function (GOF).

Methods: To measure the mechanisms induced by alterations in STAT1 activity, we collected multimodal high-dimensional immune-profiling and immunometabolic functional data from >24 STAT1 GOF and several STAT1 LOF patients and age matched controls. >7 Aicardi-Goutières-Syndrome (AGS) patients were included a disease control for chronic interferon signaling.

Results: This cohort allows us to begin to differentiate the effects of interferon signaling vs isolated alterations in STAT1 activity on CD8T function. In all three groups we find a reduced capacity of CD8T to produce interferon-gamma upon stimulation. STAT1 GOF CD8T show up-regulations in activation markers such as CD38, while AGS CD8T additionally express Eomes and Tbet. In contrast STAT1 LOF CD8T up-regulate inhibitory receptors. Preliminary data further suggests that certain interferon stimulated genes correlate with the expression levels of these activation markers.

Conclusions: Thus, by studying these three groups we are gaining novel insights into the mechanisms by which altered STAT1 activity vs chronic interferon stimulation cause CD8T dysfunction.

Disclosure: No.

Keyword: STAT1 GOF, STAT1 LOF, Aicardi-Goutiere Syndrome, CD8 T cells, STAT, exhaustion

PS006

APSID JUNIOR: AUTOIMMUNITY IN A LARGE COHORT of INBORN ERRORS of IMMUNITY! – EXPERIENCE FROM A TERTIARY CARE CENTER IN SOUTH INDIA

PARALLEL SESSION 03: IEI IN THE WORLD (IAPIDS SESSION)

Rachna Shanbhag Mohite[1], Stalin Ramprakash[2], Cp Raghuram[2], Neha Singh[1], Ananthvikas Jayaram[3], Chetan Ginigeri[4], Harish Kumar[4], Udhaya Kotecha[5], Sagar Bhattad[1]
[1]Aster CMI Hospital, Pediatric Immunology & Rheumatology, Bangalore, India, [2]Aster CMI Hospital, Pediatric Hemato-oncology, Bangalore, India, [3]Neuberg Anand, Pathology, Bangalore, India, [4]Aster CMI Hospital, Pediatrics, Bangalore, India, [5]Neuberg Supratech reference laboratories, Genetics, Gujarat, India

Background and Aims: Autoimmunity can be the first clinical presentation or sequel of Inborn Errors of Immunity (IEI). Molecular genetics and next-generation sequencing technologies have increased our understanding of the complex relationships between IEI and autoimmune diseases.Aim: To study the profile of autoimmune manifestations in patients with IEI at a tertiary care center in Bangalore, India.

Methods: A retrospective review of clinical records of 241 patients with IEI was performed.They were categorized according to the International Union of Immunological Societies (IUIS), PID Committee Report on IEI (2019).Patients who had autoimmune manifestations at presentation or during the course of their illness were included in the study.

Results: The most common IEIs noted were Severe Combined Immune Deficiency (SCID) (38,15.7%) followed by phagocytic disorders and antibody deficiency diseases.A total of 67 autoimmune manifestations were noted in 55 (22.8%) patients. Male to female ratio in this subgroup was 2.5:1. Amongst them, autoimmunity was the key or only manifestation in 20 (8.2%) patients.The most common manifestation in our cohort was inflammatory colitis (29%) followed by autoimmune cytopenia (20%), autoimmune endocrinopathy (12.7%), and arthritis (12.7%). Inflammatory colitis was common among patients with phagocytic disorders. Pyoderma gangrenosum, systemic lupus erythematosus, and Kawasaki disease were also reported.Patients received immunosuppression in the form of steroids (n=36), azathioprine (n=5), cyclosporine (n=2),methotrexate (n=2), rituximab (n=3),sirolimus (n=1), adalimumab (n=1) and infliximab (n=1). The overall survival was 76% in the “autoimmune” cohort.

Conclusions: Autoimmunity is a frequent manifestation in patients with IEI. Managing autoimmunity in patients with IEI is a challenge, due to their inherent predisposition to infections.

Disclosure: No.

Keywords: Autoimmunity, Primary Immune deficiency, Inflammatory colitis, Inborn errors of immunity, Autoimmune cytopenia, arthritis

PS007

PATIENTS WITH CTLA-4 INSUFFICIENCY HAVE DISTINCT INTESTINAL MICROBIOME SIGNATURES

PARALLEL SESSION 04: IEI AND MICROBIOME

Mate Krausz[1,2,3], Noriko Mitsuiki[2], Michele Proietti[2,4,5], Bodo Grimbacher[2,3,6,7,8]
[1]Albert-Ludwigs-University of Freiburg, Faculty of Biology, Freiburg, Germany, [2]Medical Center, Faculty of Medicine, Albert-Ludwigs-University of Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [3]Medical Center, Faculty of Medicine, Albert-Ludwigs-University of Freiburg, Department of Rheumatology And Clinical Immunology, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [4]Department of Rheumatology and Clinical Immunology, Hannover Medical University, Hannover, Germany, [5]Resolving Infection Susceptibility (RESIST) – Cluster of Excellence 2155, Hanover Medical School, Satellite Center Freiburg, Freiburg, Germany, [6]University of Freiburg, Cibss - Centre For Integrative Biological Signalling Studies, Freiburg, Germany, [7]DZIF – German Center for Infection Research, Satellite Center Freiburg, Germany, Freiburg, Germany, [8]Resolving Infection Susceptibility (RESIST) - Cluster of Excellence 2155, Hannover Medical School, Satellite Center Freiburg, Freiburg, Germany

Background and Aims: CTLA-4 insufficiency is a monogenetic condition caused by heterozygous mutations in CTLA4 that is characterized by immune dysregulation, including autoimmune enteropathy. The disease presents with a reduced (~70%) penetrance, so we hypothesized that affected and unaffected CTLA4 mutation carriers have distinct intestinal microbiome signatures compared to each other and to healthy controls, and that the microbiome may identify patients with disease-related organ involvements.

Methods: We collected stool samples and clinical data from healthy donors (HDs, n=178), affected (n=33) and unaffected CTLA-4 patients (n=8) and performed 16S rRNA sequencing. We also compared samples from patients with and without a history of specific organ involvement (enteropathy, splenomegaly, lymphadenopathy, GLILD).

Results: Affected patients had a significantly decreased alpha-diversity (Shannon), compared to unaffected carriers and HDs. Moreover, CTLA-4 patients with a history of specific organ involvement had decreased alpha-diversity (not significant). Additionally, we identified significantly different taxa in affected and unaffected CTLA-4 mutation carriers. We found that the Proteobacteria were significantly enriched in affected patients, compared to unaffected carriers and controls. Furthermore, we could identify various taxa that are the main drivers of the differences between affected and unaffected mutation carriers. In affected individuals Veillonella, Escherichia, and Haemophilus were enriched, in unaffected individuals Ruminococcaceae, Tenericutes, and Lachnospiraceae were expanded. Some of these taxa are known to be correlated with inflammatory bowel disease.

Conclusions: Here we show, that affected CTLA4 mutation carriers have distinct intestinal microbiome structures, and that the microbiome may be a relevant disease modifier. Our results could serve as a basis for further interventional studies.

Disclosure: No.

Keywords: microbiome, disease modifiers, CTLA4

PS008

INTERFERON-DRIVEN IMMUNE DYSREGULATION IN COMMON VARIABLE IMMUNODEFICIENCY ASSOCIATED ENTEROPATHY IS EXACERBATED BY NOROVIRUS INFECTION

PARALLEL SESSION 04: IEI AND MICROBIOME

Valentina Strohmeier[1], Geoffroy Andrieux[2], Susanne Unger[1], Anna Pascual-Reguant[3], Adam Klocperk[4], Maxmillian Seidl[5], Otavio Cabral Marques[6], Marleen Eckert[1], Michele Proietti[1], Bodo Grimbacher[1], Anja Hauser[3], Melanie Boerries[2], Peter Hasselblatt[7], Klaus Warnatz[1]
[1]Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany, [2]Medical Center - University of Freiburg, Institute of Medical Bioinformatics And Systems Medicine, Freiburg im Breisgau, Germany, [3]Charité - Universitätsmedizin Berlin, Department of Rheumatology And Clinical Immunology, Berlin, Germany, [4]2nd Faculty of Medicine, Charles University and University Hospital in Motol, Department of Immunology, Prague, Czech Republic, [5]Heinrich Heine University and University Hospital of Duesseldorf, Institute of Pathology, Düsseldorf, Germany, [6]Institute of Biomedical Sciences, University of São Paulo, Department of Immunology, x, Brazil, [7]Medical Center – University of Freiburg, Department of Medicine Ii, Freiburg im Breisgau, Germany

Background and Aims: About 15% of patients with common variable immunodeficiency (CVID) develop a small intestinal enteropathy, resembling celiac disease with regard to histopathology but evolves from a distinct and poorly defined pathogenesis that has been linked in some cases to chronic norovirus infection. While Interferon-driven inflammation is known as a prominent feature of CVID enteropathy, it still remains unknownit still remains unknown whether norovirus (NV) infection may contribute to it.

Methods: Duodenal biopsies of CVID patients, stratified according to enteropathy with and without villous atrophy (VA), the presence of IgA^+ plasma cells and the NV status were investigated by flow-cytometry, multi-epitope-ligand cartography (MELC), bulk RNA sequencing and RT-qPCR.

Results: In our study the development of severe enteropathy in forms of VA, was connected with the lack of intestinal (IgA^+) plasma cells (PC), a T helper 1 (TH1)/T helper 17 (TH17) cell imbalance and increased recruitment of $Granzyme^+CD8^+$ T cells and pro-inflammatory macrophages to the affected site. An Interferon (IFN)-signature occurred in early enteropathy stages and aggravated with increasing severity of histopathological changes. Chronic NV infection exacerbated this signature when compared to stage-matched NV-negative samples.

Conclusions: Our study suggests that IFN signaling and T-cell cytotoxicity are driving mechanisms during the development of CVID enteropathy. NV infection induces locally high IFN-driven inflammation, usually only seen in VA, already at less severe histological stages. Thus, revealing the impact of the different drivers of the pathological IFN signature may allow for more targeted treatment strategies in CVID enteropathy and supports the goal of viral elimination.

Disclosure: No.

Keywords: CVID, Enteropathy, Norovirus

PS009

IMMUNE TOLERANCE DEFECTS IN INDIVIDUALS WITH PATHOGENIC MUTATIONS IN THE KAPPA LIGHT CHAIN

PARALLEL SESSION 05: B AND T CELL TOLERANCE CHECKPOINTS

Julius Köppen[1], Diego Kyburz[2], Camillo Ribi[3], Ramiz Saramati[1], Marten Trendelenburg[4], Timo Hautala[5], Mike Recher[1,6]
[1]University Hospital Basel, Immunodeficiency Group, Basel, Switzerland, [2]University Hospital Basel, Rheumatology, Basel, Switzerland, [3]University Hospital Lausanne, Allergology And Immunology, Lausanne, Switzerland, [4]University Hospital Basel, Clinical Immunology, Basel, Switzerland, [5]University of Oulu, Biomedicine, Oulu, Finland, [6]University Hospital Basel, Outpatient Clinics Immunology, Basel, Switzerland

Background and Aims: Germline homozygous or compound heterozygous mutations in the gene encoding the constant domain of the immunoglobulin κ light chain (IGKC) may cause kappa light deficiency. Only few cases have been reported since its first characterisation, with very variable susceptibility to infections. κ light chain expression is involved in the process of B cell receptor (BCR) editing, a pivotal autoimmune checkpoint. Thus, IGKC mutations might predispose to autoimmunity.

Methods: We screened our inborn errors of immunity cohort consisting of 360 patients by Sanger sequencing for rare IGKC mutations. In addition, we screened 490 individuals of the Swiss SLE Cohort Study and are currently screening 500 patients enrolled into a Swiss Rheumatoid Arthritis cohort. IGKC mutation carriers were characterised clinically. We comprehensively evaluated the immune-phenotype including κ vs λ light chain expression on B cell subpopulations by flow-cytometry.

Results: So far, we have identified five individuals carrying the heterozygous c.T258G mutation in IGKC. This mutation changes an essential cysteine involved in disulphide bonds. Only one mutation carrier had kappa light chain deficiency in the serum. However, all expressed predominantly λ light chains on the surface of peripheral B cells implicating pathologic receptor editing. All mutation carriers had autoimmune disease, which in the majority was life-threatening.

Conclusions: We present evidence that the c.T258G IGKC missense variant in heterozygous state disturbs B cell receptor editing with high penetrance. The clinical associations found indicate a considerable penetrance of the c.T258G IGKC mutation to drive human autoimmune disease.

Disclosure: No.

Keywords: Immune Dysregulation, B cell receptor editing, Autoimmunity, B cell development

PS010

HYPERMORPHIC HETEROZYGOUS VARIANTS IN ZAP70 UNDERLIE AUTOIMMUNE DISEASE

PARALLEL SESSION 05: B AND T CELL TOLERANCE CHECKPOINTS

Caspar Van Der Made[1], Ruben Smeets[2], Annet Simons[3], Janneke Schuurs-Hoeijmakers[3], Emil Vorsteveld[3], Sonja De Munnik[3], Judith Potjewijd[4], Maaike Vreeburg[5], Hans Koenen[2], Gijs Van Well[6], Mihai Netea[1], Alexander Hoischen[3], Frank Van De Veerdonk[1]
[1]Radboud University Medical Center, Internal Medicine, Radboud Center For Infectious Diseases (rci), Nijmegen, Netherlands, [2]Radboud University Medical Center, Laboratory Medicine, Laboratory Medical Immunology, Nijmegen, Netherlands, [3]Radboud University Medical Center, Human Genetics, Nijmegen, Netherlands, [4]Maastricht University Medical Center+, Department of Internal Medicine, Division of Immunology, Maastricht, Netherlands, [5]Maastricht University Medical Center+, Department of Clinical Genetics, Maastricht, Netherlands, [6]Maastricht University Medical Center+, Department of Pediatrics, Division of Infectiology-immunology, Maastricht, Netherlands

Background and Aims: The tyrosine kinase ZAP-70 plays a crucial role in relaying proximal T cell antigen receptor signalling. Biallelic loss-of-function mutations in ZAP70 consequently cause a severe combined immunodeficiency with defective $CD4^+$ T cell functioning and $CD8^+$ T cell lymphopenia. Moreover, there has been a report of a ZAP70 variant (p.Arg360Pro) conferring a weak hypermorphic effect in two siblings with autoimmune disease, although not fully penetrant. In this study, we have investigated the functional impact of two novel heterozygous missense variants in ZAP70 carried by six patients with multiple autoimmune diseases.

Methods: An exome-wide research-based reanalysis was performed in three unrelated index patients. Segregation of rare, non-synonymous candidate genes in affected family members was investigated using Sanger sequencing. Functional tests were conducted to test pathogenicity and encompassed ex vivo stimulation of isolated peripheral blood mononuclear cells, ELISA for cytokine production and phosphoflow cytometry analysis.

Results: In index patients 1 and 2, an identical heterozygous missense variant (p.(Leu325Phe)) was identified. Index patient 3 carried another, private heterozygous missense variant (p.(Val114Phe)). All variants showed complete segregation in affected family members. An increased basal phosphorylation of ZAP70 was observed in PBMCs isolated from the patients, suggesting a compromised autoinhibitory state. Furthermore, in patients with the p.Leu325Phe variant, basal IFNgamma production and T cell activation after TCR stimulation were also elevated compared to controls.

Conclusions: In patients from three families with autoimmune disease, we identified rare, heterozygous missense variants in ZAP70. These hypermorphic variants led to increased basal ZAP-70 phosphorylation and augmented T-cell signalling, suggesting a novel mutational mechanism.

Disclosure: No.

Keywords: ZAP-70, Immune Dysregulation, autoimmune disease, hypermorphic variants

PS011

NEWBORN SCREENING IN SWITZERLAND: TRECS AND KRECS

PARALLEL SESSION 06: IEI NEWBORN SCREENING

Maarja Soomann[1], Seraina Prader[1], Susanna Sluka[2], Tayfun Güngör[3], Jana Pachlopnik Schmid[1], Johannes Trück[1]
[1]University Children's Hospital Zurich, Immunology, Zurich, Switzerland, [2]University Children's Hospital Zurich, Swiss Newborn Screening Laboratory, Zurich, Switzerland, [3]University Children's Hospital Zurich, Stem Cell Transplantation, Zurich, Switzerland

Background and Aims: Since January 1, 2019 levels of T cell receptor and kappa-deleting recombination excision circles (TREC, KREC) are measured as a part of the Swiss newborn screening program. We present findings of these first three years and compare outcomes of SCID patients to a historical cohort.

Methods: In all newborns with abnormal first screening, data on their medical history, laboratory findings and management were recorded in a centralised database.

Results: In total, 340 patients had abnormal findings on screening (0.13% of all tested newborns). Eleven patients (3%) had severe immunodeficiency: eight had severe combined immunodeficiency (SCID, 2.7/year) and three had agammaglobulinemia. Furthermore, 36 patients (11%) had less severe immunodeficiencies. Seven SCID patients (88%) underwent hematopoietic stem cell transplantation at a median age of 4.5 months. One patient (12%) died of a viral infection after transplantation. Compared to a historical cohort of 15 SCID patients diagnosed over a period of 12 years (1.3/year), age at diagnosis and transplantation, mortality (33% vs 12%) and morbidity were lower in SCID patients identified by newborn screening. In 251 patients (74%), abnormal screening results were transient and likely due to a variety of factors including prematurity, maternal immunosuppression, asphyxia, and trisomy 21.

Conclusions: The first three years of the Swiss newborn screening program have helped to identify a substantial number of children with severe immunodeficiencies. The number of patients diagnosed per year exceeds that of the previous 12 years by more than two times, suggesting that some children died before the introduction of screening without being diagnosed.

Disclosure: No.

Keywords: newborn screening, TREC, Agammaglobulinemia, KREC, SCID

PS012

LESSONS LEARNED FROM FIVE YEARS of NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY (SCID) IN ISRAEL

PARALLEL SESSION 06: IEI NEWBORN SCREENING

Atar Lev[1], Idan Sharir[1], Nufar Marcus[2], Shlomo Almashanu Almashanu[3], Raz Somech[4]
[1]Sheba medical center, Pediatric Department A And The Immunology Service, Ramat Gan, Israel, [2]Schneider Children's Medical Center, Allergy And Immunology Unit, Petach Tikva, Israel, [3]Sheba medical center, The National Newborn Screening Program, Ministry of Health, Ramat Gan, Israel, [4]Sheba Medical Center, Pediatrics, Immunology, Ramat Gan, Israel

Background and Aims: Background: Implementation of newborn screening (NBS) programs for severe combined immunodeficiency (SCID) have advanced diagnosis and management of affected infants and undoubtedly improved their outcomes. Reporting long-term follow-up of such programs is of great importance. Objective: Here we report a five-year summary of the NBS program for SCID in Israel.

Methods: Immunological and genetic assessments, clinical analyses and outcome data from all infants screened positive were evaluated and summarized.

Results: A total of 937,953 Guthrie cards were screened for SCID. A second Guthrie card was requested on 1169 occasions (0.12%) that resulted in 142 referrals (0.015%) for further validation tests. Flow cytometry immune-phenotyping, TREC measurement in peripheral blood, and expression of TCRVb repertoire for validation of positive cases revealed specificity and sensitivity of 93.7% and 75.9%, respectively, in detecting true cases of SCID. Altogether, 32 SCID and 110 non-SCID newborns were diagnosed, making the incidence of SCID in Israel as high as 1: 29,000 births. The most common genetic defects in this group were associated with mutations in DCLRE1C and IL7R genes. No infant with SCID was missed during the study time. Twenty-two SCID patients underwent hematopoietic stem cell transplantation (HSCT) that resulted in a 91% survival rate.

Conclusions: NBS for SCID should be ultimately applied globally, specifically to areas with high rates of consanguineous marriages. Accumulating data from follow-up studies on NBS for SCID will enable improving diagnosis and treatment and will enrich our understanding of immune development in health and disease.

Disclosure: No.

Keywords: primary immunodeficiency, Hematopoietic stem cell transplantation, Severe combined immunodeficiency, T cell lymphopenia, newborn screening, Dry blood spots

PS013

SHARPIN HETEROZYGOUS MUTATION IS RESPONSIBLE FOR AUTOIMMUNITY, INFLAMMATORY MANIFESTATIONS AND PRIMARY IMMUNE DEFICIENCY

PARALLEL SESSION 07: AUTOINFLAMMATORY DISEASES

Boris Sorin[1], Marie-Claude Stolzenberg[1], Jérôme Hadjadj[1], An Thys[2], Laura Barnabei[1], Marion Malphettes[3], Nicolas Bidère[2], Frédéric Rieux-Laucat[1]
[1]IMAGINE institut, INSERM UMR1163, Université Paris Cité, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, Paris, France, [2]CRCINA, Signaling In Oncogenesis, Angiogenesis, And Permeability, Nantes, France, [3]Hôpital Saint Louis, Department of Clinical Immunology, Paris, France

Background and Aims: LUBAC is a heterotrimeric complex composed of SHARPIN, HOIL-1 and HOIP. LUBAC is involved in NFkB pathway activation and cell survival. Patients with complete HOIL-1 or HOIP deficiency suffer from inflammatory manifestations and immune deficiency. We identified by whole exome sequencing a heterozygous SHARPIN mutation in a patient with autoimmunity, inflammatory manifestations and primary antibody deficiency. We aimed to study the link between this mutation and the disease of the patient.

Methods: To study the mutation's impact on the production, stability and function of the protein we transiently transfected HEK293T cells and complemented SHARPIN$^{-/-}$ Jurkat cells by lentiviral infection. We also evaluated LUBAC-dependent functions in patient's PBMCs and SV40-transformed fibroblasts.

Results: The mutation led to a premature STOP codon and the diminished production of a non-functional truncated protein. Patient's cells presented a decreased TNFα and IL-1β-induced canonical NFkB activation and an excess of TNFα -induced cell death. Patient's monocytes secreted higher amount of IL6 after IL-1β stimulation than healthy controls. Anti-cytokine biotherapies (anti-TNFα and IL1receptor antagonist) led to a partial improvement of the patient's inflammatory manifestations.

Conclusions: We describe the first dominant hypomorphic SHARPIN mutation in a patient with autoimmunity, inflammatory manifestations and primary immune deficiency. Clinical manifestations and experimental data are similar, although milder, to those described in HOIL-1 or HOIP deficient patients. Study of such rare inborn errors of immunity contribute to a better understanding of inflammatory and autoimmune diseases and lead to identification of new therapeutic targets.

Disclosure: No.

Keywords: NFkB pathway, Programmed cell death, inborn error of immunity, Autoimmunity, LUBAC, SHARPIN

PS014

ABERRANT INFLAMMATORY RESPONSES TO TYPE I INTERFERON IN STAT2 OR IRF9 DEFICIENCY

PARALLEL SESSION 07: AUTOINFLAMMATORY DISEASES

Florian Gothe[1], Jarmila Stremenova Spegarova[1], Catherine Hatton[1], Helen Griffin[1], Thomas Sargent[1], Sally Cowley[2], William James[2], Anna Roppelt[3], Anna Shcherbina[3], Fabian Hauck[4], Hugh Reyburn[5], Christopher Duncan[6], Sophie Hambleton[7]
[1]Translational and Clinical Research Institute, Immunity And Inflammation Theme, Newcastle upon Tyne, United Kingdom, [2]Sir William Dunn School of Pathology, James And Lillian Martin Centre For Stem Cell Research, Oxford, United Kingdom, [3]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [4]Dr. von Hauner Children's Hospital, Pediatrics, Munich, Germany, [5]Spanish Center for Biotechnology, Immunology And Oncology, Madrid, Spain, [6]The Newcastle upon Tyne Hospitals NHS Foundation Trust, Infection And Tropical Medicine, Newcastle upon Tyne, United Kingdom, [7]The Newcastle upon Tyne Hospitals NHS Foundation Trust, Children's Immunology Service, Newcastle upon Tyne, United Kingdom

Background and Aims: Inflammatory phenomena such as hyperinflammation or hemophagocytic lymphohistiocytosis are a frequent yet paradoxical accompaniment to viral susceptibility in patients with impairment of type I IFN (IFN-I) signalling caused by deficiency of STAT2 or IRF9. We hypothesized that altered and/or prolonged IFN-I signalling contributes to inflammatory complications in these patients.

Methods: We explored the signalling kinetics and residual transcriptional responses of IFN-stimulated primary cells from individuals with complete loss of either STAT1, STAT2 or IRF9 as well as gene-edited iPSC-derived macrophages.

Results: Deficiency of any ISGF3 component suppressed but did not abrogate IFN-I receptor signalling, which was abnormally prolonged in keeping with insufficient induction of negative regulators such as USP18. In cells lacking either STAT2 or IRF9, this late transcriptional response to IFNα2b mimicked the effect of IFNγ.

Conclusions: Our data suggest a model wherein the failure to limit an ineffective antiviral response leads to immune dysregulation. Aberrant IFNAR signalling in STAT2- and IRF9-deficient cells switches the transcriptional output to a prolonged, IFNγ-like response and likely contributes to clinically overt inflammation in these individuals.

Disclosure: No.

Keywords: type I interferon, antiviral immunity, ISGF3, type II interferon, HLH, GAF

PS015

LONG-TERM OUTCOMES AFTER THYMUS TRANSPLANTATION IN COMPLETE DIGEORGE SYNDROME

PARALLEL SESSION 08: THYMIC IEI

Alexandra Kreins, Evey Howley, Zainab Golwala, Matthew Buckland, Austen Worth, Graham Davies
Great Ormond Street Hospital, Immunology, London, United Kingdom

Background and Aims: Congenital athymia is most frequently associated with complete DiGeorge Syndrome (cDGS). More than 100 cDGS patients have been treated by thymus transplantation (TT)[1,2], including at Great Ormond Street Hospital (GOSH) which offers the only European TT programme, with overall survival of 75-80%. Post-TT, absolute T-cell counts, including naïve T-cells, remain suboptimal. Nevertheless, typically sufficient immune reconstitution is achieved for clearance of pre-existing and acquired infections, as well as discontinuation of antibiotic prophylaxis and immunoglobulin replacement treatment (IgRT). We report long-term outcomes post-TT, including long-term quality of T-cell immunity, which have not previously been described in detail.

Methods: We analysed clinical and laboratory outcomes for cDGS patients with more than 3 years follow-up post-TT.

Results: 24 cDGS patients treated between 2009-2018 were included, with a median follow up time of 6.7 years to date (3.4-13.1). No late deaths occurred. At last follow-up, median T-cell counts (/μL) were: $CD3^+$ 720, $CD4^+$ 500, naïve $CD4^+$ 110, $CD4^+$ recent thymic emigrants 92, $CD8^+$ 180, naïve $CD8^+$ 60. Diverse T-cell receptor repertoires persist over time. 19 patients successfully discontinued IgRT and started/completed immunisations. Chronic autoimmunity is common post-TT, with 12 patients suffering autoimmune thyroiditis and 1 autoimmune haemolytic anaemia (AIHA). 2 patients remain on long-term immunomodulatory treatments for either AIHA or inflammatory disease. All bar one patients >5 years of age attend school.

Conclusions: After successful TT in cDGS, satisfactory T-cell immunity is maintained for at least several years facilitating an improved quality of life. References: [1]Markert et al 2022; [2]Davies et al 2017.

Disclosure: No.

Keywords: thymus, thymus transplantation, Digeorge Syndrome, long-term follow up, T-cell immunity

PS016

LOSS of HOXA3 CAUSES LARYNGEAL DYSMORPHIA, THYMIC APLASIA AND SEVERE COMBINED IMMUNODEFICIENCY (SCID)

PARALLEL SESSION 08: THYMIC IEI

Sarah Dinges[1,2,3], Anke Hirschfelder[4], Johannes Grünhagen[5,6], Dimitrios Wagner[1,7], Olga Staudacher[3,8], Luisa Klein[9], Uwe Kölsch[8], Karl-Ulrich Schnuck[10], Lia Puder[11], Christoph Czernik[9], Marcus Mall[1,3,12], Nadine Unterwalder[8], Christian Meisel[8], Christoph Bührer[9], Horst Von Bernuth[1,2,3,8]
[1]Charité – Universitätsmedizin Berlin, Germany, Berlin Institute of Health, Berlin, Germany, [2]Charité — Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany, Center For Regenerative Therapies (bcrt), Berlin, Germany, [3]Charité-Universitätsmedizin Berlin, Pediatric Respiratory Medicine, Immunology And Critical Care Medicine, Berlin, Germany, Berlin, Germany, [4]Charité — Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Department of Phoniatrics & Pedaudiology, Berlin, Germany, [5]Labor Berlin GmbH, Department of Human Genetics, Berlin, Germany, [6]Charité — Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institute For Medical Genetics And Human Genetics, Berlin, Germany, [7]Charité — Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin Center For Advanced Therapies (becat), Berlin, Germany, [8]Labor Berlin Charité-Vivantes GmBH, Immunology, Berlin, Germany, [9]Charité — Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Neonatology, Berlin, Germany, [10]Vivantes Klinikum im Friedrichshain, Children's Hospital, Berlin, Germany, [11]Charité — Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Pediatric Oncology/hematology, Berlin, Germany, [12]Deutsche Zentren der Gesundheitsforschung (DZG), German Center For Lung Research (dzl), Berlin, Germany

Background and Aims: Severe combined immunodeficiency (SCID) is due to genetic defects intrinsic to hematopoietic cells, or, less frequently, impaired thymic epithelium. Human thymic aplasia is reported for mutations in TBX1, TBX2, FOXI3, CHD7, FOXN1 or PAX1. For the first time, we present a case of complete HOXA3 deficiency and thymus aplasia. Homebox (HOX) genes pattern the embryonic anterior–posterior axis.
Methods: Disease phenotype and immunological characteristics were captured. Whole-exome and Sanger sequencing and segregation analysis were conducted.
Results: Thymic aplasia, laryngopharyngeal dysmorphia, resulting in dysphagia and apnoea, and dysmorphia of face, neck and ears characterize the disease. The immunological phenotype fulfills criteria of SCID (CD3+ T cells 10/µl, naive CD4+RA+CCR7+ T cells 4%, γ/δ+ T cells 20%, and absent lymphocyte transformation upon stimulation with PHA, all data from 5th day post natum). Levels of NK cells were normal. Humoral immunity was characterized by normal absolute B cells, and a hyper IgM phenotype (IgG 8.5 g/l, IgA < 0,1 g/l and IgM 0.45 g/l and 0,29 g/l after one month). Sequencing showed a biallelic nonsense mutation. The disorder is autosomal recessive.
Conclusions: Complete HOXA3-deficiency is the seventh genetic and third autosomal recessive immunodeficiency with thymus aplasia in humans. Derivatives of several pharyngeal arches and pouches are impaired, suggesting that the role of HOXA3 in embryogenesis is not restricted to the third pharyngeal arch, where the thymus originates. Compared to other conditions with thymic aplasia, our findings suggest that HOXA3 is downstream to TBX1, CHD7 and FOXI3 and upstream to FOXN1 in human thymus organogenesis.

Disclosure: No.

Keywords: thymus organogenesis, SCID, HOXA3, thymic aplasia

PS017

JAK-INHIBITOR TREATMENT of INBORN ERRORS of IMMUNITY WITH DYSREGULATED JAK/STAT SIGNALLING, AN ESID AND EBMT INBORN ERRORS WORKING PARTY STUDY

PARALLEL SESSION 09: TREATMENT - NOVEL/TARGETED

Marco Fischer[1,2,3], Peter Olbrich[4], Jérôme Hadjadj[5], Shahrzad Bakhtiar[6], Vincent Barlogis[7], Philipp Von Bismarck[8], Marketa Bloomfield[9], Deniz Cagdas[10], Martin Castelle[11], Alice Y Chan[12], Shanmuganathan Chandrakasan[13], Pierre Cougoul[14], Etienne Crickx[15], Angela Deyà-Martínez[16], Susan Farmand[17], Luis Ignacio Gonzalez-Granado[18], David Hagin[19], Leif G Hanitsch[20], Fabian Hauck[21], José Ivorra Cortés[22], Kai Kisand[23], Ayca Kiykim[24], Timothy Ronan Leahy[25], Joris Van Montfrans[26], Brigitte Nelken[27], Suhag Parikh[13], Jan Ramakers[28], Jacques Rivière[29], Yulia Rodina[30], Pérsio Roxo Júnior[31], Sarah Salou[2], Fabien Touzot[32], Ekrem Unal[33], Mikko R J Seppänen[34], Olaf Neth[35], Michael H Albert[21], Stephan Ehl[1,2], Benedicte Neven[11], Carsten Speckmann[2]
[1]Institute for Immunodeficiency, Center For Chronic Immunodeficiency, Medical Center-university of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany, [2]Medical Center - University of Freiburg, Division of Pediatric Hematology And Oncology, Department of Pediatrics And Adolescent Medicine, Faculty of Medicine, Freiburg, Germany, [3]University Children's Hospital Zurich, Division of Immunology And Children's Research Center, Zurich, Switzerland, [4]Hospital Universitario Virgen del Rocío, Pediatric Infectious Diseases, Rheumatology And Immunology Unit, Instituto De Biomedicina De Sevilla, Ibis/universidad De Sevilla/csic, Red De Investigación Traslacional En Infectología Pediátrica Ritip, Seville, Spain, [5]Hôpital Cochin, APHP-Centre Université de Paris (CUP), Department of Internal Medicine, National Referral Center For Rare Systemic Autoimmune Diseases, Paris, France, [6]University Hospital Frankfurt, Division For Stem Cell Transplantation, Immunology And Intensive Care Medicine, Department For Children And Adolescents Medicine, Frankfurt am Main, Germany, [7]Latimone University Hospital, Pediatric Hematology Unit, Marseille, France, [8]University Hospital Schleswig-Holstein, Clinic For General Pediatrics, Kiel, Germany, [9]Charles University in Prague and University Hospital in Motol, Department of Immunology, 2nd Faculty of Medicine, Prague, Czech Republic, [10]Hacettepe University Medical School, Department of Pediatric Immunology, Ankara, Turkey, [11]Necker Children's Hospital, Assistance Publique-Hôpitaux de Paris, Université De Paris, Institut Imagine Institut Des Maladies Genetiques, Paris, France, [12]University of California, Division of Pediatric Allergy Immunology Bmt, Division of Pediatric Rheumatology, Department of Pediatrics, San Francisco, United States of America, [13]Aflac Cancer and Blood Disorder Center, Department of Pediatrics, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, United States of America, [14]Oncopole, Institut Universitaire Du Cancer De Toulouse, Toulouse, France, [15]Centre Hospitalier Universitaire Henri-Mondor, Assistance Publique-Hôpitaux de Paris (AP-HP), Internal Medicine Department, Université Paris-est Créteil (upec), Créteil, France, [16]Hospital Sant Joan de Déu, Clinical Immunology And Primary Immunodeficiencies Unit, Pediatric Allergy And Clinical Immunology Department, Barcelona, Spain, [17]University Medical Center Hamburg-Eppendorf, Division of Pediatric Stem Cell Transplantation And Immunology, Hamburg, Germany, [18]Hospital 12 Octubre; Research Institute Hospital 12 octubre (i+12); Complutense University School of Medicine, Primary Immunodeficiencies Unit, Department of Pediatrics, Madrid, Spain, [19]Tel-Aviv Sourasky Medical Center, Allergy And Clinical Immunology Unit, Tel-Aviv, Israel, [20]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Institute of Medical Immunology, Berlin, Germany, [21]Dr. von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-Universität München, Department of Pediatrics, Munich, Germany, [22]Hospital Universitari i Politècnic La Fe, Rheumatology Department, Valencia, Spain, [23]University of Tartu, Institute of Biomedicine And Translational Medicine, Tartu, Estonia, [24]Istanbul University-Cerrahpasa, Pediatric Allergy And Immunology, Istanbul, Turkey, [25]Children's Health Ireland at Crumlin, Department of Paediatric Immunology And Infectious Diseases, Dublin, Ireland, [26]Wilhelmina's Children Hospital, Department of Pediatric Immunology And Infectious Diseases, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [27]Centre hospitalier universitaire regional de Lille, Pediatric Hematology Unit, Lille, France, [28]Hospital Universitari Son Espases, Department of Pediatrics, Palma, Spain, [29]Hospital Universitari Vall d'Hebron, Pediatric Infectious Diseases And Immunodeficiencies Unit, Vall D'hebron Barcelona Hospital Campus, Barcelona, Spain, [30]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Department of Immunology, Moscow, Russian Federation, [31]University of São Paulo, Division of Immunology & Allergy, Dept.of Pediatrics, Ribeirão Preto Medical School, São Paulo, Brazil, [32]CHU Sainte-Justine, Department of Pediatrics, Université De Montréal, Montréal, Canada, [33]Erciyes University Faculty of Medicine, Department of Pediatric Hematology And Oncology, Kayseri, Turkey, [34]University of Helsinki and HUS Helsinki University Hospital, Rare Disease Center, Children's Hospital, And Adult Primary Immunodeficiency Outpatient Clinic, Inflammation Center, Helsinki, Finland, [35]Hospital Universitario Virgen del Rocío; Instituto de Biomedicina de Sevilla, IBiS/Universidad de Sevilla/CSIC; Red de Investigación Traslacional en Infectología Pediátrica RITIP, Pediatric Infectious Diseases, Rheumatology And Immunology Unit, Seville, Spain

Background and Aims: Inborn errors of immunity (IEI) with dysregulated JAK/STAT signalling can present with variable manifestations of severe immune dysregulation. Hematopoietic stem cell transplantation (HSCT) is potentially curative, however the reported treatment related mortality (TRM) of JAK/STAT patients is significant. Targeted therapies with JAK Inhibitors (JAKinib) offer a promising alternative and potentially TRM reducing bridging option. However, data on efficacy and adverse events (AE) of JAKinib treatment for IEI are limited.

Methods: Multicentre retrospective cohort study on patients with pathogenic variants in a JAK/STAT IEI-gene who have received JAKinib treatment for at least 3 months.

Results: 66 patients (74% children) were included (41 STAT1-GOF, 21 STAT3-GOF, 1 STAT1-LOF, 1 STAT5B, 1 SOCS1, 1 JAK1-GOF). Ruxolitinib was the predominantly prescribed JAKinib (82%). Improvement of general well-being was observed in 91%. However, therapeutic responses varied among underlying diseases and disease manifestations. In 41% of patients, AE were observed (i.e. infections and weight gain). AE could generally be well controlled, leading to discontinuation of treatment in only 15% among patients who suffered AE. Currently, 76% patients are maintained on JAKinib (mean treatment observation 20 months) while 17% patients have received HSCT. Drug dosing and monitoring varies considerably between individual patients and centres.

Conclusions: Our study affirms that JAKinib are an effective and generally well tolerated therapy for patients with JAK/STAT-IEI. While there was variable efficacy for different disease manifestations, severe adverse events were rare. Our data will provide the basis for a consensus process to generate treatment recommendations and for the implementation of a prospective Jakinib treatment registry.

Disclosure: No.

Keywords: Immune Dysregulation, Autoimmunity, Targeted therapy, Jakinib, JAK/STAT signalling

PS018

GENE EDITING of APDS1 T CELLS

PARALLEL SESSION 09: TREATMENT - NOVEL/TARGETED

Lucie Poggi[1,2], Loïc Chentout[1,2], Sabrina Lizot[3], Alexandre Juillerat[4], Marina Cavazzana[5,6], Philippe Duchateau[4], Julien Valton[3], Sven Kracker[1,2]
[1]Institut Imagine, U1163 Lymphohematopoiesis Lab, Paris, France, [2]Imagine Institute, Université De Paris, Paris, France, [3]Cellectis, Gene Therapy, Paris, France, [4]Cellectis, Gene Editing, New York, United States of America, [5]Necker Hospital, Pediatric Hematology-immunology And Rheumatology Unit, Paris, France, [6]Groupe Hospitalier Universitaire Ouest, Biotherapy Clinical Investigation Center, Paris, France

Background and Aims: Activated PI3kinase Delta Syndrome type 1 (APDS1) is caused by gain of function mutations affecting the PIK3CD gene. The project aims to develop a gene editing approach to correct ex vivo patient T cells and reinfuse them. This treatment may be used to treat severe viral infections, or serve as a pre-requisite for a milder conditioning before hematopoietic stem cell transplantation.

Methods: T cells were modified using a nuclease targeting the PIK3CD gene and an AAV. Nuclease cleavage frequency was assessed by digital droplet PCR. Successful editing was analyzed by flow cytometry based on the expression of a reporter gene. Phospho-AKT level and cytotoxic activity were analyzed to evaluate the functional activity of corrected T cells.

Results: A highly specific nuclease achieved a reproducible cleavage efficiency of 80% and in conjunction with the AAV a gene editing efficiency of 20% at the PIK3CD locus. High basal level of phosphorylated AKT in APDS1 patient T cells was normalized in corrected patient cells. After T cell receptor activation phosphorylation of AKT could still be induced in corrected cells. Gene editing improved the impaired cytotoxic activity of repeatedly rechallenged APDS1 patient T cells towards lymphoblastoid B cell lines in the presence of blinatumomab.

Conclusions: We developed a protocol allowing efficient gene editing of APDS1 patient T cells. Corrected APDS1 T cells displayed normalized level of AKT phosphorylation and increased cytotoxic activity indicating the potential of our approach as a new treatment for ADPS1.

Disclosure: No.

Keywords: APDS1, Gene editing, Activated PI3kinase Delta Syndrome type 1, T cell therapy, nuclease

PS019

RECESSIVE INBORN ERRORS of TYPE I IFN IMMUNITY IN CHILDREN WITH COVID-19 PNEUMONIA

PARALLEL SESSION 10: COVID-19 IN IEI

Daniela Matuozzo[1,2], Qian Zhang[1,2,3], Jérémie Le Pen[4], Danyel Lee[1,2,3], Leen Moens[4], Takaki Asano[3], Jonathan Bohlen[5], Zhyiong Liu[3], Marcela Moncada-Velez[3], Yasemin Kendir Demirkol[3], Huie Jing[6], Lucy Bizien[1,2], Astrid Marchal[1,2], Hassan Abolhassani[7,8], Selket Delafontaine[9,10], Giorgia Bucciol[10], Gulsum Ical Bayhan[11], Sevgi Keleş[12], Ayca Kiykim[13], Selda Hancerli[14], Filomeen Haerynck[15], Nevin Hatipoğlu[16], Tayfun Ozcelik[17], Guillaume Morelle[18], Mayana Zatz[19], Lisa Ng[20], David Lye[21,22], Barnaby Young[23,24], Yee-Sin Leo[21,22], Clifton Dalgard[25,26], Richard Lifton[27,28], Laurent Renia[20,22,29], Isabelle Meyts[10,30,31,32], Emmanuelle Jouanguy[33,34], Lennart Hammarström[35], Qiang Pan-Hammarström[36], Bertrand Boisson[37,38,39], Paul Bastard[33,39,40], Helen Su[41], Stéphanie Boisson-Dupuis[1,2,3], Laurent Abel[37,38,39,42], Charles Rice[4], Shen-Ying Zhang[1,3,40], Aurélie Cobat[1,2,3], Jean-Laurent Casanova[38,42,43,44,45]
[1]Institut Imagine, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1163, Paris, France, [2]University of Paris Cité, Institut Imagine, Paris, France, [3]St. Giles Laboratory of Human Genetics of Infectious Diseases, The Rockefeller University, Rockefeller Branch, New York, United States of America, [4]The Rockefeller University, Laboratory of Virology And Infectious Diseases, New York, United States of America, [5]Institut Imagine, Genetics of Infectious Disease, Paris, France, [6]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Laboratory of Clinical Immunology And Microbiology, Intramural Research Program, Bethesda, United States of America, [7]Tehran University of Medical Sciences, Research Center For Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran, Iran, [8]Karolinska Institute, Division of Clinical Immunology, Department of Biosciences And Nutrition, Stockholm, Sweden, [9]KU Leuven, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [10]KU Leuven, Laboratory Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [11]Ankara City Hospital, Yildirim Beyazit University, Ankara, Turkey, [12]Necmettin Erbakan University, Meram Medical Faculty, Division of Pediatric Allergy And Immunology, Konya, Turkey, [13]Istanbul University-Cerrahpasa, Pediatric Allergy And Immunology, Istanbul, Turkey, [14]Istanbul Faculty of Medicine, Istanbul University, Department of Pediatrics (infectious Diseases),, Istanbul, Turkey, [15]Ghent University Hospital, Department of Pediatric Pulmonology And Immunology And Pid Research Lab, Ghent, Belgium, [16]University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital,, Department of Pediatric Infection, Istanbul, Turkey, [17]Bilkent University, Department of Molecular Biology And Genetics, Bilkent-Ankara, Turkey, [18]Bicêtre Hospital, AP-HP, University of Paris Saclay, Department of General Pediatrics, Le Kremlin-Bicêtre, France, [19]University of São Paulo, Biosciences Institute, São Paulo, Brazil, [20]A*STAR Infectious Disease Labs, Agency for Science, Technology And Research, Singapore, Singapore, [21]National Centre for Infectious Diseases, National University Health System, Singapore, Singapore, [22]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore, [23]National Centre for Infectious Diseases, *, Singapore, Singapore, [24]National University of Singapore, Yong Loo Lin School of Medicine, Singapore, Singapore, [25]PRIMER, Uniformed Services University of The Health Sciences, Bethesda, United States of America, [26]Uniformed Services University of the Health Sciences, Department of Anatomy, Physiology & Genetics, Bethesda, United States of America, [27]The Rockefeller University, Laboratory of Genetics And Genomics, New York, United States of America, [28]Yale School of Medicine, Yale Center For Genome Analysis, New Haven, United States of America, [29]School of Biological Sciences, Nanyang Technological University, Singapore, Singapore, [30]KU Leuven, Department of Immunology, Microbiology And Transplantation, Laboratory of Inborn Errors of Immunity, Leuven, Belgium, [31]KU Leuven, Laboratory of Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [32]University Hospitals Leuven, Department of Pediatrics, Jeffrey Modell Diagnostic And Research Network Center, Leuven, Belgium, [33]Université Paris Descartes, Génétique Humaine Des Maladies Infectieuses, Paris, France, [34]Génétique Humaine des Maladies Infectieuses, Université Paris Descartes, Paris, France, [35]Karolinska Institutet at Karolinska University Hospital, Division of Clinical Immunology And Transfusion Medicine, Department of Laboratory Medicine, Stockholm, Sweden, [36]Karolinska Institutet, Bionut, HUDDINGE, Sweden, [37]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, New York, United States of America, [38]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1163, Paris, France, [39]Paris Cité University, Imagine Institute, Paris, France, [40]Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital For Sick Children, Paris, France, [41]Intramural Research Program, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Laboratory of Clinical Immunology And Microbiology,, Bethesda, United States of America, [42]Imagine Institute, Paris Cité University, Paris, France, [43]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, New York, United States of America, [44]Howard Hughes Medical Institute, -, New York, United States of America, [45]INSERM U1163, Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1163, Paris, France

Background and Aims: Inborn errors of type I interferon (IFN) immunity can underlie critical COVID-19 pneumonia in unvaccinated adults. The risk of COVID-19 pneumonia in unvaccinated children is much lower and remains unexplained. We tested the hypothesis that recessive inborn errors of type I IFN immunity could underlie COVID-19 pneumonia in patients < 16 years of age.

Methods: We performed an enrichment analysis focusing on rare variants in 15 candidate genes on our international cohort of 112 pediatric patients with moderate to critical COVID-19 pneumonia and 1,224 children and adults with asymptomatic or paucisymptomatic infection. We validated our findings studying the response to SARS-CoV-2 infection in patient's fibroblasts.

Results: We identified 12 children aged 1.5 to 13 years with four of the 15 known clinically recessive and biochemically complete inborn errors of type I IFN immunity: X-linked recessive TLR7 deficiency (7 children) and autosomal recessive IFNAR1 (1), STAT2 (1), or TYK2 (3) deficiencies. Fibroblasts deficient for IFNAR1, STAT2, or TYK2, are highly vulnerable to SARS-CoV-2. These 15 deficiencies are not found in children and adults with benign SARS-CoV-2 infection without pneumonia ($p = 1.2x10^{-11}$).

Conclusions: Our findings suggest that three of the 14 known AR inborn errors of type I IFN immunity underlie COVID-19 pneumonia in ~4% of children. We also found XR TLR7 deficiency in ~6% of children and 8.9% of boys with pneumonia. We provide evidence that recessive and complete defects at these four loci can underlie ~10% of cases of COVID-19 pneumonia in hospitalized children.

Disclosure: No.

Keywords: Inborn errors of immunity, type I interferon, pediatric patients, Recessive deficiencies, COVID-19, Pneumonia

PS020

IDENTIFICATION of HOST GENETIC VARIANTS IN THE CYTOSOLIC DNA SENSOR POL III IN PATIENTS WITH CRITICAL COVID-19

PARALLEL SESSION 10: COVID-19 IN IEI

Anne Hollensen[1], Sofie Jørgensen[1], Lili Hu[1], Michelle Thomsen[1], Aurora Pujol[2], Emmanuelle Jouanguy[3], Rebeca Perez De Diego[4], Aurélie Cobat[3], Jean-Laurent Casanova[5], Trine Mogensen[1]
[1]Aarhus University, Department of Biomedicine, Aarhus C, Denmark, [2]Hospital Duran i Reynals, Idibell, Barcelona, Spain, [3]Université Paris Descartes, Génétique Humaine Des Maladies Infectieuses, Paris, France, [4]IdiPAZ Institute for Health Research, La Paz Hospital, Laboratory of Immunogenetics of Human Diseases, Madrid, Spain, [5]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, New York, United States of America

Background and Aims: The underlying pathogenesis explaining why some individuals develop life-threatening COVID-19 disease remains incompletely understood. In this study we aim to identify gene variants predisposing specifically to vary rare cases of critical COVID-19 in young individuals without co-morbidities.

Methods: By whole exome sequencing we have identified potential disease-causing host gene variants in younger patients with critical COVID-19.

Results: We have revealed an accumulation of mutations in genes encoding the innate cytosolic DNA sensor RNA polymerase III (POL III) in younger patients with critical COVID-19. In peripheral blood mononuclear cells (PBMCs) isolated from patients with identified POL III gene variants, we have shown reduced type I interferon (IFN) responses to SARS-CoV-2 and the POL III agonist poly(dAdT). Likewise, inhibition of POL III in the pulmonary cell line A549 resulted in reduced IFN response to SARS-CoV-2. Currently, we are further scrutinizing the impact of POL III gene variants on the development of critical COVID-19 by investigating how the DNA sensor POL III is sensing infections with RNA-viruses, like SARS-CoV-2. We hypothesize that mitochondrial DNA released into the cytosol due to SARS-CoV-2-induced cellular stress during infection is sensed by POL III and mediating induction of IFN expression.

Conclusions: By regulating the IFN response to SARS-CoV-2 POL III seems to be important for prevention of development of critical COVID-19. Studies to examine the molecular mechanism, whereby host DNA may serve an antiviral role during SARS-CoV-2 infection are ongoing. Hence, this study provides new knowledge on the role of cytosolic DNA sensing and POL III in severe viral infections.

Disclosure: No.

Keywords: SARS-CoV-2, RNA polymerase III, COVID-19

PS021

CHARACTERIZATION of HEMATOPOIETIC STEM CELL FUNCTIONS IN PATIENTS WITH ADENOSINE DEAMINASE 2 DEFICIENCY

PARALLEL SESSION 11: IEI AND HEMATOLOGICAL DISEASE/BM FAILURE

Cristina Mesa Nunez[1], Raisa Jofra Hernández[1], Federica Barzaghi[2], Luca Basso-Ricci[1], Emanuela Pettinato[1], Stefania Crippa[1], Pamela Quaranta[1], Diego Gilioli[1], Serena Scala[1], Raffaella Di Micco[1], Maria Ester Bernardo[1,2,3], Luigi Naldini[1,3], Alessandro Aiuti[1,2,3], Alessandra Mortellaro[1]
[1]San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), Irccs San Raffaele Scientific Institute, Milan, Italy, [2]Pediatric Immunohematology and Bone Marrow Transplantation Unit, Irccs Sanraffaele Scientific Institute, Milan, Italy, [3]Vita-Salute San Raffaele University, ., Milan, Italy

Background and Aims: The deficiency of adenosine deaminase 2 (DADA2) is an inborn error of immunity caused by loss-of-function mutations in the ADA2 gene. Manifestations include vasculopathy and immunological and hematological abnormalities. It is unknown how ADA2 loss causes bone marrow (BM) failure, and understanding these mechanisms is essential for developing new targeted therapies.

Methods: We analyzed the BM composition in patients and evaluated the toxicity and efficacy of ADA2 gene transfer in patients' hematopoietic stem-progenitor cells (HSPCs).

Results: HSPCs and the primitive compartment were significantly reduced in patients' BM compared with healthy donors (HDs). Although reduced in number, patients' HSPCs showed normal clonogenic and differentiation potential. We also characterized patients' mesenchymal stromal cells (MSCs), critical elements interacting with HSPCs in the BM. They exhibited a reduced clonogenic capacity and low levels of primitive marker expression, while senescence markers increased compared with HDs. To assess whether gene therapy could represent a potent treatment for DADA2, we developed a lentiviral vector (LV) to restore constitutively ADA2 expression in patients' HSPCs. HSPCs transduction allowed efficient delivery of the functional ADA2 enzyme in patients' CD34-derived cells without signs of toxicity. Transduced HSPCs infused into immunocompromised mice demonstrated that ADA2-modified cells supported a multilineage reconstitution with a polyclonal integration pattern.

Conclusions: Our results indicate that the loss of ADA2 leads to a reduced number of primitive progenitors in the HSPC pool and an exhausted MSC phenotype. LV-mediated ADA2 reconstitution seems a promising approach to re-establish stable ADA2 activity and correct the hematological manifestations in patients with DADA2.

Disclosure: No.

Keywords: Hematopoietic stem cells, Adenosine deaminase 2 deficiency, gene therapy, Bone marrow failure

PS022

LOW CTLA-4 EXPRESSION BY NBEAL2 DEFICIENT CONVENTIONAL T CELLS AND IMMUNE DYSREGULATION IN GRAY PLATELET SYNDROME.

PARALLEL SESSION 11: IEI AND HEMATOLOGICAL DISEASE/BM FAILURE

Laure Delage[1,2], Francesco Carbone[3], Quentin Riller[1], Jean-Luc Zachayus[4], Erwan Kerbellec[2], Armelle Buzy[4], Marie-Claude Stolzenberg[5], Marine Luka[3], Georges Kalouche[6], Alizée Michel[1], Sonia Meynier[1], Camille De Cevins[3], Aurélien Corneau[7], Nathalie Neveux[8], Sébastien Roudières[4], Brieuc Pérot[9], Mathieu Fusaro[10,11], Christelle Lenoir[12], Olivier Pellé[1], Mélanie Parisot[13], Marc Bras[14], Rémi Favier[15], Sébastien Héritier[15], Guy Leverger[15], Anne-Sophie Korganow[16], Capucine Picard[10,17], Sylvain Latour[12], Bénédicte Collet[18], Alain Fischer[19,20,21], Benedicte Neven[22,23], Aude Magerus[24,25], Mickael Ménager[9], Benoit Pasquier[2], Frédéric Rieux-Laucat[1]
[1]Université Paris Cité, Immunogenetics of Pediatric Autoimmune Diseases, Imagine Institute, Inserm Umr 1163, Paris, France, [2]Sanofi, Checkpoint Immunology, Immunology And Inflammation Therapeutic Area,, Vitry-sur-Seine, France, [3]Imagine Institute, Labtech Single-cell@imagine, Paris, France, [4]Molecular Biology and Genomics, Translational Sciences, Sanofi, Chilly-Mazarin, France, [5]IMAGINE institut, INSERM UMR1163, Université Paris Cité, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, Paris, France, [6]Sanofi, Cellomics, Translational Sciences,, Chilly-Mazarin, France, [7]Sorbonne Université, Ums037, Pass, Plateforme De Cytométrie De La Pitié-salpêtrière Cyps, Paris, France, [8]Paris University, Laboratory of Biological Nutrition, Ea 4466, Faculty of Pharmacy,, Paris, France, [9]Imagine Institute, Laboratory of Inflammatory Responses And Transcriptomic Networks In Diseases, Atip-avenir, Paris, France, [10]APHP, Study Center For Primary Immunodeficiencies, Paris, France, [11]Toulouse Institute for Infectious and Inflammatory Diseases (INFINITy), Inserm U1291, Toulouse, France, [12]Université Paris Cité, Institut Imagine, Laboratory of Lymphocyte Activation And Susceptibility To Ebv Infection, Inserm Umr 1163, Paris, France, [13]Paris Cite University, Genomics Core Facility, Institut Imagine-structure Fédérative De Recherche Necker, Inserm U1163 Et Inserm Us24/cnrs Uar3633, Paris Descartes Sorbonne, Paris, France, [14]Université Paris Cité, Bioinformatics Platform, Structure Fédérative De Recherche Necker, Inserm Umr1163, Imagine Institute, Paris, France, [15]Assistance Publique-Hôpitaux de Paris, French National Reference Center For Platelet Disorders, Armand Trousseau Children Hospital, Paris, France, [16]Tertiary Center for Primary Immunodeficiency, Strasbourg University Hospital, Department of Clinical Immunology And Internal Medicine, National Reference Center For Systemic Autoimmune Diseases (cnr Reso, Strasbourg, France, [17]Necker Children's Hospital, Assistance Publique-Hôpitaux de Paris, Université De Paris, Institut Imagine Institut Des Maladies Genetiques, Paris, France, [18]Centre Hospitalier de Roubaix, Pediatric Unit, Roubaix, France, [19]Collège de France, Collège De France, Paris, France, [20]Imagine Institute, Université De Paris, Paris, France, [21]Necker Hospital, Pediatric Hematology-immunology And Rheumatology Unit, Paris, France, [22]Necker Hospital for Sick Children, Pediatric Immunology, Hematology And Rheumatology Unit, Paris, France, [23]Imagine Institute, Paris Cité University, Paris, France, [24]Imagine Institute, Immunogenetic of Pediatric Autoimmune Diseases, Paris, France, [25]Université Paris Cité, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases,, Paris, France

Background and Aims: Recessive mutations in the NBEAL2 gene lead to gray platelet syndrome (GPS), a bleeding disorder characterized by macrothrombocytopenia and α-granule-deficient platelets. A proportion of NBEAL2-deficient patients present immune system abnormalities (autoimmune disease, autoantibodies, leukopenia, etc) – suggesting a role for NBEAL2 in immune homeostasis and tolerance. And the mechanism behind the development of autoimmunity remains unclear.

Methods: NBEAL2 role in primary human T cells was investigated by mass spectrometry interactome study, CRISPR-Cas-9 knock-down and single-cell RNA sequencing.

Results: In a mass spectrometry interactome study, 76 NBEAL2 partners were found in primary T cells, including LRBA (a member of the BEACH family, like NBEAL2). Recessive LRBA mutations cause autoimmunity and lymphocytic infiltration through defective CTLA-4 trafficking. We found that NBEAL2 deficiency leads to low CTLA-4 expression in patients' effector T cells but not in their regulatory T cells. The NBEAL2-LRBA-CTLA-4 interaction was confirmed by immunoprecipitation. NBEAL2 knock-down in primary T cells also led to low CTLA-4 expression. Lastly, single cell RNAseq analyses of NBEAL2 and LRBA deficient lymphocytes uncovered an elevated IL6-STAT3 signature in LRBA patients, possibly reflecting their low CTLA-4 expression in regulatory T cells.

Conclusions: Our results show that NBEAL2 is involved in the regulation of CTLA-4 expression in conventional T cells and provide a molecular rationale for considering CTLA-4-immunoglobulin therapy in patients with GPS and autoimmune disease.

Disclosure: J-L.Z., E.K., A.B., G.K., C.dC., S.R., and B.P. are employees of Sanofi, France. J-L.Z., E.K., A.B., G.K., C.dC., S.R., L.D. and B.P. may hold shares and/or stock options in the company. Other authors have nothing to disclose.

Keywords: CTLA-4, NBEAL2, Autoimmunity, LRBA, gray platelet syndrome, BEACH-domain-containing protein

PS023

UNSUPERVISED PHENOTYPE EXPRESSION PROFILING AND LONGITUDINAL MONITORING IN INBORN ERRORS of IMMUNITY WITH IMMUNE DYSREGULATION BY MEANS of THE IDDA2.1 'KALEIDOSCOPE' SCORE

PARALLEL SESSION 12: ARTIFICIAL INTELLIGENCE IN IEI

Markus Seidel
Medical University Graz, Pediatric Hematology-oncology, Graz, Austria

Background and Aims: Clinical scores (measures, indices, scales, or similar) may be used in inborn errors of immunity (IEI) to support making a diagnosis or to classify an IEI, to assess and monitor the disease severity over time, and to guide treatment decisions.

Methods: We developed a user-friendly 22-parameter score for evaluating the immune deficiency and dysregulation activity (IDDA) that includes graded organ involvement and disease burden, intended for prospective monitoring of all IEI with immune dysregulation.

Results: To extend the utility from LRBA deficiency (IDDA version 1), we included hemophagocytic lymphohistiocytosis into the parameter list; and we modified the calculation of the numerical score to correct for very low performance scales. A new accompanying feature, the kaleidoscope function, is enabled by plotting the IDDA2.1 parameters as radar chart or heatmap which illustrates phenotypical similarities and variances between different patients or conditions. The discriminative power of this method was confirmed by unsupervised hierarchical clustering of phenotype manifestation frequencies of 18 representative IEI (including predominantly antibody deficiencies and susceptibility to EBV and lymphoproliferation) in analogy to genotype expression arrays.

Conclusions: The IDDA2.1 kaleidoscope score may be used for prospective monitoring of patients with IEI with immune dysregulation, e.g., in patient registries or clinical trials. A recently launched ESID registry study will collect data and apply unsupervised machine learning algorithms to detect similarities of patterns in training cohorts consisting of patients with known monogenic IEI to assess potentially predictive values in diagnosis finding, complication monitoring, and to suggest phenotype-driven, "semi-targeted" therapy options for undiagnosed patients.

Disclosure: Research funds (one-time donations paid to the Research Unit at the Medical University Graz or Division of Pediatric Hematology-Oncology): * 1/2021-12/2021: Takeda [Hypogammaglobulinemia (Subcutaneous IgG, hyaluronic acid, immune globulin (human))] * 1-1

Keywords: primary immune regulatory disorders (PIRD), phenotype, morbidity, ESID registry, clinical score, clinical measure tool

PS024

A PROTEOME-BASED APPROACH FOR THE DIAGNOSIS of INBORN ERRORS of IMMUNITY

PARALLEL SESSION 12: ARTIFICIAL INTELLIGENCE IN IEI

Fumiaki Sakura[1], Hirokazu Kanegane[2], Shigeaki Nonoyama[3], Hidenori Ohnishi[4], Takahiro Yasumi[5], Osamu Ohara[6], Satoshi Okada[1]
[1]Hiroshima University Graduate Schools of Biomedical and Health Sciences, Pediatrics, Hiroshima, Japan, [2]Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Pediatrics And Developmental Biology, Tokyo, Japan, [3]National Defense Medical College, Pediatrics, Saitama, Japan, [4]Gifu University Graduate School of Medicine, Pediatrics, Gifu, Japan, [5]Kyoto University Graduate School of Medicine, Pediatrics, Kyoto, Japan, [6]Kazusa DNA Research Institute, Applied Genomics, Chiba, Japan

Background and Aims: Monogenic germline defects cause Human Inborn Errors of Immunity (IEI). While more than 450 responsible genes have been identified due to advances in next-generation sequencing technology, there is still room for improvement in the efficiency of genetic diagnosis. Recently, proteomics using peripheral blood mononuclear cells (PBMCs) has been well studied. However, previous proteomic studies for PBMCs have had a limitation in the coverage of protein (about 3000). Thereby, more comprehensive data is needed to gain rational insight into the molecular mechanisms underlying aberrant immune systems. This study aimed to elucidate the pathophysiology of IEI using PBMCs' proteomics as the first-tier diagnosis of IEI, and to gain a deeper understanding of genomic etiology using integrated RNA-seq.

Methods: PBMCs were obtained from 70 IEI patients without genetic diagnosis and six healthy subjects. PBMCs' proteomic data obtained from mass spectrometry-based proteomics were optimized by data processing and were employed to explore B- and T-cell dysfunction and elucidate pathogenic proteins.

Results: Data processing yielded optimized data for 6498 proteins among 63 IEI cases and six healthy controls. Comprehensive proteomics covered proteins even in the minor cell fractions in PBMCs and identified cell-deficient cases based on B- and T-cell specific protein profiles. Furthermore, the diagnostic analysis identified the disease-causing protein in four cases, two of which intriguingly showed no significant findings in RNA-seq.

Conclusions: Proteomics provides a deeper insight into the pathogenesis of IEI and improves the efficiency for genetic diagnosis by up to 6%. These findings suggest the utility of a proteomics based diagnostic approach for IEI.

Disclosure: No.

Keywords: Proteomics, Genetic diagnosis, RNA-seq, Inborn errors of immunity

20th ESID Biennial Meeting Anniversary

ORAL COMMUNICATION

OC001

LOSS-OF-FUNCTION MUTATIONS IN PDLIM1 ABROGATE TH17 DIFFERENTIATION BY T-CELL EXHAUSTION IN HUMANS AND MICE

ORAL COMMUNICATIONS SESSION 01: B CELL T-CELL BIOLOGY

Christoph Geier[1,2,3], Akiko Sugimoto[4], Aya Jodo[4], Alexander Leiss-Piller[2], Kai Sauerwein[2,5], Raphael Rossmanith[2,6], Boglarka Ujhazi[7], Krisztian Csomos[7], Martha Eibl[2], Jolan Walter[8], Hermann Wolf[2,9], Takashi Tanaka[4]
[1]University Medical Center Freiburg, Department of Rheumatology And Clinical Immunology, Freiburg, Germany, [2]Immunology Outpatient Clinic, Immunology Outpatient Clinic, Vienna, Austria, [3]University Medical Center Freiburg, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [4]Laboratory for Inflammatory Regulation, Riken Center For Integrative Medical Sciences (ims), Yokohama, Japan, [5]Danube University Krems, Center of Experimental Medicine, Krems an der Donau, Austria, [6]Institute of Molecular Biosciences, University of Graz, Graz, Austria, [7]University of South Florida, Division of Allergy And Immunology, Department of Pediatrics, St. Petersberg, United States of America, [8]Morsani College of Medicine, University of South Florida, Division of Allergy And Immunology, Department of Pediatrics, Tampa, United States of America, [9]Sigmund Freud Private University, Medical School, Vienna, Austria

Background and Aims: PDLIM1, is a member of LIM proteins, that negatively regulates NF-κB-mediated signaling by sequestering p65 in the cytoplasm and suppressing its nuclear translocation. The role of PDLIM1 in human and murine T cell biology remains elusive.

Methods: Whole Exome sequencing was performed in a patient with early onset immune dysregulation and recurrent bacterial infections, born to healthy consanguineous parents, which identified a homozygous loss-of-function mutation in PDLIM1. The immunological phenotype was recapitulated in a PDLIM1 loss-of-function mouse model.

Results: The patient initially presented with immune dysregulation and enhanced proinflammatory cytokine production during infancy and early childhood. At older age, the patient's phenotype shifted to recurrent staphylococcal infection due to a loss of peripheral Th17 cells. Similarly, young Pdlim1$^{-/-}$ mice showed enhanced NF-κB-dependent Th1 and Th17 cell differentiation with exaggerated expression of markers associated with overactivation and premature immunosenescence/exhaustion on Th17 cells. The immunological phenotype was completely reversed in elderly Pdlim1$^{-/-}$ mice with suppressed proinflammatory response and abrogated Th1/17 cell differentiation.

Conclusions: These data identify PDLIM1 as a novel regulator of Th17 differentiation causing inborn error of immunity in humans.

Disclosure: No.

Keywords: T cell, PDLIM1, Th17, Inborn errors of immunity

OC002

IMPAIRED LYMPHOCYTE TRAFFICKING AND PLATELET ACTIVATION IN A PATIENT WITH DE NOVO MUTATION IN RAP1B

ORAL COMMUNICATIONS SESSION 01: B CELL T-CELL BIOLOGY

Marta Benavides-Nieto[1,2,3], Frédéric Adam[4], Emmanuel Martin[5], Chantal Lagresle-Peyrou[6,7], Guillaume Morelle[1,8], Charlotte Boussard[1,8], Isabelle Callebaut[9], Alexandre Kauskot[4], Miao Feng[4], Christelle Repérant[4], Jean-Claude Bordet[10], Chantal Brouzes[11], Christine Bole-Feysot[1,12], Cécile Masson[1,12], Mohammed Zarhrate[1,12], Damien Bodet[13], Jérémie Rouger-Gaudichon[13], Odile Minckes[13], Nathalie Lambert[14], Mathieu Fusaro[14], Capucine Picard[1,5,8,14], Jean-Pierre De Villartay[1,2], Despina Moshous[1,2,8]
[1]Université Paris Cité, Imagine Institute, Paris, France, [2]Genome Dynamics in the Immune System Laboratory, Inserm, Umr1163, Imagine Institute, Paris, France, [3]Supported by the ESID Research Grant (ERG), 2021/2022, Amsterdam, Netherlands, [4]INSERM, UMR_S 1176, Université Paris-saclay, Le Kremlin-Bicêtre, France, [5]Laboratory of Lymphocyte Activation and Susceptibility to EBV Infection, Inserm, Umr 1163, Institut Imagine, Paris, France, [6]Biotherapy Clinical Investigation Center, Groupe Hospitalier Universitaire Ouest , Assistance Publique Des Hôpitaux De Paris (ap-hp), Paris, France, [7]Laboratory of Human Lymphohematopoiesis, Inserm Umr 1163, Imagine Institute, Paris, France, [8]Department of Pediatric Hematology, Immunology and Rheumatology (UIHR), Hôpital Universitaire Necker-enfants Malades, (ap-hp), Paris, France, [9]Muséum National d'Histoire Naturelle, UMR CNRS 7590, Institut De Minéralogie, De Physique Des Matériaux Et De Cosmochimie, Sorbonne Université, Paris, France, [10]Laboratoire d'Hémostase, Centre De Biologie Est, Hospices Civils De Lyon, Bron, France, [11]Laboratory of Onco-hematology, Hôpital Universitaire Necker-enfants Malades, Paris, France, [12]Genomics Core Facility, Institut Imagine-Structure Fédérative de Recherche Necker, Inserm Umr 1163, Inserm Us24/cnrs Ums3633, Paris, France, [13]Department of Pediatric Hematology and Oncology, University Hospital of Caen, Caen, France, [14]Study Center for Primary Immunodeficiencies, Hôpital Universitaire Necker-enfants Malades, (ap-hp), Paris, France

Background and Aims: Ras-related protein 1b (Rap1b) belongs to the Ras-superfamily of small GTPases. Its active form, GTP-Rap1, mediates integrin activation in platelets and lymphocytes thereby regulating adhesion and migration (Stefanini-2018; Shimonaka-2003).

Methods: Whole exome sequencing (WES), Next generation sequencing (NGS), RAP1B-overexpression, functional analysis.

Results: We investigated a boy presenting with neonatal thrombocytopenia, neutropenia, anaemia, low monocyte counts, absolute lymphopenia (balanced lymphocyte subsets, decreased naïve CD4+ and CD8+ T-cells) and profound hypogammaglobulinemia. WES revealed a heterozygous, unknown and predicted deleterious, de novo variant c.35G>A, p.G12E in RAP1B. G12 is located in the RAP1B active site. Interestingly, G12V leads to constitutively activated Rap1 (Scrima-2008). The patient presented an abnormal increase in PBMC migration and integrin activation in resting platelets, as well as increased GTP-RAP1 expression and altered cell cycle in B-EBV cells. G12E and G12V-RAP1B overexpression in a megakaryocytic cell line recapitulated integrin overactivation pattern and abnormal increase in RAP1B-GTP activity (also demonstrated in HEK293T cells) supporting that G12E is a gain-of-function (GOF) mutation. Interestingly, NGS identified RAP1B c.35G>A as a somatic mutation. Variant allele frequency (VAF) in patient's peripheral blood cells decreased over time, while VAF in bone marrow cellular subsets remained stable, suggesting that RAP1B-G12E confers a negative advantage preferentially in the peripheral cell compartments.

Conclusions: We identified the first RAP1B-G12E mutation in a patient with combined immunodeficiency associated to severe platelet dysfunction. We show that this mutation is a de novo somatic GOF mutation suggesting that monoallelic RAP1B mutations should be considered as a novel cause of inborn errors of immunity associated to thrombocytopathy.

Disclosure: No.

Keywords: integrin activation, thrombocytopathy, primary immunodeficiency, Ras superfamily of small GTPases, combined immunodeficiency, Ras-related protein 1b (RAP1B)

OC003

ALTERED T CELL DIFFERENTIATION ASSOCIATED WITH ACTIVATED PI3 KINASE DELTA

ORAL COMMUNICATIONS SESSION 01: B CELL T-CELL BIOLOGY

Pamela Schwartzberg, Jennifer Cannons, Dominic Golec, Andrea Pichler
National Institutes of Health, National Institute of Allergy And Infectious Diseases, Bethesda, United States of America

Background and Aims: Activated PI3K-delta syndrome (APDS) is a primary immunodeficiency caused by heterozygous activating mutations of Pik3cd, resulting in dysregulated immunity, recurrent respiratory infections and lymphoproliferation, yet underlying mechanisms behind these phenotypes remain unclear.

Methods: Using patient samples and a mouse model ($Pik3cd^{E1020K/+}$ mice), we have evaluated CD4 and CD8 T cell function both in culture and in vivo in response to infectious agents, evaluating cellular phenotypes, metabolism, gene expression and chromatin organization.

Results: We find that $Pik3cd^{E1020K/+}$ $CD8^+$ T cells exhibited accelerated differentiation to short-lived effectors, associated with increased mTORC1 and c-Myc pathways, as well as altered metabolic, transcriptional and epigenetic circuits characterized by a pronounced IL-2/STAT5 signature associated with heightened IL-2 responses that prevented differentiation to memory-like cells in the presence of IL-15.. Conversely, $Pik3cd^{E1020K/+}$ $CD8^+$ T cells failed to sustain expression of proteins critical for maintenance of long-lived memory cells, including TCF1, and mounted inadequate central memory responses in vivo with enhanced generation of recently-described long-lived effector populations. We now have examined responses to chronic infection using Clone 13 LCMV as a model pathogen, where we find that $Pik3cd^{E1020K/+}$ mice lose TCF1+ progenitor $CD8^+$ T cells, leading to an altered balance of effector and exhausted cells associated with increased immunopathology. Similarly, we find altered differentiation of CD4 cells from $Pik3cd^{E1020K/+}$ mice, with increased inflammatory cytokine production and immunopathology in vivo.

Conclusions: Our data position PI3Kd as a central hub integrating multiple signaling nodes that promote an accelerated effector T cell program at the expense of central memory.

Disclosure: No.

Keywords: Activated PI3 Kinase Delta Syndrome, TCF1, metabolism, chromatin, Effector T cells

OC004

DISTINCT CD8 T CELL POPULATIONS WITH DIFFERENTIAL EXHAUSTION PROFILES ASSOCIATE WITH SECONDARY COMPLICATIONS IN COMMON VARIABLE IMMUNODEFICIENCY

ORAL COMMUNICATIONS SESSION 01: B CELL T-CELL BIOLOGY

Adam Klocperk[1], David Friedmann[2], Emilia Schlaak[3], Susanne Unger[4], Ondrej Vladyka[1], Zuzana Parackova[5], Sigune Goldacker[2], Anna Sediva[5], Bertram Bengsch[3], Klaus Warnatz[6]
[1]2nd Faculty of Medicine, Charles University and University Hospital in Motol, Department of Immunology, Prague, Czech Republic, [2]Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Center For Chronic Immunodeficiency (cci), Freiburg im Breisgau, Germany, [3]Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Clinic For Internal Medicine Ii, Freiburg im Breisgau, Germany, [4]University of Zurich, Institute of Experimental Immunology, Zurich, Switzerland, [5]Faculty Hospital in Motol, Department of Immunology, Prague, Czech Republic, [6]Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany

Background and Aims: Common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency, with heterogeneous clinical presentation. Our goal was to analyze CD8 T cell homeostasis in patients with infection only CVID, compared to those additionally affected by dysregulatory and autoimmune phenomena.

Methods: Flow and mass cytometry evaluation of peripheral blood of 40 patients with CVID and 17 healthy donors.

Results: CD8 T cells are skewed in patients with CVID, with loss of naïve and increase of effector memory stages, expansion of cell clusters with high functional exhaustion scores, and a highly activated population of cells with immunoregulatory features, producing IL-10. These findings correlate to clinically widely used B-cell-based EURO classification. Features of exhaustion, including loss of CD127, CD28 and expression of TIGIT and PD-1 in CD8 T cells are strongly associated with interstitial lung disease and autoimmune cytopenias, whereas CD8 T cell activation with elevated HLA-DR and CD38 expression predict non-infectious diarrhea.

Conclusions: We demonstrate features of advanced differentiation, exhaustion, activation and immunoregulatory capabilities within CD8 T cells of CVID patients. Assessment of CD8 T cell phenotype may allow risk-assessment of CVID patients, and provide new insights into CVID pathogenesis, including a better understanding of mechanisms underlying T cell exhaustion and regulation.

Disclosure: No.

Keywords: CVID, regulation, CyTOF, complication, T cells, exhaustion

OC005

DOMINANT INTERFERING CARD11 VARIANTS DISRUPT JNK SIGNALING IN T CELLS

ORAL COMMUNICATIONS SESSION 01: B CELL T-CELL BIOLOGY

Bradly Bauman[1,2], Andrew Frank[3], Gauthaman Sukumar[1,4], Clifton Dalgard[3,4,5], Alice Y Chan[6], Andrew Snow[2]
[1]Henry M. Jackson Foundation for the Advancement of Military Medicine, -, Bethesda, United States of America, [2]Uniformed Services University of the Health Sciences, Pharmacology And Molecular Therapeutics, Bethesda, United States of America, [3]Uniformed Services University of the Health Sciences, Student Bioinformatics Initiative, Center For Military Precision Health, Bethesda, United States of America, [4]Uniformed Services University of the Health Sciences, The American Genome Center, Center For Military Precision Health, Bethesda, United States of America, [5]Uniformed Services University of the Health Sciences, Department of Anatomy, Physiology & Genetics, Bethesda, United States of America, [6]University of California, Division of Pediatric Allergy Immunology Bmt, Division of Pediatric Rheumatology, Department of Pediatrics, San Francisco, United States of America

Background and Aims: Although previous studies implicated c-Jun N-terminal kinase 1 and 2 (JNK1/2) in helper $CD4^+$ T cell differentiation, mechanisms governing JNK signaling and function in human lymphocytes remain nebulous. CARD11 is a lymphocyte-specific scaffold protein connecting antigen receptor (AgR) engagement to transcriptional programs (e.g. NF-κB) responsible for effector cell survival, proliferation, and differentiation. Beyond NF-κB, CARD11 is also required for AgR-induced mTORC1 and JNK2 signaling. We sought to define the impact of dominant interfering (DI) CARD11 variants on JNK signaling and JNK-dependent transcription in T cells.

Methods: We transfected CARD11 knockout (KO) Jurkat T cells with wild-type (WT) and DI CARD11 expression plasmids to assess effects on AgR-induced JNK signaling. RNA sequencing was performed on mitogen-activated WT and CARD11 KO T cells with or without JNK inhibition to define JNK-dependent transcriptomic changes.

Results: We found that AgR-dependent JNK1 and JNK2 phosphorylation is CARD11-dependent. Furthermore, heterozygous DI CARD11 mutations derived from patients with CARD11-associated atopy with dominant interference of NF-κB signaling (CADINS) disease disrupted AgR-dependent JNK1/2 phosphorylation and c-Jun accumulation with variable potency, mirroring the extent of impaired NF-κB activation. Intriguingly, JNK inhibition in WT Jurkat and primary $CD4^+$ T cells resulted in elevated expression of GATA3, the master transcriptional regulator of Th2 cell differentiation.

Conclusions: Our novel findings suggest that defective CARD11-dependent JNK signaling in $CD4^+$ T cells may contribute to severe allergic disease manifestations noted in CADINS patients, unveiling a new potential therapeutic target.

Disclosure: No.

Keywords: JNK, atopy, CADINS, NF-kB, T cells, CARD11

OC006

HYPOMORPHIC LCK MUTANT RESULTS IN IMMUNODEFICIENCY AND INTESTINAL INFLAMMATION

ORAL COMMUNICATIONS SESSION 01: B CELL T-CELL BIOLOGY

Victor Lui[1], Manfred Hönig[2], Klaus Schwarz[3], Elena Hsieh[1]
[1]University of Colorado Anschutz Medical Center, Immunology And Microbiology, Aurora, United States of America, [2]University Hospital of Ulm, Germany, Bone Marrow Transplant, Ulm, Germany, [3]University Ulm, Institute For Transfusion Medicine, Ulm, Germany

Background and Aims: Partial T cell primary immunodeficiency disorders are a group of inborn errors of immunity (IEI) that have partial reduction of T cell number/function and are commonly associated with autoimmune and inflammatory complications. T cell receptor (TCR) signaling is initiated by Lymphocyte cell-specific protein-tyrosine kinase (LCK). A novel homozygous mutation in LCK (p.Pro440Ser, LCK P440S) was identified in two siblings who were born to consanguineous parents, presenting with T lymphopenia, recurrent viral and fungal infections, and gastrointestinal inflammatory complications. Hypothesis: The P440S mutation impairs LCK expression/function such that T cell-mediated intestinal immunity is dysfunctional, leading to intestinal inflammation (colitis). Aim 1: Determine effect of the P440S mutation on LCK expression/function in TCR signaling. Aim 2: Determine etiology of colitis in mice harboring Lck P440S (lck mut).

Methods: We generated a cell line and a mouse model that harbor the mutant kinase, and performed downstream immunophenotypic and functional assessments.

Results: The P440S mutation results in shorter protein half-life, decreased protein expression, and defective TCR signaling responses. Similarly to the lck-/- mice, the lck Mut mice demonstrate impaired thymocyte development with T cell lymphopenia, and skewed memory phenotype of peripheral T cells. However, unlike the lck-/-, only the lck mut mice develop colitis, suggesting that the partial loss of Lck function drives colitis development.

Conclusions: Our findings explain the aberrant immunological presentation of the human P440S patients, advance our understanding of intestinal inflammation in the context of partial T cell defects, and establish a model system with which to develop therapies against intestinal inflammation in IEI.

Disclosure: No.

Keywords: Lck, T cell development, Primary Immunodeficiency disorders, T cell signaling, Immune Dysregulation, Very early onset inflammatory bowel disease

OC007

UNEXPECTEDLY LOW PROPORTION of DONOR B CELLS ALLOWS FOR B-CELL FUNCTION POST HSCT IN PATIENTS WITH B-POS SCID

ORAL COMMUNICATIONS SESSION 01: B CELL T-CELL BIOLOGY

Eva Jacobsen, Abdallah Khazaleh, Andrea Hänsler, Carmen Blum, Ulrike Tengler, Gudrun Kirsch, Kerstin Felgentreff, Ingrid Furlan, Klaus Debatin, Wilhelm Friedrich, Ansgar Schulz, Manfred Hönig
University Medical Center Ulm, Germany, Department of Pediatrics And Adolescent Medicine, Ulm, Germany

Background and Aims: In patients with B-cell positive severe combined immunodeficiency (B+ SCID) due to mutations in IL2RG, B-cell function after HSCT depends on the engraftment of donor B lymphocytes. To study development and function of autologous and donor B-cells in patients with mixed chimerism after HLA-haploidentical HSCT, we analyzed blood samples of 12 long term surviving patients (1 to 34 years of follow up) with B+ SCID. All patients developed normal specific humoral immune function and are independent of Ig-substitution.

Methods: We used staining with allele-specific antibodies targeting HLA-molecules to characterize the maturation stages of donor- and autologous B-cells by flow-cytometry.

Results: We demonstrate a complete lack of switched memory B-cells (CD19+IgM-CD27+) in the autologous compartment but detected a percentage of up to 19% of CD27+ in CD19+ autologous cells, which were identified as IgM+CD27+ marginal-zone (MZ)-like B-cells. Class switched memory B-cells were strictly confined to donor derived B-cells and surprisingly a proportion of 0.9% of donor B-cells detected in peripheral blood was found sufficient to allow for normal B-cell function. Beyond that we found a negative correlation between the proportion of donor-cells and the percentage of switched memory B-cells in the donor derived B-cell compartment indicating a relative lack of naïve B-cells in patients with low B-cell-donorchimerism.

Conclusions: We identified unexpectedly low proportions (0,9-17%) of donor B-cells in the peripheral blood in 4/12 patients as sufficient for normal B-cell function, and further specified the phenotypic, transcriptional and epigenetic consequences of common-gamma-chain deficiency in autologous B-cells in the presence of normal T-cell function.

Disclosure: No.

Keywords: B-cell positive SCID, B-cell maturation and function, HLA-haploidentical Hematopoietic stem cell transplantation (HLA-haplo HSCT), HLA-chimerism analysis

OC008

THE ABACHAI CLINICAL TRIAL PROTOCOL: SAFETY AND EFFICACY of ABATACEPT (S.C.) IN PATIENTS WITH CTLA-4 INSUFFICIENCY OR LRBA-DEFICIENCY – ESTABLISHMENT of A DISEASE-SPECIFIC SCORING SYSTEM

ORAL COMMUNICATIONS SESSION 02: AUTOINFLAMMATION AND IMMUNE DYSREGULATION

Mate Krausz[1,2,3], Annette Uhlmann[2,4], Ina Rump[1], Gabriele Ihorst[4], Sigune Goldacker[1], Georgios Sogkas[5], Reinhold Schmidt[5], Manuel Feißt[6], Laia Alsina[7], Ingunn Dybedal[8], Mike Recher[9], Sara Posadas-Cantera[10], Klaus Warnatz[11], Bodo Grimbacher[1,2,12,13,14]
[1]Medical Center – University of Freiburg, Faculty of Medicine, Department of Rheumatology And Clinical Immunology, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [2]University Hospital Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [3]Albert-Ludwigs-University of Freiburg, Faculty of Biology, Freiburg, Germany, [4]Medical Center, Faculty of Medicine, Albert-Ludwigs-University of Freiburg, Clinical Trials Unit, Freiburg, Germany, [5]Hannover Medical School, Rheumatology And Immunology, Hannover, Germany, [6]Medical Center – University of Heidelberg, Institut Für Medizinische Biometrie Und Informatik, Heidelberg, Germany, [7]Hospital Sant Joan de Déu, Allergy And Clinical Immunology Department, Esplugues del Llobregat, Spain, [8]Oslo University Hospital, Rikshospitalet, Oslo, Norway, [9]University Hospital Basel, Outpatient Clinics Immunology, Basel, Switzerland, [10]Medical Center, University of Freiburg, Germany, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [11]Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany, [12]DZIF – German Center for Infection Research, Satellite Center Freiburg, Germany, Freiburg, Germany, [13]Albert-Ludwigs University, Freiburg, Cibss – Centre For Integrative Biological Signalling Studies, Freiburg, Germany, [14]RESIST – Cluster of Excellence 2155, Hanover Medical School, Satellite Center Freiburg, Freiburg, Germany

Background and Aims: CTLA-4 insufficiency and LRBA-deficiency are both complex immune dysregulation syndromes with an underlying regulatory T cell dysfunction due to the lack of CTLA-4 protein. As anticipated, the clinical phenotypes of CTLA-4 insufficiency and LRBA deficiency are similar. Main manifestations include hypogammaglobulinemia, lymphoproliferation, autoimmune cytopenia, immune-mediated respiratory, gastrointestinal, neurological, and skin involvement, which can be severe and disabling. The rationale of this clinical trial is to improve clinical outcomes of affected patients by substituting the deficient CTLA-4 by administration of CTLA4-Ig (abatacept) as a causative personalized treatment. Our objective is to assess the safety and efficacy of abatacept for patients with CTLA-4 insufficiency or LRBA deficiency. The study will also establish a CTLA4- and LRBA-specific disease-severity scoring system and investigate how treatment with abatacept affects the patients' quality of life.

Methods: ABACHAI is a phase IIa prospective, non-randomized, open-label, single arm multi-center trial. Altogether 20 adult patients will be treated with abatacept 125 mg s.c. on a weekly basis for 12 months, including (1) patients already pretreated with abatacept, and (2) patients not pretreated, starting with abatacept therapy at the baseline study visit. For the evaluation of drug safety infection control during the trial, for efficacy, a newly developed CHAI-Morbidity Score will be used.

Results: The trial was fully recruited in March 2022; altogether 18 CTLA-4 and 2 LRBA patients were included.

Conclusions: The trial is registered in the German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS) with the identity number DRKS00017736. Final results of this clinical trial are expected for 2023.

Disclosure: The study ist supported German Federal Ministry for Education and Research (BMBF) through a grant to the German Auto-Immunity Network (GAIN) [grant 01GM1910B]. The trial medication is provided by Bristol-Myers Squibb (BMS, New York, USA) [grant IM101-774]

Keywords: Abatacept, clinical trial protocol, disease severity score, immunodeficiency, CTLA-4 insufficiency, LRBA deficiency

OC009

LRBA DRIVES ACTIN CYTOSKELETON DYNAMICS THROUGH INTERACTION WITH MYOSIN-9

ORAL COMMUNICATIONS SESSION 02: AUTOINFLAMMATION AND IMMUNE DYSREGULATION

Vanessa Zeidler[1], Elena Sindram[2,3,4], Emily Mace[5], Bodo Grimbacher[1,6,7,8,9], Laura Gámez-Díaz[1]
[1]Center for Chornic Immunodeficiency (CCI), Institute For Immunology, University Medical Center Freiburg, Freiburg, Germany, [2]Albert-Ludwigs-University of Freiburg, Spemann Graduate School of Biology And Medicine (sgbm), Freiburg, Germany, [3]Albert-Ludwigs-University of Freiburg, Faculty of Biology, Freiburg, Germany, [4]Medical Center Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency, Freiburg, Germany, [5]Vagelos College of Physicians and Surgeons, Columbia University, New York City, United States of America, [6]Satellite Center Freiburg, German Center For Infection Research (dzfi), Freiburg, Germany, [7]Satellite Center Freiburg, Resolving Infection Susceptibility (resist) - Cluster of Excellence 2155 To Hannover Medical School, Freiburg, Germany, [8]Center for Integrative Biological signaling Studies (CIBSS), University of Freiburg, Freiburg, Germany, [9]University Hospital Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Freiburg, Germany

Background and Aims: LPS-responsive beach-like anchor protein (LRBA) is an essential regulator of cytotoxic T-lymphocyte antigen-4 (CTLA 4) trafficking in regulatory T cells. Hence, loss of LRBA (as observed in LRBA deficiency) decreases the extracellular expression of CTLA4 leading to uncontrolled T-cell activation. However, this mechanism does not explain the poor humoral response frequently observed in LRBA-deficient patients, suggesting an additional role of LRBA in B-lymphocytes.

Methods: Using a combination of SILAC (stable isotope labelling by amino acids cell culture) with IP (immunoprecipitation) and MS (mass spectrometry) in human B cells, we identified 63 potential LRBA interactor proteins, of which 12 were associated with cytoskeleton dynamics.

Results: Following validation experiments, we found that LRBA is in close proximity with Myosin-9 (MYH9), a conventional non-muscle myosin, essential for cell migration, endocytosis, as well as for the maturation of the immune synapse. In fact, we observed a reduced chemokine-driven migration of LRBA-KO Ramos B-cells towards C-X-C motif chemokine 12 (CXCL12) in comparison to wild-type cells. In addition, we observed that loss of LRBA impairs the B-cell receptor (BCR) internalization and the BCR-mediated phagocytosis of IgM-coated beads in Ramos B-cells. Moreover, we detected a trend towards a delayed antigen internalization, as well as an abnormal immune synapse formation in the absence of LRBA. Taken together, our results indicate that the LRBA:MYH9 interaction is essential for cytoskeleton-dependent immune function in B-cells.

Conclusions: Disruption may lead to B-cell abnormalities, contributing to the defective humoral immune response, as observed in patients with LRBA deficiency.

Disclosure: No.

Keywords: LRBA, cytoskeleton, Migration, Myosin 9, phagocytosis

OC010

IMPACT of CASPASE 10 MUTATIONS IN AUTOIMUNE LYMPHOPROLIFERATIVE SYNDROME OUTCOME

ORAL COMMUNICATIONS SESSION 02: AUTOINFLAMMATION AND IMMUNE DYSREGULATION

Solange Andrea Moreno Yanino[1], Blanca Viñuales Colell[1], Olivier Pellé[1], Frédéric Rieux-Laucat[2], Aude Magerus[1]
[1]Imagine Institute, Immunogenetic of Pediatric Autoimmune Diseases, Paris, France, [2]1. Institut National de la Santé et de la Recherche Médicale, Mixed Research Unit 1163, Laboratory of Immunogenetics of Paediatric Autoimmunity-Necker Enfants Malades Hospital, PARIS, France

Background and Aims: The Autoimmune Lymphoproliferative Syndrome (ALPS) is a rare genetic disorder with early-onset non-infectious non-malignant lymphoproliferative disease and autoimmune cytopenia. The main genetic defects involved in ALPS are mutations affecting the death receptor FAS or its ligand (FASLG). CASPASE 10 (CASP10) variants have been also described in ALPS patients, but their causal role remains debated given their high frequencies in the general population. The aim of this work was to elucidate the impact of those CASP10 variants on the apoptosis function of lymphocytes from healthy individuals.

Methods: By using the in-house IMAGINE- bioinformatic tool “Polyweb” (including more than 70 000 samples) we identified healthy carriers of CASPASE 10 mutations. By using a well described and routinely used apoptosis assays, we compared the apoptosis function in B-EBV and in activated T cells from healthy individuals carrying wild-type (wt) CASP10 or one of the 3 controversial CASP10 variants: p.401fs (c.1202-1208 del), p.Y446 (c.1337 A>G) and p.V410I (c.1228 G>A), either heterozygous or homozygous.

Results: The proportions of FAS- or TRAIL-sensitive lymphocytes were strictly similar between the CASP10 wt and mutated cells. Moreover, the apoptosis function remained totally preserved in lymphocytes carrying a homozygous deletion leading to a complete CASPASE 10 expression defect.

Conclusions: The results showed that CASPASE 10 is dispensable for the FAS- and TRAIL-induced apoptosis in lymphocytes from healthy individuals, thereby ruling-out a functional role of the previously described CASP10 variants in ALPS patients.

Disclosure: No.

Keyword: ALPS, caspase 10, homozygous, variants, apoptosis, role

OC011

SINGLE-CELL TRANSCRIPTOMICS EXPLORATION of PATIENTS WITH STING-ASSOCIATED VASCULOPATHY WITH ONSET IN INFANCY (SAVI)

ORAL COMMUNICATIONS SESSION 02: AUTOINFLAMMATION AND IMMUNE DYSREGULATION

Camille De Cevins[1,2], Laure Delage[3,4], Marine Luka[1,5], Alain Fischer[6,7,8], Franck Augé[2], Galina Boldina[2], Frédéric Rieux-Laucat[9], Mickael Ménager[1,5]
[1]Imagine Institute, Laboratory of Inflammatory Responses And Transcriptomic Networks In Diseases, Atip-avenir, Paris, France, [2]Sanofi, Artificial Intelligence & Deep Analytics (aida) Group, Data & Data Science (dds), Chilly-Mazarin, France, [3]Imagine Institute, Immunogenetic of Pediatric Autoimmune Diseases, Paris, France, [4]Université Paris Cité, Immunogenetics of Pediatric Autoimmune Diseases, Imagine Institute, Inserm Umr 1163, Paris, France, [5]Imagine Institute, Labtech Single-cell@imagine, Paris, France, [6]Collège de France, Collège De France, Paris, France, [7]Imagine Institute, Université De Paris, Paris, France, [8]Necker Hospital, Pediatric Hematology-immunology And Rheumatology Unit, Paris, France, [9]1. Institut National de la Santé et de la Recherche Médicale, Mixed Research Unit 1163, Laboratory of Immunogenetics of Paediatric Autoimmunity- Necker Enfants Malades Hospital, PARIS, France

Background and Aims: SAVI (STING associated vasculopathy with onset in infancy) is an interferonopathy characterized by inflammation of several organs. SAVI is due to mutations in STING1, which codes for STING, whose activation by cytosolic dsDNA triggering the production of type-I interferon (IFN). These mutations lead to constitutive IFN signalling and sustained inflammation. To better understand SAVI, we aim to define which pathways are dysregulated in PBMCs of patients and identified the ones that are under the direct and/or indirect control of this excessive and uncontrolled type-I IFN production. These dysregulated pathways could later be used for a better understanding of SAVI pathophysiology and open new areas of research and potential therapeutic treatments.

Methods: Two single-cell RNAseq datasets have been generated on PBMCs. A first dataset on SAVI patients revealed some cell-type specific molecular mechanisms of SAVI. A second dataset was created to establish the kinetic of response to type-I IFN: PBMCs from healthy blood donors were stimulated at several timepoints using IFNβ. The transcriptome from 100,000 single cells allowed us to identify the molecular pathways and transcription factors specific to IFN and compare them to SAVI patients.

Results: SAVI patients were found to have drastic lymphopenia, associated with a T cell hyperactivation, exhaustion and apoptosis. This T cell hyperactivation was not reproduced by type-I IFN stimulation. We also observed strong hyperinflammation in monocytes associated with ER stress.

Conclusions: Our results suggest an hyperinflammation of monocytes associated with cellular/ER stress which triggers T lymphocytes hyperactivation, senescence and apoptosis

Disclosure: No.

Keywords: single-cell RNAseq, SAVI, type I interferon, Pediatric disease

OC012

AN UPDATE of THE INTERNATIONAL REGISTRY ON COVID-19 RELATED HYPERINFLAMMATION IN CHILDREN AND YOUNG ADULTS (HYPERPED-COVID)

ORAL COMMUNICATIONS SESSION 02: AUTOINFLAMMATION AND IMMUNE DYSREGULATION

Roberta Caorsi[1], Alessandro Consolaro[1], Claudia Bracaglia[2], Francesca Minoia[3], Marco Cattalini[4], Paul Brogan[5], Carine Wouters[6], Andrea Taddio[7], Fabio Candotti[8], Isabelle Meyts[9], Fabrizio De Benedetti[2], Nicolino Ruperto[10], Marco Gattorno[1]
[1]IRCCS Giannina Gaslini Institute, Pediatric Rheumatology, Genova, Italy, [2]IRCCS Ospedale Pediatrico Bambino Gesù, Division of Rheumatology, Roma, Italy, [3]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlnico, Pediatric Department, Milano, Italy, [4]Pediatrics Clinic, Department of Clinical and Experimental Sciences, University of Brescia, Asst Spedali Civili Di Brescia, Brescia, Italy, [5]UCL GOS Institute of Child Health, Division of Rheumatology, London, United Kingdom, [6]KU Leuven, Pediatric Rheumatology And Immune-inflammatory Diseases, Leuven, Belgium, [7]Institute for Maternal and Child Health IRCCS "Burlo Garofolo" and Univerisity of Trieste, Pediatric Rheumatology, Trieste, Italy, [8]Division of Immunology and Allergy, Chuv, Lausanne, Switzerland, [9]KU Leuven, Department of Immunology, Microbiology And Transplantation, Laboratory of Inborn Errors of Immunity, Leuven, Belgium, [10]IRCCS Giannina Gaslini Institute, Pediatric Rheumatology, Printo, Genova, Italy

Background and Aims: The Multisystem Inflammatory Syndrome in Children (MIS-C), is a serious inflammatory condition characterized by a systemic inflammation with multiorgan failure, that can occur in children and young adults after COVID-19 infection. Ain of the study is to create an International multicenter collection of patients with MIS-C involving the main pediatric networks committed in the care of patients with hyperinflammatory conditions.

Methods: a steering committee constituted by representatives of ERN-RITA, PRES, ESID and ISSAID and with the coordination of PRINTO developed a shared form to collect clinical manifestations, laboratory features, response to treatment and outcome of patients with MIS-C. The registry is available online on PRINTO and ESID websites (www.printo.it , www.ESID.org).

Results: Currently, more than 1000 patients from 44 centers of 20 countries worldwide have been included in the study; completed data are available for 688 patients. 56 (8%) patients were younger than 2 years, 173 (25%) 2-6 years, 279 (41%) between 6-12 years, while 180 (26%) patients were older than 12 years. 234 (34%) patients required ICU admission; 51 (7.4%) patients presented long term sequaele and 7 (1%) patients died. Mucocutaneous manifestation were observed in 85.2% of patients, hematological in 84.7%, gastrointestinal in 80.8%, cardiovascular in 52.3%, lymphoid organ in 51.7%, respiratory in 34.6%, musculoskeletal in 31.5%, neurological in 19%, genito-urinary in 10.9%. 576 patients (84%) recieved Ig infusions and 572 (83%) corticosterois; 78 (11%) were treated with biologics.

Conclusions: The first analysis confirms that MISC is a severe inflammatory condition, requiring anti-inflammatory treatment. Even if the mortality rate is low, one third of patients required ICU admission.

Disclosure: No.

Keyword: MIS-C, COVID19, registry

OC013

EXOME SEQUENCING IN EARLY-ONSET OR FAMILIAL SYSTEMIC LUPUS ERYTHEMATOSUS

ORAL COMMUNICATIONS SESSION 02: AUTOINFLAMMATION AND IMMUNE DYSREGULATION

Maud Tusseau[1], Quentin Riller[2], Marie Jeanpierre[2], Anne-Laure Mathieu[3], Héloïse Reumaux[4], Eric Hachulla[5], Gaetan Lesca[6], Brigitte Bader-Meunier[7], Frédéric Rieux-Laucat[2], Alexandre Belot[1]
[1]Centre International de Recherche en Infectiologie, Inserm U1111, Lyon, France, [2]Université Paris Cité, Immunogenetics of Pediatric Autoimmune Diseases, Imagine Institute, Inserm Umr 1163, Paris, France, [3]21 avenue Tony Garnier, Ciri U1111, LYON, France, [4]Univ Lille, CHU Lille, Urgences Pédiatriques Maladies Infectieuses Et Rhumatologie Pédiatrique, LILLE, France, [5]Univ. Lille, CHU Lille, Département De Médecine Interne Et Immunologie Clinique, Centre De Référence Des Maladies Systémiques Et Auto-immunes Rares Du Nord-ouest, LILLE, France, [6]Lyon University Hospitals, Lyon, France, Department of Genetics,, LYON, France, [7]Necker Hospital for Sick Children, Pediatric Immunology, Hematology And Rheumatology Unit, Paris, France

Background and Aims: Systemic lupus erythematosus is an autoimmune disease characterized by the production of antibodies against nucleic acids and an upregulation of type-I interferon in most patients. The etiology of the disease is unexplained in most cases but is thought to involve both genetic and environmental factors.

Methods: We selected from our national lupus biobank patients fulfilling at least one of the following criteria: (1) male patients, (2) onset of the disease < 12 years old, (3) family history of autoimmune diseases and we performed whole exome sequencing in 118 families using Illumina technology. We used in silico panels in a diagnosis-based approach and explore the whole data to identify new disease-causing genes.

Results: We identified pathogenic or probably pathogenic variations (according to ACMG classification) in genes related to inborn errors of immunity in 6 patients (ADAR, C1QA, PSTPIP1, IRAK4, PTPN11, COPA). A genetic diagnosis involving a gene never related to lupus (MAN1B1, ETV6, BAZ2B, IGHMBP2) was identified in 4 patients (3,3%). Ten percent of families present a variation of undetermined significance. Besides, the research approach revealed many candidate genes, among which SOCS1 and PTPN2 were confirmed as disease causing thanks to collaboration and functional studies.

Conclusions: This study confirms the interest of exome sequencing in preselected lupus patients with a diagnosis rate of 13% of monogenic SLE. It demonstrates the superiority of the exome over panel sequencing in lupus, with a genetic diagnosis in unexpected genes in 3,3% percent of cases and the possibility of discovery-based approaches.

Disclosure: No.

Keywords: Exome sequencing, monogenic lupus, pediatric lupus, NGS

OC014

RAC2 MUTATIONS AND IMMUNE DEFICIENCY – FUNCTIONAL SPECTRUM of AN INTERNATIONAL COHORT

ORAL COMMUNICATIONS SESSION 02: AUTOINFLAMMATION AND IMMUNE DYSREGULATION

Svetlana Sharapova[1], Agnes Donko[2], Louis Marois[3], Christine Winterbourn[4], Louisa Ashby[4], Timi Martelius[5], Mikko R J Seppänen[6], Jennifer Leiding[7], Jolan Walter[8], Timothy Trojan[9], Paul Martin[10], Jenna Bergerson[2], Nicholas Campbell[11], Kuang Hsiao[12], Emilia Falcone[3], Steven Holland[2], Thomas Leto[2], Amy Hsu[2]
[1]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Research Department, Minsk, Belarus, [2]National Institutes of Health, National Institute of Allergy And Infectious Diseases, Bethesda, United States of America, [3]Montreal Clinical Research Institute, Department of Medicine, Montreal (Quebec), Canada, [4]University of Otago, Pathology And Biomedical Science, Christchurch, New Zealand, [5]Helsinki University Central Hospital, Inflammation Center / Infectious Diseases, Helsinki, Finland, [6]University of Helsinki and HUS Helsinki University Hospital, Rare Disease Center, Children's Hospital, And Adult Primary Immunodeficiency Outpatient Clinic, Inflammation Center, Helsinki, Finland, [7]Johns Hopkins All Children's Hospital, Immunology, St. Petersburg, United States of America, [8]Johns Hopkins All Children's Hospital, St. Petersburg, Division of Allergy/immunology, Department of Pediatrics, St.Petersburg, United States of America, [9]Allergy Partners of Oklahoma, Allergy, Enid, United States of America, [10]Duke University School of Medicine, Pediatrics, Durham, United States of America, [11]University of Laval, Hematology, Quebec City, Canada, [12]University of Aukland, School of Medicine, Aukland, New Zealand

Background and Aims: Mutations in RAC2, were first identified in neonates carrying RAC2 dominant negative, p.D57N, who presented with severe neutrophil defects and T-cell lymphopenia. Subsequently, dominant-activating mutations were reported in patients with combined immunodeficiency/immunodysregulation (CIID) or SCID. We assembled an international cohort of 48 published and unpublished patients with RAC2 mutations to characterize the spectrum of disease.

Methods: Clinical and immunologic phenotypes of 48 germline-mutant RAC2 patients were obtained from referring physicians and literature reports. Heterologous expression assays including superoxide production, PAK1 binding, AKT activation were used to characterize RAC2 variant effects. Protein stability was determined by western blot.

Results: Patient presentation varied by mutation; five patients presented as SCID with reticular dysgenesis, five as neonatal neutrophil deficiency (D57N), and 38 as CIID. Patients with dominant, active RAC2 variants with high protein stability (Q61R, Q61K) presented in the first days of life with SCID and absent lymphocytes. Activating variants with lower stability (I21S, E62K, N92K, N92S) presented as CIID with lymphopenia, detectable by newborn screening but presenting later with recurrent sinopulmonary and viral infections. A third class of mutations with unstable transcript or protein were phenotypic only in homozygosity (W56*, R68W). Severity of phenotype and initial clinical presentation was correlated with protein stability - increased stability led to neonatal presentation and dominant mutations with decreased stability had later clinical onset.

Conclusions: Clinical presentation of RAC2 mutation-bearing patients is determined by a combination of protein activity and stability. Heterologous expression and analysis is useful for deciphering the molecular basis of the clinical phenotype.

Disclosure: No.

Keywords: RAC2, genotype phenotype, cohort

OC015

INVESTIGATING THE PATHOPHYSIOLOGY of LUNG DISEASE IN STAT3-HYPER IGE SYNDROME

ORAL COMMUNICATIONS SESSION 03: INNATE IMMUNE DEFECTS

Verena Haefner[1,2,3,4], David Kutschke[3], Carola Voss[3,4], Christine Wolf[1,2], Renate Effner[1,2], Tobias Stoeger[3,4], Ellen Renner[1,2,5], Beate Hagl[1,2]
[1]Technical University of Munich, Translational Immunology In Environmental Medicine, School of Medicine, Klinikum Rechts Der Isar, Munich, Germany, [2]Helmholtz Zentrum Munich, Translational Immunology, Institute of Environmental Medicine, Neuherberg, Germany, [3]Helmholtz Zentrum Munich, Institute of Lung Health And Immunity, Comprehensive Pneumology Center, Neuherberg, Germany, [4]German Center for Lung Research, (dzl), Munich, Germany, [5]Technical University of Munich, Department of Pediatrics, School of Medicine, Klinikum Rechts Der Isar, Munich, Germany

Background and Aims: STAT3-hyper IgE syndrome (STAT3-HIES) patients suffer from recurrent lung infections, leading to tissue destructive changes with pneumatocele formation and severe lung defects. To improve the pulmonary therapy of STAT3-HIES patients, we aim to better understand the pathophysiology underlying the destructive lung disease.

Methods: Using a transgenic mouse model (mutStat3) with a STAT3-HIES like immunologic phenotype carrying the dominant negative mutation Stat3-ΔV463 (Steward-Tharp et al. Blood 2014), we model lung infections by inducing acute lung injury with intratracheal instillation of lipopolysaccharide (LPS). Inflammatory responses and tissue injury were analyzed by quantification of bronchoalveolar lavage (BAL) cells, ELISA, and protein quantification of BAL fluid. Lung tissue was collected for histology and expression analysis.

Results: Instillation of LPS induced lung injury in a dosage-dependent manner in wildtype (wt) and mutStat3 mice as shown by an overall increase in BAL protein concentrations with higher levels in mutStat3 compared to wt samples. We found increased immune cell infiltration predominantly neutrophils and increased TNFalpha release into the air space significant higher in mutStat3 compared to control animals. Quantification of immunohistologically stained lung tissue with pro surfactant protein C (pro-SpC) as a marker for alveolar type II (AT2) cells, showed reduced positive pro-SpC cells in lung tissue in mutStat3 compared to wt mice after LPS challenge.

Conclusions: Our in vivo mutStat3 mouse model of lung injury indicates a higher susceptibility to pulmonary tissue damage with elevated lung inflammation and deficient epithelial recovery in STAT3-HIES after pulmonary injury.

Disclosure: No.

Keywords: STAT3-HIES, STAT3, hyper-IgE syndrome, chronic lung disease, Pulmonary Injury

OC016

PATHOGENESIS of STAT1 GAIN-OF-FUNCTION PRIMARY IMMUNODEFICIENCY

ORAL COMMUNICATIONS SESSION 03: INNATE IMMUNE DEFECTS

Alexander Mckenna[1], Adriana Albuquerque[1], Joe Mcdowell[1], Katya Minskaia[1], Jesmeen Maimaris[1], Jonathan Lambourne[2], Li Songling[3], Daron Standley[3], Emma Morris[1], Siobhan Burns[1]
[1]University College London, Institute of Immunity And Transplantation, London, United Kingdom, [2]Royal London NHS Foundation Trust, Immunology, London, United Kingdom, [3]Osaka University, Immunology Frontier Research Center, Osaka, Japan

Background and Aims: Germline, monoallelic, gain-of-function (GOF) mutations in STAT1 cause an ultra-rare form of primary immunodeficiency (PID) through overactivation of the Janus-associated kinase STAT1 signalling pathway. Heightened basal levels of STAT1 protein have previously been shown to be a key driver of disease[1 2] but the exact mechanism of STAT1 GOF still remains unclear.

Methods: A nanoBRET system was developed to investigate the conformations adopted by STAT1 dimers pre- and post-IFNγ stimulation in STAT1 ($^{-/-}$) cell lines lentivirally transduced with wild-type or GOF STAT1. Nuclear localisation and transcriptomics were assessed in the same cell lines pre- and post-IFN stimulation, and in response to Ruxolitinib.

Results: We show that the majority of GOF mutations destabilise the inactive dimeric conformations of STAT1 and promote the adoption of an active-like conformation at baseline. In contrast, some mutations stabilise the active conformation and induce stronger DNA binding, suggesting that discreet GOF mutations function through different mechanisms. We show that the nuclear localisation sequence is exposed in the active orientation, and that consequently, GOF mutants had greater nuclear presence at baseline. Transcriptomic analysis detailed that STAT1-mediated gene expression was induced under inactive status for GOF mutants and that each mode of pathogenesis has unique gene expression signatures. We compared the clinical phenotypes described for different for STAT1 GOF mutations and identified that patients with mutations that stabilise the active conformation are more likely to experience autoimmune complications.

Conclusions: This work has identified alternative modes of pathogenesis for STAT1 GOF which may explain clinical heterogeneity.

Disclosure: No.

Keywords: gain-of-function, pathogenesis, STAT1

OC017

IMMUNOGENETICS ASSOCIATED WITH SEVERE COCCIDIOIDOMYCOSIS

ORAL COMMUNICATIONS SESSION 03: INNATE IMMUNE DEFECTS

Amy Hsu[1], Agnieszka Korzeniowska[1], Cynthia Aguilar[1], Jingwen Gu[1], Eric Karlins[1], Andrew Oler[1], Gang Chen[2], Glennys Reynoso[1], Joie Davis[1], Alexandria Chaput[3], Tao Peng[3], Jennifer Stoddard[4], Julie Niemela[4], Sergio Rosenzweig[4], Alexandra Freeman[5], Christa Zerbe[1], Kenneth Olivier[6], Richard Boucher[2], Heather Hickman[1], Jeffrey Frelinger[3], Joshua Fierer[7], Lisa Shubitz[3], Thomas Leto[1], George Thompson[8], John Galgiani[3], Michail Lionakis[1], Steven Holland[1]
[1]National Institutes of Health, National Institute of Allergy And Infectious Diseases, Bethesda, United States of America, [2]UNC-Chapel Hill, Marisco Lung Institute And Cystic Fibrosis Research Center, Chapel Hill, United States of America, [3]University of Arizona College of Medicine, Valley Fever Center For Excellence, Tucson, United States of America, [4]NIH, Immunology Service, Department of Laboratory Medicine, Bethesda, United States of America, [5]Laboratory of Clinical Immunology and Microbiology, National Institutes of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Laboratory of Clinical Immunology And Microbiology, Bethesda, United States of America, [6]National Institutes of Health, National Heart Lung And Blood Institute, Bethesda, United States of America, [7]University of California San Diego School of Medicine, Dept of Pathology And Medicine, La Jolla, United States of America, [8]University of California Davis, Dept of Medical Microbiology And Immunology, Davis, United States of America

Background and Aims: Disseminated coccidioidomycosis (DCM) is caused by Coccidioides, pathogenic fungi endemic to Western United States and Mexico. While exposure is common, pneumonia is thought to occur in ~3% of residents annually with <1% of those developoing disseminated disease.

Methods: We enrolled DCM patients, performed whole-exome sequencing and assessed cytokine production in peripheral blood mononuclear cells. Confocal microscopy co-localized DECTIN-1 and fungal endospores. Transfection demonstrated DECTIN-1, DUOX1 and DUOXA1 roles in β-glucan-stimulated H_2O_2 production. RNA was sequenced from STAT3-mutated, autosomal-dominant Hyper-IgE syndrome (AD-HIES) patients' respiratory tissues. Duox1$^{-/-}$ mice were infected with Coccidioides.

Results: In an exploratory set of 67 DCM patients, two had haploinsufficient STAT3 mutations. Defects in β-glucan sensing and response were seen in 34/67 (50.7%) cases. Damaging CLEC7A (n=14) and PLCG2 (n=11) variants were found and PBMC from patients with these variants produced less β-glucan-stimulated TNF-α than healthy controls (P<0.005). Using ancestry matched controls, damaging variants in CLEC7A and PLCG2 were over-represented in DCM (P=0.0206, P=0.015, respectively) including CLEC7A Y238* (P=0.0105) and PLCG2 R268W (P=0.0025). In a validation cohort of 112 DCM patients PLCG2 R268W (P=0.0276), CLEC7A I223S (P=0.044) and CLEC7a Y238* (P=0.0656) were confirmed. Fifteen discovery cohort patients had heterozygous DUOX1 or DUOXA1 variants which impaired H_2O_2 production in transfected cells. AD-HIES patient airway epithelial cells had decreased DUOX1/DUOXA1 transcripts. Duox1$^{-/-}$ mice had increaed morbidity and mortaligy following Coccidoiodes infection.

Conclusions: Patients with DCM have impaired β-glucan sensing or responsiveness affecting H_2O_2 production. Genetically impaired Coccidioides recognition and cellular response decrease inflammatory cytokine production and underlie susceptibility to disseminated coccidioidomycosis.

Disclosure: No.

Keywords: fungal infection, Coccidioidomycosis, Population genetics

OC018

RECOMBINANT INTERFERON GAMMA RESTORES ALTERED IMMUNOMETABOLISM IN CGD

ORAL COMMUNICATIONS SESSION 03: INNATE IMMUNE DEFECTS

Mariolina Bruno[1], Charlotte Kröger[2], Bowen Zhang[3], Anaísa Ferreira[1], Ruiqi Liu[1], Rutger Röring[1], Athanasios Ziogas[1], Laszlo Groh[1], Viola Klück[1], Simone Moorlag[1], Priya Debisarun[1], Nico Janssen[1], Diletta Rosati[1], Jorge Saiz[4], Orsi Gaal[5], Humberto Ferreira[3], Martina Uelft[2], Stefanie Herresthal[2], Matthias Becker[2], Lisa Holsten[2], Sophie Müller[2], Michael Kraut[2], Jonas Schulte-Schrepping[2], Lorenzo Bonaguro[2], Kristian Händler[2], Joachim Schultze[2], Cristina Cunha[6], Coral Barbas[4], Leo Joosten[1], Mihai Netea[1], Yang Li[3], Anna Aschenbrenner[2], Agostinho Carvalho[6], Frank Van De Veerdonk[1]
[1]Radboud University Medical Center, Internal Medicine, Nijmegen, Netherlands, [2]University of Bonn, Department For Genomics & Immunoregulation, Life And Medical Sciences Institute (limes), Bonn, Germany, [3]Hannover Medical School (MHH), Twincore, Centre For Experimental And Clinical Infection Research, Hannover, Germany, [4]Universidad San Pablo-CEU, Centre For Metabolomics And Bioanalysis (cembio), Chemistry And Biochemistry Department, Pharmacy Faculty, Madrid, Spain, [5]Iuliu Haţieganu University of Medicine and Pharmacy, Department of Medical Genetics, Cluj-Napoca, Romania, [6]University of Minho, Life And Health Sciences Research Institute (icvs), Braga, Portugal

Background and Aims: Chronic granulomatous disease (CGD) is characterized by recurrent life-threatening infections and hyperinflammatory complications.It is caused by mutations in the NADPH oxidase complex and the consequent loss of reactive oxygen species (ROS) production. Recombinant human interferon gamma (rIFNγ) is used as prophylaxis to reduce the risk of severe infections, but the mechanisms behind its efficacy in CGD are still unknown.

Methods: We compared the immune and metabolic profile of immmune cells from CGD patients with healthy controls using scRNAseq analysis, ATACseq profiling, ELISA, proteomics, Seahorse and metabolomics. Finally, we investigated the effect of in vitro rIFNγ treatment on some of those parameters.

Results: We found that innate immune myeloid cells from CGD patients are epigenetically and functionally reprogrammed to have a hyperactivated immune status. In parallel, they present an impaired in vitro induction of trained immunity. CGD monocytes have deficient intracellular amino acids levels and have profound functional metabolic defects, both at the glycolytic and mitochondrial level. In vitro treatment with rIFNγ restored these myeloid metabolic defects and reduced abnormal IL-1β and IL-6 production in response to fungal stimuli in CGD monocytes, suggesting that prophylactic rIFNγ efficacy in CGD patients has a metabolic basis.

Conclusions: Learning more about the immunometabolic defects underlying diseases will not only give new insight into their pathogenesis but, beyond CGD, might open doors for efficient and targeted immunotherapy aimed at correcting these defects. In conclusion, our findings address a new avenue of research exploring the consequences of a defective NADPH oxidase complex in the metabolic rewiring of immune cells.

Disclosure: No.

Keywords: CGD, rIFNγ immunotherapy, cytokines, NADPH OXİDASE, ROS

OC019

NOX2-DERIVED ROS CONTROL THE INFLAMMATORY RESPONSE BY REGULATING GASDERMIN D CLEAVAGE

ORAL COMMUNICATIONS SESSION 03: INNATE IMMUNE DEFECTS

Daniela Stanga[1], Eric Bonneil[2], Emilie Heckel[1], Jennifer Leiding[3], Guilhem Cros[4], Isabel Fernandez[5], Etienne Caron[6], Jean-Sebastien Joyal[7], Fabien Touzot[8]
[1]CHU Sainte-Justine Research Center, Immunology And Microbiology, Montreal, Canada, [2]Institute for Research in Immunology and Cancer, Université de Montréal, Biochemistry, Montréal, Canada, [3]University of South Florida, Department of Pediatrics, St. Petersburg, United States of America, [4]Centre Hospitalier de l'Université de Montréal, Immunology, Montréal, Canada, [5]Université de Montréal, Immunology And Microbiology, Montréal, Canada, [6]Université de Montréal, Department of Pharmacology, Montréal, Canada, [7]CHU Sainte-Justine, Université de Montréal, Department of Pediatrics, Université De Montréal, Montréal, Canada, [8]CHU Sainte-Justine, Department of Pediatrics, Université De Montréal, Montréal, Canada

Background and Aims: Chronic Granulomatous Disease is a mendelian disorder caused by loss-of-function mutations genes encoding subunits of the NADPH oxidase complex 2. Increasing reports have underlined the role of the NLRP3 inflammasome in the pathophysiology of inflammation in CGD. However, the precise mechanism provoking a disproportionate inflammatory response in CGD patients remains elusive. Interestingly, the NOX2-deficiency model – characterized by defective production of cytosolic Reactive Oxygen Species (ROS) is at odds with the classical concept that chronic inflammation is caused by prolonged and sustained ROS production. These opposite views suggest that efficient regulation of the inflammatory response requires a well-balanced ROS signaling. The objective of our study is to refine the precise role of cytosolic ROS in regulating inflammation and discover alternative strategies for treating chronic inflammatory diseases.

Methods: We assessed the dynamics of the inflammatory response in NOX2-deficient patients' primary monocytes and a CRISPR-engineered NOX2-deficient phagocytic THP-1 cell line.

Results: We show that the defective redox signaling in CGD phagocytes is responsible for post-translational priming of the pyroptosome as evidenced by an enhanced oligomerization of its principal component ASC. NOX2 deficiency also increases the phosphorylation of GasderminD (GSDMD) at Serine 252, an amino acid that seems critical for its pyroptotic activity. Interestingly, GSDMD cleavage further activates the NLRP3 inflammasome by facilitating the release of mitochondrial DNA in the cytosol and by lowering the intracellular K+ concentration through GSDMD membrane pores.

Conclusions: We unveil the pivotal role of GSDMD in the amplification of the inflammatory response in CGD, paving the way for targeted therapies.

Disclosure: No.

Keywords: Chronic Granulomatous Disease, Pyroptosome, Gasdermin D, Post-translational modification, NLRP3 inflammasome

OC020

A NOVEL HETEROZYGOUS GERMLINE STAT6 VARIANT AS A LIKELY MONOGENIC CAUSE of A NOVEL PRIMARY ATOPIC DISORDER

ORAL COMMUNICATIONS SESSION 03: INNATE IMMUNE DEFECTS

Lucia Pacillo[1,2], Cristina Cifaldi[1,2], Beatrice Rivalta[1,2], Donato Amodio[3], Silvia Di Cesare[1,2], Paola Zangari[3], Chiara Passarelli[4], Alessandro Fiocchi[5], Paolo Palma[1,3], Andrea Finocchi[1,6], Gigliola Di Matteo[1,2], Caterina Cancrini[1,2]
[1]Tor Vergata University, Department of Systems Medicine, Rome, Italy, [2]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Research Unit of Primary Immunodeficiencies,, Roma, Italy, [3]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Unit of Clinical Immunology And Vaccinology,, Roma, Italy, [4]IRCCS Bambino Gesù Children Hospital, Laboratory of Medical Genetics, Rome, Italy, [5]IRCCS Bambino Gesù Children Hospital, Pediatric Allergology Unit,, Rome, Italy, [6]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Unit of Immune And Infectious Diseases, Unit of Immunology And Vaccinology,, Roma, Italy

Background and Aims: Hyperactive or constitutive STAT6 signalling is associated to increased Th2 differentiation, responsible of allergic inflammation. STAT6 variants have been associated to food allergies[1] and STAT6 somatic mutations have been identified in 11% of follicular lymphoma.[2] Recently, STAT6 variants have been detected in two patients with profound allergic immunedysregulation.[3]

Methods: We describe a clinical case of allergic immunedysregulation. Diagnostic work-up included immunologic investigations using FACS analysis, clinical exome sequencing (CES) and proteomic approach through Olink assay.

Results: A 21yo-girl presented early-onset refractory atopic dermatitis, recurrent respiratory infections, severe asthma, multiple inhalants, drugs and food severe allergies, HPV-negative laryngeal papillary hyperplasia, gastrointestinal disorders with not-specific mucosal infiltrate and chronic EBV infection. Diagnostic work-up showed hyper-eosinophilia, hyper-IgE (699-12550 kU/L), positive RAST and ISAC test for multiple allergens, normal Ig levels, normal frequency of Tcells and Tregs, reduced frequency of Th17cells, normal circulating Tfhcells, slightly reduced Bcells frequency with normal Bcell maturation, reduced in vitro Tcell proliferation and Bcell antibodies production. CES disclosed a de novo heterozygous mutation in STAT6 gene (c.1255G>A; p.D419N), predicted pathogenic by ACGM (CADD score 31) not reported in gnomAD, but described in follicular lymphoma. Proteomic analysis showed a baseline higher percent-change in IL-4 level compared to healthy control.

Conclusions: We suggest that the mutation identified in our patient could be responsible of her clinical phenotype and could be stated as a novel Primary Atopic Disorder. More functional studies are ongoing to confirm its pathogenic role and to suggest a targeted therapeutical choice. [1]Allergy. 2018 Jun;73(6):1337-1341. [2]Blood. 2015 Jan 22;125(4):668-79. [3]medRxiv preprint doi:10.1101/2022.04.25.22274265

Disclosure: No.

Keywords: stat6, primary atopic disorder, Inborn errors of immunity, HyperIgE syndromes, food allergy, Immune Dysregulation

OC021

GTF3A DEFICIENCY IN HUMANS PREDISPOSES TO HERPES SIMPLEX ENCEPHALITIS BY ABROGATING TRANSCRIPTION of THE HOST-DERIVED RIG-I LIGAND RNA5SP141

ORAL COMMUNICATIONS SESSION 03: INNATE IMMUNE DEFECTS

Leslie Naesens[1,2], Santoshi Muppala[3], Jung-Hyun Lee[3], Josephine Nemegeer[4], Delfien Bogaert[5], Dhiraj Acharya[3], Katrien Staes[4], Veronique Debacker[2], Pieter De Bleser[4], Marieke De Bruyne[6], Elfride De Baere[6], Michiel Van Gent[3], Bart N. Lambrecht[7], Jens Staal[4], Tessa Kerre[8], Rudi Beyaert[4], Jonathan Maelfait[4], Simon Tavernier[2], Michaela Gack[3], Filomeen Haerynck[2]
[1]Ghent University, Internal Medicine And Pediatrics, Ghent, Belgium, [2]Ghent University, Primary Immune Deficiency Research Laboratory, Department of Internal Diseases And Pediatrics, Centre For Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis And Research Centre, Ghent, Belgium, [3]Cleveland Clinic, Florida Research And Innovation Center, Port Saint Lucie, United States of America, [4]University Ghent, Vib Center For Inflammation Research, Zwijnaarde, Belgium, [5]Ghent University Hospital, Primary Immunodeficiency Research Lab, Center For Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis And Research Center, Ghent, Belgium, [6]Ghent University, Biomolecular Medicine, Ghent, Belgium, [7]VIB-UGhent Center for Inflammation Research, Laboratory of Mucosal Immunology, Ghent, Belgium, [8]Ghent University Hospital, Department of Hematology, Ghent, Belgium

Background and Aims: Monogenic defects in type I interferon (IFN-I) signaling components have been identified in patients with herpes simplex encephalitis (HSE), emphasizing inborn errors of immunity underlying pathogenesis. In vitro studies demonstrate that the cytoplasmic RNA sensor RIG-I, which is well known to restrict RNA viruses, also critically contributes to the innate immune responses to DNA viruses including HSV-1.

Methods: We identified compound heterozygous mutations in the gene GTF3A in a family afflicted by HSE in early childhood. We studied primary patient cells as well as several CRISPR/Cas9-edited GTF3A mutant cells.

Results: GTF3A encodes for the transcription factor TFIIIA, which is part of the Pol III complex. We confirmed that the patient TFIIIA mutants have an impaired promoter-binding ability. We tested HSV-1 replication in the patient fibroblasts and GTF3A mutant cells and observed enhanced viral replication. To understand the underlying mechanism, we took an unbiased approach and searched for novel transcriptional targets of TFIIIA by ChIP-seq analysis and identified the pseudogene RNA5SP141, previously described as a RIG-I agonist. We found that RNA5SP141 is upregulated following HSV-1 infection and that this induction is abrogated in primary patient cells, in GTF3A gene-edited mutant cells, and upon targeted knockdown using siRNA. Finally, we explored the downstream effects of impaired RNA5SP141 expression on anti-herpesviral immunity and found abrogated RIG-I activation and markedly diminished induction of antiviral genes during HSV-1 infection.

Conclusions: Our work unveils a novel role for TFIIIA, acting as a moonlighting protein that regulates innate immune responses to HSV-1 by transcriptional regulation of the host-derived RNA5SP141 RIG-I ligand.

Disclosure: No.

Keywords: HSV-1 encephalitis, Inborn errors of immunity, Innate Immunity, RIG-I, type I interferon, Viral susceptibility

OC022

COMPARISON of EFFICACY AND SAFETY of IL-1 RECEPTOR INHIBITOR (ANAKINRA) AND STEROIDS (PREDNISOLONE) IN TREATMENT of GRANULOMATOUS COMPLICATIONS IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE

ORAL COMMUNICATIONS SESSION 04: THERAPY

Daria Yukhacheva[1], Yulia Rodina[1], Alexandra Laberko[1], Anna Roppelt[1], Vasiliy Burlakov[1], Elena Deripapa[1], Nelly Kan[1], Ilyuza Valimukhametova[2], Galina Tereshchenko[3], Galina Novichkova[4], Anna Shcherbina[1]
[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [2]Clinical Rehabilitation Research Center for patients in remission "Russkoye pole", Immunology, Chekhov, Russian Federation, [3]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Radiology, Moscow, Russian Federation, [4]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Medical Director, Moscow, Russian Federation

Background and Aims: Chronic granulomatous disease (CGD) is a well described primary immunodeficiency with a "classic" infectious phenotype. Granulomatous complications present another significant problem in CGD, occur in 70-80% of the patients, and are difficult to diagnose and treat.

Methods: We report results of granulomas treatment in 30 CGD patients. Granulomas were present predominantly in the lungs (26 patients) and liver (8 patients). Antibacterial and antifungal therapy failed to resolve the lesions. For granulomas treatment 12 patients received prednisolone (1 mg/kg/day for 2 weeks, 0.5 mg/kg/day for 2 weeks, then 0.3 mg/kg/day for 1-4 months) and 18 patients - anakinra (8-10 mcg/kg daily for 2 weeks - 6 months). Complete response to treatment was defined as more than 75% reduction of granulomas size.

Results: We demonstrate that complete response to prednisolone was achieved in 37.8% patients with lung granulomas, and in 25.0% with liver granulomas ($p<0.01$); and 75.0% of the patients receiving prednisolone developed moderate adverse events (AE), 33.3% - severe AE, and 25.0% - life-threatening AE, including pulmonary aspergillosis. 3/12 patients had more than one AE. Complete response to anakinra was achieved in 90.0% of patients with lung granulomas, and in 75.0% with liver granulomas ($p<0.01$). In this group, 5.6% had mild AE (local reaction at the injection site) and 11.1% had moderate AE (neutropenia), no severe AE was recorded.

Conclusions: We report that IL-1 receptor inhibitor (anakinra) is more effective and safe for the treatment of liver and lung granulomas in CGD patients as compared to the traditionally used steroids.

Disclosure: No.

Keywords: chronic granulomatous disease, granulomatous complications, lung and liver granulomas, treatment, anakinra

OC023

INTERIM SAFETY AND EFFICACY ANALYSIS of AN ONGOING LONG-TERM OPEN-LABEL EXTENSION STUDY of LENIOLISIB FOR PATIENTS WITH ACTIVATED PI3K DELTA SYNDROME (APDS) THROUGH DECEMBER 2021

ORAL COMMUNICATIONS SESSION 04: THERAPY

V. Koneti Rao[1], Sharon Webster[1], Anna Sediva[2], Alessandro Plebani[3], Catharina Schuetz[4], Anna Shcherbina[5], Niall Conlon[6], Tanya Coulter[7], Virgil Dalm[8], Antonino Trizzino[9], Yulia Zharankova[10], Elaine Kulm[11], Julia Körholz[4], Vassilios Lougaris[3], Yulia Rodina[5], Klaus Kucher[12], Kath Radford[13], Jason Bradt[14], Gulbu Uzel[1]
[1]National Institutes of Health, National Institute of Allergy And Infectious Diseases, Bethesda, United States of America, [2]Charles University, Department of Immunology, 2nd Faculty of Medicine, Prague, Czech Republic, [3]University of Brescia, ASST Spedali Civili of Brescia, Pediatrics Clinic, Department of Clinical And Experimental Sciences, Brescia, Italy, [4]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Pediatric Immunology, Dresden, Germany, [5]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Department of Immunology, Moscow, Russian Federation, [6]St James's Hospital, and Trinity College Dublin School of Medicine, Department of Immunology, Dublin, Ireland, [7]Belfast Health and Social Care Trust, Regional Immunology Services of Northern Ireland, Belfast, United Kingdom, [8]Erasmus MC University Medical Center, Department of Internal Medicine, Division of Allergy & Clinical Immunology And Department of Immunology, Rotterdam, Netherlands, [9]ARNAS Civico Di Cristina Benfratelli Hospital, Department of Pediatric Hematology And Oncology, Palermo, Italy, [10]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Clinic, Minsk, Belarus, [11]Frederick National Laboratory for Cancer Research, Clinical Research Directorate, Bethesda, United States of America, [12]Novartis, Institutes For Biomedical Research, Basel, Switzerland, [13]Novartis Pharmaceuticals, Uk Limited, London, United Kingdom, [14]Pharming Healthcare Inc, Clinical Development, Warren, United States of America

Background and Aims: Pathogenic variants in genes encoding PI3Kδ (PIK3CD, PIK3R1) causing kinase hyperactivity can result in the primary immunodeficiency and regulatory disorder activated PI3Kδ syndrome. We previously reported use of molecularly targeted inhibition of hyperactive PI3Kδ with investigational drug leniolisib in a phase 3 RCT (NCT02435173). Here we describe interim analysis outcomes from the ongoing open-label, single-arm, long-term extension study (NCT02859727).

Methods: Thirty-seven patients with APDS aged ≥12 years were enrolled globally. Patients were exposed to leniolisib through 5 years, including 20 patients ≥ 96 weeks, and 5 patients approximately 5 years.

Results: Sustained reduction of lymphoproliferation as well as immune reconstitution was notable. The latter included: increased naïve B cells, decreased transitional B cells, reduced PD-1+ and senescent T cells through Extension Day (ED) 252. Immunoglobulin replacement therapy (IRT) infusions were reduced; four patients discontinued IRT; results were maintained. At 2 years, mean improvement in physical component summary and mean change in general health scale of the SF-36 suggest improved HRQoL. Leniolisib was well tolerated; 32/37 patients experienced AEs Grades 1-3. The majority were Grade 1 (55%), with no Grade 4 AEs. Study drug related AEs occurred in 13.5% of patients. One patient with significant comorbidities (history included disseminated mycoplasma infection and cardiomyopathy) suffered cardiac arrest resulting in death at ED794 determined not related to study drug. This was the only discontinuation. No SAEs were suspected related to leniolisib.

Conclusions: These results demonstrate long-term leniolisib administration with exposure through 5 years was well-tolerated in patients with APDS, with continued improvement in lymphoproliferation and immunophenotype.

Disclosure: Novartis Pharma AG and Pharming Group NV funded the research. KK and KR are employees of Novartis Pharma AG, and KK is also a shareholder. JB is an employee of Pharming Healthcare, Inc. EK is funded by NCI Contract No. 75N91019D00024.

Keywords: APDS, PI3K, PIK3CD, PIK3R1, leniolisib, primary immunodeficiency

OC024

ALLOGENEIC HSCT FOR STAT3-DN HYPER IGE SYNDROME – AN INTERNATIONAL SURVEY

ORAL COMMUNICATIONS SESSION 04: THERAPY

Christo Tsilifis[1,2], Christina Oikonomopoulou[3], Ramya Uppuluri[4], Masakatsu Yanagimachi[5], Ásgeir Haraldsson[6], Melanie Wong[7], Steven Keogh[8], Paul Gray[9], Richard Mitchell[10,11], Peter Ciznar[12], Corina Gonzalez[13], Mary Slatter[1,2], Venetia Bigley[1,14], Alexandra Freeman[15], Austen Worth[16], Andrew Gennery[1,2]
[1]Newcastle University, Translational And Clinical Research Institute, Newcastle upon Tyne, United Kingdom, [2]Great North Children's Hospital, Children's Haematopoietic Stem Cell Transplant Unit, Newcastle upon Tyne, United Kingdom, [3]Agia Sofia Children's Hospital, Stem Cell Transplant Unit, Athens, Greece, [4]Apollo Hospitals, Paediatric Haemato-oncology, Chennai, India, [5]Kanagawa Children's Medical Center, Department of Haematology/oncology, Yokohama, Japan, [6]Landspitali - University Hospital, Children's Hospital Iceland, Reykjavik, Iceland, [7]Children's Hospital at Westmead, Immunology And Allergy, Westmead, Australia, [8]Children's Hospital at Westmead, Oncology, Westmead, Australia, [9]Sydney Children's Hospital, Immunology And Infectious Diseases, Randwick, Australia, [10]Sydney Children's Hospital, Kids Cancer Centre, Randwick, Australia, [11]University of New South Wales, School of Women & Children's Health, Sydney, Australia, [12]Children's University Hospital Bratislava, National Institute of Children's Diseases, Clinical Immunology Service, Pediatric Department, Bratislava, Slovak Republic, [13]National Institutes of Health, Immune Deficiency Cellular Therapy Branch, National Cancer Institute, Bethesda, United States of America, [14]Freeman Hospital, Northern Centre For Bone Marrow Transplantation, Newcastle upon Tyne, United Kingdom, [15]Laboratory of Clinical Immunology and Microbiology, National Institutes of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Laboratory of Clinical Immunology And Microbiology, Bethesda, United States of America, [16]Great Ormond Street Hospital, Department of Immunology And Gene Therapy, London, United Kingdom

Background and Aims: Allogeneic HSCT may cure the haematopoietic components of STAT3-DN hyper-IgE syndrome (STAT3-DN-HIES), though experience on long-term outcomes is limited.

Methods: A survey of international patients undergoing allogeneic HSCT with STAT3-DN-HIES was conducted.

Results: We identified 21 patients receiving 23 grafts. Median age at HSCT was 13.2 years (range: 3.0–25.7) with median follow-up 3.32 years (range: 0.96–25.9). HSCT indications were recurrent infection (n=18) and lymphoma (peripheral T-cell; high-grade non-Hodgkin's; n=3). Lung disease typical of STAT3-DN-HIES was present pre-transplant in 19/21 patients and chronic infection at HSCT in 18/21. Patients received peripheral blood stem cells (n=12) or bone marrow (n=11) from matched family donors (n=9), unrelated donors matching ≥9/10 HLA loci (n=13) and one TCRαβ/CD19-depleted haploidentical donor, using busulfan- (n=6), treosulfan- (n=11), and melphalan-based (n=6) conditioning regimens, with serotherapy in 19/21 procedures. Peri-transplant morbidity included acute graft-versus-host disease (9/21, grade 3-4 in 3 patients), graft rejection/failure (2/21), and intensive care admission (3/21). Two patients died, from graft-versus-host disease and from disseminated adenoviral infection. At 3 years, overall and event-free survival (defined as survival without graft failure or second procedure) were 89.6% and 85.7% respectively. At data collection, in 19 survivors, median donor chimerism was 100%, median IgE 1720IU/L (range: 10–11813), and Th17 lymphocytes were present in 9/9 patients tested. Survivors reported improvement in lung disease (n=16/19) and reduced infection (n=16/19).

Conclusions: Successful HSCT results in restoration of Th17-IL-17 immunity, improvement in lung and skin disease, and good event-free survival in STAT3-DN-HIES patients with significant pre-transplant morbidity. Further exploration of quality-of-life impact may aid patient selection.

Disclosure: No.

Keywords: Job's, allogeneic, HSCT, hyper IgE, STAT3, Lymphoma

OC025

ALLOGENEIC TRANSPLANTATION FOR HIGH RISK PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE (CGD)

ORAL COMMUNICATIONS SESSION 04: THERAPY

Elizabeth Kang[1], Corin Kelly[1], Mark Parta[2], Harry Malech[1]
[1]National Institutes of Health, Lcim, Bethesda, United States of America, [2]Frederick National Laboratory for Cancer Research, Clinical Research Directorate, Bethesda, United States of America

Background and Aims: Bone marrow transplantation (BMT) can cure CGD-related infections, and inflammatory disease. Older patients and those with resistant fungal infections, severe inflammatory bowel disease (IBD), or hypoxemic lung disease are often ineligible for transplant. We have devised a BMT regimen to transplant these patients.

Methods: Conditioning: Campath (1mg/kg over 5d), Busulfan (5mg/kg over 2d) and TBI (300cGy) with post-transplant cyclophosphamide (100mg/kg in 2d) and sirolimus. Patients with C-reactive protein (CRP)>100 were normally excluded as this is an indicator of high mortality; however 5 received exceptions for transplant because of life-threatening recalcitrant infections.

Results: Number: 28 plus 5 with CRP>100 off protocol. Follow up: 6 months to 5 years Donors: 30 Matched unrelated, 3 Matched related Ages: Mean 30 (6-58), Gender: 4F, 29M, CGD type: GP91 (25, incl.1 skewed lyonized female), P47 (6), P67 (1), P22 (1) BMT indications: pulmonary disease (7), IBD (12), active infection (17) Outcomes: 28 ‘eligible’ (all 33 patients)

OS	EFS (≥ 1year)	GvHD (I-II)	GvHD (III-IV)	Chronic GvHD
96.4% (81.8%*)	92.9%**	2: stage 1 skin GvHD 2: stage 1 GI GvHD	0	0
*All 5 patients with elevated CRPs>100, 100% mortality.	**1 death; 1 graft failure who survived			

Conclusions: Low dose Busulfan with TBI, Campath, post-transplant cyclophosphamide and sirolimus for BMT of CGD patients (CRP<100) results in improved engraftment rates with minimal GvHD. Patients not eligible for transplant at other centers, due to infection, lung inflammation, and/or severe colitis, tolerated the conditioning with resolution of their CGD complications. However, patients with CRP>100 at initiation of conditioning should not be transplanted.

Disclosure: No.

Keywords: hypoxemic lung disease, Graft versus Host Disease, Chronic Granulomatous Disease, Infection, Allogeneic Transplantation, Inflammatory bowel disease

OC026

INTERIM RESULTS FROM AN ONGOING PHASE 1/2 STUDY of LENTIVIRAL-MEDIATED EX-VIVO GENE THERAPY FOR PEDIATRIC PATIENTS WITH SEVERE LEUKOCYTE ADHESION DEFICIENCY-I (LAD-I)

ORAL COMMUNICATIONS SESSION 04: THERAPY

Claire Booth[1], J. Sevilla[2], G. Rao[3], M Lopez[3], E Almarza[3], D Terrazas[4], J. Zubicaray[2], M González-Vicent[2], Kritika Chetty[1], Gráinne O'Toole[1], Jinhua Xu-Bayford[1], E Nicoletti[3], A Fernandes[4], C Kuo[4], S De Oliveira[4], T Moore[4], G Choi[3], M Zeini[3], C Mesa-Núñez[5], A Thrasher[1], J Bueren[5], J Schwartz[3], Donald Kohn[4]
[1]University College London, Great Ormond Street Hospital, Division of Infection And Immunity, London, United Kingdom, [2]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER-ISCIII) and Hospital Infantil Universitario Niño Jesús (HIUNJ), Fundación Para La Investigación Biomédica, Madrid, Spain, [3]Rocket Pharmaceuticals, Inc., Clinical Development, Cranbury, United States of America, [4]University of California, Los Angeles, Departments of Microbiology, Immunology & Molecular Genetics, Pediatrics, And Molecular & Medical Pharmacology, Los Angeles, United States of America, [5]Centro de Investigaciones Energéticas Medioambientales y Tecnológicas (CIEMAT), Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER-ISCIII) and Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD), Unidad Mixta De Terapias Avanzadas, Madrid, Spain

Background and Aims: LAD-I results from mutations in ITGB2 encoding the β2-integrin CD18. Severe LAD-I (<2% CD18+ polymorphonucleocytes [PMNs]) causes severe infections, impaired wound healing, and childhood mortality. Allogeneic hematopoietic stem cell transplant is curative; efficacy is limited by donor availability, graft-versus-host disease, and graft failure. RP-L201-0318 (NCT03812263), employs autologous CD34+ cells transduced with a lentiviral vector carrying ITGB2.

Methods: Patients ≥3 months old with severe LAD-I were enrolled. HSCs were collected via apheresis after mobilization with granulocyte-colony-stimulating-factor and plerixafor and transduced ex-vivo. Myeloablative busulfan conditioning preceded RP-L201. Patients are followed for safety and efficacy including survival to age 2 and ≥1-year post-infusion, peripheral blood [PB] PMN CD18 expression, PB vector copy number [VCN], neutrophilia improvement, decreased infections/hospitalizations, resolution of skin/periodontal abnormalities.

Results: Nine patients (ages 5mos-9yrs) received RP-L201, with 3–24-month available follow-up. RP-L201 cell doses ranged from 2.8x106 to 10x106 CD34+ cells/kg with a drug product VCN from 1.8-3.8. All 9 demonstrated sustained PMN CD18 restoration and VCN >0.1integration. At 1 year, the OS rate is 100% per Kaplan-Meier estimate. The patient with 24 months follow-up showed ~40% PMN CD18 expression with 1.53 PB VCN. Baseline skin lesions resolved with no new infection-related hospitalizations. Subsequent 8 patients were followed for 3-18 months, demonstrating PMN CD18 expression of 25.6-86.6%. Neutrophilia resolved uniformly. Hospitalizations and severe infections were significantly reduced following therapy. The safety profile has been highly favorable with no RP-L201-related SAEs.

Conclusions: RP-L201 confers durable reversal of the severe LAD-I phenotype with improved clinical course in 9 of 9 patients.

Disclosure: Disclosures for Dr. Claire Booth, MBBS, PhD: SOBI: Consultancy, Honoraria; Orchard Therapeutics: Consultancy, Honoraria; Takeda: Honoraria; Rocket Pharmaceuticals, Inc.: Consultancy. GSK: Honoraria.

Keywords: Lentivirus Vectors, Clinical Gene Therapy, primary immunodeficiency, Leukocyte Adhesion Deficiency-I (LAD-I)

OC027

ETOPOSIDE FOR PRIMARY HLH – BETTER THAN ITS REPUTATION.

ORAL COMMUNICATIONS SESSION 04: THERAPY

Svea Ledig[1], Katharina Wustrau[2], Udo Kontny[3], Silke Westphal[4], Patrick Hundsdörfer[5], Norbert Jorch[6], Johanna Scheer-Preiss[7], Dominik Schneider[8], Sujal Ghosh[9], Nora Naumann-Bartsch[10], Dirk Holzinger[11], Shahrzad Bakhtiar[12], Christine Mauz-Körholz[13], Christof Kramm[14], Rita Beier[15], Wolfgang Behnisch[16], Monika Streiter[17], Alfred Längler[18], Rhoikos Furtwängler[19], Bernd Gruhn[20], Michaela Nathrath[21], Ümmügül Behr[22], Meinolf Siepermann[23], Lars Fischer[24], Antje Redlich[25], Alexandra Russo[26], Matthias Dürken[27], Fabian Hauck[28], Martina Ahlmann[29], Martin Irnich[30], Heiko-Manuel Teltschik[31], Peter Lang[32], Manfred Hönig[2], Ansgar Schulz[2], Sharon Choo[33], Bruce Crooks[34], Renata Formankova[35], Marianne Ifversen[36], Thais Murciano-Carrillo[37], Itziar Astigarraga[38], Juana Gil Herrera[39], Tal Ben-Ami[40], Joanne Yacobovich[41], Iwona Malinowska[42], Michael Jordan[43], Melissa Hines[44], Julie-An Talano[45], Jana Pachlopnik Schmid[46], Kai Lehmberg[1], Stephan Ehl[47]
[1]University Medical Center Eppendorf, Division of Pediatric Stem Cell Transplantation, Hamburg, Germany, [2]Pediatric Immunology, Rheumatology and Stem Cell Transplantation, Ulm University Hospital, Department of Pediatrics And Adolescent Medicine, Pediatric Immunology, Ulm, Germany, [3]RWTH Aachen University Hospital, Section of Pediatric Hematology, Oncology And Stem Cell Transplantation, Aachen, Germany, [4]Augsburg University Hospital, Swabian Children's Cancer Center, Augsburg, Germany, [5]Helios Klinikum Berlin-Buch, Pediatric Oncology And Hematology, Berlin, Germany, [6]University Ostwestfalen-Lippe, Clinic For Pediatrics And Adolescent Medicine, Hematology/oncology, Bielefeld, Germany, [7]Städtisches Klinikum Braunschweig, Center For Pediatric And Adolescent Medicine, Pediatric Hematology And Oncology, Braunschweig, Germany, [8]Klinikum Dortmund gGmbH - Westphalian Children's Center, Clinic For Pediatrics And Adolescent Medicine, Dortmund, Germany, [9]Center of Child and Adolescent Health, Medical Faculty, Heinrich Heine University, Department of Pediatric Oncology, Hematology And Clinical Immunology, Düsseldorf, Germany, [10]University Clinic Erlangen, Clinic For Children And Adolescents, Erlangen, Germany, [11]Essen University Hospital, Pediatric Immunology, Rheumatology And Stem Cell Transplantation, Essen, Germany, [12]University Hospital Frankfurt, Division For Stem Cell Transplantation, Immunology And Intensive Care Medicine, Department For Children And Adolescents Medicine, Frankfurt am Main, Germany, [13]University Children's Hospital Giessen and Medical Faculty, Martin-Luther University of Halle-Wittenberg, Pediatric Hematooncology, Giessen, Germany, [14]Göttingen University Medical Center, Department of Pediatrics And Adolescent Medicine, Pediatrics I, Hematology/oncology, Göttingen, Germany, [15]Hannover Medical School, Pediatric Hematology And Oncology, Hannover, Germany, [16]Heidelberg University Hospital, Center For Pediatrics And Adolescent Medicine, Hematology/oncology, Heidelberg, Germany, [17]Klinikum am Gesundbrunnen Heilbronn, Clinic For Pediatrics And Adolescent Medicine, Hematology/oncology, Heilbronn, Germany, [18]University of Witten/Herdecke; Faculty of health, Professorship for integrative Pediatrics, Department of Pediatrics, Herdecke, Germany, [19]Saarland University Hospital, Department of Pediatric Oncology And Hematology, Homburg, Germany, [20]Jena University Hospital, Department of Pediatrics, Jena, Germany, [21]Kassel Hospital, Pediatric Hematology And Oncology, Psychosomatics And Systemic Diseases, Kassel, Germany, [22]Gemeinschaftsklinikum Mittelrhein, Pediatric Hematology And Oncology, Kemperhof Koblenz, Koblenz, Germany, [23]Kliniken der Stadt Köln gGmbH, 22 Children's Hospital Cologne, Pediatric Oncology/ Hematology, Köln, Germany, [24]Leipzig University Hospital AöR, University Hospital And Polyclinic For Children And Adolescents, Pediatric Oncology, Leipzig, Germany, [25]University Hospital Magdeburg, Pediatric Clinic, Pediatric Hematology And Oncology, Magdeburg, Germany, [26]University Mainz, Center For Pediatric And Adolescent Medicine, Pediatric Hematology/ Oncology, Mainz, Germany, [27]Mannheim University Hospital, Department of Pediatrics And Adolescent Medicine, Mannheim, Germany, [28]Dr von Hauner Children's Hospital, University Hospital, Ludwig Maximilians Universität München, Division of Pediatric Immunology And Rheumatology, Department of Pediatrics, Munich, Germany, [29]University Children`s Hospital Münster, Department of Pediatric Hematology And Oncology, Münster, Germany, [30]Asklepios Klinik Sankt Augustin GmbH, Sankt Augustin Children's Hospital, Sankt Augustin, Germany, [31]Olgahospital - Clinical Center Stuttgart, Center For Pediatric, Adolescent And Women's Medicine, Pediatric Oncology, Hematology And Immunology, Stuttgart, Germany, [32]Tübingen University Hospital, Clinic For Children And Adolescents, Dept. I Hematology/oncology, Tübingen, Germany, [33]The Royal Children's Hospital Melbourne, Department of Allergy And Immunology, Melbourne, Australia, [34]IWK Health, Halifax, Paediatric Haematology/oncology, Nova Scotia, Canada, [35]University Hospital Motol, 35 Department of Pediatric Haematology And Oncology, Prague, Czech Republic, [36]Rigshospitalet, Department of Pediatrics And Adolescent Medicine Copenhagen University Hospital, Copenhagen, Denmark, [37]Vall d'Hebron University Hospital, Pediatric Hematology And Oncology, Barcelona, Spain, [38]Cruces University Hospital, UPV/EHU, Biocruces Bizkaia Health Research Institute, Barakaldo, Spain, [39]Hospital General Universitario Gregorio Marañón, Division of Immunology, Madrid, Spain, [40]Kaplan Medical Center Rehovot, Pediatric Hematology-oncology Unit, Rehovot, Israel, [41]Schneider Children's Medical Center of Israel, Sackler School of Medicine, Tel Aviv University, Department of Pediatric Hematology Oncology, Tel Aviv, Israel, [42]Medical University of Warsaw, Department of Oncology, Pediatric Hematology, Clinical

Transplantology And Pediatrics, Warsaw, Poland, [43]Cincinnati Children's Hospital Medical Center, Bone Marrow Transplantation & Immune Deficiency, Cincinnati, United States of America, [44]St. Jude Children's Research Hospital, Division of Critical Care Histiocytosis Team, Memphis, United States of America, [45]Medical College of Wisconsin, Department of Pediatrics Hematology/oncology/bmt, Milwaukee, United States of America, [46]University Children's Hospital Zurich – Eleonorenstiftung, Pediatric Immunology, Zurich, Switzerland, [47]Medical Center-University of Freiburg, Center For Chronic Immunodeficiency, Institute For Immunodeficiency, Freiburg, Germany

Background and Aims: Primary hemophagocytic lymphohistiocytosis (pHLH) is a life-threatening hyperinflammatory syndrome that develops in patients with a genetic predisposition (FHL2-5, CHS, GSII, SAP, XIAP). In previous HLH-94 and HLH-2004 studies, etoposide-based treatment followed by hematopoietic stem cell transplantation (HSCT) led to 50% and 59% overall survival in pHLH patients, respectively. Contemporary data are lacking, but are essential to put novel treatment approaches (emapalumab, alemtuzumab, ruxolitinib) into perspective.

Methods: We evaluated all primary HLH patients registered in the international Histiocyte Society/ESID HLH registry 2016 - 2021 with one-year follow-up.

Results: Among 78 patients, 54 had FHL2-5, 13 had GS2/CHS, 8 had XLP1/2 and 3 had undefined pHLH. 10 patients were diagnosed without symptoms, 8 of them were transplanted and all 10 were alive and well. Among 67 symptomatic patients, 93% fulfilled HLH-2004 criteria, while 3 presented with CNS-HLH and 2 had less than 5 HLH criteria. 8 patients (4 FHL) only received IVIG/steroids/ cyclosporine A, while 59 received major HLH-directed drugs (first-line etoposide in 90%). 32% of patients received at least one additional major drug (mostly alemtuzumab). 65 patients underwent HSCT, 7 died before HSCT. At the 1-year follow-up, overall 63/78 (81%) patients were alive. 74% of patients receiving first-line etoposide were alive after 1 year.

Conclusions: Contemporary prognosis of pHLH patients receiving first-line etoposide-based therapy is better than anticipated, suggesting important advances in early diagnosis, supportive therapies and HSCT procedures. However, salvage therapies were used in 1/3. Importantly, early HSCT of asymptomatic siblings resulted in 100% survival, emphasizing the potential benefit of newborn screening.

Disclosure: No.

Keywords: HLH, HLH-registry, Hyperinflammation, Etoposide

OC028

THERAPEUTIC GENE EDITING of T CELLS CORRECTS CTLA4 INSUFFICIENCY.

ORAL COMMUNICATIONS SESSION 04: THERAPY

Thomas Fox[1], Ben Houghton[2], Lina Petersone[1], David Sansom[1], Siobhan Burns[1], Alex Mckenna[1], Lucy Walker[1], Claire Booth[1], Emma Morris[1]
[1]University College London, Division of Infection And Immunity, London, United Kingdom, [2]University College London, Department of Child Health, London, United Kingdom

Background and Aims: Background: Heterozygous mutations in CTLA4 result in an inborn error of immunity (IEI) (also known as primary immunodeficiency) with a severe clinical phenotype. Autologous T cell gene therapy may offer a cure without the immunological complications of allogeneic stem cell transplantation. Aims: We set out to devise a CRISPR/Cas9/AAV6 gene editing strategy to correct CTLA4 insufficiency in T cells.

Methods: We evaluated several universal gene editing strategies that enable correction of most disease-causing mutations with a single edit; the first that inserts the CTLA4 cDNA in exon 1, and a second that inserts the CTLA4 cDNA at the 3'end of the first intron of CTLA4.

Results: Superior editing efficiencies were obtained with the intronic approach compared to the other editing strategies. Functional studies using CTLA4 transendocytosis (TE) assays, demonstrated restoration of CD80 and CD86 internalization in the edited CD4+ T cells. Gene editing of T cells isolated from patients with CTLA4 insufficiency restored CTLA4 expression and rescued transendocytosis of CD80 and CD86 in vitro. Using a similar approach, gene corrected T cells from CTLA4$^{-/-}$ mice engrafted in immunodeficient mice at clinically relevant frequencies and rescued mice from fatal lymphoproliferation and autoimmunity.

Conclusions: Together these data demonstrated that CTLA4 edited T cells survived in vivo, expressed CTLA4 and were able to control the clinical phenotype of CTLA4 insufficiency, providing a powerful proof-of-principle of our T cell GT approach. Our data provide proof-of-concept that gene editing can restore CTLA4 function in T cells demonstrating the potential of this approach to treat CTLA4 insufficiency.

Disclosure: No.

Keywords: gene therapy, Gene editing, Autoimmunity, CTLA4 insufficiency, Immune Dysregulation

OC029

RECESSIVE YET MOSAIC CBL DEFICIENCY BY SEGMENTAL UPD IN IDENTICAL TRIPLETS WITH PULMONARY DISEASE

ORAL COMMUNICATIONS SESSION 05: NOVEL DEFECTS AND MECHANISMS

Jonathan Bohlen[1], Masato Ogishi[2], Marine Michelet[3], Zarah Janda[1], Anna-Lena Neehus[4], Marlene Pasquet[5], Jeremie Rosain[1], Emmanuelle Six[1], Lori Buetow[6], Isabelle Andre[1], Cindy Ma[7], Feroj Syed[6], Taushig Khan[8], Emmanuelle Jouanguy[1], Nico Marr[8], Stuart Tangye[7], Danny Huang[6], Eric Delabesse[9], Vivien Beziat[1], Laurent Abel[10], Jacinta Bustamante[11], Jean-Laurent Casanova[12]
[1]Institut Imagine, Genetics of Infectious Disease, Paris, France, [2]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, New York, United States of America, [3]Hospital Center University De Toulouse, Pneumologie, Toulouse, France, [4]Institut Imagine, Laboratory of Human Genetics of Infectious Diseases, Paris, France, [5]Hospital Center University De Toulouse, Hemato-immunology, Toulouse, France, [6]The Beatson Institute for Cancer Research, Huang Lab, Glasgow, United Kingdom, [7]Garvan Institute, Tangye Lab, Darlinghurst, Australia, [8]Sindra Medicine, Marr Lab, CFV+W Ar-Rayyan, Qatar, Qatar, [9]Institut Universitaire de Cancérologie de Toulouse, Department of Haematology, Toulouse, France, [10]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1163, Paris, France, [11]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Paris, France, [12]Howard Hughes Medical Institute, -, Washington, United States of America

Background and Aims: Rare missense variants are frequently detected by next-generation DNA sequencing but the deleterious functional consequence of these is often difficult or impossible to establish with computational means.

Methods: We utilize a database of regulatory post-translational modifications, accumulated from thousands of scientific papers, to search missense variants that affect post-translational modification sites known to regulate the protein activity.

Results: Using this approach, we identified three patients, monochorionic triamniotic identical triplets, with a homozygous variant, p.Y371C, in CBL. The patients suffer from recurrent pneumonia and emphysema associated with an excess of transitional B cells and moncytosis. The variant is loss-of-function affecting the phosphorylation site required for CBL function . The triplets have inherited the CBL mutation from their father by segmental uniparental disomy (UPD) mosaicism. Surprisingly, the mosaic distribution of the mutant allele is exactly identical between the three siblings, affecting bone marrow and peripheral blood, oral mucosa but not hair and fingernails. The homozygosity rate in whole blood is above 95%, explaining the homogeneity of the immunological phenotype between the three siblings.

Conclusions: In summary we discovered and described a novel inborn error of immunity (IEI): autosomal recessive, yet mosaic CBL deficiency, causing recurrent pneumonia, myeloproliferation and a B-cell defect. To date, this report represents the first IEI in monozygotic triplets.

Disclosure: No.

Keywords: UPD, Mosaicism, Myeloproliferation, CBL, IEI, Pulmonary Disease

OC030

AN IRF4 MUTATION AFFECTING THE INTERFERON ACTIVATION DOMAIN IS ASSOCIATED TO AN AUTOSOMAL DOMINANT PRIMARY B CELL IMMUNODEFICIENCY

ORAL COMMUNICATIONS SESSION 05: NOVEL DEFECTS AND MECHANISMS

Romane Thouenon[1,2], Loïc Chentout[1,2], Nidia Moreno-Corona[1,2], Lucie Poggi[1,2], Emilia Puig Lombardi[3], Benedicte Hoareau[4], Yohann Schmitt[5], Chantal Lagresle-Peyrou[1,2,6], Jacinta Bustamante[7,8,9], Isabelle Andre[1,2], Marina Cavazzana[2,6,10], Anne Durandy[1], Jean-Laurent Casanova[7,9,10,11], Galicier Lionel[12,13], Jehane Fadlallah[12,13], Alain Fischer[2,10,14], Sven Kracker[1,2]
[1]Institut Imagine, Human Lymphohematopoiesis Laboratory, Paris, France, [2]Imagine Institute, Université De Paris, Paris, France, [3]Imagine Institute, Paris-descartes Bioinformatics Platform, Paris, France, [4]Sorbonne Université, Plateforme De Cytométrie De La Pitié-salpêtrière Cyps, Paris, France, [5]Imagine Institute, Genomics Core Facility, Paris, France, [6]Groupe Hospitalier Universitaire Ouest, Biotherapy Clinical Investigation Center, Paris, France, [7]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Paris, France, [8]Paris Hospital, Study Center For Primary Immunodeficiencies, Paris, France, [9]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, New York, United States of America, [10]Necker Hospital, Pediatric Hematology-immunology And Rheumatology Unit, Paris, France, [11]Howard Hughes Medical Institute, -, Washington, United States of America, [12]Hôpital Saint Louis, Clinical Immunology Department, Paris, France, [13]Hôpital Saint Louis, National Reference Center For Castleman Disease, Paris, France, [14]Collège de France, Collège De France, Paris, France

Background and Aims: Three patients from a multigeneration family suffer since early childhood from recurrent respiratory tract infections associated to hypogammaglobulinemia and requiring Ig substitution. Skin manifestations and early hair greying were reported for all patients. Whole exome sequencing identified a novel heterozygous missense IRF4 mutation located in the sequence coding for the interferon activation domain. Our study aimed to characterize functional consequences of this mutation for the immune system.

Methods: Time-of-flight mass cytometry was performed to characterize the immune phenotype. Molecular analysis included luciferase reporter assays, transcriptomic and proteomic approaches. Ectopic expression and functional analysis were performed in naive T and B lymphoblastoid cell lines.

Results: Blood immunophenotyping of all patients indicated a striking absence of plasma cells. Lower proportion of naïve and elevated proportion of terminal effector T lymphocytes were observed in both CD4 and CD8 cell subsets. Luciferase reporter assays (containing three main IRF4 binding elements) revealed variably modified transcriptional activity for mutant IRF4 protein, depending on the analyzed element. Although chromatin immunoprecipitation experiments showed similar binding of wild type and mutated IRF4 to these elements, rapid immunoprecipitation mass spectrometry of endogenous proteins identified unexpected cofactors bound to DNA IRF4 complexes. Ectopic expression of mutant IRF4 in naïve T cells was associated with a rapid loss of naïve markers. Experiments performed in lymphoblastoid B cell lines correlated the presence of the mutant IRF4 protein to a loss of pro-plasmablast gene expression.

Conclusions: We report the phenotypic and functional investigation of a novel dominant immune deficiency caused by an IRF4 missense heterozygous mutation.

Disclosure: No.

Keywords: Interferon Regulatory Factor 4, Plasma cell, hypogammaglobulinemia, T and B cell differentiation, Terminal effector T cells, combined immunodeficiency

OC031

A NOVEL INBORN ERROR of IMMUNITY CAUSED BY MUTATIONS IN NFKBID

ORAL COMMUNICATIONS SESSION 05: NOVEL DEFECTS AND MECHANISMS

Jasper Cornish[1,2], Alba Parra-Martínez[3,4,5], Marina Garcia-Prat[3,4,5], Malena Perez-Lorenzo[3,4,5], Andrea Martín-Nalda[3,4,5], Clara Franco Jarava[5,6,7], Jacques Rivière[3,4,5], Roger Colobran[5,6,7,8], Maryam Rashidi[2,9], James Vince[2,9], Jo Douglass[10,11], Melanie Bahlo[2,12], Pere Soler-Palacin[3,4,5], Charlotte Slade[1,2,10], Vanessa Bryant[1,2,10]
[1]The Walter and Eliza Hall Institute of Medical Research, Immunology, Parkville, Australia, [2]Melbourne University, Medical Biology, Parkville, Australia, [3]Vall d'Hebron Barcelona Hospital Campus, Infection In Immunocompromised Pediatric Patients, Barcelona, Spain, [4]Vall d'Hebron Barcelona Hospital Campus, Pediatric Infectious Diseases And Immunodeficiencies Unit, Barcelona, Spain, [5]Jeffrey Modell Foundation, Diagnostic And Research Center For Primary Immunodeficiencies, Barcelona, Spain, [6]Vall d'Hebron Barcelona Hospital Campus, Immunology Division, Barcelona, Spain, [7]Vall d'Hebron Institute of Research (VHIR), Translational Immunology, Barcelona, Spain, [8]Vall d'Hebron Barcelona Hospital Campus, Department of Clinical And Molecular Genetics, Barcelona, Spain, [9]The Walter and Eliza Hall Institute of Medical Research, Inflammation, Parkville, Australia, [10]Royal Melbourne Hospital, Clinical Immunology And Allergy, Parkville, Australia, [11]Royal Melbourne Hospital, Medicine, Parkville, Australia, [12]The Walter and Eliza Hall Institute of Medical Research, Population Health And Immunity, Parkville, Australia

Background and Aims: The NF-κB family of transcription factors are essential for immune function. Mutations in NFKB1 and NFKB2 are the most prevalent monogenic causes of Common Variable Immunodeficiency (CVID). NF-κB activity is regulated by the IκB family of inhibitor proteins, including 3 atypical nuclear IκBs (Bcl-3, IκBζ, and IκBNS) that bind to NF-κB dimers at target gene promoters to provide additional regulation. Disruption of any one of these interactions may thus have significant impact on immune responses. We identified biallelic loss-of-function mutations in NFKBID (encoding IκBNS) in 3 unrelated patients with antibody deficiency complicated by significant immune dysregulation. Two adult patients were identified (Royal Melbourne Hospital, Australia; Vall d'Hebron Hospital, Barcelona, Spain) and one child (Royal Children's Hospital, Australia). Aims: 1. Characterise the clinical spectrum of NFKBID-deficiency 2. Determine the cellular and regulatory consequences of NFKBID-deficiency

Methods: Comprehensive clinical and immunological characterisation of 3 patients was performed. IκBNS null leukocyte cell lines were generated (Jurkat, THP-1, Bjab) by CRISPR/Cas9 editing, representing key immune cell lineages with specific point mutations introduced, and NF-κB activity assessed.

Results: Both adult IκBNS-deficient patients developed a progressive dysregulatory immune phenotype with shared clinical features of severe dermatitis, autoimmune cytopenia and recurrent respiratory infections We identified defects in NFκB signalling both upstream and downstream of IκBNS, suggesting atypical IκB inhibitors also regulate expression and function of classical IκBs and underlie severe disease in patients.

Conclusions: Mutations in NFKBID represent a new inborn error of immunity due to aberrant NF-κB signalling and disruption of classical IκB inhibiror proteins.

Disclosure: No.

Keywords: NF-κB, IEI, NFKBID, Inflammation, IgE, IκB

OC032

NOVEL PRIMARY IMMUNODEFICIENCY ASSOCIATED WITH BIALLELIC VARIANTS IN CWF19L2

ORAL COMMUNICATIONS SESSION 05: NOVEL DEFECTS AND MECHANISMS

James Poulter[1], Fatima Nadat[2], Elanor O'Callagham[3], Dylan Lawless[4,5], Evie Robson[6], Alaa Alghamdi[1], Jacquelyn Bond[4], Ailsa Rose[1], Daniel Peckham[6], Clive Carter[2], Gina Doody[7], Sinisa Savic[2,3]
[1]University of Leeds, Leeds Institute of Medical Research, Leeds, United Kingdom, [2]St James's University Hospital, Clinical Immunology And Allergy, Leeds, United Kingdom, [3]University of Leeds, Leeds Institute of Rheumatic And Musculoskeletal Medicine, Leeds, United Kingdom, [4]University of Leeds, Leeds Institute of Medical Research At St James's University Hospital, Leeds, United Kingdom, [5]Global Health Institute, School of Life Sciences, Lausanne, Switzerland, [6]University of Leeds, Leeds Cystic Fibrosis Trust Strategic Research Centre, Leeds, United Kingdom, [7]University of Leeds, School of Medicine, Leeds, United Kingdom

Background and Aims: CWF19L2 is a part of the post-mRNA release spliceosomal complex and is responsible for pre-mRNA splicing into its mature form. Here we present a compound heterozygous mutations (c.2200C>T, p.Gln734Ter; c.2251T>C, p.Cys751Arg) in a family with microcephaly, autism and immunodeficiency.

Methods: WES was used to identify biallelic CW19L2 variants. Immunological assessment included immunophenotyping, functional T and B cell assessment and neutrophil assays. Knockdown experiments using HEK293 cells were used to study cell division.

Results: Affected sibling pair presented with early onset bronchiectasis and recurrent sinopulmonary infections. Immunoglobulin profile showed reduction in IgM, but normal IgG and IgA levels. Lymphocyte populations and T cell proliferation in the probands were normal with the exception of a reduction in naïve T-cells. T-cell recall response to range of viral antigens was detectable. Patient peripheral blood B cells were able to differentiate in vitro and secrete IgM, IgA and IgG in the culture, following T dependent stimulation. Neutrophil burst test was normal but neutrophil migration was severely impaired in the probands. RNA sequencing from the proband identified increased expression of genes associated with the adaptive immune response and T cell receptor signalling, and a decrease in genes associated with the inflammatory response, chemokine-mediated signalling and actin cytoskeleton. CWF19L2 knockdown in HEK293 resulted in reduced cellular proliferation, increased asymmetric cell division, increased time required to complete mitosis and increased number of cells failing to complete mitosis.

Conclusions: These results suggest that biallelic loss of function variants in CW19L2 result in a novel primary immunodeficiency characterised by cytoskeleton defects and impaired neutrophil migration.

Disclosure: No.

Keywords: spliceosome, CWF19L2, Bronchiectasis, neutrophil chemotaxis

OC033

HETEROZYGOUS LOSS of MAP4K1 ENCODING FOR HEMATOPOIETIC PROGENITOR KINASE 1 (HPK1), A NEGATIVE REGULATOR of TCR SIGNALING, CAN LEAD TO IMMUNE DYSREGULATION

ORAL COMMUNICATIONS SESSION 05: NOVEL DEFECTS AND MECHANISMS

Meri Kaustio[1], Katariina Nurmi[2], Kristiina Silventoinen[2], Kirsten Nowlan[2], Kim Le[2], Silvia Taglieri[1], Virpi Glumoff[3], Kari Eklund[2], Mikko R J Seppänen[4], Eliisa Kekäläinen[2], Juha Grönholm[2], Kristiina Aalto[5], Timi Martelius[6], Janna Saarela[1]
[1]University of Helsinki, Institute of Molecular Medicine Finland (fimm), Helsinki, Finland, [2]University of Helsinki, Translational Immunology Research Program, Helsinki, Finland, [3]University of Oulu, Research Unit of Biomedicine, Oulu, Finland, [4]University of Helsinki and HUS Helsinki University Hospital, Rare Disease And Pediatric Research Centers, Helsinki, Finland, [5]University of Helsinki and Helsinki University Hospital, New Children's Hospital, Pediatric Research Center, Helsinki, Finland, [6]Helsinki University Hospital, Inflammation Center/infectious Diseases, Helsinki, Finland

Background and Aims: MAP4K1 encodes for hematopoietic progenitor kinase 1 (HPK1) which negatively regulates TCR and BCR signaling in lymphocytes. MAP4K1-knockout mice show increased T cell proliferation, secretion of proinflammatory cytokines, and susceptibility to autoimmunity. In humans, decreased levels of HPK1 have been found in patients with psoriatic arthritis and systemic lupus erythematosus but evidence of direct causality between HPK1 and human immune disorders is lacking.

Methods: We employed genotyping and exome sequencing to identify the underlying genetic defect in a multigenerational pedigree with nine affected individuals exhibiting dominantly inherited autoimmunity/inflammation. RT-PCR, RNA-sequencing, flow cytometry and western blotting were utilized for patient characterization and analysis of candidate variant effects.

Results: Symptoms in the studied pedigree included prolonged fevers of unknown cause and recurrent joint inflammation, as well as untypical Still's disease, Kawasaki disease and urticaria in one patient, and HLH in another. Genetic linkage analysis indicated highest probability of disease variant at the genomic location chr19:35079781-45414451 (hg19, maximum LOD-score 2.067), where exome sequencing identified a novel splice-site variant in MAP4K1 (NM_007181:exon23:c.1778+2T>G). RT-PCR and western blotting confirmed altered splicing of MAP4K1 and loss of HPK1 protein production from the variant allele in patient-derived PBMCs. The patients had normal immune cell composition but exhibited increased levels of proinflammatory cytokines in their plasma. Gene Set Enrichment Analysis of RNA-sequencing data indicated increased expression of genes involved in NF-κB-mediated TNFα signaling and inflammatory responses in patient PBMCs. Further functional tests are pending.

Conclusions: Heterozygous loss of MAP4K1/HPK1 is a possible novel cause of autoinflammation and autoimmunity.

Disclosure: No.

Keywords: TCR signaling, HLH, MAP4K1/HPK1, Genetics, Inflammation, Autoimmunity

OC034

HUMAN OTULIN HAPLOINSUFFICIENCY IMPAIRS CELL-INTRINSIC IMMUNITY TO STAPHYLOCOCCAL ALPHA-TOXIN

ORAL COMMUNICATIONS SESSION 05: NOVEL DEFECTS AND MECHANISMS

András Spaan[1,2], Anna-Lena Neehus[3,4,5], Emmanuel Laplantine[6], Frederoik Staels[7], Masato Ogishi[1], Yoann Seeleuther[5], Franck Rapaport[1], Keenan Lacey[8], Erika Van Nieuwenhove[7,9], Maya Chrabieh[3,5], David Hum[1], Melanie Migaud[3,5], Araksya Izmiryan[5,10], Lazaro Lorenzo[5], Tatiana Kochetkov[1], Dani Heesterbeek[2], Bart Bardoel[2], Ashley Dumont[8], Kerry Dobbs[11], Solenne Chardonnet[12], Søren Heissel[13], Timour Baslan[14], Peng Zhang[1], Rui Yang[1], Dusan Bogunovic[15], Herman Wunderink[2], Pieter-Jan Haas[2], Henrik Molina[13], Griet Van Buggenhout[16,17], Stanislas Lyonnet[5], Luigi Notarangelo[11], Mikko R J Seppänen[18], Robert Weil[6], Analia Seminario[19], Héctor Gomez-Tello[20], Carine Wouters[7,21], Mehrnaz Mesdaghi[22], Mohammad Shahrooei[23,24], Xavier Bossuyt[23], Erdal Sag[25], Rezan Topaloglu[26], Seza Ozen[25], Helen Leavis[27], Maarten Van Eijk[28], Liliana Bezrodnik[19], Lizbeth Blancas Galicia[29], Alain Hovnanian[5,10,30], Aude Nassif[31], Brigitte Bader-Meunier[5], Benedicte Neven[32,33], Isabelle Meyts[34,35], Rik Schrijvers[36], Anne Puel[1,3,5], Jacinta Bustamante[1,3,5,37], Ivona Aksentijevic[38], Dan Kastner[38], Victor Torres[8], Stephanie Humblet-Baron[7], Adrian Liston[7,39,40], Laurent Abel[1,3,5], Bertrand Boisson[1,3,5], Jean-Laurent Casanova[1,3,5,41]
[1]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, New York, United States of America, [2]University Medical Center Utrecht, Utrecht University, Department of Medical Microbiology, Utrecht, Netherlands, [3]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1163, Paris, France, [4]Hannover Medical School, Institute of Experimental Hematology, Rebirth Research Center For Translational And Regenerative Medicine, Hannover, Germany, [5]Paris Cité University, Imagine Institute, Paris, France, [6]Centre d'Immunologie et des Maladies Infectieuses, Sorbonne University, Inserm U1135, Cnrs Erl8255, Paris, France, [7]KU Leuven, Laboratory For Adaptive Immunology, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [8]New York University Grossman School of Medicine, Department of Microbiology, New York, United States of America, [9]Utrecht University, Department of Pediatric Rheumatology And Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands, [10]INSERM U1163, Laboratory of Genetic Skin Diseases, Paris, France, [11]NIAID, NIH, Laboratory of Clinical Immunology And Microbiology, Division of Intramural Research, Bethesda, United States of America, [12]Plateforme Post-génomique de la Pitié-Salpêtrière, Sorbonne University, Inserm, Ums Production Et Analyse De Données En Sciences De La Vie Et En Santé, Pass, Paris, France, [13]The Rockefeller University, Proteomics Resource Center, New York, United States of America, [14]Memorial Sloan Kettering Cancer Center, Cancer Biology And Genetics Program, New York, United States of America, [15]Mount Sinai, Icahn School of Medicine, New York, United States of America, [16]KU Leuven, Department of Human Genetics, Leuven, Belgium, [17]University Hospitals Leuven, Center For Human Genetics, Leuven, Belgium, [18]University of Helsinki and HUS Helsinki University Hospital, Rare Disease And Pediatric Research Centers, Helsinki, Finland, [19]Children's Hospital Ricardo Gutierrez, Center For Clinical Immunology, Immunology Group, Buenos Aires, Argentina, [20]Poblano Children's Hospital, Immunology Department, Puebla, Mexico, [21]University Hospitals Leuven, Department of Pediatrics, Leuven, Belgium, [22]Shahid Beheshti University of Medical Sciences, Department of Allergy And Clinical Immunology, Mofid Children's Hospital, Tehran, Iran, [23]KU Leuven, Clinical And Diagnostic Immunology, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [24]Sina Medical Complex, Specialized Immunology Laboratory of Dr. Shahrooei, Ahvaz, Iran, [25]Hacettepe University, Department of Pediatric Rheumatology, Ankara, Turkey, [26]Hacettepe University, Department of Pediatric Nephrology, Ankara, Turkey, [27]University Medical Center Utrecht, Utrecht University, Department of Rheumatology & Clinical Immunology, Utrecht, Netherlands, [28]University Medical Center Utrecht, Utrecht University, Department of Intensive Care Medicine, Utrecht, Netherlands, [29]National Institute of Pediatrics, Immune Deficiencies Laboratory, Mexico City, Mexico, [30]Necker Hospital for Sick Children, Department of Genetics, Paris, France, [31]Institut Pasteur, Centre Médical, Paris, France, [32]Necker Hospital for Sick Children, Pediatric Immunology, Hematology And Rheumatology Unit, Paris, France, [33]Necker Hospital for Sick Children, Laboratory of Immunogenetics of Pediatric Autoimmunity, Inserm U1163, Paris, France, [34]KU Leuven, Laboratory of Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [35]University Hospitals Leuven, Department of Pediatrics, Jeffrey Modell Diagnostic And Research Network Center, Leuven, Belgium, [36]KU Leuven, Allergy And Clinical Immunology Research Group, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [37]AP-HP, Study Center For Primary Immunodeficiencies, Necker Hospital For Sick Children, Paris, France, [38]National Human Genome Research Institute, Inflammatory Disease Section, Bethesda, United States of America, [39]KU Leuven, Vib Center For Brain And Disease Research, Leuven, Belgium, [40]Babraham Research Campus, Immunology Programme, Babraham Institute, Cambridge, United Kingdom, [41]Howard Hughes Medical Institute, -, New York, United States of America

Background and Aims: Staphylococcus aureus is a major bacterial pathogen with a global impact on human health. The molecular basis of interindividual clinical variability upon exposure to and infection with S. aureus is unclear. Most cases of severe staphylococcal disease remain unexplained.

Methods: We aimed to discover human genetic and immunological determinants of severe staphylococcal disease in a genome-wide manner. We tested for genetic homogeneity in a cohort of patients with unexplained life-threatening staphylococcal disease in the exomes of 105 cases and 1,274 controls.

Results: We found enrichment for rare heterozygous OTULIN variants in patients with severe staphylococcal disease. OTULIN is a linear deubiquitinase and negative regulator of NF-κB-signaling encoded by a gene on chromosome 5p. Probands heterozygous for deleterious OTULIN variants suffered from episodes of life-threatening skin or pulmonary necrosis. Their disease was typically triggered by S. aureus infections. Haploinsufficiency was the mechanism of dominance and was both biochemically and clinically phenocopied in patients with the more common 5p- (Cri-du-Chat) chromosomal deletion syndrome. Blood leukocyte subsets were developmentally and functionally unaffected. In dermal fibroblasts, OTULIN haploinsufficiency increased the levels of linear ubiquitin, but TNF-receptor NF-κB-signaling remained intact. The OTULIN-dependent accumulation of caveolin-1 in dermal fibroblasts — but not leukocytes — facilitated the cytotoxic damage inflicted by the staphylococcal virulence factor α-toxin. Naturally elicited antibodies against α-toxin contributed to incomplete clinical penetrance.

Conclusions: By disrupting cell-intrinsic immunity to α-toxin in fibroblasts, human OTULIN haploinsufficiency underlies life-threatening staphylococcal disease of the skin and lungs.

Disclosure: No.

Keywords: caveolin-1, OTULIN, Haploinsufficiency, 5p- syndrome, Staphylococcus aureus, alpha-toxin

OC035

BIALLELIC MUTATION IN DNA POLYMERASE DELTA 3 AS A NOVEL CAUSE of SEVERE COMBINED IMMUNODEFICIENCY WITH DEVELOPMENTAL DEFECTS

ORAL COMMUNICATIONS SESSION 05: NOVEL DEFECTS AND MECHANISMS

Maria Rodrigo Riestra[1], Bethany Pillay[1], Mathijs Willemsen[2], Lisa Ehlers[1], Selket Delafontaine[1], Marjon Wouters[1], Anneleen Hombrouck[1], Kate Sauer[3], Cecilia Dominguez Conde[4], Kaan Boztug[5], Luigi Notarangelo[6], Stephanie Humblet-Baron[2], Giorgia Bucciol[1], Leen Moens[1], Isabelle Meyts[1]
[1]KU Leuven, Laboratory Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [2]KU Leuven, Laboratory For Adaptive Immunology, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [3]AZ Sint-Jan Bruges, Paediatrics, Brugge, Belgium, [4]Wellcome Sanger Institute, Wellcome Genome Campus, Cambridge, United Kingdom, [5]St. Anna Children's Hospital, Pediatrics And Adolescent Medicine, Vienna, Austria, [6]NIAID, NIH, Laboratory of Clinical Immunology And Microbiology, Division of Intramural Research, Bethesda, United States of America

Background and Aims: The DNA polymerase δ complex, comprising catalytic subunit POLD1, and accessory subunits POLD2, POLD3 and POLD4, is essential for DNA synthesis and central to genome integrity (Loeb and Monnat, 2008). Biallelic loss-of-function mutations in POLD1 and POLD2, leading to reduced functionality of the polymerase δ complex, were reported previously (Conde et al. 2019, Cui et al. 2020, Nichols-Vinueza et al. 2021). The phenotype of polymerase δ deficient patients combines immunodeficiency, developmental abnormalities, and replicative stress and has implicated the DNA polymerase δ complex in T and B cell development. The aim of this study is to validate a mutation in POLD3 as a novel cause of inborn error of immunity.

Methods: We performed molecular and functional analysis of the mutant DNA polymerase δ complex, assessed cell cycle progression as well as replication-associated DNA damage by means of imaging/standard flow cytometry.

Results: We identified a homozygous missense variant (c.1118CA>C; p.K373T) in POLD3 in a patient with severe combined immunodeficiency. The patient exhibited decreased numbers of naïve T cells associated with a restricted T-cell receptor repertoire and a defect in the early stages of T-cell receptor recombination. Protein expression of POLD1, POLD2 and POLD3 tends to be decreased in patient fibroblasts, associated with a marked defect in S-phase entry and an enhanced numbers of double-strand DNA break foci. Rescue of the phenotype will be presented. The patient received hematopoietic stem cell transplantation and is now two years old.

Conclusions: We describe a homozygous mutation in POLD3 as a novel cause of severe combined immunodeficiency.

Disclosure: No.

Keywords: polymerase delta deficiency, Severe combined immunodeficiency, biallelic POLD3 mutation, replication stress, DNA lesions, TCR oligoclonality

OC036

HUMAN INHERITED IL-7 DEFICIENCY IS MILDER THAN IL-7R DEFICIENCY

ORAL COMMUNICATIONS 06: LATE BREAKING ABSTRACTS

Carlos Arango-Franco[1,2,3], Masato Ogishi[4], Susanne Unger[5], Ottavia Delmonte[6], Julio Orrego[2], Margarita Velasquez-Lopera[7], Andrés Zea-Vera[8,9], Juan Sanchez[2,10], Julian Rojas[2], Ahmad Yatim[4], Lucia Erazo-Borras[1,2,3], Jonathan Bohlen[1,3], Majistor Maglorius Renkilaraj[1,3], Yoann Seeleuthner[1], Luis Correa-Londoño[7], Axel Cederholm[11], Alejandro Gallon[2], Pedro Goncalves[12], Jean-Marc Doisne[12], Kathryn Payne[5], Liran Horev[13], Bénédicte Charmeteau De-Muylder[14], Jesús Álvarez Álvarez[2], Diana Arboleda[2], Lizeth Pérez-Zapata[2], Marcela Moncada-Velez[2,4], Yolanda Caicedo[15], Boaz Palterer[6], Tina Nguyen[16], Cindy Ma[16], Juan Alzate[17], Felipe Cabarcas[17], Taushig Khan[18], Darawan Rinchai[4], Tim Waterboer[19], Jean-Luc Pretét[20], Nico Marr[18], Stéphanie Boisson-Dupuis[3,4], Vivien Beziat[1,3], Emmanuelle Jouanguy[1,3], Jacinta Bustamante[1,3,4,21], Dimitra Kiritsi[22], João Barata[23], Nils Landegren[11], James Di Santo[12], Laurent Abel[1,3,4], Stuart Tangye[16], Luigi Notarangelo[6], Rémi Cheynier[14], Andrea Lisco[24], Ken Natsuga[25], Andrés Arias[2,4,10], José Franco[2], Klaus Warnatz[5], Jean-Laurent Casanova[1,3,4,26,27], Anne Puel[1,3,4]
[1]Necker Hospital, Laboratory of Human Genetics of Infectious Diseases, Paris, France, [2]Primary Immunodeficiencies Group, Department of Microbiology And Parasitology, School of Medicine, University of Antioquia, Medellin, Colombia, [3]Imagine Institute, University of Paris Cité, Paris, France, [4]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, New York, United States of America, [5]Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany, [6]National Institutes of Health, Laboratory of Clinical Immunology And Microbiology, Bethesda, United States of America, [7]Universidad de Antioquia, Facultad de Medicina, Sección De Dermatología Centro De Investigaciones Dermatológicas (ciderm), Medellin, Colombia, [8]Hospital Universitario del Valle, Clinical Immunology Clinic, Cali, Colombia, [9]Universidad del Valle, Microbiology Department, Cali, Colombia, [10]University of Antioquia, Microbiology School, Medellin, Colombia, [11]Uppsala University, Department of Medical Biochemistry And Microbiology, Uppsala, Sweden, [12]Institut Pasteur, Innate Immunity Unit, Paris, France, [13]University Medical Center, Department of Dermatology, Hadassah-hebrew University Medical Center, Jerusalem, Israel; The Center For Genetic Diseases of The Skin And Hair, Hadassah-hebrew, jerusalem, Israel, [14]Université Paris Cité, CNRS, INSERM, Institut Cochin, Paris, France, [15]Clinica Farallones, Infectologia Pediátrica,, Cali, Colombia, [16]Garvan Institute of Medical Research, Immunology, Darlinghurst, Australia, [17]Universidad de Antioquia, Centro Nacional De Secuenciación Genómica Cnsg, Medellin, Colombia, [18]Hamad Bin Khalifa University, College of Health and Life Sciences, Research Branch, Sidra Medicine, Doha, Qatar, [19]German Cancer Research Center (DKFZ), Infections And Cancer Epidemiology, Heidelberg, Germany, [20]Bourgogne Franche-Comté University, Ea3181, 25030, Besançon, France, [21]Paris Hospital, Study Center For Primary Immunodeficiencies, Paris, France, [22]University Medical Center of Freiburg, Department of Dermatology, Freiburg, Germany, [23]Universidade de Lisboa, Instituto De Medicina Molecular João Lobo Antunes, Faculdade De Medicina, lisboa, Portugal, [24]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Laboratory of Immunoregulation, Maryland, United States of America, [25]Hokkaido University Graduate School of Medicine, Department of Dermatology, Sapporo, Japan, [26]Necker Hospital, Pediatric Hematology-immunology And Rheumatology Unit, Paris, France, [27]Howard Hughes, Medical Institute, Washington, United States of America

Background and Aims: Infants with bi-allelic *IL7R* loss-of-function rare variants have severe combined immune deficiency (SCID), without autologous T lymphocytes but normal counts of B and NK lymphocytes ($T^-B^+NK^+$ SCID). We investigated seven patients with bi-allelic *IL7* rare variants and combined immunodeficiency (CID). We aimed at performing a comprehensive molecular, biochemical, cellular, and immunological characterization of human AR IL-7 deficiency

Methods: We reviewed medical records, established pedigrees, performed whole exome-sequencing (WES), Sanger sequencing, deep immunophenotyping by spectral flow cytometry, scRNA seq, and functional tests for seven patients with permanent lymphopenia and multiple infectious diseases.

Results: We report seven adults aged 22 to 63 years from five kindreds of three ancestries with bi-allelic *IL7* rare variants and combined immunodeficiency (CID), with detectable blood T lymphocytes but selective $CD4^+$, MAIT, and iNKT cell lymphopenia. Decreased blood counts of T-cell receptor excision circle (TRECs), recent thymic emigrant T cells, and naïve $CD4^+$ T cells, with reduced TCR diversity, all attest to an impaired thymic output *in vivo*. Peripheral $CD4^+$ T cells also proliferate poorly but produce normal levels of cytokines *in vitro*. Nevertheless, the patients are homozygous for three different *IL7* variants, which are all biochemically deleterious. Moreover, the IL-7 protein is undetectable in the patients' samples tested, unlike in healthy controls.

Conclusions: These findings show that inherited human IL-7 deficiency is milder than IL-7R deficiency, implying that other IL-7R-binding cytokines, such as thymic stromal lymphopoietin (TSLP), govern the IL-7-independent development of a significant range and proportion of human T cells.

Disclosure: No.

Keywords: combined immunodeficiency, human papilloma virus, Interleukin-7, mycobacterial disease, cryptococcal disease, histoplasmosis

OC037

INHERITED FLT3 LIGAND (FLT3LG) DEFICIENCY UNDERLIES SEVERE CUTANEOUS PAPILLOMAVIRUS INFECTION

ORAL COMMUNICATIONS 06: LATE BREAKING ABSTRACTS

Mana Momenilandi[1,2], Jiafen Hu[3], Hossein Esmaeilzadeh[4], Anna-Lena Neehus[1], Antoine Guerin[5], Erika Della Mina[5], Antoine Fayand[6], Romain Lévy[7], David Langlais[8], Hassan Rokni-Zadeh[9], Majid Changi-Ashtiani[10], Yoann Seeleuther[1], Corentin Le Floc'H[1], Marie Materna[1], Anais Pereira[1], Margareta Wuyts[11], Masato Ogishi[12], Jouni Uitto[13], Hassan Vahidnezhad[13], Jean-Luc Pretét[14], Nico Marr[15], Isabelle Meyts[16], Laurent Abel[1], Jacinta Bustamante[17], Tim Waterboer[18], Cindy Ma[19], Stuart Tangye[5], Nico Lachmann[20], Neil Christensen[21], Mohammad Shahrooei[11], Xavier Bossuyt[11], Jean-Laurent Casanova[17,22,23], Vivien Beziat[24,25]
[1]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1163, Paris, France, [2]Imagine institute, Immunology, Paris, France, [3]Pennsylvania State University College of Medicine, Department of Pathology And Laboratory Medicine, Pennsylvania, United States of America, [4]Shiraz University of Medical Sciences, Department of Allergy And Clinical Immunology, Namazi Hospital,, Shiraz, Iran, [5]Garvan Institute of Medical Research, Immunology, Darlinghurst, Australia, [6]Sorbonne Université, Department of Internal Medicine, Paris, France, [7]Hôpital Necker-Enfants Malades, Pediatric Immunology-hematology And Rheumatology Unit, Paris, France, [8]McGill University, Department of Human Genetics, Montréal, Canada, [9]Zanjan University of Medical Sciences (ZUMS), Department of Medical Biotechnology, Zanjan, Iran, [10]Institute for Research in Fundamental Sciences (IPM), School of Mathematics, Tehran, Iran, [11]KU Leuven, Clinical And Diagnostic Immunology, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [12]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, New York, United States of America, [13]Thomas Jefferson Univerrsity, Department of Dermatology And Cutaneous Biology, Philadelphia, United States of America, [14]Bourgogne Franche-Comté University, Ea3181, 25030, Besançon, France, [15]Sindra Medicine, Marr Lab, CFV+W Ar-Rayyan, Qatar, Qatar, [16]KU Leuven, Laboratory of Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [17]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Paris, France, [18]German Cancer Research Center (DKFZ),, Infections And Cancer Epidemiology, Heidelberg, Germany, [19]Garvan Institute, Tangye Lab, Darlinghurst, Australia, [20]Hannover Medical School, Institute of Experimental Hematology, Hannover, Germany, [21]Pennsylvania State University College of Medicine, Department of Microbiology And Immunology, Pennsylvania, United States of America, [22]Howard Hughes Medical Institute, -, Washington, United States of America, [23]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, New York, United States of America, [24]Institut Imagine, Genetics of Infectious Disease, Paris, France, [25]University of Paris, Laboratory of Human Genetics of Infectious Diseases, Paris, France

Background and Aims: We studied three siblings with disseminated and recalcitrant HPV2$^+$ common warts, but no mutations in known genes underlying inborn errors of immunity associated with severe human papillomavirus (HPV) infection.

Methods: The patients were adults suffering from failure to thrive, recurrent respiratory infections, diarrhea, polyarthritis, and severe disseminated warts from childhood. All family members underwent whole-exome sequencing and linkage analysis followed by Sanger sequencing. WT and mutants FLT3LG cDNA were characterized using overexpression systems. Patients' blood and skin samples were investigated using mass cytometry (CyTOF) and imaging mass cytometry (IMC). Endogenous FLT3LG levels were investigated and complemented in primary T cells using a lentiviral system.

Results: The patients were homozygous for a loss of function variant in the *FLT3LG* gene, affecting all functional isoforms. FLT3LG was absent in the plasma of the patients. T cells of the patients lacked FLT3LG expression *in vitro* and were rescued using lentiviral transduction. The patients had nearly absent circulating dendritic cells count, reduced B cells subpopulations, and monocytopenia, whereas other leukocyte subsets were normal. Their T cell function was not affected. Their Immunoglobulin blood levels were normal except for elevated IgA. Their Langerhans cells were in normal numbers in the skin. Serological assays demonstrated exposure to multiple HPV of all genera, suggesting specific susceptibility to HPV2 in the patients.

Conclusions: Inherited human FLT3LG deficiency results in quantitative defects of multiple myeloid and lymphoid subsets, particularly DCs, impairing immunity to various infectious agents, most notably cutaneous HPV2.

Disclosure: Funding: This work was supported by a grant from ANRS (Maladies infectieuses émergentes, Inserm) within a doctoral program funding context.

Keywords: Inborn errors of immunity, HPV infection, Primary Immune deficiency, FLT3 ligand

OC038

HUMAN INHERITED RIPK3 DEFICIENCY IN HERPES SIMPLEX ENCEPHALITIS

ORAL COMMUNICATIONS 06: LATE BREAKING ABSTRACTS

Zhiyong Liu, Eduardo J. Garcia Reino, Jean-Laurent Casanova, Shen-Ying Zhang
Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, New York, United States of America

Background and Aims: Herpes simplex virus-1 (HSV-1) encephalitis (HSE) is the commonest sporadic encephalitis in the Western world. Inborn errors of TLR3-dependent type I IFN immunity in cortical neurons underlie forebrain HSE due to uncontrolled viral growth and subsequent cell death.

Methods: We performed whole-exome sequencing (WES) on an HSE patient from France, and identified two predicted to be loss-of-function (pLOF) heterozygous mutations in *RIPK3*: p. Arg422* (c.1264 C>T) and p.Pro493fs9* (c.1475 C>CC). Sanger sequencing of DNA from the patient and her parents confirmed both mutations in the patient and showed that Arg422* (R422*) was inherited from the mother and Pro493fs9* (P493fs9*) from the father.

Results: RIPK3 is a ubiquitous cytoplasmic kinase regulating cell death outcomes, including apoptosis and necroptosis in particular. *In vitro*, the R422* and P493fs9* RIPK3 proteins impaired cellular necroptosis upon TLR3 or TNFR1 stimulation, and ZBP1/DAI-mediated necroptotic cell death following HSV-1 infection. The patient's fibroblasts displayed no detectable RIPK3 expression. Following TNFR1 or TLR3 stimulation, the patient's cells did not undergo apoptosis or necroptosis. Following HSV-1 infection, the cells supported excessive viral growth despite the normal induction of IFN-beta. This phenotype was, nevertheless, rescued by the application of exogenous type I IFN. The patient's human pluripotent stem cell (hPSC)-derived cortical neurons displayed impaired cell death and enhanced viral growth following HSV-1 infection, as did isogenic RIPK3-knockout hPSC-derived cortical neurons.

Conclusions: Inherited RIPK3 deficiency therefore confers a predisposition to HSE, by impairing the cell death-dependent control of HSV-1 in cortical neurons independently of type I IFN immunity.

Disclosure: No.

Keywords: HSE, HSV-1, RIPK3, Necroptosis, apoptosis, Cell Intrinsic Immunity

OC039

AUTOSOMAL DOMINANT STAT6 GAIN of FUNCTION CAUSES ATOPY ASSOCIATED WITH LYMPHOMA

ORAL COMMUNICATIONS 06: LATE BREAKING ABSTRACTS

Jesmeen Maimaris[1,2], Ekaterina Minskaya[1], Adriana Albuquerque[1], Persephone Jenkins[3], Richard Grace[4], Fernando Moreira[5], Bodo Grimbacher[6], N Ihr Bioresource–Rare Diseases Consortium[7], Emma Morris[1,2], Siobhan Burns[1,2]
[1]Institute of Immunity and Transplantation, University College London, Ucl Division of Infection And Immunity, London, United Kingdom, [2]The Royal Free London NHS Foundation Trust, Immunology, London, United Kingdom, [3]University College London, Institute of Immunity And Transplantation, London, United Kingdom, [4]East Sussex Hospitals NHS Trust, Department of Haematology, Eastbourne, United Kingdom, [5]Royal Free Hospital, Department of Immunology, PQ, United Kingdom, [6]Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany, [7]Cambridge University Hospital, Nihr Bioresource, Cambridge, United Kingdom

Background and Aims: The transcription factor STAT6 (Signal Transducer and Activator of Transcription 6) is a key regulator of T-helper 2 (Th2)- mediated allergic inflammation via the IL-4 JAK (Janus kinase)/STAT signalling pathway. We identified a novel heterozygous germline mutation STAT6 c.1255G>C, p.D419H, in a kindred affected by early-onset atopic dermatitis, food allergy, eosinophilic asthma, and follicular lymphoma.

Methods: Analysis of D419H STAT6 expression and functional activity in transduced HEK293T cells and in patient skin fibroblasts and peripheral blood mononuclear cells (PBMC).

Results: We observed consistently higher STAT6 and phosphorylated STAT6 levels at baseline and following IL-4 stimulation in D419H cell lines and primary cells compared to wild type controls. The pSTAT6/STAT6 ratios were unchanged between D419H and control cells suggesting that elevated pSTAT6 levels resulted from higher total STAT6 expression. JAK inhibition with the selective JAK1/JAK2 inhibitor, ruxolitinib, reduced pSTAT6 levels in D419H HEK293T cells and patient PBMC but did not reduce STAT6 levels in patient PBMC. Increased nuclear levels of STAT6 were seen in patient fibroblasts at baseline and increased nuclear levels of STAT6 and pSTAT6 after IL-4 stimulation. We also observed higher transcriptional upregulation of downstream genes (XBP-1 and EPAS-1) in patient PBMC.

Conclusions: Discussion: Our study confirms STAT6 gain of function (GOF) as a novel genetic cause of early onset atopic disease. The clinical association of lymphoma in our family along with previous data linking somatic STAT6 D419H mutations to follicular lymphoma suggest that patients with STAT6 GOF disease are at higher risk of lymphomagenesis.

Disclosure: No.

Keywords: stat6, Gain of function, Lymphoma, JAK-STAT, atopy

OC040

SEVERE ALLERGIC DYSREGULATION DUE TO A GAIN of FUNCTION MUTATION IN THE TRANSCRIPTION FACTOR STAT6

ORAL COMMUNICATIONS 06: LATE BREAKING ABSTRACTS

Safa Baris[1,2], Mehdi Benamar[3], Qian Chen[3], Mehmet Cihangir Catak[1,2], Jason Fong[3], Michel Massaad[4,5], Asena Pinar Sefer[1,2], Altan Kara[6], Royala Babayeva[1,2], Sevgi Bilgic Eltan[1,2], Ayse Yucelten[7], Emine Bozkurtlar[8], Leyla Cinel[8], Elif Karakoc-Aydıner[1,2], Yumei Zheng[9], Hao Wu[9], Ahmet Ozen[1,2], Klaus Schmitz-Abe[3,10], Talal A. Chatila[3]
[1]Marmara University, The Isil Berat Barlan Center For Translational Medicine, İstanbul, Turkey, [2]Marmara University, Pediatric Allergy And Immunology, Istanbul, Turkey, [3]Harvard Medical School, Division of Immunology, Boston Children's Hospital And Department of Pediatrics, Boston, United States of America, [4]American University of Beirut, Department of Experimental Pathology, Immunology, And Microbiology, Beirut, Lebanon, [5]American University of Beirut Medical Center, Department of Pediatrics And Adolescent Medicine, Beirut, Lebanon, [6]TUBITAK, Gene Engineering And Biotechnology Institute, Istanbul, Turkey, [7]Marmara University, Department of Dermatology, İstanbul, Turkey, [8]Marmara University, Department of Pathology, İstanbul, Turkey, [9]Boston Children's Hospital, Program In Molecular And Cellular Medicine, Department of Pediatrics, Boston, United States of America, [10]Boston Children's Hospital, The Manton Center For Orphan Disease Research, Boston, United States of America

Background and Aims: Inborn errors of immunity (IEI) have been implicated in causing immune dysregulation, including allergic diseases. The signal transducer and activator of transcription 6 (STAT6) is a key regulator of allergic responses. We sought to characterize a novel gain of function (GOF) STAT6 mutation identified in a child with severe allergic manifestations.

Methods: We performed whole-exome and targeted gene sequencing, lymphocyte characterization, and molecular and functional analyses of mutated STAT6.

Results: We report a child with a novel mutation in the DNA binding domain of STAT6 who presented with severe atopic dermatitis, eosinophilia, and elevated IgE. Naive lymphocytes from the affected patient displayed increased TH2 and suppressed TH1 and TH17 cell responses. The mutation augmented both basal and cytokine-induced STAT6 phosphorylation without affecting dephosphorylation kinetics. Treatment with the Janus kinase 1/2 inhibitor ruxolitinib reversed STAT6 hyperresponsiveness to IL-4, normalized TH1, and TH17, suppressed the eosinophilia, and improved the patient's atopic dermatitis.

Conclusions: We identified a novel IEI due to STAT6 GOF mutation that gave rise to severe allergic dysregulation. Janus kinase inhibitor therapy could represent an effective targeted treatment for this disorder. Supported by National Institutes of Health, Grant number: R01AI128976 and Scientific and Technological Research Council of Turkey, Grant number: 318S202.

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Keyword: Inborn errors of immunity, primary atopic disorders, STAT6, IL-4

OC041

HETEROZYGOUS VARIANTS IN THE DNA-BINDING DOMAIN of C-MYB MAY AFFECT NORMAL B/T CELL DEVELOPMENT

ORAL COMMUNICATIONS 06: LATE BREAKING ABSTRACTS

Bas Smits[1], Thalia Hartley[2], Ester Dunnebach[3], Marije Bartels[4], Kim Boycott[2], Kristin Kernohan[2], David Dyment[2], Jacques Giltay[5], Elie Haddad[6], Olga Jarinova[2], Joris Van Montfrans[7], Annette Van Royen-Kerkhof[7], Lars Van Der Veken[5], Monique De Witte[8], Stefan Nierkens[9], Anne Pham-Huy[10], Helen Leavis[11]
[1]UMC Utrecht, Pedriatric Immunology, Utrecht, Netherlands, [2]Children's Hospital of Eastern Ontario, Research Institute, Ottowa, Canada, [3]UMC Utrecht, Center For Translational Immunology, Utrecht, Netherlands, [4]UMC Utrecht, Department of Pediatric Hematology, Utrecht, Netherlands, [5]University Medical Center Utrecht, Genetics, Utrecht, Netherlands, [6]CHU Sainte-Justine, Department of Pediatrics, Montreal, Canada, [7]Wilhelmina's Children Hospital, Department of Pediatric Immunology And Infectious Diseases, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [8]UMC Utrecht, Department of Hematology, Utrecht, Netherlands, [9]Princess Maxima Centre for Paediatric Oncology, Department of Pediatric Immunology And Infectious Diseases, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [10]Children's Hospital of Eastern Ontario, Infectious Diseases, Ottawa, Canada, [11]University Medical Center Utrecht, Utrecht University, Department of Rheumatology & Clinical Immunology, Utrecht, Netherlands

Background and Aims: Background: Temperospatial mouse models have identified *MYB* as a key player in transcription factor networks involved in myeloid and lymphoid cell development. In mice CD8+ cells *MYB* has been shown to control central memory stemness, through *Tcf7* and *Bcl2* upregulation and *Zeb2* repression. However, inborn errors of immunity related variant of *MYB* have never been reported.

Methods: Methods: T cells from three healthy donors and one patient were cultured for 0, 24, 72 & 120h. Peak c-Myb, Tcf7, Bcl2 expression and Zeb2 repression were compared using RT-PCR and flowcytometry.

Results: Results: A 22-year-old Dutch male presented with a CVID phenotype at age 3, with absent peripheral B cells. At age 19 he developed bone marrow dysplasia, reduced NK cell counts and reduced CD8+ naive T cell fractions and telomeropathy. An unrelated French-Canadian patient presented with a similar but worse at the age of 3 years, including T cell lymphocytopenia. Trio exome sequencing detected *de novo* heterozygous DNA binding domain variants in *MYB,* respectively causing p.(Lys182Arg) and p.(Lys128Arg) substitutions. Both variants were at conserved nucleotides, were not reported in healthy controls and were indicated as potentially damaging. RT-PCR showed a trend towards lower peak expression of c-*Myb, Tcf7 and Bcl2* in p.(Lys182Arg) cells, while peak repression of *Zeb2* was normal. Flowcytometry showed significantly hampered c-Myb and Tcf7 expression, especially in CD8+ T cells ($p<0.01$ & $p<0.01$).

Conclusions: Conclusion: Here we describe the first two patients with *de novo* heterozygous DNA binding domain variants of c-Myb, possibly causing combined immunodeficiency and bone marrow dysfunction.

Disclosure: No.

Keywords: MYB, Inborn errors of immunity, primary immunodeficiencies, Telomeropathies, Bone marrow failure

OC042

HUMAN IRF1 GOVERNS PHAGOCYTIC IFN-GAMMA IMMUNITY TO MYCOBACTERIA BUT NOT CELL-INTRINSIC IFN-ALPHA/BETA IMMUNITY TO VIRUSES

ORAL COMMUNICATIONS 06: LATE BREAKING ABSTRACTS

Jeremie Rosain[1], Anna-Lena Neehus[1], Jeremy Manry[1], Rui Yang[2], Jérémie Le Pen[3], Wassim Daher[4], Zhiyong Liu[2], Yi-Hao Chan[2], Natalia Tahuil[5], Ozden Turel[6], Mathieu Bourgey[7], Masato Ogishi[2], Jean-Marc Doisne[8], Tom Le Voyer[1], Antoine Guerin[9], Paul Bastard[1], Irf1 Consortium[10], Stéphanie Boisson-Dupuis[2], Nico Marr[11], Stuart Tangye[12], Qian Zhang[2], James Di Santo[8], Shen-Ying Zhang[2], Charles Rice[3], Vivien Beziat[1], Nico Lachmann[13], David Langlais[14], Jean-Laurent Casanova[2,15], Philippe Gros[7], Jacinta Bustamante[1]
[1]Institut Imagine, Laboratory of Human Genetics of Infectious Diseases, Paris, France, [2]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, New York, United States of America, [3]The Rockefeller University, Laboratory of Virology And Infectious Diseases, New York, United States of America, [4]Institut de Recherche en Infectiologie de Montpelier, Montpellier University, Montpellier, France, [5]Del Niño Jesus Hospital, Department of Immunology, San Miguel de Tucuman, Argentina, [6]Hannover Medical School, Institute of Experimental Hematology And Rebirth Center For Regenerative And Translational Medicine, Hannover, Germany, [7]McGill University, Departement of Biochemistry, Montréal, Canada, [8]Institut Pasteur, Innate Immunity Unit, Paris, France, [9]University of NSW, Garvan Institute of Medical Research, Darlinghurst, Australia, [10]*, *, *, France, [11]Sidra Medicine, Department of Immunology, Doha, Qatar, [12]Garvan Medical Research Institute, Immunology, Darlinghurst, Australia, [13]Hannover Medical School, Institute of Experimental Hematology, Hannover, Germany, [14]McGill University, Department of Human Genetics, Montréal, Canada, [15]Howard Hughes Medical Institute, -, Washington, United States of America

Background and Aims: Inborn errors of human IFN-γ immunity underlie mycobacterial diseases, whereas inborn errors of IFN-α/β immunity underlie viral diseases. Both types of IFNs induce the transcription factor IRF1.

Methods: We investigated two unrelated children with inherited complete IRF1 deficiency and early-onset, multiple, life-threatening diseases caused by weakly virulent mycobacteria. These children had no history of severe viral disease, despite exposure to many viruses, including SARS-CoV-2, which is life-threatening in individuals with impaired IFN-α/β immunity.

Results: We found that the IRF1-dependent response to IFN-γ is, both quantitatively and qualitatively, much greater than that to IFN-α/β *in vitro*. Monocyte-derived macrophages and iPSC-derived macrophages from the two patients showed no upregulation of at least 20% of the target genes normally induced by IFN-γ. This resulted, in IRF1-deficient myeloid cells, in complete lack IFN-γ-dependant cell intrinsic immunity to intramacrophagic bacteria and mycobacteria. By contrast, cell-intrinsic IFN-α/β immunity to diverse viruses, including SARS-CoV-2, was intact.

Conclusions: Human IRF1 is, thus, largely redundant for antiviral IFN-α/β immunity. By contrast, human IRF1 is an essential enhancer of IFN-γ immunity to mycobacteria in myeloid cells.

Disclosure: No.

Keywords: IRF1, interferon-gamma, myeloid cells, Macrophages, Mycobacteria

WORKING PARTY

WP001

LENTIVIRAL HEMATOPOIETIC STEM AND PROGENITOR CELL GENE THERAPY FOR WISKOTT-ALDRICH SYNDROME: SAFETY AND CLINICAL BENEFIT IN 23 PATIENTS UP TO 10.5 YEARS of FOLLOW-UP

WORKING PARTY 01: INBORN ERRORS

Francesca Ferrua[1,2], Maria Pia Cicalese[1,2,3], Stefania Giannelli[2], Sabina Cenciarelli[1,3], Federico Fraschetta[1], Stefania Galimberti[4], Elena Albertazzi[2], Carmen Caputo[2], Maria Ester Bernardo[1,2,3], Federica Barzaghi[1,2], Francesca Tucci[1,2], Giulia Consiglieri[1,2], Valeria Calbi[1,2], Valentina Sofia[1,3], Daniele Canarutto[1,2,3], Federica Salerio[2], Jillian Baker[5], Catherine Gaud[6], Marco Rabusin[7], Antonino Trizzino[8], Toru Uchiyama[9], Julia Upton[10], Horst Von Bernuth[11,12], Masafumi Onodera[13], Chris Dott[14], Russell Jones[14], Christine Rivat[14], Koen Van Rossem[14], Maria Grazia Valsecchi[4], Fabio Ciceri[3,15], Luigi Naldini[2,3], Alessandro Aiuti[1,2,3]
[1]IRCCS San Raffaele Scientific Institute, Pediatric Immunohematology And Bone Marrow Transplantation Unit, Milano, Italy, [2]IRCCS San Raffaele Scientific Institute, San Raffaele Telethon Institute For Gene Therapy (sr-tiget), Milano, Italy, [3]Vita-Salute San Raffaele University, ., Milano, Italy, [4]University of Milano – Bicocca, Bicocca Bioinformatics Biostatistics And Bioimaging B4 Center, School of Medicine And Surgery, Monza, Italy, [5]The Hospital for Sick Children, Unity Health Toronto (st. Michael's Hospital), Toronto, Canada, [6]Centre hospitalier universitaire Felix Guyon, Service D'immunologie Clinique, Saint Denis Cedex Ile de la Reunion, France, [7]IRCCS Burlo Garofolo, Department of Oncohematology, Institute For Maternal And Child Health, Trieste, Italy, [8]ARNAS Civico Di Cristina Benfratelli Hospital, Department of Pediatric Hematology And Oncology, Palermo, Italy, [9]National Center for Child Health and Development, Division of Molecular Pathogenesis, Department of Human Genetics, Tokyo, Japan, [10]The Hospital for Sick Children, University of Toronto, Department of Pediatrics, Division of Immunology And Allergy, Toronto, Canada, [11]Charité – Universitätsmedizin Berlin, Department of Pediatric Respiratory Medicine, Immunology And Critical Care Medicine, Berlin, Germany, [12]Berlin Institute of Health (BIH), Bih Center For Regenerative Therapies (bcrt), Berlin, Germany, [13]National Center for Child Health and Development, Department of Human Genetics, Tokyo, Japan, [14]Orchard Therapeutics (Europe) Limited, ., London, United Kingdom, [15]IRCCS San Raffaele Scientific Institute, Department of Hematology And Stem Cell Transplantation, Milano, Italy

Background and Aims: Wiskott-Aldrich Syndrome (WAS) can be treated with allogeneic hematopoietic stem cell transplantation (HSCT). However, HSCT outcome is hampered by limited donor availability and potential complications, with higher risks in older subjects. Gene therapy (GT) is currently being studied as an alternative treatment.

Methods: OTL-103 is an investigational autologous hematopoietic stem and progenitor cell (HSPC) GT composed of $CD34^+$ HSPCs transduced ex vivo with a self-inactivating lentiviral vector encoding human WAS Cdna under endogenous promoter control.

Results: At data cut, 23 patients have been treated with OTL-103, as part of phase I/II (n=8) or III (n=6) clinical trials or Expanded Access Program (EAP) (n=9), with median follow-up of 3.6 years (range: 0.4-10.5). All received rituximab and reduced-intensity conditioning pre-GT. Median age at treatment was 3.1 years (range: 1.0-35.1). Seventeen patients received fresh OTL-103, while six received cryopreserved formulation. All were alive, except one EAP subject who died early post-GT due to deterioration of a pre-existing neurological condition. To date, no GT-related adverse events or signs of insertional mutagenesis have been reported. Integrated efficacy analysis performed in trials' subjects showed sustained engraftment of gene-corrected cells, leading to marked increase of WASP expression in platelets and lymphocytes. This resulted in improved platelet count and T-cell functionality, with substantial reduction of moderate/severe bleedings and severe infections. Bleeding and antimicrobial prophylaxis was stopped. Eczema improved and clinical autoimmunity resolved.

Conclusions: Our data show that lentiviral GT for WAS is well tolerated and leads to sustained clinical benefit, highlighting its potential as an alternative treatment for WAS patients.

Disclosure: No.

Keywords: Wiskott-Aldrich Syndrome, thrombocytopenia, gene therapy, primary immunodeficiency, Platelet disorder

WP002

INNOVATIVE PRE-TRANSPLANT CONDITIONINGS FOR IMMUNE DYSREGULATION DISORDERS

WORKING PARTY 01: INBORN ERRORS

Fatemeh Asgari[1], Martina Di Verniere[1], Elena Draghici[1], Marita Bosticardo[2], Luigi Notarangelo[2], Anna Villa[1,3], Maria Carmina Castiello[1,3]
[1]San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), Ircss San Raffaele Scientific Institute, Milan, Italy, [2]Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, Niaid, Nih, Bethesda, United States of America, [3]Milan Unit, Istituto di Ricerca Genetica e Biomedica (IRGB), Consiglio Nazionale Delle Ricerche (cnr), Milan, Italy

Background and Aims: Hematopoietic stem cell transplantation (HSCT) is the only cure for severe immune dysregulation. Conditioning regimens are crucial for successful HSCT to eliminate resident hematopoietic stem/progenitor cells (HSPCs), but current chemo/radiotherapy conditionings may induce severe toxicities. We demonstrated the efficacy of non-genotoxic conditioning with anti-CD45 mAb conjugated with saporin (CD45-SAP) in Recombination Activating gene (Rag1)-deficient mouse models. To maximize the therapeutical potential of CD45-SAP, we are optimizing a protocol based on CD45-SAP combined with a low dose of clinically relevant chemotherapies, treosulfan and fludarabine (Treo/Flu), in distinct preclinical models.

Methods: We tested the depletion activity of a full dose of Treo/Flu (7g/1g /Kg) in Rag1-knock-out (KO), Rag1-F971L and Wiskott-Aldrich Syndrome gene (Was)-KO mice, showing a spectrum of immunodeficiency and autoimmunity. We assessed, in Rag1-KO mice, the engraftment and immune reconstitution achieved by lower doses of Treo/Flu with or without CD45-SAP (3mg/kg). Transgenic mice were transplanted with wild-type (WT) Lineage negative cells (Lin-). Depletion activity, engraftment and immunological reconstitution were assessed by flow cytometry, histology, and ELISA.

Results: Full Treo/Flu dose efficiently depletes HSPCs and lymphoid progenitors in all mouse models resulting in high myeloid chimerism and immune cell reconstitution in Rag1-KO mice transplanted with WT Lin- cells. The combination of CD45-SAP with low doses of Treo/Flu showed a dose dependent synergistic effect increasing both myeloid chimerism and immune recovery, as compared to CD45-SAP alone.

Conclusions: Preliminary data show that CD45-SAP combined with low doses of Treo/Flu allows robust immune reconstitution in Rag1-KO mice, paving the way for further studies in the other immune disorders.

Disclosure: No.

Keywords: immunodeficiency, conditioning, anti-CD45–saporin, engraftment, immune reconstitution, Hematopoietic stem cell transplantation

WP003

LATE-ONSET ENTERIC VIRUS INFECTION ASSOCIATED WITH HEPATITIS (EVAH) IN TRANSPLANTED SCID PATIENTS

WORKING PARTY 01: INBORN ERRORS

Quentin Riller[1], Jacques Fourgeaud[2], Julie Bruneau[3], Suk See De Ravin[4], Grace Smith[5], Mathieu Fusaro[6], Samy Meriem[7], Aude Magerus[1], Marine Luka[8], Ghait Abdessalem[8], Ludovic Lhermitte[9], Anne Jamet[2], Emmanuelle Six[10], Alessandra Magnani[6], Martin Castelle[11], Romain Lévy[11], Mathilde Lecuit[11], Benjamin Fournier[11], Sarah Winter[11], Michaela Semeraro[12], Graziella Pinto[13], Hanene Abid[2], Nizar Mahlaoui[14], Nathalie Cheikh[15], Benoit Florkin[16], Pierre Frange[11], Eric Jeziorski[17], Felipe Suarez[18], Françoise Sarrot-Reynauld[19], Dalila Nouar[20], Dominique Debray[21], Florence Lacaille[21], Capucine Picard[6], Philippe Pérot[22], Béatrice Regnault[22], Nicolas Da Rocha[22], Camille De Cevins[23], Laure Delage[1], Brieuc Pérot[23], Angélique Vinit[24], Francesco Carbone[8], Camille Brunaud[1], Manon Marchais[1], Marie-Claude Stolzenberg[1], Vahid Asnafi[9], Thierry Molina[3], Frédéric Rieux-Laucat[1], Luigi Notarangelo[25], Stefania Pittaluga[26], Jean-Philippe Jais[7], Despina Moshous[11], Stephane Blanche[11], Harry Malech[27], Marc Eloit[22], Marina Cavazzana[28], Alain Fischer[29], Mickael Ménager[23], Benedicte Neven[1]
[1]Imagine Institute, Immunogenetic of Pediatric Autoimmune Diseases, Paris, France, [2]APHP, Microbiology, Paris, France, [3]APHP, Pathology, Paris, France, [4]NIH, Laboratory of Clinical Immunology And Microbiology, Bethesda, United States of America, [5]NIH, Center For Cancer Research, Bethesda, United States of America, [6]APHP, Study Center For Primary Immunodeficiencies, Paris, France, [7]APHP, Biostatistics, Paris, France, [8]Imagine Institute, Labtech Single-cell@imagine, Paris, France, [9]APHP, Onco-hematology, Paris, France, [10]Institut Imagine, Genetics of Infectious Disease, Paris, France, [11]Necker Children's Hospital, Assistance Publique-Hôpitaux de Paris, Université De Paris, Institut Imagine Institut Des Maladies Genetiques, Paris, France, [12]APHP, Necker, Cic, Paris, France, [13]APHP, Necker, Endocrinology, Paris, France, [14]HOPITAL NECKER, Ceredih & Uihr, PARIS, France, [15]University Hospital of Besançon, Pediatric Hematology Oncology Unit, Besançon, France, [16]CHR Citadelle, Immuno-hémato -rhumatologie Pédiatrique, Liege, Belgium, [17]University of Montpellier, CHU Montpellier, Department of Pediatrics, Infectious Diseases, And Immunology, Montpellier, France, [18]Necker, APHP, Hematology Department,, Paris, France, [19]Centre Hospitalier Universitaire Grenoble Alpes, Service De Médecine Interne, La Tronche, France, [20]CHRU Tours, Service D'immunologie clinique Et D'allergologie, Tours, France, [21]Necker, APHP, Pediatric Liver Unit, Paris, France, [22]Pasteur Institute, Pathogen Discovery Laboratory, Paris, France, [23]Imagine Institute, Laboratory of Inflammatory Responses And Transcriptomic Networks In Diseases, Atip-avenir, Paris, France, [24]Sorbonne Université, Cyps Platform, Paris, France, [25]NIAID, NIH, Laboratory of Clinical Immunology And Microbiology, Division of Intramural Research, Bethesda, United States of America, [26]National Institutes of Health, Nci, Bethesda, United States of America, [27]National Institutes of Health, Lcim, Bethesda, United States of America, [28]Groupe Hospitalier Universitaire Ouest, Biotherapy Clinical Investigation Center, Paris, France, [29]Collège de France, Collège De France, Paris, France

Background and Aims: Allogenic hematopoietic stem cell transplantation (HSCT) and gene therapy (GT) are potentially curative treatments of severe combined immunodeficiency (SCID). Nevertheless, late-onset manifestations are not uncommon including hepatitis.
Methods: SCID patients with late-onset hepatitis post HSCT or GT were investigated using multi-omics, pathology and metagenomics.
Results: Eleven patients developed persistent hepatitis at a median time of 6 years for SCID related to IL2RG (n=10) or DCLRE1C (n=1) deficiency (SCIDH+). Clinical consequences of this condition can be severe, up to death (n=3). It was associated with the detection of enteric viruses (Aichi virus, Norovirus and Sapovirus) in liver and/or stools, which were not found in stools of healthy asymptomatic similarly transplanted patients (n=12, SCIDH-). Mass-cytometry analysis on peripheral blood mononuclear cells of 6 SCIDH+ compared to 7 SCIDH- identified an expansion of $CD38^{high}$ $HLA\text{-}DR^{high}$ $CD127^{low}$ CD8+ T cells. Type I and II IFN signatures identified by scRNAseq were mostly but not exclusively found in CD8+ T cells. Among a cohort of 114 long-term survivors post HSCT or GT for SCID, hepatitis was strongly associated with absence of myeloablation, split chimerism and defective B cell function.
Conclusions: Overall, this condition characterized by enteric virus infection associated with hepatitis (named EVAH) represents 25% of SCID patients who did not receive myeloablation and were on immunoglobulin replacement. Partially myeloablative re-transplantation or GT could reconstitute T and B cell immunity and lead to remission of hepatitis, concomitantly to viral clearance, as observed in 5 patients. Beyond SCID, a same dysimmune process could occur in inherited or acquired B-cell defects.

Disclosure: No.

Keyword: SCID, transplantation, hepatitis, enteric viruses, interferon

WP004

EXPLORING THE OLIGOGENIC ASPECTS of COMMON VARIABLE IMMUNODEFICIENCIES USING ORVAL

WORKING PARTY 02: GENETICS

Marie Nabout[1], Isabelle Vandernoot[2], Sofia Papadimitriou[3], Youssef Bouysran[2], Sophie Henrard[1], Jean-Christophe Goffard[4]
[1]ULB – CUB Hôpital Erasme, Internal Medicine, ANDERLECHT, Belgium, [2]ULB – CUB Hôpital Erasme, Center of Human Genetics, ANDERLECHT, Belgium, [3]Université Libre de Bruxelles, Ibsquare, Ixelles, Belgium, [4]ULB – CUB Hôpital Erasme, Internal Medicine, Anderlecht, Belgium

Background and Aims: Common variable immunodeficiency (CVID) is a heterogeneous disease with various clinical presentations. Currently, less than 20% of cases of CVID have a known genetic cause, considered as monogenic but not following a mendelian inheritance pattern in most of the cases. More complex genetic scenarios like oligogenic inheritance must be considered. ORVAL, Oligogenic Resource for Variant AnaLysis, is a novel bioinformatics platform designed for the prediction and exploration of candidate disease-causing oligogenic variant combinations. This study aim to unravel networks of candidate pathogenic variants combinations in a cohort of CVID patients.

Methods: This retrospective study included 35 CVID patients for whom clinical exome sequencing did not disclose a monogenic cause. Clinical exome data of the 35 subjects and of 1536 controls were analysed through ORVAL, focusing on 479 genes associated with immune disorders. Combinations found in at least 2 CVID patients where selected as potential candidate pathogenic variant combinations if not found in controls.

Results: Variant combinations predicted to be pathogenic were statistically significantly higher among CVID patients compared to controls. 3 unrelated couples of patients shared the same multiple combinations considered as pathogenic. None of these combinations were found in the control cohort. Clinical and B cells phenotype similarities were found in each couple of patients with the same candidate disease-cause associations.

Conclusions: ORVAL platform is a promising tool to address the oligogenic nature of CVID. Our results need to be replicated in an independent cohort of cases and controls. Real impact of these variant combinations at a molecular level needs further confirmation.

Disclosure: No.

Keywords: Common variable immunodeficiency, Oligogenic, ORVAL, Etiology, Genetics

WP005

RESOLVING INCOMPLETE PENETRANCE IN PRIMARY IMMUNODEFICIENCIES (PIDS): VIA MONOALLELIC EXPRESSION (MAE)

WORKING PARTY 02: GENETICS

O'Jay Stewart[1], Conor Gruber[1], Roosheel Patel[1], Dusan Bogunovic[2]
[1]Icahn School of Medicine at Mount Sinai, Precision Immunology Institute, New York, United States of America, [2]Mount Sinai, Icahn School of Medicine, New York, United States of America

Background and Aims: BACKGROUND: Primary Immunodeficiencies (PIDs) are monogenic disorders of the immune system. Phenotypic variability of PIDs provide challenges studying and clinically managing these inborn errors. Recent studies indicate that up to 10% of autosomal genes randomly commit to expression of a single allele, termed monoallelic expression (MAE). Unlike X-inactivation or imprinting, MAE of genes is not specific to gene clusters or a single chromosome and leads to a diverse population of cells at the transcript level. Despite an increase in the understanding of MAE, both the functional and mechanistic impact in disease is unknown. AIM: Identify the contribution of monoallelic expression to the phenotypic variability of primary immunodeficiencies.

Methods: METHODS: Single T cells were sorted from healthy donor PBMCS (n=6) and expanded into monoclonal populations (n=57). Genomic DNA was isolated from donors for WES and 431 PID genes were examined for exonic heterozygous SNPs. Bulk RNA-seq of the clonal populations was used to determine allele specific expression of PID genes.

Results: RESULTS: WES identified 172 PID genes with heterozygous SNPs from the 6 donors. RNA-seq data from 18 clones in 4 donors identified 15 PID genes that display allelic bias. While MAE occurs in 7 of the assessed PID genes.

Conclusions: CONCLUSIONS: Using this system of monoclonal T cell populations, 7 genes which cause primary immunodeficiencies were found to be regulated by 83tandardiza expression. Almost all the identified genes have reports of incomplete penetrance. Mutations in 3 of these genes are known to cause autosomal dominant inherited disease, facilitating further study in patient samples.

Disclosure: No.

Keywords: Genetics, immunodeficiency, gene expression, innate-immunity, incomplete penetrance

WP006

CHRONIC MUCOCUTANEOUS CANDIDIASIS DISEASE DUE TO A NOVEL DUPLICATION MUTATION of IL17RC

WORKING PARTY 02: GENETICS

Kosuke Noma[1], Miyuki Tsumura[1], Takaki Asano[1], Yoko Mizoguchi[1], Takayo Shoji[2], Satoshi Okada[1]
[1]Hiroshima University, Pediatrics, Hiroshima, Japan, [2]Shizuoka Children's Hospital, Pediatric Infectious Diseases, Shizuoka, Japan

Background and Aims: Chronic Mucocutaneous Candidiasis (CMC) is a condition characterized by recurrent or persistent infections of the nails, skin, oral and genital mucosa caused by Candida albicans. CMC disease (CMCD) refers to patients with CMC as the predominant clinical phenotype without the other significant clinical manifestations. Autosomal recessive (AR) IL-17RC deficiency is a rare CMCD, with only three cases reported so far. Now, there is no in vitro functional evaluation system for the pathogenicity of IL17RC mutations and that makes a diagnosis difficult.

Methods: We herein studied a Japanese girl with IL-17RC deficiency who suffered from CMCD. We developed a new in vitro system for functional validation of IL17RC mutations and confirmed her genetic pathogenicity as IL-17RC deficiency.

Results: The patient is a seven-year-old Japanese girl who has developed early-onset oral and cutaneous candidiasis from the age of three months. She had no episodes with a susceptibility to other pathogens. Her clinical phenotype thus clearly showed CMCD. Genetic testing identified a novel homozygous IL17RC duplication (Chr3: 9,971,476-9,971,606 dup(+131bp)). This duplication caused a premature stop codon by frameshift, producing a truncated IL-17RC protein. Our new evaluation system based on IL17RC knockout HeLa cells revealed this duplication mutation was loss-of-function, while polymorphisms, for which homozygotes was reported in general population, were validated as isomorphic. The patient's fibroblasts did not respond to IL-17A, which was restored by introducing WT IL17RC, suggesting that identified mutation caused patient's clinical phenotype.

Conclusions: Our new evaluation system for IL17RC mutations was accurate and can be useful for the diagnosis of IL-17RC deficiency.

Disclosure: No.

Keywords: CMC, IL17RC, CMCD

WP011

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION ACTIVITY FOR INBORN ERRORS of IMMUNITY (IEI) IN RUSSIAN FEDERATION

WORKING PARTY 04: REGISTRY

Alexandra Laberko[1,2], Anna Mukhina[3], Elena Machneva[4], Elena Skorobogatova[4], Olga Paschenko[5], Tatiana Bykova[6], Larisa Vahonina[7], Irina Kondratenko[5], Anna Shcherbina[2], Larisa Fechina[7], Ludmila Zubarovskaya[6], Dmitry Balashov[8], Alexander Rumiantsev[2]
[1]Newcastle University, Translational And Clinical Research Institute, Newcastle upon Tyne, United Kingdom, [2]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [3]Russian National Association of Experts in Primary Immunodeficiency Registry, Registry, Moscow, Russian Federation, [4]Russian Children's Clinical Hospital of the N.I. Pirogov Russian National Research Medical University, Hematopoietic Stem Cell Transplantation, Moscow, Russian Federation, [5]Russian Children's Clinical Hospital of the N.I. Pirogov Russian National Research Medical University, Immunology, Moscow, Russian Federation, [6]RM Gorbacheva Children Research Institute, Pavlov University, Hematopoitic Stem Cell Transplantation, St.Petersburg, Russian Federation, [7]Sverdlovsk Regional Children Hospital №1, Institute of Medical Cell Technologies, Hematopoietic Stem Cell Transplantation, Ekaterinburg, Russian Federation, [8]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Hematopoietic Stem Cell Transplantation, Moscow, Russian Federation

Background and Aims: Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative modality for IEI. The number of HSCTs has been rising worldwide. The availability of HSCT for IEI patients in Russia is poorly studied.

Methods: The data were collected from four Russian centers performing HSCT in pediatric IEI patients and Russian Primary Immunodeficiency Registry.

Results: From 1997 to the end of 2020, 511 allogeneic HSCTs were performed in 452 patients with IEI; 88 (19%) had severe combined immunodeficiency (SCID), 157 (35%) other combined immunodeficiencies, 94 (21%) phagocyte disorders, 78 (17%) diseases of immune dysregulation, and 35 (8%) other IEI. The median age at IEI diagnosis was 1 year (range 0-18). The median age at HSCT was 2.3 years (range 0.1-19.6 years). The median number of HSCTs per year was 3 in 1997-2009, 15 in 2010-2015 and 60 in 2015-2020. For the first HSCT a matched unrelated donor was used in 216 patients, a matched related donor in 74 and a mismatched related donor in 161 (135 with TCRαβ/CD19 depletion, 16 CD34 selection, 7 post-HSCT cyclophosphamide and 2 campath-in-bag depletion); in second HSCTs in 12 of 56 patients the same donor was used. The median FU in survivors was 4.5 years (range 1-25). Overall survival was: in SCID patients 57%, in non-SCID patients 78% ($p<0.001$); in those who had severe morbidity at HSCT 65% and those with no morbidity 86% ($p<0.001$).

Conclusions: The availability of HSCT for IEI has been rising in Russia. Implementation of newborn screening for SCID might dramatically improve survival in this group of patients.

Disclosure: No.

Keywords: inborn error of immunity, Hematopoietic stem cell transplantation, Severe combined immunodeficiency, unrelated donor, related donor, combined immunodeficiency

WP012

LYMPHOPROLIFERATIVE DISEASES IN THE XLP1 SYNDROME

WORKING PARTY 04: REGISTRY

Marina Dockes[1], Nizar Mahlaoui[2,3,4], Julie Bruneau[5], Benedicte Neven[2,3,4], Despina Moshous[2,3,4], Stephane Blanche[2,4], Fanny Fouyssac[6], Sebastien Humbert[7], Claire Fieschi[8], Olivier Hermine[1,3,4], Alain Fischer[2,3,4,9], Felipe Suarez[1,3,4], Morgane Cheminant[1,3,4]
[1]Necker, APHP, Hematology Department,, Paris, France, [2]Necker Hospital, Pediatric Hematology-immunology And Rheumatology Unit, Paris, France, [3]Necker Hospital, French National Reference Center For Primary Immunodeficiencies, Paris, France, [4]Imagine Institute, Université De Paris, Paris, France, [5]Necker, APHP, Pathology, Paris, France, [6]Nancy University Hospital, Pediatric Onco-hematology, Nancy, France, [7]CRHU Jean Minjoz, Iternal Medicine, Besancon, France, [8]Saint Louis Hospital, Immuno-hematology, Paris, France, [9]Collège de France, Collège De France, Paris, France

Background and Aims: X-linked lymphoproliferative disease type 1 (XLP1) patients have a high risk of monoclonal lymphoproliferative diseases (LPD). A precise and actualized description of LPDs in XLP1 patients is lacking.

Methods: We conducted a retrospective analysis of genetically identified XLP1 patients from the CEREDIH registry having presented an LPD before allogenic stem cell transplantation.

Results: Eighteen out of 43 XLP1 patients developed at least one LPD and 6 presented two LPDs. Median age at diagnosis of the first malignancy was 12 years old [IQR 7-20]. The LPD was the first manifestation of the XLP1 syndrome in 16/18 patients. Out of 25 LPDs, 21 were B-cell neoplasms (9 diffuse large B-cell lymphomas, 7 Burkitt,1 Hodgkin, 1 lymphoblastic lymphoma, 3 unspecified), one was an NK/T-cell lymphoma and two were unspecified. Five out of 11 LPDs were not EBV-associated. Thirteen out of 14 LPDs had extranodal localizations, the most frequent being the digestive tract (6/14) and the central nervous system (4/14). Eleven out of 13 patients received high dose 86tanda-chemotherapy, one received only Rituximab and the last one received Brentuximab alone. All patients who received 86tanda-chemotherapy except one reached complete remission. Five patients received an allogenic transplantation. With a median follow-up of 6.9 years, 5-year overall survival after LPD was 77%.

Conclusions: LPDs occur at a high rate in XLP1 patients, most often present as aggressive B-cell lymphomas with a high incidence of extranodal disease and are not always associated to EBV. All medical records and centralized pathology will be reviewed.

Disclosure: No.

Keywords: Lymphoma, EBV, X-linked lymphoproliferative disease, Hemophagocytic Lymphohistiocytosis, lymphoproliferative disease

WP013

PHENOTYPE CAPTURE TOOL – A WEB-BASED TOOL TO COLLECT HPO-CODED PHENOTYPE

WORKING PARTY 04: REGISTRY

Luiza Campos[1], Olga Shamardina[2], Daniel Greene[3], Ernest Turro[3], Siobhan Burns[1,4]
[1]UCL, Institute of Immunity And Transplantation, London, United Kingdom, [2]University of Cambridge, Department of Medicine, Cambridge, United Kingdom, [3]Mount Sinai, Icahn School of Medicine, New 87tan, United States of America, [4]The Royal Free London NHS Foundation Trust, Immunology, London, United Kingdom

Background and Aims: The INTREPID project aims to evaluate the utility of specific Human Phenotype Ontology (HPO) terms for distinguishing known primary immunodeficiency disorders (PID) and enabling genetic diagnosis from whole genome sequence data. To improve and standardize HPO data collection, we aimed to develop a tool for PID phenotype capture.

Methods: We developed a web-based Phenotype Capture Tool (PCT), which allows the user to easily browse and input HPO terms for individual patients. We also developed a training package focused on selection of HPO terms for PID. To provide quality control for data entry, access to the tool is only given to clinicians and researchers after a training session with practice cases used to 87tandardiza selection of HPO terms.

Results: We have now used the PCT tool to enter HPO phenotype for over 300 patients and have trained 8 users. The number and specificity of HPO terms used to create a phenotype profile increased after training. The range of terms used also expanded, covering more categories of abnormalities such as abnormal infection history or vaccine reactions, lymphoproliferation, autoimmune/autoinflammation, and abnormal test results.

Conclusions: To achieve better output of the algorithms of statistic association, the set of HPO terms chosen to represent a phenotypic profile must be as specific as possible and represent the most relevant observations. The use of the PCT after a training session improves the quality and 87tandardization of data input. We intend to make our PCT and training course publicly available as a resource for the PID community.

Disclosure: No.

Keywords: Whole genome sequencing, HPO, Genetic diagnosis, human phenotype ontology

WP014

SLAVIC FOUNDER MUTATION IN UNC13D GENE IN PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS FROM BELARUS AND UKRAINE

WORKING PARTY 06: PID CARE IN DEVELOPMENT

Aleksandra Kupchinskaya[1], Ekaterina Polyakova[2], Inga Sakovich[2], Irina Pakhomova[2], Viktoria Belobokova[2], Katsiaryna Vashkevich[2], Tatyana Ermilova[2], Mikhail Belevtsev[2], Tatsiana Shman[2], Sviatlana Charniauskaya[2], Larysa Kostuchenko[3], A Stepanyuk[4], Olga Aleinikova[2], O Dorosh[4], Jolan Walter[5,6], Svetlana Sharapova[2]
[1]Belarussian Centre for Pediatric Oncology, Hematology and Immunology, Research Department, Минск, Belarus, [2]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Research Department, Borovlyany, Belarus, [3]West-Ukrainian Specialized Children's Medical Center, Pediatric Department, Lviv, Ukraine, [4]Lviv Regional Children's Specialized Clinical Hospital, Hematology Department, Lviv, Ukraine, [5]Johns Hopkins All Children's Hospital, St. Petersburg, Division of Allergy/immunology, Department of Pediatrics, St.Petersburg, United States of America, [6]Massachusetts General Hospital for Children, Division of Allergy And Immunology, Boston, United States of America

Background and Aims: Hemophagocytic lymphohistiocytosis (HLH) is polygenetic disease caused by mutations in genes associated with granule-dependent lymphocyte-mediated cytotoxicity (PRF1, UNC13D, STX11, STXBP2, LYST, AP3B1, AP3D1 RAB27A, XIAP, SH2D1A).

Methods: We describe the clinical and immunological manifestations and mutation spectrum in HLH cohort (n=19) diagnosed in Belarus (n=15) and Ukraine (n=4) since 1991-2022.

Results: Enrolled patients were residents of Belarus (n=14), Ukraine (n=4) and Kazakhstan (n=1). Genetic diagnose of HLH was established in 12/19 patients, NK activity was checked in 5/19. UNC13D gene variants were revealed in 10 patients (4 patients from 2 families from Ukraine; 6-from 4 families, Belarus); 3 unrelated Belarusian and Ukrainian families had c.2346_2349delCTCC(p.R782fs in homozygous state, 4pts out of 2 families (Belarus)-in heterozygous compound. Also variants in XIAP(n=2) were detected. One patient is alive after HSCT, one patient waiting for HSCT, 17 children died, 3 after HSCT, 8 were genetically diagnosed postmortem. 3/19pts had an "atypical" presentation, age of manifestation and death was 9m/2.5yr; 1.5yr/2.5yr, and 2yr/19yr (genetic diagnosis was established post-mortem in 3/3). "Atypical" manifestation was-lymphoproliferation (n=3), neurological presentation (brain cysts/epilepsy (n=1), disseminated encephalitis (n=1). Hemophagocytosis was not manifested biochemically during all period of observation; a small number of phagocytic macrophages were detected once in one patient's bone marrow.

Conclusions: Our cohort of patients demonstrated a repeated mutation in the UNC13D gene-c.2346_2349delCTCC(p.R782fs), which may be associated with the "founder effect" in Slavic countries. Atypical manifestation causes difficulties in rapid diagnosis, fast sequencing of all PID genes are necessary for establishing correct diagnosis and start appropriate treatment.

Disclosure: No.

Keywords: UNC13D, founder mutation, HLH

WP015

IMMUNODEFICIENCY REGISTRY: A REPORT FROM BELARUS (2007-2021)

WORKING PARTY 06: PID CARE IN DEVELOPMENT

Mikhail Belevtsev[1], Svetlana Sharapova[1], Irina Guryanova[1], Yulia Zharankova[2], Svetlana Aleshkevich[2], Ekaterina Polyakova[1], Inga Sakovich[1], Valeria Pugacheva[1], Katsiaryna Skapavets[1], Tatiana Volodashchik[1], Viktoria Kazak[1], Lubov Zherko[2], Aleksandra Kupchinskaya[1], Tatiana Uglova[1], Alexander Migas[1], Andrei Salivonchik[3], Maria Shitikova[1], Olga Khurs[4], Olga Aleinikova[1], Angelika Solntseva[1], László Maródi[5]
[1]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Research Department, Borovlyany, Belarus, [2]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Outpatient Department, Borovlyany, Belarus, [3]The Republican Research Centre for Radiation Medicine and Human Ecology, Immunology Department, Gomel, Belarus, [4]Republican Medical Center «Mother and Child», Research Department, Minsk, Belarus, [5]Rockefeller University, Laboratory of Human Genetics of Infectious Diseases, New York, United States of America

Background and Aims: Primary immunodeficiencies (PIDs) are heterogeneous disorders, characterized by variable clinical and immunological features. We report on data collected from the Belarussian PID registry.

Methods: Clinical and laboratory data was collected from Belarusian patients with PIDs, treated at the Belarusian Research Center for Pediatric Oncology, Hematology and Immunology in the Minsk Region and the Republican Research Center for Radiation Medicine and Human Ecology in Gomel.

Results: Collaboration with the J Project, the Jeffrey Modell Foundation significantly expands the possibilities of helping patients with PIDs in Belarus. The prevalence of PID in Belarus is 6.23 per 100,000 inhabitants. At the beginning of 2022, 621 cases of PIDs were registered, more than half of the patients were genetically confirmed diagnosed (62.8%, n=390). Based on the updated IUIS classification of 2019, PID distribution in Belarus showed that predominantly antibody deficiencies (32.53%, n=202) account for the majority of cases, followed by combined immunodeficiencies with associated or syndromic features (28.34%, n=176), complement deficiencies (14.98%, n=93), diseases of immune dysregulation (8.21%, n=51), immunodeficiencies affecting cellular and humoral immunity (7.25%, n=45) and congenital defects in phagocyte number or function (4.99%, n=31), autoinflammatory disorders (1.77%, n=11), bone marrow failure (1.13%, n=7), defects of innate immunity (0.81%, n=5). The distribution of patients with PID in the regions of Belarus is almost the same, however the prevalence of Ataxia-telangiectasia and Nijmegen syndrome is higher in Western Belarus.

Conclusions: Data from the PID Registry of Belarus contribute to the expansion of clinical knowledge about PID, help in the development of new diagnostic procedures and treatments.

Disclosure: No.

Keyword: registry

WP016

PROSPECTIVE STUDY of EFFICACY AND SAFETY of ROMIPLOSTIM VERSUS ELTROMBOPAG IN PATIENTS WITH WISKOTT-ALDRICH SYNDROME .

WORKING PARTY 06: PID CARE IN DEVELOPMENT

Anna Khoreva[1], Yulia Rodina[1], Dmitry Pershin[1], Kirill Voronin[2], Daria Yukhacheva[1], Galina Novichkova[3], Alexey Maschan[4], Anna Shcherbina[1]
[1]Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [2]Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, Department of Bioinformatics And Medical Statistics, Moscow, Russian Federation, [3]Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, General Director, Moscow, Russian Federation, [4]Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, Department of Pediatric Hematology And Oncology, Moscow, Russian Federation

Background and Aims: Wiskott-Aldrich syndrome (WAS) is a life-threatening primary immunodeficiency, associated with bleeding risk due to thrombocytopenia. We previously demonstrated that romiplostim is effective for thrombocytopenia treatment in 60% of WAS patients.

Methods: In this open-label prospective study WAS patients (0-18 years) were treated with romiplostim or eltrombopag. We assessed platelet response, proportion of patients additionally achieving platelet response by changing an arm of treatment, bleeding severity and adverse events. Criteria for switching were lack of efficacy, loss of long-term response and adverse events.

Results: 21 patients underwent randomization. Mean age was 2.6 years [range 0.2-15.2]; mean platelet level, 23×10^9/L [range 4-49]. The incidence of achieving platelet response did not differ between romiplostim (7/11 [64%]) and eltrombopag (5/10[50%]; 95% CI, 0.07-4.4; P=0.67) groups. 5/11 (45%) participants in romiplostim group and 6/10 (60%) in eltrombopag group required switch of therapy. Conversion to the alternative arm of treatment allowed to attain durable response in 1 non-responder in romiplostim group and in 2 non-responders in eltrombopag group. 1 eltrombopag responder was switched to romiplostim due to the severe adverse event (ALT/AST increase >3 norms) after 17 months of therapy and continued to have complete response. The number of patients with grade 2-4 bleeding at baseline declined from 91% to 27% in romiplostim group and from 70% to 10% in eltrombopag group after 1 month of treatment (p=0.864).

Conclusions: Both romiplostim and eltrombopag are effective in WAS. We demonstrate that in cases of inefficiency switching to the another agonist is beneficial.

Disclosure: No.

Keyword: Wiskott-Aldrich syndrome, romiplostim, eltrombopag, bleeding, thrombocytopenia

POSTER DISCUSSION

PP001

CLINICAL AND IMMUNOLOGICAL OUTCOMES of HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR INBORN ERRORS of IMMUNITY (IEIS): 20 YEARS' EXPERIENCE FROM A 220 PATIENTS' MONOCENTRIC COHORT

POSTER DISCUSSION 01: THERAPIES

Giulia Baresi[1], Fulvio Porta[1], Elena Soncini[1], Stefano Rossi[1], Arnalda Lanfranchi[2], Marta Comini[2], Alessandra Beghin[2], Federica Bolda[2]
[1]Children's Hospital, Spedali Civili, Brescia, Italy,, Oncohematology And Bone Marrow Transplant (bmt) Unit, Brescia, Italy, [2]ASST Spedali Civili di Brescia, Stem Cell Laboratory, Section of Hematology And Blood Coagulation, Clinical Chemistry Laboratory, Diagnostic Department, Brescia, Italy

Background and Aims: IEIs are a heterogeneous group of diseases presenting with susceptibility to infectious diseases, autoinflammatory/autoimmune manifestations, and increased risk of developing malignancies. HSCT represents the only curative approach.

Methods: Monocentric retrospective analysis of 220 patients treated with HSCT for IEIs at the Pediatric BMT Unit of Brescia between year 2000 and 2020.

Results: Overall survival was 73,2%, with lower survival rates in patients receiving non-myelosuppressive regimens ($p<0,001$) or HSCT without preconditioning regimen ($p=0,047$) rather than those treated with myeloablative or reduced intensity conditioning. Immunological reconstitution showed T-cell restoration in 93,7% of patients and B-cell restoration in 87,17% of patients. Graft failure occurred mostly in severe combined immune deficiency patients, both T-B- and T-B+ (31,8% and 22,8% respectively), followed by combined immune deficiency patients (18,2%). Median time of graft failure after first HSCT was 1,8 months. Infectious episodes at HSCT or viral reactivation mainly affected patients transplanted from cord blood units, while using HLA-mismatched donor resulted in a reduction of viral reactivation average time ($p=0,006$). Anti-thymocyte globulin for graft versus host disease (GvHD) prophylaxis resulted in higher incidence of immune reconstitution on CD4+ and CD19+ ($p<0,05$) cells and a lower median time of immunoglobulin replacement treatment ($p<0,005$). GvHD occurred in 53,3% of all cases; hepatic veno-occlusive disease and transplant-associated microangiopathy occurred in 3,4% and 2,7% of the patients respectively. 4,7% of patients developed post-HSCT malignancies.

Conclusions: Our results confirm the effectiveness of HSCT as a curative treatment for IEIs, with excellent long-term survival rate and effective immunological reconstitution.

Disclosure: No.

PP002

DONOR-DERIVED VIRUS-SPECIFIC T CELL INFUSION FOR TREATMENT AND PROPHYLAXIS of VIRUS INFECTIONS POST-HEMATOPOIETIC STEM CELL TRANSPLANT

POSTER DISCUSSION 01: THERAPIES

Hannah Kinoshita[1], Mariah Jensen-Wachspress[2], Catherine Bollard[3], Allistair Abraham[3], Michael Keller[4]
[1]Children's National Hospital, Department of Hematology Oncology, Washington, United States of America, [2]Children's National Hospital, Cellular Enhancement And Technologies For Immunotherapy Program, Washington, United States of America, [3]Children's National Hospital, Department of Bone Marrow Transplantation, Washington, United States of America, [4]Children's National Hospital, Department of Allergy And Immunology, Washington, United States of America

Background and Aims: Hematopoietic-stem-cell transplantation (HSCT) remains the only curative option for many patients with relapsed and/or high-risk malignant diseases, immunodeficiency disorders and hemoglobinopathies. In the case of mis-matched transplant donors, immunosuppression is required post-transplant to prevent graft-versus-host disease (GVHD), increasing the risk of virus infections before immune reconstitution is achieved. Use of multi-virus-specific T cells (mVST) therapy following HSCT is a novel treatment for virus infection and reactivation, which can help to restore antiviral immunity, including targeting of latent and respiratory viruses.

Methods: We developed a novel "first-in-human" mVST product targeting 6 viruses (12 antigens). Recipients of allogeneic-HSCT were enrolled on a phase-I dose-escalation ($1x10^7/m^2$–$5x10^7/m^2$ /dose) trial evaluating rapidly-expanded, donor-derived mVSTs targeting CMV, EBV, adenovirus, HHV6, BK virus and human-parainfluenza-3 for prophylaxis or treatment of target viruses.

Results: Sixteen patients received mVSTs post-HSCT, including 7 patients with inborn errors of immunity. Six patients received mVSTs as prophylaxis, of whom 67% (n=4/6) remained virus-free post-infusion. Two patients (n=2/6) had reactivation of EBV post-infusion, requiring rituximab treatment. of the 10 patients receiving mVSTs for treatment, 80% displayed partial or complete response to the target virus(es) post-infusion. Two patients had persistent viral disease post-infusion. Only one patient developed de novo grade III GVHD post-infusion. Two patients developed cytokine-release syndrome and one patient developed immune reconstitution inflammatory syndrome. Immunobiology studies of post-infusion patient samples including interferon-γ ELISpot assay and single-cell sequencing are ongoing.

Conclusions: These data provide evidence that this novel mVST therapeutic is safe and elicits antiviral activity for the treatment and prophylaxis of viral infections post-allogeneic transplant.

Disclosure: No.

Keywords: Virus-specific T cells, Adoptive immunotherapy, Hematopoietic stem cell transplant

PP003

FLOW CYTOMETRY-BASED DRUG SCREENING TO FIND DRUG CANDIDATES THAT RESTORE WASP IN MEGAKARYOCYTE AND PLATELET FUNCTION

POSTER DISCUSSION 01: THERAPIES

Rhaissa Vieira[1], Lia Gonçalves Pinho[2], Julien Record[3], Anna Ericksson[4], Anna-Lena Gustavsson[4], Lisa Westerberg[3]
[1]Karolinska Institutet, Microbiology, Tumor And Cell Biology, Solna, Sweden, [2]Karolinska Institutet, Department of Microbiology Tumor And Cell Biology, Stockholm, Sweden, [3]Karolinka Institutet, Microbiology, Tumor And Cell Biology, Solna, Sweden, [4]Science for Life Laboratory Stockholm, Department of Medical Biochemistry & Biophysics, Solna, Sweden

Background and Aims: Wiskott-Aldrich syndrome (WAS) is a severe immunodeficiency disease divided into classical WAS, with a severe outcome, and a milder form X-linked thrombocytopenia (XLT). Thrombocytopenia and small platelets are the most consistent finding among patients. To identify new treatment strategies, we developed a flow cytometry-based drug screening approach to find a drug candidate that could stabilize WASp preventing the rapid degradation and/or reducing the platelet overactivation observed in WAS/XLT patients.

Methods: CRISPR/Cas9, Flow Cytometry

Results: The flow cytometry-based drug screening was performed in a high throughput mode using the Prestwick library that contains 1276 FDA-approved and EMA-approved drugs, pre-spotted in plates by the Chemical Biology Consortium Sweden. After hit validation, two compounds (PTW-LW01 and PTW-LW02) were confirmed to increase WASp levels in the MEG-01 cell line mutated to express a XLT-related mutation, WAS R86C. Orthogonal analysis demonstrated that both compounds can increase WASp levels using another XLT mutation, WAS L39P. Moreover, the PTW-LW02 compound presented with lower toxicity effects in vitro and better scores in SwissADME webtool analysis, favoring its drug-likeness.

Conclusions: With this innovative flow cytometry-based approach, especially suited for cells in suspension, we identify two potential compounds that increase the availability of WASp in cells carrying different mutations related to XLT clinical outcomes.

Disclosure: No.

Keywords: Megakaryocyte, Drug screening, flow cytometry, WAS, X-linked thrombocytopenia

PP004

PERSISTENT HYPOGAMMAGLOBULINEMIA POST RITUXIMAB: AN UNDERLYING PRIMITIVE IMMUNODEFICIENCY?

POSTER DISCUSSION 01: THERAPIES

Carmela Giancotta[1], Beatrice Rivalta[1,2], Chiara Rossetti[2], Donato Amodio[1], Lucia Pacillo[1,2], Emma Concetta Manno[1], Veronica Santilli[1], Paola Zangari[1], Andrea Gioacchino Rotulo[1], Nicola Cotugno[1,2], Caterina Cancrini[1,2], Andrea Finocchi[1,2], Paolo Palma[1,2]
[1]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Roma, Italy, [2]Tor Vergata University, Department of Systems Medicine, Rome, Italy

Background and Aims: Rituximab(RTX) an anti-CD20-monoclonal-antibody, is used to treat autoimmune and hematological disorders. Transient hypogammaglobulinemia is a common effect related to the use of RTX. Immunoglobulin replacement therapy(IGRT) is necessary to prevent severe infections but guidelines about the length of therapy are lacking.

Methods: We retrospectively included 17 pediatrics patients(9 male, 8 female) that received RTX for different diseases without a previous diagnosis of PID(although extensive immunological investigations previous-RTX were not performed): 7 with nephrotic syndrome, 2 each with lymphoblastic leukemia, Burkitt's lymphoma, autoimmune hepatitis, one each with Berger's disease/persistent lymphadenopathy, autoimmune thrombocytopenia, glomerulonephritis and PTLD after liver transplantation.

Results: Six months after RTX, hypogammaglobulinemia(IgG serum level<2 DS for age) was found in all patients. 13 patients perform IGRT once a month for recurrent infections and/or lack of specific antibodies response. Low IgG levels and/or recurrence of infections suddenly appeared when Ig replacement therapy suspension was attempted. The other 4 patients (3 with nephrotic syndrome and one with autoimmune hepatitis), were asymptomatic with normal B-cell compartment replenishment and IGRT was not started.

Conclusions: Patients following RTX treatment may develop hypogammaglobulinemia and recurrent infection, demonstrating a failure of B-cell recovery. The incidence of these events is unknown for the lack of studies in various cohorts of patients; some patients have recurrent infections while others are relatively asymptomatic. Some reports show how a proportion of patients with post-RTX B-cell lymphopenia/hypogammaglobulinemia are later diagnosed with a PID. Hence, extend the cohort with an extensive immunological follow-up previous/post-RTX is mandatory to identify patients that could benefit from continuous IGRT.

Disclosure: No.

Keywords: hypogammaglobulinemia, B cell replenishment, immunoglobulin replacement therapy, RITUXIMAB, primary immunodeficiency

PP005

IMPACT of GRAFT FUNCTION ON HEALTH STATUS AND QUALITY of LIFE IN 112 LONG TERM SURVIVORS WHO RECEIVED AN HSCT FOR A PID

POSTER DISCUSSION 01: THERAPIES

Audrey Petit[1], Benedicte Neven[2], Victoria Min[3], Despina Moshous[2], Martin Castelle[4], Maya Allouche[5], Nizar Mahlaoui[2], Sandrine Visentin[1], Arthur Sterin[1], Pascal Auquier[1], Mohamed Boucekine[1], Alaa Mustafa Shawket[1], Capucine Picard[4], Gérard Michel[1], Alain Fischer[6], Vincent Barlogis[1]
[1]CHU de la Timone, Pediatric Hematology, Marseille, France, [2]Necker Hospital for Sick Children, Pediatric Immunology, Hematology And Rheumatology Unit, Paris, France, [3]CHU de la Timone, Pediatric Oncology, Marseille, France, [4]Necker Children's Hospital, Assistance Publique-Hôpitaux de Paris, Université De Paris, Institut Imagine Institut Des Maladies Genetiques, Paris, France, [5]Assistance Publique Hopitaux Marseille, Immunology, Marseille, France, [6]Necker Hospital, Pediatric Hematology-immunology And Rheumatology Unit, Paris, France

Background and Aims: Hematopoietic stem cell transplantation (HSCT) for Primary Immune Deficiencies (PIDs) is now considered in a broadening spectrum of patients aiming primarily to improve long-term survival and health. Our study focuses on how the health and quality of life (HRQoL) of 5-year post-HSCT survivors are affected.

Methods: We conducted a multicenter prospective follow-up program enrolling PID patients included in the CEREDIH registry, transplanted during childhood with a minimum of 5-year follow-up. Answers from self-reported French Childhood Immune Deficiency Long-term Cohort (F-CILC) and 36-item Short Form (SF-36) questionnaires were compiled. A full donor chimerism at last follow-up, no chronic GVHD during follow-up and normal CD3+ lymphocytes count according to age at last follow-up were considered as a satisfactory graft function.

Results: 112 survivors were included with a time from HSCT ranging from 5 to 37 years. In multivariate analysis an unsatisfactory graft function was significantly associated with a poor and very poor health (OR 2,6 CI 95%: 1,1-5,9 p:0,028) and to a very poor health (OR 3,6 CI 95%: 1,1-13, p:0,049). Patients with a very poor health had a significantly worse HRQoL.

Conclusions: It has been established that transplanted PID patients fare better than non-transplanted patients. Our results show that about half of them are affected by an altered health with a correlation to both an unsatisfactory graft function and a long-term impaired quality of life. Despite major progress in the outcome after HSCT for PIDs, survivors still face significant challenges that require persistent surveillance and research.

Disclosure: No.

Keywords: long-term follow up, graft function, HSCT, quality of life

PP006

C-TERMINAL DOMAIN COPA MUTATIONS IN SIX CHILDREN FROM THREE UNRELATED FAMILIES WITH AUTOSOMAL DOMINANT COPA SYNDROME

POSTER DISCUSSIONS 02: IMMUNE MECHANISMS

Selket Delafontaine[1], Tarin Bigley[2], Alberto Iannuzzo[3], Bram Mylemans[4], Ruchit Rana[5], Katrien Jansen[6], Catherine Cassiman[7], Philippe Demaerel[8], Rik Schrijvers[9], Xavier Bossuyt[10], Giorgia Bucciol[11], Karen Willekens[12], Anniek Corveleyn[12], Bram Boeckx[13], Marco Baggio[14], Dieter Lambrechts[13], Arnout Voet[4], Carla Davis[5], Megan Cooper[2], Jérôme Delon[3], Leen Moens[11], Isabelle Meyts[14]
[1]KU Leuven, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [2]Washington University in St. Louis, Department of Pediatrics, Division of Rheumatology/immunology, St. Louis, United States of America, [3]Cochin Institute (Institut Cochin - CNRS - INSERM - Université Paris Cité), Département Infection-immunité-inflammation, Paris, France, [4]KU Leuven, Department of Chemistry, Leuven, Belgium, [5]Baylor St. Luke's Medical Center, Department of Medicine, Houston, United States of America, [6]University Hospitals Leuven, Department of Pediatrics, Leuven, Belgium, [7]University Hospitals Leuven, Department of Ophtalmology, Leuven, Belgium, [8]University Hospitals Leuven, Department of Radiology, Leuven, Belgium, [9]KU Leuven, Allergy And Clinical Immunology Research Group, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [10]KU Leuven, Clinical And Diagnostic Immunology, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [11]KU Leuven, Laboratory Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [12]University Hospitals Leuven, Center For Human Genetics, Leuven, Belgium, [13]KU Leuven, Department of Oncology, Leuven, Belgium, [14]KU Leuven, Laboratory of Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium

Background and Aims: Dominant heterozygous loss-of-function mutations affecting the N-terminal domain of coatomer protein complex subunit-α, COPA, cause COPA syndrome, a type I interferonopathy[1,2]. We aim to contribute to the elucidation of the pathophysiology of COPA syndrome.
Methods: Whole exome sequencing in three unrelated families detected three novel COPA mutations, affecting the C-terminal domain of COPA, in six children. COPA expression, COPI formation, type I IFN response, STING activation, ER stress and NF-κB activation were assessed in peripheral blood, primary and HEK293T cells.
Results: Clinical manifestations included alveolar haemorrhage, neuroinflammation, nephritis and arthritis. P1 successfully underwent a hematopoietic stem cell transplantation, P2 succumbed due to macrophage activation syndrome. WES revealed a private nonsense variant (c.3424C>T, p.Arg1142*, P1) and two missense variants (c.3172C>T, p.Arg1058Cys, P2 and c.3038G>C, p.Cys1013Ser, P3-6), all predicted pathogenic. The truncated R1142* protein, overexpressed in HEK293T cells, impaired the binding to COPB2 and COPE in co-immunoprecipitation assay. Although this binding remained intact for the missense variants, biomodelling predicted a disturbed COPI stability. We detected increased induced ER stress and NF-κB nuclear translocation in patient LCLs and fibroblasts of P1. Patients demonstrate an increased type I IFN signalling and a Golgi-localized accumulation of STING in R1142* fibroblasts. In contrast, HEK293T cells overexpressing WT STING and mutant COPA demonstrate a reduced phosphorylation of IRF3 and ISG expression, through a dominant negative mechanism.
Conclusions: C-terminal domain COPA mutations cause a broad dysregulation of pro-inflammatory signalling pathways, including the type I IFN response. References: (1) Watkin et al. Nat Genet. (2015).
(2) Lepelley et al. J Exp Med. (2020).
Disclosure: No.

Keywords: COPA, COPI, intracellular transport, autoinflammation, ER stress, Type I interferonopathy

PP007

PREDOMINANTLY ANTIBODY DEFICIENCY AND ENHANCED PI3K SIGNALLING IN B CELLS of A PATIENT WITH A HETEROZYGOUS MISSENSE VARIANT IN SYK

POSTER DISCUSSIONS 02: IMMUNE MECHANISMS

Emily S.J. Edwards[1,2], Julian Bosco[2,3], Josh Chatelier[2,3], Go Hun Seo[4], Pei Mun Aui[1,2], Robyn O'Hehir[1,2,3], Menno Van Zelm[1,2,3]
[1]Monash University, Immunology And Pathology, Melbourne, Australia, [2]JMF Centre Melbourne, The Jeffrey Modell Diagnostic And Research Centre For Primary Immunodeficiencies, Melbourne, Australia, [3]Alfred Hospital, Department of Allergy, Immunology And Respiratory Medicine, Melbourne, Australia, [4]3 billion Inc., 3billion Inc., Seol, Korea, Republic of

Background and Aims: Spleen tyrosine kinase (Syk) is a critical signaling molecule downstream of immune receptors, including the B-cell receptor (BCR). Four heterozygous Syk variants have been reported in six patients presenting with immunodeficiency, multiorgan inflammatory disease and diffuse large B-cell lymphoma. Variants were shown to increase phosphorylation of Syk and its downstream target ERK. Our aim is to identify and functionally validate the genetic cause of disease in a 43yo female who presented hypogammaglobulinemia, congenital heart disease and pulmonary hypertension.

Methods: Genetic analysis by whole-exome sequencing of genomic DNA was performed. Flow cytometry was performed on blood leukocytes to determine impacts on the B- and T-cell compartments and to examine phosphorylated ribosomal-S6 levels resulting from tonic and ligand-induced PI3K signaling in B- and T-cells.

Results: A novel heterozygous missense SYK variant was identified, affecting the Syk protein kinase domain (c.1769G>A; p.R590Q). This residue is highly conserved across vertebrates. Total B- and T-cell numbers were within the normal range, whereas unswitched and class-switched B-cell numbers, and serum IgG were reduced. Tonic and ligand-induced levels of phosphorylated-S6 were normal in T-cells but were dramatically increased in the patient's B-cells, inline with Syk expression in B- but not T-cells.

Conclusions: The observed enhanced PI3K signaling supports that the identified novel heterozygous SYK variant has a gain-of-function effect and underlies immunodeficiency in this patient. Phosphorylated-S6 represents a functional assay for the validation of genetic variants that activate BCR signaling, findings of which provide an evidence-base for treatment with available therapies targeting the PI3K pathway.

Disclosure: No.

Keywords: functional genomics, predominantly antibody deficiency, SYK, BCR signalling, PI3K pathway

PP008

SOMATIC REVERTANT MOSAICISM CORRELATING WITH CLINICAL IMPROVEMENT IN A PATIENT WITH TNFRSF9 (CD137) DEFICIENCY

POSTER DISCUSSIONS 02: IMMUNE MECHANISMS

Roger Colobran[1,2,3], Marina Garcia-Prat[3,4,5], Alba Parra-Martínez[3,5,6], Clara Franco Jarava[1,7,8], Daniel Álvarez-Sierra[1,9], Aina Aguiló-Cucurull[10], Jacques Rivière[4,11,12], Andrea Martín-Nalda[4,11,13], Pere Soler-Palacin[4,11,12], Ferran Casals[14], Laia Alsina[15], Montserrat Torrent[16], Laura Batlle-Masó[3,5]
[1]Vall d'Hebron Research Institute (VHIR), Translational Immunology, Barcelona, Spain, [2]Universitary Hospital Vall d'Hebron, Immunology Division, Genetics Department, Barcelona, Spain, [3]Jeffrey Modell Foundation Diagnostic and Research Center for Primary Immunodeficiencies, Diagnostic And Research Center For Primary Immunodeficiencies, Barcelona, Spain, [4]Vall d'Hebron Barcelona Hospital Campus, Infection In Immunocompromised Pediatric Patients, Barcelona, Spain, [5]Vall d'Hebron University Hospital, Pediatric Infectious Diseases And Immunodeficiencies Unit, Barcelona, Spain, [6]Vall d'Hebron Barcelona Hospital Campus, Infection In Immunocompromised Pediatric Patients, Barcelona, Catalonia, Spain, [7]Jeffrey Modell Foundation, Diagnostic And Research Center For Primary Immunodeficiencies, Barcelona, Spain, [8]Vall d'Hebron Barcelona Hospital Campus, Immunology Division, Barcelona, Catalonia, Spain, [9]Vall d'Hebron Barcelona Hospital Campus, Immunology Division, Barcelona, Catalonia, Spain, [10]Vall d'Hebron Barcelona Hospital Campus, Immunology Division, Barcelona, Spain, [11]Vall d´Hebron Hospital, Pediatric Infectious Diseases And Immunodeficiencies Unit, Hospital Universitari Vall D'hebron (huvh), Vall D'hebron Research Institute (vhir), Universitat Autònoma De Barcelona, Catalonia, Spain. Jeffrey Modell Excellence Centre, Barcelona, Spain, [12]Jeffrey Modell Foundation Diagnostic and Research Center for Primary Immunodeficiencies, Barcelona, Barcelona, Spain, [13]Vall d´Hebron Hospital, Pediatric Infectious Diseases And Immunodeficiencies Unit, Barcelona, Spain, [14]Universitat de Barcelona (UB), Department of Genetics, Microbiology And Statistics, Barcelona, Spain, [15]Hospital Sant Joan de Déu, Allergy And Clinical Immunology Department, Esplugues del Llobregat, Spain, [16]Hospital Santa Creu i Sant Pau, Paediatric Hematopoietic Transplant Unit, Barcelona, Spain

Background and Aims: Reversion mosaicism is a naturally occurring event involving a spontaneous correction of a pathogenic mutation in somatic cells. TNFRSF9 (CD137/4-1BB) deficiency is a recently described IEI characterized by lymphocytic defects with early-onset EBV-associated lymphoma.
Methods: We used Sanger sequencing, whole-exome sequencing (WES), deep-amplicon sequencing (DAS) and single-cell RNA sequencing (scRNAseq) in total blood and specific cell populations.
Results: We report a patient who at 12 years of age developed a severe EBV-associated hemophagocytic lymphohistiocytosis episode. No genetic defects were found at that time and she underwent HSCT from an HLA identical brother with good engraftment. In the following 8 years the patient could not control the EBV, with recurrent reactivations, lymphoproliferation and EBV-associated smooth muscle tumor. Then, the patient experienced a spontaneous decrease in EBV viral load. Using WES we identified a homozygous stop-gain variant in TNFRSF9. Strikingly, the HSCT donor was also homozygous but without overt clinical symptoms. The presence of small, unexpected peaks in Sanger sequencing of blood samples lead us to suspect a possible somatic reversion event. Using DAS we confirmed the presence of two independent somatic reversion events: a second-site mutation in the same codon (STOP to missense) and a "back mutation" (STOP to wild-type). The revertants were specifically located at CD8-T cells (absent in neutrophils, B cells and CD4-T cells) in which scRNAseq experiments are ongoing.
Conclusions: We report the first case of reversion mosaicism in CD137 deficiency associated with clinical improvement, which may point the way to gene therapy strategies in this IEI.

Disclosure: No.

Keywords: Somatic reversion, somatic mosaicism, Next generation sequencing, CD137 deficiency, EBV infection

PP009

ALVEOLAR ORGANOIDS AS A HUMAN MODEL TO STUDY LUNG DISEASE IN STAT3-HYPER-IGE SYNDROME

POSTER DISCUSSIONS 02: IMMUNE MECHANISMS

Miriam Kastlmeier[1], Andreas Eberherr[2,3], Christine Wolf[2,3], Andre Maaske[2,3], Ejona Rusha[4], Anna Pertek[4], Micha Drukker[4,5], Tobias Stoeger[1], Ellen Renner[2,3], Carola Voss[1], Beate Hagl[2,3]
[1]Helmholtz Zentrum Munich, Lung Health And Immunity, Neuherberg, Germany, [2]Technical University of Munich, Translational Immunology In Environmental Medicine, Munich, Germany, [3]Helmholtz Zentrum Munich, Translational Immunology In Environmental Medicine, Neuherberg, Germany, [4]Helmholtz Zentrum Munich, Institute of Stem Cell Research, Neuherberg, Germany, [5]Leiden Academic Centre for Drug Research (LACDR), Division of Drug Discovery And Safety, Leiden, Netherlands

Background and Aims: Air-filled pneumatoceles are one of the characteristic findings of chronic lung disease in STAT3-hyper-IgE syndrome (STAT3-HIES). To investigate the pathophysiology of the alveolar epithelium we have established alveolar organoids as a human model.

Methods: Primary STAT3-HIES patient fibroblasts were reprogramed toward induced pluripotent stem cells (iPSCs). The disease-causing STAT3 mutation p.R382W was corrected using CRISPR/Cas9-mediated adenine base editing (Eberherr et al. CRISPRJ 2021). Untreated and genetically corrected patient iPSCs were differentiated to alveolar organoids. Alveolar epithelial cell identity of enriched differentiated cells was confirmed by immunofluorescence staining of surfactant protein C. Organoids were stimulated with interleukin 6 (IL6) and soluble IL6 receptor (sIL6R)and expression of the STAT3 target gene SOCS3 was assessed using quantitative real-time PCR.

Results: Genetically corrected STAT3-R382W (cSTAT3-R382W) organoids showed improved expression of the STAT3 target gene SOCS3 after stimulation with IL6/sIL6R compared to untreated STAT3-R382W organoids. An increased cell proliferation in cSTAT3-R382W organoids compared to unrepaired organoids hint to a positive effect by the gene repair which might benefit epithelial recovery after lung injury.

Conclusions: Our first experiments showed, that alveolar organoids are a promising human model to study the pathophysiology of lung disease and to investigate alveolar homeostasis and function in STAT3-HIES. By comparing alveolar function of corrected and untreated STAT3-HIES organoids we aim to gain insights into the therapeutic effect of gene repair on lung pathophysiology. Reference: Eberherr AC et al. Rescue of STAT3 Function in Hyper-IgE Syndrome Using Adenine Base Editing. CRISPR J. 2021 Apr;4(2):178-190.

Disclosure: No.

Keywords: gene therapy, STAT3, STAT3-HIES, hyper-IgE syndrome, chronic lung disease, organoid

PP010

TYPE 1 IFN REGULATION of HIF1A SWITCHES ENERGY METABOLISM ENHANCING INFLAMMATION THROUGH CYTOKINE PRODUCTION IN AGS

POSTER DISCUSSIONS 02: IMMUNE MECHANISMS

Maxime Batignes[1], Marine Luka[1], Tinhinane Fali[1], Camille De Cevins[1], Surabhi Jagtap[1], Victor Garcia-Paredes[1], Francesco Carbone[2], Benedicte Neven[3], Marie-Louise Frémont[4], Alice Lapelley[4], Yanick Crow[4], Alain Fischer[5], Mickael Ménager[1,2]
[1]Imagine Institute, Laboratory of Inflammatory Responses And Transcriptomic Networks In Diseases, Atip-avenir, Paris, France, [2]Imagine Institute, Labtech Single-cell@imagine, Paris, France, [3]Necker Hospital for Sick Children, Pediatric Immunology, Hematology And Rheumatology Unit, Paris, France, [4]Imagine Institute, Aicardi-goutières Syndrome And Type 1 Interferonopathies, Paris, France, [5]Collège de France, Collège De France, Paris, France

Background and Aims: Nucleic acid sensors in the cytoplasm are specialized in detecting invasive RNA/DNA from pathogens like viruses driving defensive mechanisms throught type 1 interferon (IFN). Some genetic mutations affecting genes involved in nucleic acid sensing cause uncontrolled IFN production leading to disruption of brain development characterizing of Aicardi-Goutières Syndrome (AGS). Here, our objective is to use innovative single cell approaches to better apprehend AGS pathogenesis expecting to unveil new therapeutic approaches for patients.

Methods: We used single-cell RNA sequencing (scRNAseq) on peripheral blood mononuclear cells from healthy controls and from AGS patients to explore genes and pathways dysregulated in AGS. We also developed an in vitro cellular model on monocyte derived dendritic cells knock down for AGS associated gene by short-hairpin RNA inference.

Results: Analysing scRNAseq data, we described an impairment of glycolysis and an upregulation of oxidative phosphorylation associated with mitochondrial stress in AGS patients. Importantly, this metabolic switch was associated with a strong IFN signature. We identified a drastic loss of the transcription factor hypoxia induce factor 1 A (HIF1A) expression and its associated targets in patients, that have never been reported before. Using in vitro model of AGS, we found that chemical stabilization of HIF1A revert energy metabolism switch, reduce IFN-induce protein 10 (IP-10) production and attenuate mitochondrial stress.

Conclusions: We identified that, along uncontrolled type 1 IFN production, AGS patients suffers from metabolic switch linked to a specific downregulation of HIF1A transcriptional program. We also reported that chemical HIF1A stabilization could decrease cytokine production, unveiling promising therapeutic approaches in AGS.

Disclosure: No.

Keywords: Type 1 interferon, Pediatric disease, Aicardi-Goutières syndrome, Autoimmunity, Energy metabolism

PP011

CONGENITAL ATHYMIA AS A FEATURE of DIGEORGE SYNDROME IN PATIENTS WITH MONOGENIC TBX1 DEFICIENCY

POSTER DISCUSSIONS 02: IMMUNE MECHANISMS

Maarja Soomann[1], Adam Klocperk[2], Martin Castelle[3], Eduardo López Granados[4], Jennifer Leiding[5], Despina Moshous[3], Anna Sediva[2], Austen Worth[1], Graham Davies[1], Alexandra Kreins[1]
[1]Great Ormond Street Hospital, Immunology, London, United Kingdom, [2]2nd Faculty of Medicine, Charles University and University Hospital in Motol, Immunology, Prague, Czech Republic, [3]Necker Hospital for Sick Children, Pediatric Immunology, Hematology And Rheumatology Unit, Paris, France, [4]La Paz University Hospital, Immunology, Madrid, Spain, [5]Johns Hopkins All Children's Hospital, Immunology, St. Petersburg, United States of America

Background and Aims: Haploinsufficiency of the T-box transcription factor TBX1 underlies DiGeorge Syndrome (DGS) in most patients with microdeletions of chromosome 22q11.2. Heterozygous TBX1 point mutations have been reported in association with DGS features, including congenital heart disease (CHD) and hypoparathyroidism. The association with thymic hypo- and aplasia is not yet well described in humans. We report monogenic TBX1 deficiency in a case series of athymic DGS patients.

Methods: We identified 7 patients with heterozygous TBX1 mutations, including 3 previously reported. All were referred for consideration of thymus transplantation (TT). Clinical questionnaires facilitated data collection.

Results: Six patients were diagnosed because of infections, including pneumonia, BCGosis and disseminated viraemia (mean age: 2.5 months). One patient was diagnosed by newborn screening. They all displayed at least one other DGS feature, including hypoparathyroidism (n=6), minor CHD (n=1), velopharyngeal insufficiency (n=2), dysmorphisms (n=5), deafness (n=4) and neurodevelopmental anomalies (n=4). Four patients developed Omenn Syndrome. All patients had negligible proportions of naïve ($CD45RA^+CD27^+$) T-cells (max. 3% of $CD4^+$ T-cells). Three patients succumbed to viraemias (CMV, adenovirus) before corrective therapy could be attempted. Two patients underwent TT, whereas the remaining 2 patients received haematopoietic cell transplantation (HCT) in the context of disseminated viraemia. At last follow up, treated patients have $CD3^+$ T-cell counts between 450-970/µl. Higher absolute counts of naïve $CD4^+$ T-cells were documented post-TT (max. 200/µl and 480/µl) vs post-HCT (max 40/µl and 72/µl).

Conclusions: Monogenic TBX1 deficiency can be associated with athymia, requiring early diagnosis and referral for corrective treatment, ideally TT.

Disclosure: No.

Keywords: TBX1, thymus transplantation, Digeorge Syndrome, haematopoietic cell transplantation

PP012

DISSECTING THE ROLE of LRBA IN AUTOPHAGY AND ITS IMPACT ON ANTIGEN PRESENTATION

POSTER DISCUSSION 03: IMMUNE DYSREGULATION

Laura Gámez-Díaz[1], Marie-Céline Deau[2], Elena Sindram[3,4,5], Laura-Anne Ligeon[6], Pablo Sanchez-Martin[7], Angelika Rambold[2], Christian Münz[6], Claudine Kraft[7], Bodo Grimbacher[1,8,9,10,11]
[1]University Hospital Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [2]Medical Center, Faculty of Medicine, Albert-Ludwigs-University of Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency, Freiburg, Germany, [3]Medical Center Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency, Freiburg, Germany, [4]Albert-Ludwigs-University of Freiburg, Spemann Graduate School of Biology And Medicine (sgbm), Freiburg, Germany, [5]Albert-Ludwigs-University of Freiburg, Faculty of Biology, Freiburg, Germany, [6]Viral Immunobiology, Institute of Experimental Immunology, Zurich, Switzerland, [7]Institute of Biochemistry and Molecular Biology, Zbmz, Faculty of Medicine, University of Freiburg, Freiburg, Germany, [8]Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany, [9]Satellite Center Freiburg, German Center For Infection Research (dzfi), Freiburg, Germany, [10]Satellite Center Freiburg, Resolving Infection Susceptibility (resist) - Cluster of Excellence 2155 To Hannover Medical School, Freiburg, Germany, [11]Center for Integrative Biological signaling Studies (CIBSS), University of Freiburg, Freiburg, Germany

Background and Aims: Biallelic mutations in lipopolysaccharide responsive beige-like anchor protein (LRBA) lead to a severe clinical syndrome presenting with immunodeficiency and immunodysregulation. Previously, we suggested reduced autophagy as the biological cause for the aberrant humoral response in LRBA-deficient patients; however, the molecular mechanisms and its impact on autophagy-dependent immune functions remained unknown.

Methods: Hence, we screened for LRBA-interacting proteins using in silico and proteome-wide approaches.

Results: We found that LRBA interacts with the phosphoinositide 3-kinase regulatory subunit 4 (PIK3R4) and the FYVE And Coiled-Coil Domain Autophagy Adaptor 1 (FYCO-1). Interestingly, both proteins play essential roles during early and late autophagy, respectively. Specifically, PIK3R4 facilitates the production of phosphatidylinositol-3 phosphate (PI(3)P) and thereby the recruitment of DFCP-1 and WIPI2. In fact, LRBA-KO cells showed impaired production of PI(3)P leading to reduced autophagosome formation. In addition, blockade of the autophagosome-lysosome fusion and accumulation of enlarged autophagosomes, accompanied by an atypical lysosomal positioning, were observed in LRBA-KO cells; possibly due to loss of LRBA-FYCO1 interaction. Immunologically, we observed that accumulation of enlarged autophagosomes led to an enhanced antigen presentation and a strong T-cell response. Noteworthy, autophagy is a major intracellular degradation system that delivers cytoplasmic proteins to lysosomes for MHC class II loading.

Conclusions: Taken together, our data suggests that i) LRBA is part of a large protein machinery serving at different stages of autophagy, and ii) loss of LRBA impacts the targeting of cytosolic antigens for autophagy degradation, enhancing antigen presentation. The latter could contribute to the exacerbated T-cell infiltration and autoimmune manifestations in LRBA-deficient patients.

Disclosure: No.

Keywords: FYCO1, antigen presentation, immunedysregulation, LRBA, Autophagy, PIK3R4

PP013

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN CHILDREN WITH GRISCELLI SYNDROME : EXPERIENCE AND OUTCOMES

POSTER DISCUSSION 03: IMMUNE DYSREGULATION

Ezgi Cay[1], Ahmet Sezer[2], Veysel Karakulak[2], Dilek Ozcan[2], Atıl Bisgin[3], Hatice Ilgen Sasmaz[4], Derya Ufuk Altıntaş[2]
[1]Cukurova University , Faculty of Medicine, Paediatrics, Adana, Turkey, [2]Cukurova University , Faculty of Medicine, Allergy And Immunology, Adana, Turkey, [3]Cukurova University , Faculty of Medicine, Medical Genetics, Adana, Turkey, [4]Cukurova University , Faculty of Medicine, Hematology, adana, Turkey

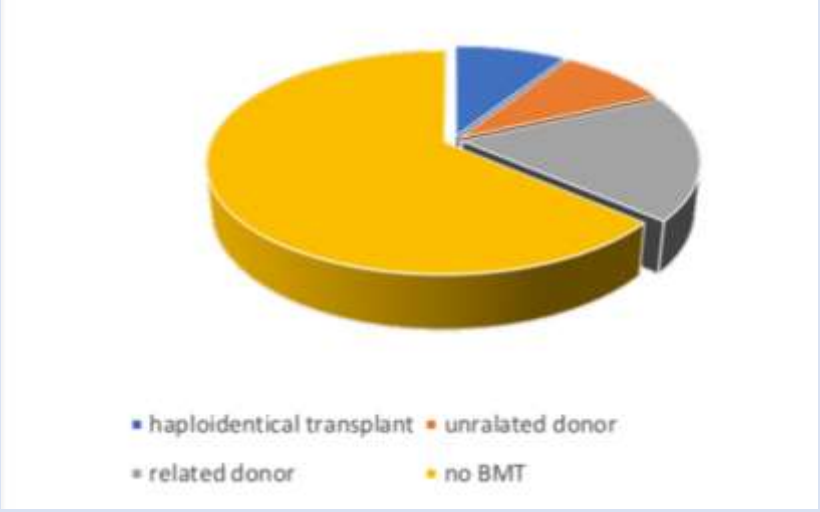
Background and Aims: Griscelli Syndrome is a rare autosomal recessive inherited syndrome that causes immunodeficiency. Hemophagocytic Lymphohistiocytosis (HLH) which is characterized by high mortality may develop due to Griscelli. We aimed to evaluate patients who developed HLH secondary to Griscelli.

Methods: Twelve patients were enrolled in the study. All patients met at least 5 of 8 diagnostic criteria of HLH 2004. Symptoms and laboratory parameters at the time of diagnosis of HLH and laboratory parameters during treatment were evaluated. HLH 2004 protocol was used in the treatment.

Results: The first presentation finding in 10 patients was HLH. One patient presented with CNS involvement and 1 patient with immunodeficiency findings. Genetic mutation was RAB27A in 10 patients. Mean age at diagnosis was 7 months. All patients received intravenous immunoglobulin and corticosteroid therapy. A statistically significant decrease was detected in ferritin, fibrinogen and CRP levels after treatment compared to before treatment (Table1). Three patients died during follow-up. Family related allogeneic bone marrow transplantation (BMT) was performed in 3 patients and unrelated BMT was performed in 1 patient. Remission was observed in 3 of the 4 transplanted patients. Unrelated transplantation was performed for the second time in 1 patient due to the lack of engraftment and remission was observed after the second transplantation (Table2).

Table 1. Pre- and post-treatment laboratory findings in patients

Labaratory Parameters	Pre-Treatment	Post-Treatment	*p*
WBC (n/mm³)	3500 (2171 -12.700)	5300 (2350 -18.200)	0.168
Absolute Neutrophil Count	1200 (300-8000)	1900 (0 – 16.200)	0.091
Absolute Lymphocyte Count	1770 (900 - 4600)	2500 (600 – 4700)	0.646
Hemoglobin (g/dL)	9.4±1.6	10.1±1.8	0.164
Platelet (µL)	88.000 (10.000 -852.000)	280.000 (57.000 – 387.000)	0.062
LDH (U /L)	329 (200-483)	281 (177 -561)	0.441
Fibrinogen (mg/dl)	129 (100 – 297)	250 (118 – 291)	0.016
Ferritin ng/ml)	1353 ± 672	469 ± 278	<0.001
Trigliycerides (mg/dl)	375 ± 166	255 ±137	0.110
AST (U/L)	35 (21 – 479)	37 (13 – 241)	0.350
ALT (U/L)	39 ± 20	48 ± 32	0.334
Albumin (g/L)	34.5 ± 7	35.2 ± 7	0.589
CRP (mg/L)	15.6 (1 - 79)	5 (1 - 9)	0.028



Conclusions: HLH may be the one of the first manifestations of patients with Griscelli. Ferritin, fibrinogen and CRP can be used as a marker in the evaluation of response to treatment. BMT is an important treatment option for patients to survive and to prevent relapse.

Disclosure: No.

Keywords: Griscelli Syndrome, Bone Marrow Transplantation, Hemophagocytic Lymphohistiocytosis

PP014

EXPANDING THE CLINICAL AND IMMUNOLOGICAL PHENOTYPES AND NATURAL HISTORY of MALT1 DEFICIENCY

POSTER DISCUSSION 03: IMMUNE DYSREGULATION

Asena Pinar Sefer[1], Hassan Abolhassani[2], Franziska Ober[3], Basak Kayaoglu[4], Sevgi Bilgic Eltan[1], Altan Kara[5], Baran Erman[6], Naz Surucu Yilmaz[4], Cigdem Aydogmus[7], Sezin Kisabacak[8], Louis-Marie Charbonnier[9], Burcu Kolukısa[1], Gholamreza Azizi[10], Tobaa Momen[11], Simuzar Aliyeva[12], Yasemin Kendir Demirkol[13], Saban Tekin[14], Ayca Kiykim[8], Omer Faruk Beser[15], Haluk Cezmi Cokugras[8], Mayda Gursel[4], Elif Karakoc-Aydıner[1], Ahmet Ozen[1], Daniel Krappmann[3], Talal A. Chatila[9], Nima Rezaei[16], Safa Baris[1]
[1]Marmara University Pendik Research and Training Hospital, Pediatric Allergy And Immunology, Istanbul, Turkey, [2]Karolinska Institute, Division of Clinical Immunology, Department of Biosciences And Nutrition, Stockholm, Sweden, [3]Research UnitCellular Signal Integration, Institute of Molecular Toxicology And Pharmacology, Helmholtz Zentrum München, Germany, [4]Middle East Technical University, Department of Biological Sciences, Ankara, Turkey, [5]TUBITAK Marmara Research Center, Gene Engineering And Biotechnology Institute, Gebze, Turkey, [6]Hacettepe University, Institute of Child Health, Ankara, Turkey, [7]University of Health Sciences, Basaksehir Cam Sakura City Hospital, Division of Pediatric Allergy And Immunology, Istanbul, Turkey, [8]Istanbul University-Cerrahpasa, Pediatric Allergy And Immunology, Istanbul, Turkey, [9]Harvard Medical School, Division of Immunology, Boston Children's Hospital And Department of Pediatrics, Boston, United States of America, [10]Alborz University of Medical Sciences, Non-communicable Diseases Research Center, Karaj, Iran, [11]Child Growth and Development Research Center, Research Institute for Primordial Prevention of Noncommunicable Disease, Isfahan University of Medical Sciences, Department of Allergy And Clinical Immunology, Isfahan, Iran, [12]Marmara University Pendik Research and Training Hospital, Pediatrics, Istanbul, Turkey, [13]University of Health Sciences, Umraniye Education and Research Hospital, Division of Pediatric Genetics, Istanbul, Turkey, [14]University of Health Sciences, Hamidiye Faculty of Medicine, Department of Basic Medical Sciences, Division of Medical Biology, Istanbul, Turkey, [15]Istanbul University, Cerrahpasa School of Medicine, Department of Pediatrics, Division of Gastroenterology, Hepatology And Nutrition, Istanbul, Turkey, [16]Tehran University of Medical Sciences, Research Center For Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran, Iran

Background and Aims: MALT1 deficiency is a combined immune deficiency characterized by recurrent infections, eczema, chronic diarrhea, and failure to thrive. Clinical and immunological characterizations of the disease have not been previously reported in large cohorts. We sought to determine the clinical, immunological, genetic features, and the natural history of MALT-1 deficiency.

Methods: The clinical, laboratory findings and treatment outcomes were evaluated in nine new MALT1-deficient patients. Peripheral lymphocyte subset analyses, cytokine secretion, and proliferation assays were performed. We also analyzed ten previously reported patients together with new patients to comprehensively evaluate genotype/phenotype correlation.

Results: The main clinical findings of the disease were recurrent infections (100%), skin involvement (100%), failure to thrive (100%), oral lesions (67%), chronic diarrhea (56%), and autoimmunity (44%). Five of our patients (56%) and seven (78%) of previously reported patients suffered from mild intermittent or severe diarrhea, causing growth retardation, FTT, malabsorption, mimicking IPEX. Eosinophilia and high IgE were observed in six (67%) and two (22%) patients, respectively. The majority of patients had normal T and NK cells, while eight (89%) exhibited reduced B cells. Most of the MALT-1 deficient patients had low $CD4^+CD25^+FOXP3^+$ Treg cells. Anti-CD3/CD28 and or Phytohemagglutinin (PHA)-stimulated T cells showed blunted expansion and reduced cytokine responses (IL-2, IL-4, IFN-

Conclusions: Human MALT1 deficiency causes a CID and/or IPEX-like disorder characterized by defective NF-κB signaling with lacking paracaspase activity. The defective Treg and T_H17 development and accompanied by impaired T- and B-cell responses determine the clinical phenotype of the patients. Our study extends the clinical spectrum of MALT1-deficient cases.

Disclosure: This work was supported by grants from the Scientific and Technological Research Council of Turkey (318S202).

Keywords: primary immunodeficiency, MALT1, combined immune deficiency, Immune Dysregulation, recurrent infections, Inborn errors of immunity

PP015

MISDIAGNOSIS of PRIMARY IMMUNE THROMBOCYTOPENIA IN CHILDREN AND ADOLESCENTS

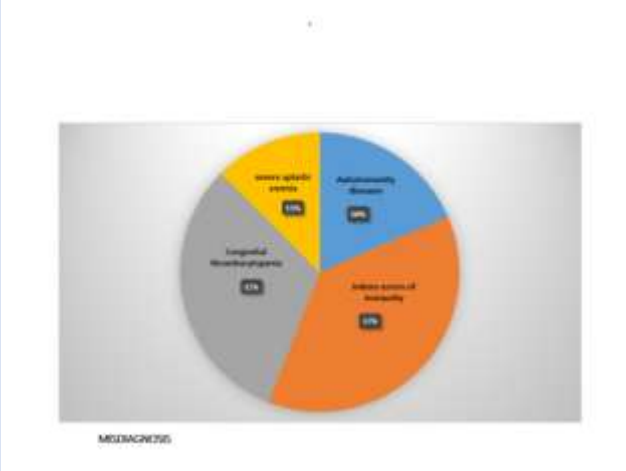
POSTER DISCUSSION 03: IMMUNE DYSREGULATION

Irene D'Alba, Lara Antonini, Alessandra Piro, Barbara Bruschi, Valeria Petroni, Simona Gobbi, Paola Coccia
AOU Ospedali Riuniti Salesi Children Hospital, Pediatric Onco-hematology, Ancona, Italy

Background and Aims: Immune thrombocytopenia is a diagnosis of exclusion which can lead to misdiagnosis. Our aim is to evalueted the misdiagnosis in a cohort of 222 patients with initial diagnosis of immune thrombocytopenia (ITP).

Methods: A retrospective observational study was conducted in a paediatric hospital in Italy between 2002 and 2022, which included children from 3 days to 20 years old diagnosed with ITP. Data were recorded from clinical charts: gender, race, age at diagnosis, laboratory data, bleeding score, vaccination, recent infection, coexisting condition, associated characteristics, outcome and treatment.

Results: A total of 222 children with an initial diagnosis of primary ITP were collected. At the time of the analysis 16 patients (7.2%) had an unequivocal diagnosis of secondary ITP or non-IT. Six patients (37.5%) received a diagnosis of Inborn errors of immunity (ALPS, ALPS-like, Artemis deficiency, CVID, Kabuki syndrome, BCL11B deficiency), 5 patients (31.5%) were congenital thrombocytopenia (2 MYH9-Related Thrombocytopenia, 1 Thrombocytopenia Absent Radius Syndrome, 1 Sitosterolemia, 1 Wilson's disease) 3 patients (18.5%) were autoimmunity diseases (LES, 2 Celiac Disease) and 2 patients (12.5%) were severe aplastic anemia. Fourteen patients developed chronic ITP (87.5%). Fourteen patients received first line treatment (IgEV, steroids) and two patients (Artemis deficiency, Kabuki syndrome) received second and third line treatment (rituximab, mycophenolate, azathioprine and eltrombopag)



Conclusions: Secondary ITP and non-IT are rare, difficult to recognize in children with suspected or newly diagnosed ITP. Some manifestations of the underlying disease may emerge only during the follow-up period. Well-defined and validated diagnostic workflow would be needed for timely diagnosis and right management.

Disclosure: No.

Keywords: Inborn errors of immunity, misdiagnosis, Primary Immune Thrombocytopenia

PP016

EFFECTS of THE HETEROZYGOUS TNFRSF13B P.C104R VARIANT ON THE EXPRESSION of APOPTOSIS-ASSOCIATED GENES IN THREE UNRELATED PATIENTS WITH DIFFERENT DEGREES of CLINICAL PENETRANCE

POSTER DISCUSSION 03: IMMUNE DYSREGULATION

Marcelo Teocchi[1], Janine Schincariol Sabino[1], Lia Furlaneto Marega[1], Marcus Vinícius Costa Pedroni[1], Dulcinéia Martins De Albuquerque[2], Fernando Ferreira Costa[2], Maria Marluce Dos Santos Vilela[1]
[1]University of Campinas, Center For Investigation In Pediatrics, Campinas, Brazil, [2]University of Campinas, Hematology And Hemotherapy Center, Campinas, Brazil

Background and Aims: Common variable immunodeficiency is mainly characterized by hypogammaglobulinemia, immunization failure, and infection susceptibility, although other important clinical manifestations may coexist.

Methods: Three patients manifesting different degrees of lymphoproliferation, hypogammaglobulinemia and autoimmunity – from very mild (P03), mild-to-moderate (P01), to severe (P02) – were identified through WES/PID-panel as carriers of the pathological p.C104R variant of TNFRSF13B (CD267). To clarify the pathophysiological mechanisms behind these manifestations, 12 out of 92 apoptosis-associated genes whose expression was previously quantified in patients were selected for statistical analyses, including IL10 and IL10RA. Additionally, viability and CD267 expression in CD19+ and CD19+CD27+ cells were assessed by flow cytometry.

Results: revealed a dysregulation in the apoptosis signaling pathways, inversely correlated with the degree of clinical manifestations. BCL2L1 ($P<0.0001$, for P01), BCL2L14 ($P<0.0001$, for P01; $P=0.0524$, for P03), FASLG ($P=0.0354$, for P03), IL10RA ($P=0.0078$, for P02), and TP53 ($P=0.0190$, for P01) were found to be significantly modified in patients compared to controls. For P02, the only patient to use sirolimus, the expression of 24 genes (27.59%) was altered after its intake. Except for P02, patients' CD19+CD27+ cells were not diminished, but their CD267 expression, as well as the apoptotic rate, was accompanied by an increased number of viable cells.

Conclusions: The ability of the organism to modulate the expression of apoptosis-associated genes might represent an important mechanism to counterbalance the deleterious consequences caused by the TNFRSF13B defect. Our findings indicate potential biomarkers and targets for a tailored therapy for these patients who, despite having the same disease, might be considered as unique entities.

Disclosure: No.

Keywords: cell death, primary antibody deficiencies, death domain receptors, penetrance, Inborn errors of immunity, rapamycin

PP017

AGE ASSOCIATED B-CELLS AS A PREDICTOR of RESPONSE TO BNT162B2 IN PEOPLE WITH INBORN ERRORS of IMMUNITY

POSTER DISCUSSION 04: T CELL & B CELL BIOLOGY

Emily Horner[1], Juan Carlos Yam-Puc[1], Pehuén Pereyra Gerber[2], Nonantzin Beristain Covarrubias[1], Robert Hughes[1], Rebecca Boston[1], Katrin Fischer[3], Harry Robson[1], Lakmini Kahanawita[1], Magda Ali[1], Martin O'Reilly[1], Sara Lear[4], Nicholas Matheson[2], Christine Parkinson[5], James Thaventhiran[1]
[1]University of Cambridge, Mrc Toxicology Unit, QR, United Kingdom, [2]University of Cambridge, Department of Medicine, Cambridge, United Kingdom, [3]University of Cambridge, Department of Biochemistry, Cambridge, United Kingdom, [4]Cambridge University NHS Hospitals Foundation Trust, Immunology, Cambridge, United Kingdom, [5]Cambridge University Hospitals NHS Foundation Trust, Oncology, QQ, United Kingdom

Background and Aims: Age associated B cells (ABCs) are a subset of B cells associated with dysfunctional immune responses. People with inborn errors of immunity (IEI) can have elevated levels of ABCs in addition to the genetic mutations impacting their adaptive immune responses. Those with IEI are at risk of persistent SARS-CoV-2 infection and onward transmission of viral mutants. Therefore, the response of those with IEI to vaccination against SARS-CoV-2 is of interest to public and individual health.

Methods: The response to BNT162b2 vaccination of 10 healthy controls, 10 individuals with IEI, and 20 people on immune checkpoint blockade (ICB) therapy was longitudinally assessed. We used live virus neutralisation, a Luminex bead immunoassay, and flow cytometry with a specific tetramer, to assess adaptive responses. Flow cytometry and single cell sequencing were used to assess the phenotype of B cells from the peripheral blood at multiple timepoints before and after vaccination.

Results: Response to vaccination was heterogenous across participants with IEI. Pre-vaccination levels of ABCs negatively correlated with neutralisation and specific B cell response. Moreover, the ABCs of people with IEI were phenotypically similar to those in healthy controls, people on ICB therapy, and an external lupus cohort.

Conclusions: Levels of ABCs in the peripheral blood predict the ability of an individual to respond to an immune challenge. High levels of ABCs may contribute to the poor response to vaccination in some individuals with IEI. This is likely to be in mechanistically the same way as in other non IEI individuals with high levels of ABCs.

Disclosure: No.

Keywords: Inborn errors of immunity, SARS-CoV-2, Age Associated B cells, B cells, Vaccination, Neutralisation

PP018

LCK GAIN of FUNCTION VARIANT IN TWO SIBLINGS WITH SEVERE CD8 T CELL LYMPHOPENIA

POSTER DISCUSSION 04: T CELL & B CELL BIOLOGY

Mathieu Fusaro[1], Mathieu Simonin[2], Benjamin Fournier[2,3], Capucine Picard[2,3,4], Benedicte Neven[2,3], Sylvain Latour[2]
[1]Toulouse Institute for Infectious and Inflammatory Diseases (INFINITy), Inserm U1291, Toulouse, France, [2]Necker Children's Hospital, Assistance Publique-Hôpitaux de Paris, Université De Paris, Institut Imagine Institut Des Maladies Genetiques, Paris, France, [3]Necker Hospital for Sick Children, Pediatric Immunology, Hematology And Rheumatology Unit, Paris, France, [4]APHP, Study Center For Primary Immunodeficiencies, Paris, France

Background and Aims: T cell receptor (TCR) signaling is mandatory for T cell development, activation and function. The lymphocyte-specific protein tyrosine kinase (LCK) is crucial for initiation and propagation of proximal TCR signaling. We studied two siblings with profound but asymptomatic CD8 lymphopenia carrying a heterozygous inframe deletion removing the F498 in LCK (LCK F498del).

Methods: We evaluated the genetic and functional impact of the LCK F498del allele on primary T cells and Jcam1.6 cell line (LCK-deficient Jurkat cells).

Results: Parents were healthy and wild-type leading to the hypothesis of a germinal mosaicism. The deletion is located in the C-terminal tail which is important for the closed inactive conformation. Both patients had low TCR excision circles at birth with severe T CD8 lymphopenia and nearly absent MAIT cells. A moderate T CD4 lymphopenia and a progressive decrease of naïve T cells was evidenced in the elder brother. Interestingly, CD4 and CD8 co-receptors expression were decreased, a feature also present in the only patient reported with a complete LCK deficiency. Evaluation of proliferation shows no clear defect. However, we observed a decreased reactivation induced cell death, increased phosphorylation signals and an abnormal Ca^{2+} mobilization upon weak TCR engagement. Increased Ca^{2+} mobilization was confirmed in Jcam1.6 cells transfected with LCK F498del.

Conclusions: Therefore, these data suggest that the LCK F498del behaves as a gain-of-function variant in two apparently healthy children. This variant seems to lower the threshold for activation. The central or peripheral origin of the CD8 lymphopenia remains to be determined, as well as the gain-of-function mechanism.

Disclosure: No.

Keywords: primary immunodeficiency, Lck, gain-of-function, lymphopenia, TCR signaling

PP019

CHARACTERIZING AND UNRAVELLING THE VARIABLE SPECTRUM of IMMUNOGLOBULIN DEFICIENCY IN ATAXIA TELANGIECTASIA

POSTER DISCUSSION 04: T CELL & B CELL BIOLOGY

Sanami Takada[1], Thomas Weitering[1], Nienke Van Os[2], Ingrid Pico-Knijnenburg[1], Likun Du[3], Qiang Pan-Hammarström[3], Corry Weemaes[4], Michel Willemsen[2], Mirjam Van Der Burg[1]
[1]Willem-Alexander Children's Hospital Leiden University Medical Center (LUMC), Laboratory For Pediatric Immunology, Leiden, Netherlands, [2]Radboud UMC, Department of Neurology, Nijmegen, Netherlands, [3]Karolinska Institutet, Bionut, Huddinge, Sweden, [4]Radboud UMC, Department of Pediatrics, Nijmegen, Netherlands

Background and Aims: Ataxia Telangiectasia (AT) is a rare inherited disorder characterized by cerebellar ataxia, telangiectasia, immunodeficiency, and cancer susceptibility, caused by mutations in the ataxia telangiectasia mutated (ATM) gene. The immunodeficiency comprises predominantly immunoglobulin (Ig)-deficiency, mainly IgA and IgG2, with a variable spectrum of severe early-onset disease, classical AT, to mild adult-onset disease, variant AT. The exact mechanisms of the Ig-deficiency remain unelucidated.

Methods: We analyzed long-term Ig-levels, immunophenotyping, and survival time in our cohort (n=45/86). Somatic hypermutation (SHM) and class-switch junctions in B-cells were analyzed by next-generation sequencing. Furthermore, an in vitro class-switching induction assay was performed followed by RNAseq, to assess the effect of ATM-inhibition.

Results: The Ig-levels showed predominantly decreased IgG2 and IgA. Moreover, flowcytometric analysis demonstrated reduced naïve B- and T-lymphocytes and a deficiency of class-switched IgG2 and IgA memory B-cells. Only the hyper-IgM AT phenotype significantly worsened survival time, while IgA or IgG2-deficiencies did not. SHM frequencies were lowered in IgA and IgG2-deficient patients, indicating a hampered germinal center reaction. In addition, the microhomology of switch junctions was elongated, suggesting alternative end-joining during class-switch DNA-repair. The in vitro class-switching of naïve B-cells was negatively affected by ATM-inhibition. RNA-seq analysis showed that the ATM-inhibitor influenced expression levels of germinal center reaction genes.

Conclusions: Ig-deficiency in AT is caused by disturbed development of class-switched memory B-cells. Our data suggests that ATM-deficiency affects both the germinal center reaction and the choice of DNA-repair pathway in class-switch recombination. These findings greatly contribute to the understanding of the mechanism behind the Ig-deficiency in AT.

Disclosure: No.

Keywords: Ataxia Telangiectasia, ATM, immunoglobulin deficiency, class-switching, Germinal Center, DNA repair

PP020

PERSISTENT HYPOGAMMAGLOBULINEMIA AFTER RECEIVING RITUXIMAB POST-HSCT IS NOT CAUSED BY AN INTRINSIC B-CELL DEFECT

POSTER DISCUSSION 04: T CELL & B CELL BIOLOGY

Lisa Ott De Bruin[1], Ingrid Pico-Knijnenburg[1], Monique Van Ostaijen-Ten Dam[1], Thomas Weitering[1], Dagmar Berghuis[2], Arjan Lankester[2], Mirjam Van Der Burg[1]
[1]Leiden University Medical Center, Willem-alexander Children's Hospital, Department of Pediatrics, Laboratory For Pediatric Immunology, Leiden, Netherlands, [2]Leiden University Medical Center, Willem-alexander Children's Hospital, Department of Pediatrics, Pediatric Stem Cell Transplantation Program, Leiden, Netherlands

Background and Aims: Rituximab (RTX) is used after hematopoietic stem cell transplantation (HSCT) for (pre-emptive) treatment of EBV-associated post-transplantation lymphoproliferative disease or autoimmune phenomena such as autoimmune hemolytic anemia (AIHA). Persistent hypogammaglobulinemia has been observed in several patients despite normalization of B-cell levels. We aimed to study whether this is a B-cell intrinsic problem.

Methods: The LUMC-WAKZ has a database and biobank with samples of all HSCT-treated patients. Four patients with hypogammaglobulinemia a year after receiving their last dose of RTX were selected. They all received RTX to treat EBV infection or AIHA. All patients showed normal B-cell counts, but absent to low IgG positive memory B-cells. Three had absent IgA positive memory B-cells. All patients had full donor chimerism and no graft-versus-host disease. Naïve B-cells were sorted from mononuclear cells of patients and healthy controls and cultured and stimulated with CD40L, IL21, IL10 and anti-IgM to induce class switch recombination and immunoglobulin production. Switched memory B-cells were measured by flow cytometry and immunoglobulin levels by ELISA. Flow cytometry was used to analyze T cell subsets.

Results: Upon in vitro stimulation of naïve B-cells of patients and healthy controls, differentiation into switched memory B-cells was successfully induced. Secreted IgA and IgG was detected. Peripheral follicular T helper cell counts were within the normal range and comparable to age matched controls.

Conclusions: For these four post-HSCT patients, persistent hypogammaglobulinemia after RTX cannot be attributed to an intrinsic B-cell problem nor can it be explained by a reduced peripheral follicular T helper cell count.

Disclosure: No.

Keywords: hypogammaglobulinemia, RITUXIMAB, Class switch defect, B cell, SCT, IVIG

PP021

RESTORATION of FOLLICULAR T CELLS IN PATIENTS WITH WISKOTT-ALDRICH SYNDROME AFTER GENE THERAPY

POSTER DISCUSSION 04: T CELL & B CELL BIOLOGY

Maria Pia Cicalese[1,2,3], Matteo Filippini[4], Biagio Di Lorenzo[4], Cristiana Trimarchi[4], Tatiana Jofra[4], Federico Fraschetta[5], Alessandro Aiuti[2], Georgia Fousteri[4]
[1]Vita-Salute San Raffaele University, ., Milano, Italy, [2]IRCCS San Raffaele Scientific Institute, San Raffaele Telethon Institute For Gene Therapy (sr-tiget), Milano, Italy, [3]IRCCS San Raffaele Scientific Institute, Pediatric Immunohematology And Bone Marrow Transplantation Unit, Milano, Italy, [4]IRCCS San Raffaele Scientific Institute, Milan, Italy, Division of Immunology Transplantation And Infectious Diseases (ditid), Diabetes Research Institute (dri), Milan, Italy, [5]IRCCS San Raffaele Scientific Institute, San Raffaele Telethon Institute For Gene Therapy (sr-tiget), Milan, Italy

Background and Aims: Wiskott-Aldrich syndrome (WAS) is a rare X-linked primary immunodeficiency caused by mutations in the WAS gene, with increased risk of autoimmunity (AI) and lymphomas. Gene therapy (GT) represents a potential alternative to allogeneic hematopoietic stem cell transplantation (HSCT). We hypothesize that AI in WAS is determined by alterations in the quantity/quality of germinal centre (GC) responses, controlled by CD4+ T cells known as follicular helper (Tfh) and follicular regulatory T (Tfr) cells. We evaluated Tfh and Tfr cell number, phenotype, ratio and functions in patients before and after GT, and CXCL13 plasma levels.

Methods: Tfh and Tfr number, phenotype, and functional properties and CXCL13 plasma levels were determined, by flow cytometry and ELISA, in 12 WAS pre-GT and 23 WAS post-GT patients.

Results: The data show lower levels of Tfh cells (CD4+CXCR5+), their subpopulations and Tfr cells (CXCR5+FOXP3+) in WAS patients compared to healthy donors (HD). The levels of these cells, especially the Tfr population, return to normal values after year 5 from GT. Patients with a low Zhu score showed fewer alterations in Tfh cells. Surface receptors PD-1 and ICOS showed a significant decrease after GT resulting in normal values. Interestingly, WAS patients showed elevated levels of plasma CXCL13 compared to HD, decreasing after 5 years from GT.

Conclusions: GT could restore some of the defects observed in the Tfh and Tfr cells, including values of PD-1 and ICOS, and decrease CXCL13 plasma levels of WAS patients, contributing to the recovery of the humoral responses.

Disclosure: M.P. Cicalese is one of the Investigators of WAS Gene Therapy Clinical Trials sponsored by Orchard Therapeutics.

Keywords: Germinal centre, Wiskott-Aldrich Syndrome, Autoimmunity, T follicular helper cells, T follicular regulatory cells, gene therapy

PP022

OVERACTIVE WASP IN X-LINKED NEUTROPENIA LEADS TO ABERRANT B CELL DIVISION WITH DECREASED IG SWITCHING AND ACCELERATED PLASMA CELL GENERATION

POSTER DISCUSSION 04: T CELL & B CELL BIOLOGY

Minghui He, Lisa Westerberg
Karolinka Institutet, Microbiology, Tumor And Cell Biology, Solna, Sweden

Background and Aims: B cell affinity maturation takes place in germinal center (GC) and is an important feature of all vaccination approaches to obtain production of high affinity antibodies. The GC response depends on B cell migration, cell-to-cell interaction and gene editing that are coordinated by actin dynamics. Mutations that lead to loss-of-function of actin regulator WASp in B cells result in reduced marginal zone B cells and spontaneous germinal center formation associated with breakdown of self-tolerance. Activating mutations in WASp has been recently found to cause X-linked neutropenia (XLN), however, the role of B cells in XLN pathogenesis remains poorly defined.

Methods: We examined B cells from six XLN patients of which two have de novo R286W and S271F mutations in WASp, and analyzed XLN mouse models that carry the corresponding patient mutations WASp L272P or WASp I296T.

Results: XLN patients had normal naïve B cells and plasmablasts, but reduced IgA^+ B cells and memory B cells, and poor B cell proliferation. Upon immunization, XLN mice had a 2-fold reduction in germinal center B cells in spleen, however, increased generation of plasmablasts and plasma cells. In vitro, XLN B cells showed reduced Ig class switching and aberrant cell division, but had increased production of Ig switched plasma cells.

Conclusions: These results show that overactive WASp predisposes for pre-mature differentiation into plasma cells at the expense of cell proliferation and Ig class switching.

Disclosure: No.

Keyword: XLN, WASp, Germinal center, B cell, Ig switching, primary immunodeficiency

PP023

SERUM BIOMARKERS AND DNT PHENOTYPING CAN PREDICT COMPLEX FAS GENE ALTERATIONS IN ALPS-U PATIENTS

POSTER DISCUSSION 05: NEXT GENERATION SEQUENCING AND OTHER DIAGNOSTICS

Anne Rensing-Ehl[1], Myriam Lorenz[2], Marita Fuehrer[2], Wolfgang Willenbacher[3], Ella Willenbacher[3], Mario Abinun[4], Maria Elena Maccari[5], Christoph König[1], Pauline Haegele[1], Sebastian Fuchs[1], Carla Castro[1], Patrick Kury[1], Christian Klemann[6], Maximilian Heeg[1], Julian Thalhammer[1], Oliver Wegehaupt[1], Marco Fischer[1], Sarah Salou[1], Sigune Goldacker[1], Saskia Biskup[7], Philippe Chatelain[7], Volker Schuster[8], Klaus Warnatz[1], Bodo Grimbacher[1], Andrea Meinhardt[9], Fabian Hauck[10], Dirk Holzinger[11], Prasad Oommen[12], Holger Hebart[13], Karlheinz Seeger[14], Karina Butler[15], Timothy Ronan Leahy[16], Kai Lehmberg[17], Ilka Fuchs[1], Miriam Gross[1], Carsten Speckmann[1], Frédéric Rieux-Laucat[18], Aude Magerus[19], Klaus Schwarz[20], Stephan Ehl[1]
[1]University Freiburg, Center For Chronic Immunodeficiency, Freiburg, Germany, [2]University Ulm, Institute For Transfusion Medicine, Ulm, Germany, [3]Innsbruck University Hospital,, Internal Medicine V: Hemarology & Oncology, Innsbruck, Austria, [4]Newcastle University, Paediatric Immunology, Newcastle, United Kingdom, [5]University of Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency, Medical Center, Freiburg, Germany, [6]Hannover Medical School, Department of Pediatric Pulmonology, Allergy And Neonatology, Hannover, Germany, [7]Center for Human Genetics, Genetics, Tuebingen, Germany, [8]University of Leipzig, Children´s Hospital, Leipzig, Germany, [9]University Hospital Giessen, Department of Pediatric Hematology And Oncology, Giessen, Germany, [10]Dr. von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-Universität München, Department of Pediatrics, Munich, Germany, [11]University of Duisburg-Essen,, Department of Pediatric Hematology-oncology, Essen, Germany, [12]Heinrich Heine University Düsseldorf, Department of Pediatric Oncology, Hematology And Clinical Immunology,, Duesseldorf, Germany, [13]Stauferklinikum, Department of Internal Medicine, Mutlangen, Germany, [14]Charité Universitätsmedizin Berlin, Dept. of Ped. Oncology/hematology, Berlin, Germany, [15]Children's Health Ireland at Crumlin, Immunology, Dublin, Ireland, [16]Children's Health Ireland at Crumlin, Department of Paediatric Immunology And Infectious Diseases, Dublin, Ireland, [17]University Medical Center Eppendorf, Division of Pediatric Stem Cell Transplantation, Hamburg, Germany, [18]Imagine Institute, Immunogenetic of Pediatric Autoimmune Diseases, Paris, France, [19]Université Paris Cité, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases,, Paris, France, [20]Red Cross Blood Service Baden-Wuerttemberg-Hessen, Institute For Clinical Transfusion Medicine And Immunogenetics, Ulm, Germany

Background and Aims: Elevated double-negative T cells (DNT) and serum biomarkers have high diagnostic value for identifying FAS mutant patients with autoimmune lymphoproliferative syndrome (ALPS). However, in some patients with clinical features and biomarkers consistent with ALPS, germline or somatic FAS mutations cannot be found upon standard Sanger sequencing (ALPS-U). We hypothesized that complex genetic alterations in the FAS gene escaping standard sequencing could explain these cases.

Methods: Our analyses were guided by FAS expression analysis on CD57+ DNT and complemented by FAS cDNA analysis and FAS whole gene sequencing.

Results: Absent FAS expression can predict somatic loss-of-heterozygosity (sLOH), which was observed in 31/35 ALPS-FAS patients with extracellular or transmembrane mutations but only in 7/31 patients with intracellular mutations. Sixteen of 100 patients with elevated DNT and biomarkers did not show FAS mutations upon standard sequencing including DNA from sorted DNT. Ten of these patients lacked FAS expression on CD57+ DNT compatible with heterozygous “loss of expression” FAS mutations plus acquired somatic second hit in the FAS gene, enriched in DNT. Indeed, 6/9 analysed patients carried deep intronic mutations or large deletions in the FAS gene combined with sLOH detectable in DNT. Three patients had reduced FAS expression, two of which harbored mutations in the FAS promoter, reducing promoter-driven expression in reporter assays. Two patients with normal FAS expression on DNT carried FADD mutations.

Conclusions: A combination of serum biomarkers and DNT phenotyping is superior to conventional FAS sequencing in diagnosing ALPS-FAS. Most well defined ALPS-U patients carry FAS pathway mutations but require extended genetic analysis.

Disclosure: No.

Keywords: ALPS-FAS, ALPS-U, DNT, Biomarker

PP024

USE of EX VIVO T CELL DIFFERENTIATION ASSAYS IN THERAPEUTIC MANAGEMENT of GENETICALLY UNDEFINED T-B+NK+ SEVERE COMBINED IMMUNODEFICIENCY (SCID)

POSTER DISCUSSION 05: NEXT GENERATION SEQUENCING AND OTHER DIAGNOSTICS

Zainab Golwala[1], Alexandra Kreins[2], Joris Van Montfrans[3], Fanette Bernard[4], Antonio Marzollo[5], Evey Howley[1], Irene Obiri-Yeboa[1], Sabrina Lizot[6], Coco Koning[3], Matthew Buckland[1], Austen Worth[7], Stefan Nierkens[8], Isabelle Andre[9], Graham Davies[2]
[1]Great Ormond Street Hospital for Children, Immunology, London, United Kingdom, [2]Great Ormond Street Hospital, Immunology, London, United Kingdom, [3]Wilhelmina's Children Hospital, Department of Pediatric Immunology And Infectious Diseases, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [4]Geneva University Hospital, Paediatric Onco Haematology, Geneva, Switzerland, [5]Univerita degli Studi di Padova, Paediatrics, Padova, Italy, [6]Cellectis, Gene Therapy, Paris, France, [7]Great Ormond Street Hospital, Department of Immunology And Gene Therapy, London, United Kingdom, [8]Princess Maxima Centre for Paediatric Oncology, Department of Pediatric Immunology And Infectious Diseases, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [9]Toulouse Biotechnology Institute, Biotechnology, Toulouse, France

Background and Aims: Unlike other immune cells derived from hematopoietic stem cells (HSC), T-cells require maturation in the thymus. For SCID cases with isolated T-cell deficiency (T-B+NK+), it is critical to determine whether there is an intrinsic defect in hematopoietic or in thymic stromal cells to facilitate appropriate treatment with either HSC-transplantation (HSCT) or thymus-transplantation (TT). In-vitro T-cell differentiation assays have been proposed to assist clinical decision making for genetically undefined cases[1,2]. We report the use of such assays in 5 patients with undefined T-B+NK+ SCID who were referred for consideration for TT.

Methods: No 22q11.2 microdeletions nor mutations in any of the known SCID genes found in CGH arrays and clinical exomes. Therapeutic decision was based on T-cell differentiation results, clinical history +/- trio whole-genome-sequencing (WGS).

Results: All patients showed intrinsic potential for differentiation into mature T-cells on In-vitro T-cell differentiation assays. 3/5 patients had syndromic features (2 with DiGeorge Syndrome features) of which one had failure of naïve T-cell development post-HSCT. Three patients underwent TT, 2 have ongoing thymopoiesis, one died due to CMV infection prior to achieving thymopoiesis. 2/5 patients did not have syndromic features, one of these, who is post-HSCT, is still under consideration for TT whilst in the second, WGS identified a novel T-cell signalling defect and she has early immune reconstitution after HSCT.

Conclusions: Ex vivo T-cell differentiation assays can assist with therapeutic decision making in undefined T-B+NK+ SCID, but critically alongside clinical features and genetic analysis. Ref: 1.Bosticardo et al 2020; 2.Bifsha et al 2020; 3.Six et al 2011

Disclosure: No.

Keywords: thymus transplant, HSCT, SCID, T cell maturation, syndromic, thymopoiesis

PP025

GENE REGULATORY MODULES DEFINING HUMAN THYMIC REGULATORY T CELLS HELP DECIPHERING THE CONTRIBUTION of MULTIPLE VARIANTS TO PIDS

POSTER DISCUSSION 05: NEXT GENERATION SEQUENCING AND OTHER DIAGNOSTICS

Alexandre Raposo, Pedro Rosmaninho, Susana Paço, Afonso Almeida, Adriana Raymundo, Susana Silva, Ana E. Sousa
Faculdade de Medicina, Universidade of Lisboa, Instituto De Medicina Molecular João Lobo Antunes, Lisboa, Portugal

Background and Aims: Whilst most PIDs studies focus on the discovery and characterisation of new monogenic variants, the complexity and diversity of PIDs remains poorly understood. Nonetheless, recent multi-omics data revealed the contribution of single-nucleotide variants in the non-coding genome to PID variety and severity. CD4 T cells are the organisers of immune responses, with the large majority of immune-mediated diseases being associated with their disruption. CD4 T cells are committed in the thymus to at least two lineages, conventional and regulatory (Treg). We focus primarily on thymic Tregs to understand PID aetiology given their intrinsic ability to control of self-reactivity and inflammation.

Methods: Here we generated bulk RNA-seq transcriptomes and chromatin accessibility data (ATAC-seq) of both CD4 lineages from human thymuses. We quantified genome-wide transcription factor binding to respective differentially expressed genes and used this to determine the Gene Regulatory Modules (GRMs) controlling Treg identity.

Results: The transcriptional networks of direct interaction so defined allowed us to identify 2 clusters of transcription factors, the AP-1 complex and the KLF family, targeting 3 clusters of genes up-regulated in Tregs. The potential breadth of this strategy is illustrated by the identification of PID-associated targets in each of the GRMs, namely: 1) RELB, IL10RA, LYST, MAP3K14, TNFAIP3, TTC7A, G6PC3, NFKBIA; 2) TFRC, REL, NFKB2; and 3) CTLA4, STX11, which are targeted by AP-1, including BACH2, also a PID-related.

Conclusions: We suggest that the Treg GRMs are a useful tool to infer the clinical relevance of multiple variants in PIDs and to establish precise patient stratification and targeted therapies.

Disclosure: No.

Keywords: Human Thymus, Regulatory T cells, Human Multiomics, Transcriptional Networks, Inborn errors of immunity, Systems Immunology

PP026

SP110 EXPRESSION ANALYSIS FACILITATES THE DETECTION of HUMAN PATIENTS WITH TYPE I INTERFERON SIGNATURES

POSTER DISCUSSION 05: NEXT GENERATION SEQUENCING AND OTHER DIAGNOSTICS

Domenique Tschopp, Robin Hupfer, Oluwatobi Fashola, Mike Recher
University Hospital Basel, Outpatient Clinics Immunology, Basel, Switzerland

Background and Aims: The Speckled Protein 110 (SP110) encodes a PML nuclear body protein with yet to be determined cellular functions. Genetically determined loss of SP110 expression causes a highly lethal combined immunodeficiency and liver failure (veno-occlusive disease with immunodeficiency, VODI).

Methods: SP110 mRNA expression was analyzed in peripheral blood of 57 healthy controls or 80 patients with immune-dysregulation by real-time PCR together with known interferon-stimulated genes (MX1, IFIT1, ISG15, SIGLEC1, RSAD2, IFI44). Patients with defined interferonopathy due to SAMHD1 mutation served as positive controls. SP110 protein expression with and without interferon alpha stimulation was measured in SP110 competent vs. deficient Jurkat T cells and PBMC derived T cells.

Results: SP110 expression increased on mRNA and protein level following interferon alpha stimulation identifying it as an interferon stimulated gene (ISG). SP110 mRNA expression was significantly elevated in patients with immune dysregulation compared to healthy controls. When compared to established ISG's SP110 outcompeted MX1, IFIT1 and IFI44 in its ability to identify type I interferon signatures in patients with immune-dysregulation.

Conclusions: Our work establishes SP110 as an easy to measure biomarker of type I interferon signatures in vivo and suggests to implement it in future interferon signature panel analysis.

Disclosure: No.

Keywords: SP110, ISGs, primary immunodeficiency, Interferon score

PP027

SPLICING DEFECT DUE TO A SYNONYMOUS MUTATION IN DOCK2 CAUSING DOCK2 DEFICIENCY

POSTER DISCUSSION 05: NEXT GENERATION SEQUENCING AND OTHER DIAGNOSTICS

Karin Engelhardt[1], Helen Griffin[1], Angela Grainger[1], Joseph Willet[1], Mary Slatter[1,2], Zohreh Nademi[1,2], Andrew Gennery[1,2], Andrew Cant[1,2], Sophie Hambleton[1,2]
[1]Newcastle University, Translational & Clinical Research Institute, Immunity & Inflammation Theme, Newcastle Upon Tyne, United Kingdom, [2]Great North Children's Hospital, Newcastle upon Tyne Hospital NHS Foundation Trust, Children's Haematopoietic Stem Cell Transplant Unit, Newcastle upon Tyne, United Kingdom

Background and Aims: We aimed to obtain a molecular diagnosis for a patient with combined immunodeficiency presenting as severe diarrhoea, marked failure to thrive, CMV viraemia, colitis, rash, reduced T-cell proliferation and profoundly reduced naïve T cells.

Methods: After whole exome and whole genome sequencing failed to reveal a deleterious variant in a known or novel primary immunodeficiency gene, we employed the prediction programme SpliceAI to screen for variants with potential splicing defects.

Results: The homozygous variant c.1818G>A, p.V606= in DOCK2, which we initially dismissed due to its synonymous nature, caught our interest as it had a SpliceAI score of 0.86 for a splice donor gain, a MutationTaster prediction of being disease-causing and a CADD score >10. We reasoned that DOCK2 deficiency caused by aberrant splicing would be a good explanation for our patient's phenotype. We performed cDNA sequencing with RNA extracted from patient's dermal fibroblasts, and found the last 28 bp of exon 18, including the mutated nucleotide, to be missing, resulting in a frameshift and premature stop codon (p.V606Wfs*6). Western Blotting with patient's peripheral blood mononuclear cell lysate showed absence of protein expression, confirming a diagnosis of DOCK2 deficiency.

Conclusions: SpliceAI correctly predicted the presence of a cryptic exonic splice donor site due to the c.1818G>A change in DOCK2. Instead of being silent, this variant causes aberrant splicing leading to absent protein expression. c.1818G>A is thus a novel pathogenic mutation causing DOCK2 deficiency. Our experience emphasises the importance of considering the potential pathogenicity of rare synonymous variants in genes linked to monogenic disease.

Disclosure: No.

Keyword: synonymous mutation, cryptic splice site, SpliceAI, DOCK2 deficiency

PP028

SIGNIFICANT MUTATION-SPECIFIC VARIATION IN DISEASE SEVERITY AND OUTCOME FOR PATIENTS WITH STAT1 GOF MUTATIONS

POSTER DISCUSSION 05: NEXT GENERATION SEQUENCING AND OTHER DIAGNOSTICS

Alexander Mckenna[1], Joe Mcdowell[1], Eleanor O'Callaghan[1], Jesmeen Maimaris[1], Adriana Albuquerque[2], Emma Morris[3], Siobhan Burns[3,4]
[1]University College London, Institute of Immunity And Transplantation, London, United Kingdom, [2]Institute of Immunity and Transplantation, University College London, Ucl Division of Infection And Immunity, London, United Kingdom, [3]University College London, Division of Infection And Immunity, London, United Kingdom, [4]UCL, Institute of Immunity And Transplantation, London, United Kingdom

Background and Aims: Germline, monoallelic, gain-of-function (GOF) mutations in STAT1 cause an ultra-rare form of primary immunodeficiency through overactivation of the Janus-associated kinase STAT1 signalling pathway. The extremely variable clinical phenotype remains unexplained but may result from the effects of individual mutations. A detailed clinical analysis of patients with STAT1 GOF mutations was previously reported in 2016[1], but many publications since have described the clinical information of one or a small number of patients.

Methods: We conducted a systematic review of all publications describing clinical information regarding STAT1 GOF patients since Toubiana et al reported their findings. This data was collated with the original cohort and clinical data from our cohort of unreported patients in London, resulting in a database totaling 429 patients.

Results: We identified that patients harbouring a T385M mutation, the fourth most common STAT1 GOF mutation, have a 4.29x greater risk of mycobacterial infections, a 2.8x greater risk of bronchiectasis and a 2.2x greater risk of mortality in comparison to 390 patients with other GOF mutations in STAT1. Furthermore, we show that mutations located directly at the interface of a STAT1 dimer are more severe than those not, regardless of which domain they reside in. In contrast, patients with the second most common STAT1 GOF mutation, R274Q, are less likely to experience viral infections, thyroid dysfunction, bronchiectasis, and death in comparison to all other patients with STAT1 GOF mutations.

Conclusions: We provide an updated analysis of the clinical outcome of patients with STAT1 GOF mutations which can inform patient counselling and management decisions.

Disclosure: No.

Keywords: STAT1, gain-of-function, primary immunodeficiency, clinical phenotype, patient management

PP029

TYPE I INTERFERON MEDIATED NEUROPATHOLOGY IN A MOUSE MODEL of STAT2 GAIN-OF-FUNCTION

POSTER DISCUSSION 06: INNATE IMMUNE DEFECTS

Benjamin Thompson[1], Matthew Drummond[1], Henrique De Paula Lemos[1], Rui Chen[1], Kate Smith-Jackson[1], Helen Griffin[1], Stefan Geyer[2], Tracy Briggs[3], Wolfgang Weninger[2], Timothy Mohun[4], Gavin Clowry[5], Lei Huang[1], David Kavanagh[1], David Adams[6], Andrew Mellor[1], Sophie Hambleton[7,8], Christopher Duncan[1,9]
[1]Newcastle University, Clinical And Translational Research Institute, Immunity And Inflammation Theme, Newcastle upon Tyne, United Kingdom, [2]Medical University of Vienna, Division of Anatomy & Mic, Vienna, Austria, [3]University of Manchester, Manchester Centre For Genomic Medicine, Manchester Academic Health Science Centre, Manchester, United Kingdom, [4]The Francis Crick Institute, Heart Development Laboratory, London, United Kingdom, [5]Newcastle University, Biosciences Institute, Newcastle upon Tyne, United Kingdom, [6]Wellcome Trust Sanger Institute, Experimental Cancer Genetics Group, Cambridge, United Kingdom, [7]Great North Children's Hospital, Paediatric Immunology, C/o Block 2, Level 4, Clinical Resources Building, Newcastle upon Tyne, United Kingdom, [8]Newcastle University, Translational & Clinical Research Institute, Immunity & Inflammation Theme, Newcastle Upon Tyne, United Kingdom, [9]The Newcastle upon Tyne Hospitals NHS Foundation Trust, Infection And Tropical Medicine, Newcastle upon Tyne, United Kingdom

Background and Aims: Type I interferonopathies are a group of monogenic disorders associated with excessive type I interferon (IFN-I) activity. A common feature is the development of neurological disease, manifest as intracranial calcification, developmental regression, motor signs and seizures. However, the cellular and molecular mechanisms underpinning these phenotypes are ill defined, in part due to a lack of suitable animal models that recapitulate neurological disease. We have recently described a severe, ultimately fatal human type I interferonopathy associated with a homozygous missense mutation in STAT2. Here we sought to investigate its neuropathogenesis by generating a new mouse model of STAT2 'gain-of-function'.

Methods: We created C57BL/6 embryos bearing a missense mutation of the murine Stat2 R147 residue using CRISPR/Cas9 gene editing and characterised disease phenotypes using high resolution episcopic microscopy, immunophenotyping, behavioural testing and histopathological and molecular analyses, including RNA-seq.

Results: On a C57BL/6 background R147W in homozygosity was associated with embryonic lethality that was rescued by Ifnar1-/- intercross. C57BL/6.Sv129 homozygotes developed early onset neurological disease characterised by reduced locomotion, gait instability and seizures and accompanied by molecular evidence of unrestrained IFN-I activity. Key neuropathological features included microgliosis alongside vascular abnormalities and reduced expression of the neuronal marker NeuN.

Conclusions: Here we report a unique mouse model of STAT2-associated type I interferonopathy that recapitulates key aspects of the human neurological disease phenotype, highlighting the brain’s vulnerability to excessive IFN-I activity and delivering a tractable model suitable for interrogating pathomechanism and testing new therapies.

Disclosure: No.

Keywords: Type I interferonopathy, In vivo model, Neuroinflammation, Microglial activation, JAK-STAT signalling, Immunoregulation

PP030

HETEROZYGOUS DELETERIOUS MUTATION of CHUK IN A PATIENT WITH IMMUNODEFICIENCY, AUTOIMMUNITY AND LYMPHOMA

POSTER DISCUSSION 06: INNATE IMMUNE DEFECTS

Quentin Riller[1], Boris Sorin[1], Charline Courteille[1], Olivier Pellé[1], Marie-Claude Stolzenberg[1], Thomas Becquard[2], Maria Rodrigo Riestra[1], Cécile Boulanger[3], Isabelle Meyts[4], Alain Fischer[5], Veronique Baud[2], Benedicte Neven[1], Frédéric Rieux-Laucat[1]
[1]Imagine Institute, INSERM UMR1163, Immunogenetic of Pediatric Autoimmune Diseases, Paris, France, [2]INSERM, Nf-kappab, Differentiation And Cancer, Paris, France, [3]Cliniques universitaires Saint-Luc, Department of Pediatric Hemato-oncology, Bruxelles, Belgium, [4]KU Leuven, Laboratory Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [5]Imagine Institute, Collège De France, Paris, France

Background and Aims: IKKα plays a central role in the activation process of the non-canonical NF-κB pathway. We studied a patient with hypogammaglobulinemia, recurrent lung infections, alopecia totalis, ankyloblepharon, dysmorphia, coeliac disease, central hypogonadism who died from a diffuse large B-cell lymphoma. A predicted deleterious, de novo and private missense variant (p.H142R) of CHUK (encoding IKKα), affecting the catalytic domain, was found by whole-exome sequencing analysis. This study aims at deciphering the impact of this mutation and its role in the clinical phenotype of the patient.

Methods: To study the impact of the mutation on the production, stability and function of the protein we transiently transfected HEK293T with plasmids encoding IKKα. Canonical and non-canonical NF-κB activation was also assessed in patient's cells by western blot, RTqPCR and EMSA.

Results: The mutation led to the production of a partially degraded, hypomorphic IKKα protein. Non-canonical NF-κB activation was severely impaired, as assessed by the cleavage of p100 to p52, RELB binding to DNA by EMSA, and fold-increase of VCAM1 mRNA, upon LTα1β2 stimulation. In contrast, phosphorylation of p65 and degradation of IkBα were unaffected. Ectopic expression of the variant confirmed that it was unable to induce P100 phosphorylation.

Conclusions: This study described the first patient with a deleterious heterozygous CHUK mutation leading to a profound defect in the non-canonical NF-κB pathway, probably accounting for the B-cell defect, without any impact on the canonical NF-κB pathway. It remains to be determined if this variant act in a dominant negative manner and how it can lead to lymphoma and autoimmunity.

Disclosure: No.

Keyword: CHUK, IKKA, hypogammaglobulinemia, auto-immunity, lymphoma

PP031

DETRIMENTAL NFKB1 MISSENSE VARIANTS AFFECTING THE REL-HOMOLOGY DOMAIN of P105/P50

POSTER DISCUSSION 06: INNATE IMMUNE DEFECTS

Manfred Fliegauf[1,2], Matias Kinnunen[3], Sara Posadas-Cantera[1], Nadezhda Camacho-Ordonez[1,4], Hassan Abolhassani[5], Faranaz Atschekzei[6], Laia Alsina[7], Delfien Bogaert[8], Siobhan Burns[9], Joseph Church[10], Gregor Dückers[11], Alexandra Freeman[12], Lennart Hammarström[13], Leif G Hanitsch[14], Tessa Kerre[15], Robin Kobbe[16], Svetlana Sharapova[17], Kathrin Siepermann[11], Carsten Speckmann[1,18], Sophie Steiner[14], Nisha Verma[19], Jolan Walter[20,21,22], Emma Westermann-Clark[20], Sigune Goldacker[23], Klaus Warnatz[23], Markku Varjosalo[24], Bodo Grimbacher[1,2,25,26]

[1]Medical Center, University of Freiburg, Germany, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [2]University of Freiburg, Cibss - Centre For Integrative Biological Signalling Studies, Freiburg, Germany, [3]University of Helsinki, Institute of Biotechnology, Helsinki, Finland, [4]University of Freiburg, Faculty of Biology, Freiburg, Germany, [5]Karolinska Institute, Division of Clinical Immunology, Department of Biosciences And Nutrition, Stockholm, Sweden, [6]Hannover Medical School, Rheumatology/immunology, Hannover, Germany, [7]Hospital Sant Joan de Déu, Allergy And Clinical Immunology Department, Esplugues del Llobregat, Spain, [8]Ghent University Hospital, Primary Immunodeficiency Research Lab, Center For Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis And Research Center, Ghent, Belgium, [9]UCL, Institute of Immunity And Transplantation, London, United Kingdom, [10]University of Southern California and Children's Hospital Los Angeles, Department of Pediatrics, Keck School of Medicine, Los Angeles, United States of America, [11]HELIOS Children's Hospital, Helios Klinik, Krefeld, Germany, [12]Laboratory of Clinical Immunology and Microbiology, National Institutes of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Laboratory of Clinical Immunology And Microbiology, Bethesda, United States of America, [13]Karolinska Institutet at Karolinska University Hospital, Division of Clinical Immunology And Transfusion Medicine, Department of Laboratory Medicine, Stockholm, Sweden, [14]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Institute of Medical Immunology, Berlin, Germany, [15]Ghent University Hospital, Department of Hematology, Ghent, Belgium, [16]University Medical Center Hamburg-Eppendorf, Department of Pediatrics, Hamburg, Germany, [17]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Research Department, Minsk, Belarus, [18]University of Freiburg, Division of Pediatric Hematology And Oncology, Department of Pediatrics And Adolescent Medicine, Medical Center - University of Freiburg, Faculty of Medicine, Freiburg, Germany, [19]Royal Free London NHS Foundation Trust, Department of Immunology, London, United Kingdom, [20]Morsani College of Medicine, University of South Florida, Division of Allergy And Immunology, Department of Pediatrics, Tampa, United States of America, [21]Johns Hopkins All Children's Hospital, St. Petersburg, Division of Allergy/immunology, Department of Pediatrics, St.Petersburg, United States of America, [22]Massachusetts General Hospital for Children, Division of Allergy And Immunology, Boston, United States of America, [23]Institute for Immunodeficiency, Center for Chronic Immunodeficiency (CCI), Faculty of Medicine, Medical Center - University of Freiburg, Department of Rheumatology And Clinical Immunology, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany, [24]University of Helsinki, Institute of Biotechnology; Helsinki Institute of Life Science; Proteomics Unit, Helsinki, Finland, [25]Satellite Center Freiburg, Resolving Infection Susceptibility (resist) - Cluster of Excellence 2155 To Hannover Medical School, Freiburg, Germany, [26]DZIF – German Center for Infection Research, Satellite Center Freiburg, Germany, Freiburg, Germany

Background and Aims: Most of the known heterozygous pathogenic NFKB1 variants comprise deleterious defects (severe truncations, internal deletions, and frameshifts) and these collectively represent the most frequent monogenetic cause of CVID. NFKB1 encodes the transcription factor precursor p105 which undergoes proteasomal processing to generate the mature p50. While p105/p50 haploinsufficiency due to protein loss is a well-known disease mechanism, the pathogenic significance of numerous NFKB1 missense variants still remains uncertain.

Methods: We functionally characterized 47 distinct missense variants residing within the N-terminal half of p105, thus affecting both, the p105 precursor and the mature p50. Following transient overexpression of EGFP-fused mutant p105 and p50 in HEK293T cells, we used fluorescence microscopy, Western blotting, EMSA, and reporter assays to analyze their effects on subcellular localization, protein stability and precursor processing, DNA binding, and on RelA-dependent target promoter activation, respectively.

Results: We found nine missense variants to cause detrimental defects with protein loss, while two variants left protein stability unaffected but caused loss of DNA-binding activity. Seven single amino acid substitutions gained variable effects and four variants showed only minor functional impairments. For 25 of the 47 variants, the results were undistinguishable from the wildtype controls, hence their pathogenic impact remained elusive.

Conclusions: Pathogenic missense variants affecting the Rel-homology domain may cause protein-decaying defects, resembling p105/p50 haploinsufficiency, or cause DNA-binding deficiency. However, we still consider variants with a population frequency of less than 0.01% and with minor abnormalities or with neutral tests as potentially pathogenic, until suitable methods become available to prove them being benign.

Disclosure: No.

Keywords: CVID, NF-kappaB, p105/p50 haploinsufficiency, NFKB1

PP032

LIFE-THREATENING VIRAL DISEASE IN A NOVEL FORM of AUTOSOMAL RECESSIVE IFNAR2 DEFICIENCY IN THE ARCTIC

POSTER DISCUSSION 06: INNATE IMMUNE DEFECTS

Christopher Duncan[1,2], Morten Skouboe[3,4], Sophie Howarth[2], Anne Hollensen[3,4], Rui Chen[2], Malene Børresen[5,6], Benjamin Thompson[2], Jarmila Stremenova Spegarova[2], Catherine Hatton[2], Frederik Stæger[7], Mette Andersen[8], John Whittaker[2], Søren Paludan[4], Sofie Jørgensen[3,4], Martin Thomsen[4], Jacob Mikkelsen[4], Carsten Heilmann[9,10], Daniela Buhas[11,12], Nina Øbro[13], Jakob Bay[13], Hanne Marquart[13], Maite Teresa De La Morena[14,15], Joseph Klejka[16], Matthew Hirschfeld[17], Line Borgwardt[18], Isabel Forss[18], Tania Masmas[5], Anja Poulsen[5], Francisco Noya[19], Guy Rouleau[20], Torben Hansen[8], Sirui Zhou[12], Anders Albrechtsen[7], Reza Alizadehfar[19], Eric Allenspach[12,21,22], Sophie Hambleton[2,23,24], Trine Mogensen[3,4]
[1]The Newcastle upon Tyne Hospitals NHS Foundation Trust, Infection And Tropical Medicine, Newcastle upon Tyne, United Kingdom, [2]Newcastle University, Clinical And Translational Research Institute, Immunity And Inflammation Theme, Newcastle upon Tyne, United Kingdom, [3]Aarhus University Hospital, Department of Infectious Diseases, Aarhus N, Denmark, [4]Aarhus University, Department of Biomedicine, Aarhus C, Denmark, [5]Copenhagen University Hospital Rigshospitalet, Department of Paediatrics And Adolescent Medicine, Copenhagen, Denmark, [6]Statens Serum Institut, Department of Epidemiology Research, Copenhagen, Denmark, [7]University of Copenhagen, Section For Computational And Rna Biology, Department of Biology, Copenhagen, Denmark, [8]University of Copenhagen, Novo Nordisk Foundation Center For Basic Metabolic Research, Faculty of Health And Medical Sciences, Copenhagen, Denmark, [9]Copenhagen University Hospital Rigshospitalet, Department of Paediatrics And Adolescent Medicine, København Ø, Denmark, [10]Dronning Ingrid Hospital, Medical Department, Pediatric Section, Nuuk, Greenland, [11]McGill University Health Centre, Division of Genetics, Department of Specialized Medicine, Montreal, Canada, [12]McGill University, Department of Human Genetics, Montreal, Canada, [13]Copenhagen University Hospital Rigshospitalet, Department of Clinical Immunology, Copenhagen, Denmark, [14]Seattle Children's Hospital, Immunology Clinic, Seattle, United States of America, [15]University of Washington, Department of Pediatrics, Seattle, United States of America, [16]Yukon-Kuskokwim Health Corporation, Corporate Medical Director, Bethel, United States of America, [17]Alaska Native Medical Center, Maternal Child Health, Anchorage, United States of America, [18]Copenhagen University Hospital Rigshospitalet, Center For Genomic Medicine, Copenhagen, Denmark, [19]McGill University, Division of Allergy & Clinical Immunology, Montreal Children's Hospital, Montreal General Hospital, Montreal, Canada, [20]McGill University, The Neuro, Department of Neurology And Neurosurgery, Montreal, Canada, [21]Seattle Children's Research Institute, Center For Immunity And Immunotherapies, Seattle, United States of America, [22]Brotman Baty Institute for Precision Medicine, Precision Medicine, Seattle, United States of America, [23]Great North Children's Hospital, Paediatric Immunology, C/o Block 2, Level 4, Clinical Resources Building, Newcastle upon Tyne, United Kingdom, [24]Great North Children's Hospital, Newcastle upon Tyne Hospital NHS Foundation Trust, Children's Haematopoietic Stem Cell Transplant Unit, Newcastle upon Tyne, United Kingdom

Background and Aims: In recent years, type I IFN (IFN-I) signaling deficiencies have been linked to severe viral disease, including herpes encephalitis and dissemination of live attenuated virus vaccines (LAV).

Methods: We investigated five children of Inuit and related Arctic ancestries in Greenland, Canada, and Alaska, presenting with severe viral illness: meningoencephalitis following measles-mumps-rubella (MMR) vaccination as well as severe COVID-19 and influenza. All were homozygous for a SNP in the interferon alpha/beta receptor 2 (IFNAR2 p.Ser53Pro, rs1987287426). Using flow cytometry and fluorescence microscopy, we investigated the intracellular localization of the variant protein. We stimulated patient cells with IFN-I and infected with pathogenic and LAV virus to examine IFNAR signaling. Lastly, we re-introduced the wild type IFNAR2 gene into patient cells, using lentiviral transduction.

Results: Although absent from reference databases, the IFNAR2 p.Ser53Pro variant was present in unpublished genome datasets of Greenlandic and Canadian Inuits at 2.4-3.4%. Patient leukocytes did not express the variant protein on the cell surface. Concordantly, IFN-I treatment failed to establish any antiviral response, resulting in high viral titers. Reconstitution of patient cells with wild type IFNAR2 restored IFN-I-dependent antiviral defense. Mechanistic studies revealed that the variant IFNAR2 protein was present in an aberrantly glycosylated form inside the cells, failing to translocate to the cell surface.

Conclusions: We propose this novel IFNAR2 p.Ser53Pro variant to underlie severe autosomal recessive immunodeficiency conferring susceptibility to severe disease after LAV vaccination, influenza, and COVID-19 . This may have public health implications in affected Arctic populations due to its prevalence there.

Disclosure: No.

Keywords: Influenza, glycosylation, ifnar2, interferon, MMR vaccination, COVID-19

PP033

RESPIRATORY VIRAL INFECTIONS IN OTHERWISE HEALTHY HUMANS WITH INHERITED IRF7 DEFICIENCY

POSTER DISCUSSION 06: INNATE IMMUNE DEFECTS

Tessa Campbell[1], Zhiyong Liu[2], Qian Zhang[2], Marcela Moncada-Velez[2], Laura Covill[1], Peng Zhang[2], Ilad Alavi Darazam[3], Peter Bergman[4], Laurent Abel[2], Aurélie Cobat[2], Jean-Laurent Casanova[2], Isabelle Meyts[5], Yenan Bryceson[1]
[1]Karolinska Institute, Center For Hematology And Regenerative Medicine, Stockholm, Sweden, [2]Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, New York, United States of America, [3]Shahid Beheshti University of Medical Sciences, Department of Infectious Diseases And Tropical Medicine, Tehran, Iran, [4]Karolinska Institutet, Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden., Huddinge, Sweden, [5]KU Leuven, Department of Immunology, Microbiology And Transplantation, Laboratory of Inborn Errors of Immunity, Leuven, Belgium

Background and Aims: Autosomal recessive IRF7 deficiency has been previously reported in three patients with single critical influenza or COVID-19 pneumonia episodes. We have discovered four new patients, and extensively investigated the genetic, immunological, and clinical features for all seven IRF7-deficient patients from six families and five ancestries.

Methods: We functionally interrogated the patient variants using HEK293T cells cotransfected with the IRF7 variants and a luciferase reporter under IFNB. We examined IRF7 protein expression in patient cells stimulated with interferon, and assessed the function of patient plasmacytoid dendritic cells (pDCs), which express high constitutive levels of IRF7.

Results: Five patients were homozygous and two were compound heterozygous for IRF7 variants, with all variants demonstrated to be loss of function. For three patients we demonstrated complete loss of protein expression in patient cells. Consequently, analysis of IRF7 function through TLR7 and TLR9 antagonism of patient pDCs failed to induce IFN-alpha. Patients typically had one episode of pulmonary viral disease. Age at onset was surprisingly broad, from six months to 50 years. The penetrance of viral pneumonia was variable, involving SARS-CoV-2, influenza virus, respiratory syncytial virus, and adenovirus. Serological analyses indicated previous infections with many common viruses, highlighting the specific susceptibility of IRF7 patients to severe respiratory viral infections. In support, cellular analyses revealed strong antiviral immunity and expanded populations of influenza– and SARS-CoV-2–specific memory $CD4^+$ and $CD8^+$ T cells.

Conclusions: IRF7-deficient individuals are prone to viral infections of the respiratory tract but are otherwise healthy, potentially due to residual IFN-beta expression and compensatory adaptive immunity.

Disclosure: No.

Keywords: interferon, Covid, Influenza, dendritic cell, IRF7

PP034

IDENTIFICATION of A COMPOUND HETEROZYGOUS MUTATION IN DUOX2 GENE IN A INFANT AFFECTED BY IBD

POSTER DISCUSSION 06: INNATE IMMUNE DEFECTS

Lucia Pacillo[1,2], Beatrice Rivalta[1,2], Giulia Angelino[3], Simona Faraci[3], Chiara Passarelli[4], Antonio Novelli[4], Gigliola Di Matteo[1,2], Maria Chiriaco[1], Paolo Rossi[1,5], Paolo Palma[1,6], Caterina Cancrini[1,2], Paola De Angelis[3], Andrea Finocchi[1,7]
[1]Tor Vergata University, Department of Systems Medicine, Rome, Italy, [2]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Research Unit of Primary Immunodeficiencies, Rome, Italy, [3]IRCCS Bambino Gesù Children Hospital, Digestive Endoscopy And Surgery Unit, Rome, Italy, [4]IRCCS Bambino Gesù Children Hospital, Laboratory of Medical Genetics, Rome, Italy, [5]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics, Rome, Italy, [6]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Unit of Clinical Immunology And Vaccinology,, Roma, Italy, [7]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Unit of Immune And Infectious Diseases,unit of Clinical Immunology And Vaccinology, Rome, Italy

Background and Aims: Very Early Onset Inflammatory Bowel Disease (VEO-IBD) is potentially associated with genetic disorders of the intestinal epithelial barrier or inborn errors of immunity. Dual oxidase 2 (DUOX2) is expressed in the gastrointestinal epithelial cells and produces hydrogen peroxide. Biallelic DUOX2 mutations have been described only in two patients with VEO-IBD up to date.[1,2]

Methods: We describe a case of infant onset of IBD. Diagnostic work-up included histological examination of colon biopsy and clinical exome sequencing (CES).

Results: A 1-month infant born at term from uneventfully pregnancy except for IUGR, presented persistent high C-reactive protein (CRP) levels from birth. Although treated with high spectrum antibiotic therapy and negative microbiological investigations, high CRP persisted, and anemia also occurred. Positive occult blood and very high calprotectin in the stool were detected despite an attempt of milk proteins exclusion diet. Abdominal US showed thickened last ileal loop. Full endoscopy evaluation showed important colon stenosis with multiple pseudo-polypoid formations, that resulted refractory to steroid therapy, requiring a partial colic resection. Histological examination of biopsy samples showed morphological features of inflammatory bowel disease. Immunological investigations didn't show any alteration. CES disclosed a compound heterozygous mutation in DUOX2 gene: the pathogenic c.2524C>T; p.Arg842Ter (from father) and the VUS c.3175C>T;p.Arg1059Cys (from mother). Currently she's on mesalamine with clinical and histological remission 3 months after surgery.

Conclusions: Our case expands the knowledge about DUOX2 deficiency, describing a patient with infantile onset IBD presenting with intestinal pseudo-polypoid formations. Functional studies are ongoing to confirm the impact of these two mutations. [1]Gastroenterology.2017 Aug;153(2):609-611.e3. [2]Clinical Immunology (2022),https://doi.org/10.1016/j.clim.2022.109015

Disclosure: No.

Keywords: infant ibd, Inflammatory bowel disease, Dual oxidase2, Inborn errors of immunity, duox2, veo-ibd

POSTER DISPLAY

PD001

NEUTROPENIA IN X-LINKED AGAMMAGLOBULINEMIA PATIENTS MAY BE A MORE COMMON PRESENTING FEATURE THAN PREVIOUSLY REPORTED, AND WARRANTS A HIGH INDEX of SUSPICION AND IMMUNE EVALUATION

POSTER DISPLAY 01: B-CELL BIOLOGY

Nufar Marcus Mandelblit[1], Niv Soffair[2], Suhair Hanna[3], Yehonatan Pasternak[1], Oded Scheuerman[4]
[1]Schneider Children's medical center of Israel, Immunology, Petach Tikva, Israel, [2]Schneider Children's medical center of Israel, Department Pediatrics B, Petach Tikva, Israel, [3]Ruth Rappaport Children's hospital, Immunology, Haifa, Israel, [4]SCMCI, Pediatric B, Petach Tikva, Israel

Background and Aims: X linked agammaglobulinemia (XLA) is the most common cause of primary agammaglobulinemia. Other rare mutations causing a similar clinical phenotype, include mutations in the TCF3 gene. XLA typically presents with hypogammaglobulinemia, and recurrent bacterial infections. Neutropenia, has been previously described occurining in 10-26% of XLA patients. Our study was conducted to assess the prevalence and impact of neutropenia, and neutropenia related infections, as the initial presentation of XLA patients in our patient population.

Methods: A retrospective cohort study of patients diagnosed with XLA in 2 tertiary care pediatric hospitals in Israel; Schneider Children's medical center and The Rappaport Children's hospital was conducted.

Results: Out of 16 patients with XLA, 12 (75%) presented with neutropenia as part of their initial presentation. 8 had significant neutropenia related infections. 4 patients received GCSF. One patient succumbed to a fatal neutropenia related pseudomonas sepsis. After the initiation of IVIG replacement therapy, none of the patients suffered from recurring events of significant neutropenia. We also present a patient with TCF3 mutation presenting with agammaglobulinemia and severe neutropenia resolving after IVIG replacement. Previous studies have failed to explain the mechanism of neutropenia in XLA patients. This case may suggest neutropenia may be related to the agammaglobulinemic state and not to the underlying genetic disorder

Conclusions: Our study suggests neutropenia is a more prevalent manifestation of XLA than previously considered. It may be severe, causing life-threatening risks for neutropenia related infections. Serum immunoglobulin levels should be a part of the evaluation of every child with unexplained neutropenia related infections.

Disclosure: No.

Keyword: X linked agammaglobulinemia, Bruton’s agammaglobulinemia, neutropenia, hypogammaglobulinemia, TCF3

PD002

DISSECTING GERMINAL CENTER B CELL RESPONSES IN COMMON VARIABLE IMMUNODEFICIENCY

POSTER DISPLAY 01: B-CELL BIOLOGY

Kathryn Payne, Susanne Unger, Bärbel Keller, David Friedmann, Victoria Cousin, Klaus Warnatz
Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany

Background and Aims: Common Variable Immunodeficiency (CVID) represents the most common human primary immunodeficiency. It is characterised by hypogammaglobulinemia and displays signs of immune dysregulation, such as lymphadenopathy, autoimmunity and inflammatory organ manifestations in over 30% of patients. Low numbers of class switched memory B cells and plasmablasts in peripheral blood reflect a heterogenic germinal center (GC) dysfunction, providing the opportunity to dissect essential steps during memory and effector differentiation.

Methods: We combine deep phenotyping by multi-parameter cytometry, transcriptome analysis and microscopy on secondary lymphoid organs in order to identify underlying dysregulated expression profiles, molecular pathways and cellular interactions in individual CVID patients.

Results: Preliminary analysis of RNAseq data revealed T-bet-regulated gene expression in centroblast, centrocytes and memory B cells derived from CVID patient's secondary lymphoid organs confirming Th1/TfH1-driven immune dysregulation previously identified in peripheral blood.

Conclusions: Identification of informative altered molecular, cellular and histological findings in patients with immunodeficiency will shed new light on the complex GC responses in humans.

Disclosure: No.

Keywords: b cell differentiation, Germinal Center, secondary lymphoid organs, Common variable immunodeficiency, plasma cell differentiation

PD003

CLINICAL AND IMMUNOLOGICAL CHARACTERISTICS of PATIENTS WITH NFKB1 AND NFKB2 DEFICIENCY

POSTER DISPLAY 01: B-CELL BIOLOGY

Nadira Nabiyeva Cevik[1], Saliha Esenboga[1], Cansu Özdemiral[1], Hacer Neslihan Bildik[1], Togay Yılmaz[2], Nihan Avcu[2], Deniz Cagdas Ayvaz[1], Ilhan Tezcan[1]
[1]Hacettepe University School of Medicine, Pediatric Immunology, Ankara, Turkey, [2]Hacettepe University School of Medicine, Paediatrics, Ankara, Turkey

Background and Aims: Nuclear factor-kB (NF-kB) is the master regulator of transcription factors that regulate genes involved in the immune response. NF-κB signaling through its NFKB1-dependent canonical and NFKB2-dependent noncanonical pathways plays distinctive roles in a diverse range of immune processes, including cell survival and proliferation, inflammation, and the adaptive immune response.

Methods: This research was conducted in a tertiary reference center for IEI for children and adults in Turkey, Hacettepe University Department of Pediatric Immunology and retrospectively evaluated the clinical, immunological and genetic characteristics of the patients with NFKB1 or NFKB2 mutations.

Results: We presented eight patients (NFKB1(4), NFKB2 (4) mutations) from six unrelated families. Half of the patients were male. The median age at the onset of symptoms was 39 years (min-max: 2 months-51 years). The median duration of follow-up was 6 years (min-max: 1month-15 years). Two of the patients were asymptomatic at the time they were included in the study. Detailed clinical characteristics and treatments are shown in Table 1 and Figure 1.

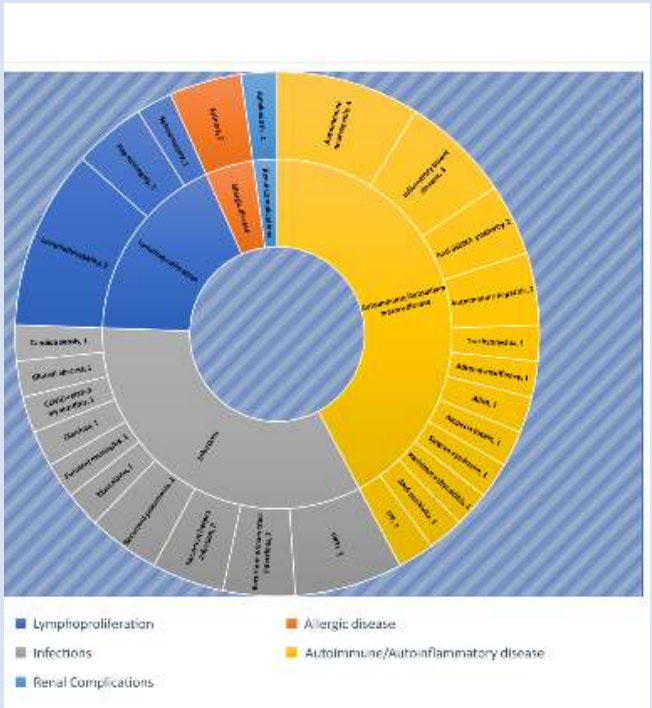


Table 1: Demographical findings of the patients

	Total
Number of patients, n	8
Sex, male n (%)	4 (50%)
Age, median, (min-max)	19 years (10 years-61 years)
Follow-up duration, median, (min-max)	6 years (1 month-15 years)
Treatments n (%)	7 (88%)
Follow-up without treatment	1(12.5%)
Antibiotic prophylaxis	7 (88%)
IgRT	6 (75%)
Immunomodulatory treatment	4 (50%)

Conclusions: NFKB1 and NFKB2 haploinsufficiencies are one of the most common genetic causes in patients with CVID phenotype. Recurrent upper and lower respiratory tract infections, autoimmune diseases, lymphoproliferation are the most common clinical findings. More severe clinical findings with viral and opportunistic microorganisms, similar to combined immunodeficiencies has been defined in the literature. In addition to IVIG and immunomodulatory treatment, HSCT may be planned in case there is unresponsive to treatment and severe autoimmune and inflammatory complications.

Disclosure: No.

Keywords: NFKB2 mutation, primary immuno deficiency, NF-κB signaling, antibody deficiency, common variable immune deficiency, NFKB1 mutation

PD004

MOLECULAR PROFILING of AUTOIMMUNE MANIFESTATIONS AFTER PEDIATRIC ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION.

POSTER DISPLAY 01: B-CELL BIOLOGY

Melanie De Gier[1], Lisa Ott De Bruin[1], Ingrid Pico-Knijnenburg[1], Joëll Bense[2], Federica Achini-Gutzwiller[2], Dagmar Berghuis[2], Arjan Lankester[2], Mirjam Van Der Burg[1]
[1]Leiden University Medical Center, Willem-alexander Children's Hospital, Department of Pediatrics, Laboratory For Pediatric Immunology, Leiden, Netherlands, [2]Leiden University Medical Center, Willem-alexander Children's Hospital, Department of Pediatrics, Pediatric Stem Cell Transplantation Program, Leiden, Netherlands

Background and Aims: Children receiving HSCT for Inborn Errors of Immunity (IEI) frequently experience long-term immunological complications like hypogammaglobulinemia, impaired vaccination response or autoimmune disease (AID), which may reflect impaired B-cell immunity. A recent study demonstrated AID to occur in 11% of HSCT-treated patients at 8 years post-transplantation. The aim of this study was to extend our understanding on the development of AID post-HSCT.

Methods: Four patients with autoimmune thyroiditis (AIT) and two with autoimmune hepatitis (AIH) after HSCT were selected together with 10 matched HSCT and healthy controls. To investigate the scope of autoreactivity, serum at AID onset was analyzed with an autoantigen array harboring 124 autoantigens. For characterization of the BCR repertoire at AID onset, IG transcripts were analyzed with a primer-based and UMI-based NGS strategy.

Results: The autoantigen profile of the AIT patients was mostly restricted to thyroglobulin, whereas the profile of the AIH patients was polyreactive. BCR repertoire analysis did not show statistically significant differences in diversity in IGG transcripts based on the Shannon Entropy and Gini-Simpson index. However, several skewed VJ combinations, comprising up to 50% of the repertoire of one post-HSCT AIT patient, were identified and appeared to be unique to the post-HSCT autoimmune repertoire. We observed a strong skewing towards certain CDR3 lengths, indicative of antigen-driven clonal dominance within the BCR repertoire.

Conclusions: In patients with AID post-HSCT we find distinctive autoantigen profiles and preferential VJ usage within a diverse overall BCR repertoire, reflecting a possible lack of proper selection against B-cell autoreactivity.

Disclosure: No.

Keywords: Hematopoietic stem cell transplantation, Autoimmunity, pediatrics, B-cell immune reconstitution, B-cell receptor repertoire, BCRseq

PD005

DISSECTION of THE BLOOD B- AND T-CELL COMPARTMENT IN AFFECTED AND NON-AFFECTED FAMILY MEMBERS of PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

POSTER DISPLAY 01: B-CELL BIOLOGY

Suzanne Comans[1], Elles Simonetti[1], Bram Van Cranenbroek[1], Eshter Van Rijssen[1], Riet Strik-Albers[2], Jacques J.M. Van Dongen[3,4], Marien De Jonge[1], Stefanie Henriet[2]
[1]Radboudumc Nijmegen, Department of Laboratory Medecine, Nijmegen, Netherlands, [2]Radboud University Nijmegen Medical Centre, Pediatric Infectious Diseases And Immunology, Nijmegen, Netherlands, [3]Leiden University Medical Cente, Department of Immunology, Leiden, Netherlands, [4]University of Salamanca (USAL), Cancer Research Centre (ibmcc, Usal-csic; Ciberonc Cb16/12/00400), Institute For Biomedical Research of Salamanca (ibsal), Department of Medicine And Cytometry Service (nucleus Research Support Platform), Salamanca, Spain

Background and Aims: In only 10% of Common Variable Immunodeficiency (CVID) patients a monogenetic disorder is identified and directly associated with the disease. However, in approximately 30% there is a positive family history. We aim to get more insight in the genetic cause of CVID by evaluating the blood lymphocyte compartment and mucosal immune state of the CVID index in relation to these of their family members.

Methods: Index patients with their family members of families with a negative (n=5), or a positive (n=4) family history for CVID were included. In peripheral blood B-cell, plasma and T-cell compartment of all participants (n=58) were analyzed using high-dimensional flowcytometry. Serum antibody levels are currently evaluated and correlated to the mucosal levels in nasal lining fluid and saliva.

Results: All CVID patients showed aberrant patterns in the B-cell, plasma cell and T-cell compartment. Surprisingly, family members of both the negative family anamnesis and positive family anamnesis families show substantial aberrancies mainly in the memory B-cell and plasma cell compartment. In addition, decreased IgA+ memory B-cells and plasma cells are widely distributed among both family categories.

Conclusions: High-dimensional flowcytometry is able to detect genealogical patterns independently of positive or negative family anamnesis suggesting a multifactorial and/or multigenetic defect underlying the physiopathology of CVID. IgA pathology seems to be an underestimated part. This highlights the additional value of high-dimensional flowcytometry in clinical practice and the need for more in dept analysis of mucosal immunity in order to optimize treatment strategies. It provides a perfect basis for further analysis to possible gene defects in CVID.

Disclosure: No.

Keywords: B-cell, Common variable immunodeficiency, flowcytometry, genetic, immunodeficiency, mucosal immunity

PD006

T CELL ABNORMALITIES IN PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA

POSTER DISPLAY 01: B-CELL BIOLOGY

Ankur Jindal, . Sanchi, Rahul Tyagi, Kanika Arora, Amit Rawat, Deepti Suri, Saniya Sharma, Rajni Sharma, Surjit Singh
Postgraduate Institute of Medical Education and Research, Pediatrics, Chandigarh, India

Background and Aims: X-Linked agammaglobulinemia (XLA) is an antibody deficiency disorder. In this study we report the T cell abnormalities in patients with XLA.

Methods: Patients with XLA and carriers of BTK gene mutation were included. Flow panel comprising of CD45, CD19, CD3, CD4, CD8, HLA-DR, CXCR5, CD45RA, CD45RO was prepared. T helper 17 and T regulatory cells expression was assessed using CD4, Foxp3 and IL-17 antibodies in patients, carriers and healthy controls. T cell proliferation responses through a carboxyfluorescein succinimidyl

Results: In this study we enrolled 22 patients, 7 carrier females and 13 healthy controls. Patients with XLA had significantly reduced $CD4^+$ helper T cells compared to carriers and healthy controls respectively (43.7100±17.32594 vs 60.2714±9.82277, p value 0.028 43.7100±17.32594 vs 57.7408±5.33696, p value 0.020). An increased proportion of $CD4^+CD45RA^+$ naïve T cells were seen in patients with XLA (53.9800±19.54011 vs 34.3186±11.14823, p value 0.030) compared to carrier females. $CD3^+CD45RO^+$ memory T lymphocytes were significantly reduced in patients with XLA (28.2595±13.51810 vs 43.1371±11.80266, p value 0.048 vs 41.2969±13.83028, p value 0.029) compared to carrier females and healthy controls respectively. $CXCR5^+CD45RA^-$ T follicular helper cells were significantly reduced in patients with XLA (4.3014±11.87242 vs 9.5243±3.04909, p value<0.01 vs 10.2291±4.18243, p value<0.01) compared to carriers and healthy controls respectively. Abnormal T cell proliferation was observed in 1 patient.

Conclusions: Patients with XLA have reduced helper, memory and follicular helper T lymphocytes, increased proportion of naïve CD4 T cells and may have mild T cell proliferation defect.

Disclosure: The study has been funded by Jeffrey Modell Foundation 'Specific Defect Research Grant' Scheme.

Keyword: XLA, T cells, IVIg, flow cytometry

PD007

THE ROLE of THE STEROID PRODUCING ENZYME CYP11A1 IN B CELL SUBSETS LINKED TO ACTIVATED PI3KDELTA SYNDROME

POSTER DISPLAY 01: B-CELL BIOLOGY

Julius Christopher Baeck[1], Olivier Papapietro[2], Sergey Nejentsev[2], Anton Enright[1], Bidesh Mahata[1], Leandra Jackson[1], Klaus Okkenhaug[1], Anita Chandra[1]
[1]University of Cambridge, Department of Pathology, Cambridge, United Kingdom, [2]University of Cambridge, Department of Medicine, Cambridge, United Kingdom

Background and Aims: The cytochrome p450 monooxygenase Cyp11a1 serves as the rate-limiting enzyme during de novo steroidogenesis by facilitating the production of pregnenolone from cholesterol. B cells are not known to produce steroids, however, Cyp11a1 was recently discovered to be highly expressed in a novel regulatory B cell subset ($CD19^+$ $IL\text{-}10^+$ $B220^-$ B cells) found in mouse model of Activated Phosphoinositide-3 Kinase δ (PI3Kδ) Syndrome (APDS), a primary immunodeficiency characterised by PI3Kδ hyperactivity. APDS patients present with immunodeficiency, autoimmunity and increased susceptibility to lymphoproliferation. To test whether Cyp11a1 activity is essential for this novel B cell subset, conditional knockout (KO) mice have been generated to assess the effect of Cyp11a1 loss on B cells homeostasis.

Methods: Changes in the lymphocyte landscape have been assessed by spectral flow cytometry and Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITE-Seq).

Results: Loss of Cyp11a1 reduced $B220^-$ B regulatory cell proportions in young and old mice. In some old mice, loss of Cyp11a1 induced splenomegaly which was accompanied by a reduction and increase in follicular and class-switched B cell proportions, respectively. CITE-Seq revealed that the reduction of B cells was accompanied by changes in the regulatory B cell niche.

Conclusions: This study emphasises a role for Cyp11a1 in $B220^-$ B cells and B cell homeostasis. Loss of Cyp11a1 impairs de novo steroidogenesis which suggests that $B220^-$ B cells could drive some pathogenic features of APDS through steroid secretion. Furthermore, B cell-intrinsic steroid production may be important for maintaining B cell populations with age.

Disclosure: No.

Keywords: APDS, PI3K, Steroids, Cyp11a1, Bcells

PD008

NON-APOPTOTIC FAS SIGNALING CONTROLS CD40-DEPENDENT MTOR ACTIVATION AND BALANCES EXTRAFOLLICULAR VERSUS GERMINAL CENTER FATE IN HUMAN B CELLS

POSTER DISPLAY 01: B-CELL BIOLOGY

Julian Staniek[1], Tomas Kalina[2], Iga Janowska[1], Geoffroy Andrieux[3], Marina Bakardjieva[2], Jitka Stancikova[2], Jan Stuchly[2], Olaf Neth[4], Peter Olbrich[5], Laia Alsina[6], Aude Magerus[7], Frédéric Rieux-Laucat[8], Vladimir Benes[9], Raquel Lorenzetti[1], Jan Raabe[1], Chiara Böhler[1], Julika Neumann[1], Rita Carsetti[10], Eva Piano Mortari[10], Manuel Fuentes[11], Benedicte Neven[12], Melanie Boerries[3], Albert Catala[13], Luis Allende[14], Reinhard Voll[1], Nils Venhoff[1], Jens Thiel[1], Luis Ignacio Gonzalez-Granado[15], Klaus Warnatz[1], Maxmillian Seidl[16], Pascal Schneider[17], Dirk Mielenz[18], Stephan Ehl[19,20], Anne Rensing-Ehl[19], Cristian Smulski[21], Marta Rizzi[22]
[1]University Medical Center Freiburg, University of Freiburg, Rheumatology And Clinical Immunology, Freiburg, Germany, [2]Second Faculty of Medicine, Charles University, Department of Paediatric Haematology And Oncology, Prague, Czech Republic, [3]Medical Center - University of Freiburg, Institute of Medical Bioinformatics And Systems Medicine, Freiburg im Breisgau, Germany, [4]Hospital Universitario Virgen del Rocío, Pediatric Infectillous Diseases, Rheumatology And Immunology Unit, Instituto De Biomedicina De Sevia, Ibis/universidad De Sevilla/csic, Red De Investigación Traslacional En Infectología Pediátrica Ritip, Seville, Spain, [5]Pediatric Infectious Diseases, Rheumatology and Immunology Unit, Hospital Universitario Virgen Del Rocío, Instituto De Biomedicina De Sevilla, Ibis/ Universidad De Sevilla/csic, Red De Investigación Traslacional En Infectología Pediátrica Ritip, Seville, Spain, [6]Hospital Sant Joan de Déu, Allergy And Clinical Immunology Department, Esplugues del Llobregat, Spain, [7]Imagine Institute, Immunogenetic of Pediatric Autoimmune Diseases, Paris, France, [8]1. Institut National de la Santé et de la Recherche Médicale, Mixed Research Unit 1163, Laboratory of Immunogenetics of Paediatric Autoimmunity- Necker Enfants Malades Hospital, PARIS, France, [9]European Molecular Biology Laboratory, Genomics Core Facility, Heidelberg, Germany, [10]Diagnostic Immunology Research Unit, Multimodal Medicine Research Area, Bambino Gesù Children's Hospital, IRCCS; Viale di San Paolo,15, Rome, Italy, Diagnostic Immunology Research Unit, Multimodal Medicine Research Area, Bambino Gesù Children's Hospital, Irccs; Viale Di San Paolo,15, Rome, Italy, Roma, Italy, [11]Cancer Research Center, Universidad de Salamanca, Department of Medicine And General Cytometry Service-nucleus, Salamanca, Spain, [12]Necker Hospital for Sick Children, Laboratory of Immunogenetics of Pediatric Autoimmunity, Inserm U1163, Paris, France, [13]Institut de Recerca Hospital Sant Joan de Déu Barcelona, Department of Hematology, Barcelona, Spain, [14]Hospital Universitario 12 de Octubre, Immunology Department, Madrid, Spain, [15]Hospital 12 Octubre; Research Institute Hospital 12 octubre (i+12); Complutense University School of Medicine, Primary Immunodeficiencies Unit, Department of Pediatrics, Madrid, Spain, [16]Heinrich Heine University and University Hospital of Duesseldorf, Institute of Pathology, Düsseldorf, Germany, [17]Faculty of Biology and Medicine, University of Lausanne, Lausanne,, Department of Biochemistry, Lausanne, Switzerland, [18]Nikolaus Fiebiger Zentrum, Friedrich Alexander University Erlangen-NürnbergFriedrich Alexander University Erlangen-Nürnberg, Division of Molecular Immunology, Department of Internal Medicine Iii, Erlangen, Germany, [19]University of Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency Medical Center-university of Freiburg, Faculty of Medicine, Freiburg, Germany, [20]Medical Center - University of Freiburg, Division of Pediatric Hematology And Oncology, Department of Pediatrics And Adolescent Medicine, Faculty of Medicine, Freiburg, Germany, [21]Centro Atómico Bariloche, Comisión Nacional de Energía Atómica, Medical Physics Department, San Carlos de Bariloche, Argentina, [22]University Medical Center Freiburg, Rheumatology And Clinical Immunology, Freiburg, Germany

Background and Aims: Defective FAS signaling causes autoimmune lymphoproliferative syndrome (ALPS). Hypergammaglobulinemia is a common feature in ALPS with FAS mutations (ALPS-FAS) but paradoxically, conventional memory cells that can derive from FAS-expressing germinal center (GC) B cells are reduced. Resistance to FAS-induced apoptosis does not explain this phenotype. We hypothesized that defective non-apoptotic FAS signaling may contribute to impaired B cell differentiation in ALPS.

Methods: We analyzed secondary lymphoid organs of ALPS-FAS patients by high-dimensional spectral flow cytometry and mass cytometry. We investigated FAS-induced signaling in activated human B cells and performed proteomic and transcriptional profiling of FAS-stimulated B cells.

Results: We found low memory B cells, reduced GC B cells and an expanded extrafollicular (EF) B cell response in ALPS. Enhanced mTOR activity has been shown to favor EF versus GC fate decision, and we found enhanced PI3K/mTOR and BCR signaling in ALPS-FAS splenic B cells. Modeling initial T-dependent B cell activation with CD40L in vitro, we showed that in FAS competent cells transient FAS ligation specifically decreased mTOR axis activation without causing apoptosis. This signal modulation was absent in B cells of ALPS-FAS patients. In the early phase of activation, FAS stimulation promoted expression of MYC and CXCR4, which are important for GC formation.

Conclusions: We suggest that non-apoptotic FAS signaling acts as molecular switch between EF versus GC fate decision via signaling modulation and transcriptional regulation. The defect of this modulatory circuit may explain the observed hypergammaglobulinemia and low memory B cell numbers in ALPS.

Disclosure: No.

Keywords: non-apoptotic, Germinal Center, extrafollicular response, B cells, FAS, ALPS

PD009

GENETIC BASIS of COMMON VARIABLE IMMUNODEFICIENCY (CVID): A MULTICENTRE EXPERIENCE FROM INDIA.

POSTER DISPLAY 01: B-CELL BIOLOGY

Rahul Tyagi[1], Ankur Jindal[1], . Sanchi[1], Himanshi Chaudhary[2], Amit Rawat[1], Kavadichanda Chengappa[3], Sagar Bhattad[4], Latika Gupta[5], Inderpaul Singh[6], Pratap Patra[7], Silky Jain[8], Vignesh Pandiarajan[1], Rajni Sharma[9], Ruchi Saka[1], Surjit Singh[9]
[1]Postgraduate Institute of Medical Education and Research, Department of Pediatrics, Advanced Pediatrics Centre, Chandigarh, India, [2]Post graduate Institute of Medical Education and Research, Department of Pediatrics, Advanced Pediatrics Centre, Chandigarh, India, [3]Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India, Clinical Immunology, Puducherry, India, [4]Aster CMI Hospital, Pediatric Immunology And Rheumatology, Department of Pediatrics,, Bengaluru, India, [5]Sanjay Gandhi Postgraduate Institute of Medical Sciences (SPGIMS), Department of Clinical Immunology And Rheumatology,, Lucknow, India, [6]Postgraduate Institute of Medical Education and research, Department of Pulmonary Medicine,, Chandigarh, India, [7]All India Institute of Medical Sciences, Patna, India., Department of Paediatrics, Patna, India, [8]Jaypee Hospital, Department of Pediatric Hemato-oncology, Noida, India, [9]Postgraduate Institute of Medical Education and Research, Pediatrics, Chandigarh, India

Background and Aims: Background: Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency (PID) characterized clinically by recurrent episodes of infections (predominantly encapsulated bacteria), autoimmunity, and malignancy. Aim: To elucidate the genetic basis of CVID in the multicentre cohort from India.

Methods: A predesigned Microsoft Excel sheet was circulated via email to all centers across the countries who are involved in the care of patients with PIDs. Data were collected from centers who agreed to take part in this multicentre study. Diagnosis of CVID was based on the European Society for Immunodeficiency (ESID) 2014 classification criteria. The genetic investigations were carried out through targeted next-generation Sequencing/Whole Exome Sequencing.

Results: In this multicentre study, we included 126 patients diagnosed to have CVID. Genetic testing could be performed on 37 patients. A pathogenic variant was observed in 17/37 patients (45.94%). These included pathogenic variants in following genes: LRBA (n=3), IRF2BP2 (n=2), XIAP (n=2), DCLRE1C (n=1), WAS (n=1), SH2D1A (n=1), STXBP2 (n=1), DOCK2 (n=1), NFKB1 (n=1), STX11 (n=1), IRF8 (n=1), AICDA (n=1) and PI3KCD (n=1). In the monogenic cohort 6/14 cases (42.85%) had autoimmune manifestations and 5/14 (36%) had bronchiectasis. IgG, IgM, and IgA levels were reduced in 100%, 86% and 86%, respectively. Infections were observed in all cases. In the monogenic group, B-cells were reduced in 6/14 (43%), and switched memory B cells were reduced in 7/8 (87.5%) cases.

Conclusions: Pathogenic variants were reported in 45.94% of patients with CVID. LRBA gene variants were the most common pathogenic variant.

Disclosure: No.

Keywords: NGS, CVID, Primary Antibody Deficiency, Whole Exome Sequencing, Primary Immunodeficiency Disease

PD010

A NOVEL SLC39A7 VARIANT AND ZIP7 DISORDER IN A B-CELL DEFICIENT JAPANESE GIRL

POSTER DISPLAY 01: B-CELL BIOLOGY

Kay Tanita[1], Wakana Ohashi[2], Fumiko Honda-Ozaki[1], Tsubasa Okano[1], Tetsu Nose[3,4], Yasunori Horiguchi[4], Zenichiro Kato[5,6], Hidenori Ohnishi[5], Kohsuke Imai[1,7], Tomohiro Morio[1], Koji Hase[2], Hirokazu Kanegane[8]
[1]Tokyo Medical and Dental University, Department of Pediatrics And Developmental Biology, Yushima, Bunkyo-ku, Tokyo, Japan, [2]Keio University, Division of Biochemistry, Tokyo, Japan, [3]Musashino Tokushukai Hospital, Pediatrics, Tokyo, Japan, [4]International University of Health and Welfare Atami Hospital, Pediatrics, Shizuoka, Japan, [5]Gifu University Graduate School of Medicine, Pediatrics, Gifu, Japan, [6]Gifu University, United Graduate School of Drug Discovery And Medical Information, Gifu, Japan, [7]National Defense Medical College, Pediatrics, Saitama, Japan, [8]Tokyo Medical and Dental University, Child Health And Development, Tokyo, Japan

Background and Aims: B-cell deficiency is a primary immunodeficiency presenting with agammaglobulinemia and recurrent infections from infancy. Most cases are X-linked agammaglobulinemia, 90% of which are known to have variants in the BTK gene. On the other hand, there are also cases in girls and cases without BTK variants, and recent developments in molecular biological techniques, including next-generation sequencing, have led to the discovery of new causative genes.

Methods: The case is a 9-year-old girl with a history of pyogenic arthritis, B-cell deficiency, and agammaglobulinemia, who was treated with immunoglobulin replacement therapy. The patient underwent whole-exome-sequencing and molecular biological scrutiny.

Results: WES revealed a novel compound heterozygous missense variants of parental origin in the SLC39A7 gene encoding ZIP7, which is responsible for zinc transport from intracellular organelles to the cytoplasm. Molecular biological scrutiny proved that one variant promotes proteasomal degradation of ZIP7 and the other causes abnormal localization of ZIP7 on the endoplasmic reticulum, demonstrating that both variants impair ZIP7 function.

Conclusions: ZIP7 deficiency, an autosomal recessive B-cell deficiency, is a relatively new immunodeficiency reported in 2019, with six cases in five families (Anzilotti et al. Nat Immunol). In the report, mice with complete deletion of ZIP7 were embryonic lethal, while mice with the missense variant seen in the patient reproduced the B-cell defect. Although the detailed pathogenesis of B-cell loss due to ZIP7 deficiency remains unclear, this is an extremely important disease in terms of the relationship between zinc and immunity, and further elucidation of its pathogenesis is warranted.

Disclosure: No.

Keywords: Autosomal Recessive Agammaglobulinemia, ZIP7, B-cell deficiency, SLC39A7, Zinc transporter

PD011

REVEALING THE MOLECULAR ROLE of WASP IN THE NUCLEUS of B CELLS.

POSTER DISPLAY 01: B-CELL BIOLOGY

Roberta D'Aulerio, Minghui He, Mariana Oliveira, Lisa Westerberg
Karolinska Institutet, Microbiology, Tumor And Cell Biology, Solna, Sweden

Background and Aims: Mutations in the WAS gene, encoding for the actin regulator WASp, cause two rare primary immunodeficiency disorders (PIDs): Wiskott-Aldrich syndrome (WAS) and X-linked neutropenia (XLN). WAS is caused by a loss-of-function mutation in the WAS protein (WASp) resulting in immunodeficiency, thrombocytopenia, and eczema. WASp overexpression causes XLN. XLN patients show common features of immune system failure and accumulated cytogenetic abnormalities, leading to a tumor-prone phenotype. WASp is a regulator of the actin cytoskeleton, required for hematopoietic cell functions including effective migration and immune synapse formation. In this context, B cell affinity maturation in the germinal center (GC) relies on processes regulated by the actin cytoskeleton, such as migration, proliferation, and genomic rearrangement. The aim of this project is to reveal the role of WASp in the nucleus driving dynamic processes like DNA synthesis, DNA repair, and chromatin remodeling.

Methods: Performing nuclear-cytosol fractionation experiments on murine XLN and WT activated B cells, as well as inducible germinal center system and through flow cytometry analysis

Results: we are able to detect, through immunoblotting, the presence of WASp in the nucleus apart from its known presence in the cytosol. Valuable is FACS analysis to track the differentiation of naïve B cells into plasma cells.

Conclusions: Considering the well-known association of N-WASp (a homologous protein of WASp in non-hematopoietic cells) with RNA Pol II and of WASp with T cell factor 1 (TCF1) in T cells, further ChIP-Seq experiments will be important to determine the function of WASp in active processes of the nucleus of B cells.

Disclosure: No.

Keywords: B cells, Nucleus, PID, Wiskott-Aldrich Syndrome, Actin

PD012

FUNCTIONAL ASSAYS IN B CELLS TO DETERMINE THE PATHOGENICITY IN ATYPICAL BTK VARIANTS.

POSTER DISPLAY 01: B-CELL BIOLOGY

Lucia Del Pino Molina[1], Yadira Bravo Gallego[2], Yolanda Soto Serrano[2], Rebeca Rodríguez Pena[2], Eduardo López Granados[2]
[1]La Paz University Hospital, Immunology. Ciberer U767, Madrid, Spain, [2]La Paz University Hospital, Immunology. Ciberer U767, Idipaz, Madrid, Spain

Background and Aims: Classical XLA male patients suffered from hypogammaglobulinemia due to the reduced or absence of B cells, and frequent infections. However, atypical case presentations have been reported. Here we present a patient with a leaky BTK mutation in the kinase domain, without history of recurrent infections. We aimed to determine the pathogenicity of this variant in BTK and the functional impact in this patient.

Methods: Clinical evaluation of the patient included a complete analysis of phenotype from peripheral blood and bone marrow due to B-cell lymphopenia. To further explored Btk functionality we selected intracellular readouts measurable by flow cytometry that reflected the strength of homeostatic signalling pathways in resting cells and after activation, Btk expression, phospho-Btk and downstream signalling readouts such as intracellular Ca2+ flux and IkBa degradation.

Results: The patient presented reduced total B-cell numbers in peripheral blood together with reduced but detectable numbers of memory B-cells and plasma cells expressing distinct immunoglobulin subclasses. The patient presented normal distribution of B cell precursor's subsets in bone marrow. Normal Btk expression and Btk phosphorylation were detected. The patient´s B cells presented normal IkBa degradation with CD40L, however failed to respond to BCR signalling and also calcium flux after stimulation with anti IgM was reduced.

Conclusions: Atypical cases reveal the need of functional assays that could aid in determining variant´s pathogenicity and to anticipate or confirm an established deterioration of the functional antibody response that would require immunoglobulin replacement therapy.

Disclosure: No.

Keywords: B cell biology, XLA, Functional Assays, flow cytometry

PD013

PROBABLE SELECTIVE IGM DEFICIENCY (SIGMD) IN A 3-YEAR-OLD GIRL

POSTER DISPLAY 01: B-CELL BIOLOGY

Benoit Brasseur[1], Catherine Draguet[2]
[1]Clinique Saint-Pierre, Paediatrics, Ottignies, Belgium, [2]CHU UCL Namur Site Dinant, Paediatrics, Dinant, Belgium

Background and Aims: Selective IgM deficiency is rare.

Methods: We present the clinical picture of a 3-year-old girl evaluated for chronic staturoponderal deficit. She's a first child of non-consanguineous moroccan parents, born eutrophic at term. She was hospitalized in NICU at day 2 for a suspicion of maternofetal infection, with empirical treatment with ampicillin and amikacin. Bacterial workup was reassuring. In the first weeks of life she developped extensive eczema. At 2 year and 9 months, she was hospitalized for a varicella complicated by corneal infection, preseptal cellulitis and Staphylococcus aureus bacteriemia, and treated with oxacilline and topical ganciclovir. Others cutaneous infections were noted, with toe infection at 2 months, and two episodes compatible with extensive Coxsackie infection (eczema coxsackiorum and hand-mouth-foot disease at 1 and nearly 3-year-old). Notably, a recent SARS-CoV2 infection followed a benign course.

Results: Recent biological work-up revealed a normal hemogram with normal lymphocytic count, slight thrombocytosis (504000/microL), normal total gammaglobulins (10,5% N : 9-19) and CH50, rather high IgA (1,85 g/L N :0,25-1,6), normal IgG (7,18g/L N : 4,6-12,4), normal IgE (16 kUA/L N : 1,5-114) and repeatedly undosable IgM (<0,21g/L N : 0,45-2). No autoimmunity was found (thyroid, celiac disease) and vaccine serologies were normal (tetanus, mumps, HBV).

Conclusions: We described a case of probable selective IgM deficiency. Polysaccharidic antipneumococcal vaccination and complete antimeningococcal vaccination (ACWY and B) are planned, and antibioprophylaxis will be discussed. Immunological follow-up is mandatory to confirm that the SIgMD stays isolated and the absence of autoimmune complications due to the young age of the patient.

Disclosure: No.

Keywords: IgM deficiency, selective, Autoimmunity, viral and bacterial infections

PD014

T-CELL-DERIVED FACTORS ARE CRUCIAL FOR THE EXPANSION of T-BETHIGHCD21LOW B CELLS

POSTER DISPLAY 01: B-CELL BIOLOGY

Bärbel Keller[1], Ina Harder[1], Valentina Strohmeier[1], Susanne Unger[1], Kathryn Payne[2], Geoffroy Andrieux[3], Melanie Boerries[3], Peter Felixberger[1], Alexandra Nieters[4], Anne Rensing-Ehl[5], Ulrich Salzer[1], Roland Elling[4], Carsten Speckmann[6], Ina Hainmann[7], Elizabeth Ralph[8], Kimberly Gilmour[9], Marjolein Wenink[10], Mirjam Van Der Burg[11,12], Hye Sun Kuehn[13], Sergio Rosenzweig[14], Uwe Kölsch[15], Horst Von Bernuth[16], Petra Kaiser-Labusch[17], Florian Gothe[18], Sophie Hambleton[19], Alexandru Vlagea[20], Ana Garcia Garcia[21], Laia Alsina[22], Gasper Markelj[23], Tadej Avcin[23], Julia Vasconcelos[24], Margarida Guedes[25], Bella Shadur[26], Danielle Avery[2], Nils Vennhoff[1], Jens Thiel[1], Satoshi Okada[27], Paul Gray[28], Gulbu Uzel[29], Jean-Laurent Casanova[30], Manfred Fliegauf[31], Bodo Grimbacher[32], Herman Eibel[1], Stephan Ehl[33], Reinhard Voll[1], Marta Rizzi[34], Polina Stepensky[26], Vladimir Benes[35], Cindy Ma[36], Claudia Bossen[37], Stuart Tangye[38], Klaus Warnatz[1]
[1]Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany, [2]Garvan Institute of Medical Research, Immunology Division, Sydney, Australia, [3]Medical Center - University of Freiburg, Institute of Medical Bioinformatics And Systems Medicine, Freiburg im Breisgau, Germany, [4]Medical Center - University of Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Faculty of Medicine, Freiburg, Germany, [5]University of Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency Medical Center-university of Freiburg, Faculty of Medicine, Freiburg, Germany, [6]University of Freiburg, Division of Pediatric Hematology And Oncology, Department of Pediatrics And Adolescent Medicine, Medical Center - University of Freiburg, Faculty of Medicine, Freiburg, Germany, [7]University Hospital Bonn, 14department of Pediatric Hematology And Oncology, Bonn, Germany, [8]Great Ormond Street Hospital; London, Immunology, London, United Kingdom, [9]Kimberly.gilmour@gosh.nhs.uk, Immunology, London, United Kingdom, [10]Erasmus MC, University Medical Center, 16department of Immunology, Rotterdam, Netherlands, [11]Leiden University Medical Center, Laboratory For Pediatric Immunology, Department of Pediatrics, Leiden, Netherlands, [12]Leiden University Medical Center, Willem-alexander Children's Hospital, Department of Pediatrics, Leiden, Netherlands, [13]NIH, 18immunology Service, Department of Laboratory Medicine, Bethesda, United States of America, [14]NIH, Immunology Service, Department of Laboratory Medicine, Bethesda, United States of America, [15]Labor Berlin Charité-Vivantes GmBH, Human Genetics, Berlin, Germany, [16]Charité — Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany, Center For Regenerative Therapies (bcrt), Berlin, Germany, [17]Prof. Hess childrens' hospital, Klinikum Bremen - Mitte, Gesundheit Nord gGmbH, Immunology, Bremen, Germany, [18]Translational and Clinical Research Institute, Immunity And Inflammation Theme, Newcastle upon Tyne, United Kingdom, [19]Newcastle University, Translational & Clinical Research Institute, Immunity & Inflammation Theme, Newcastle Upon Tyne, United Kingdom, [20]Biomedic Diagnostic Center (CDB), Hospital Clínic de Barcelona, Immunology Department, Barcelona, Spain, [21]Sant Joan de Déu-Hospital Clínic Barcelona, Clinical Immunology Unit, Barcelona, Spain, [22]Hospital Sant Joan de Déu, Allergy And Clinical Immunology Department, Esplugues del Llobregat, Spain, [23]Children's Hospital, University Medical Center Ljubljana, University of Ljubljana, Department of Allergology, Rheumatology And Clinical Immunology, Ljubljana, Slovenia, [24]Centro Hospitalar Universitário do Porto, Serviço De Imunologia, Porto, Portugal, [25]Centro Hospitalar Universitário do Porto, Pediatric Department, Porto, Portugal, [26]Hadassah Hebrew University Medical Centre, Department of Bone Marrow Transplantation And Cancer Immunotherapy, Jerusalem, Israel, [27]Hiroshima University, Pediatrics, Hiroshima, Japan, [28]Sydney Children's Hospital, Immunology And Infectious Diseases, Randwick, Australia, [29]National Institutes of Health, National Institute of Allergy And Infectious Diseases, Bethesda, United States of America, [30]Howard Hughes Medical Institute, -, Washington, United States of America, [31]Medical Center, University of Freiburg, Germany, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [32]University Hospital Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [33]University of Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency, Medical Center, Freiburg, Germany, [34]University Medical Center Freiburg, Rheumatology And Clinical Immunology, Freiburg, Germany, [35]European Molecular Biology Laboratory, Genomics Core Facility, Heidelberg, Germany, [36]Garvan Institute of Medical Research, Immunology, Darlinghurst, Australia, [37]Center for Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg, Germany, [38]Garvan Medical Research Institute, Immunology, Darlinghurst, Australia

Background and Aims: T-bet^{high}CD21^{low} B cells expand in immune dysregulation in patients with common variable immunodeficiency (CVID), but also in infection or autoimmunity. In autoimmune diseases these B cells have been associated with disease pathogenesis. The origin and role of this population is still incompletely understood. The transcription factor T-bet is strongly induced by IFNγ/anti-IgM stimulation and plays a dominant role in the

transcriptional regulation of T-bet^{high}CD21^{low} B cells. Our aim was to determine factors involved in the differentiation of T-bet^{high}CD21^{low} B cell in vivo and in vitro.

Methods: B cells of healthy controls and patients with inborn errors of immunity (IEI) were analysed by FACS ex vivo and after in vitro cultivation.

Results: In vitro cultivation of HC naïve B cells with anti-IgM, IFNγ and IL-21 with CpG or CD40L induced the differentiation of a T-bet^{high}CD21^{low} B-cell population. High expression of additional markers corroborated the phenotypic resemblance to T-bet^{high}CD21^{low} B cells ex vivo. IEI affecting IFNγR and canonical NF-κB signaling disturbed the differentiation of T-bet^{high}CD21^{low}-like B cells. While IL-21 was crucial for the differentiation in the context of CD40L stimulation, CpG-induced T-bet^{high}CD21^{low}-like B cells did not depend on IL-21. Reduced CD21^{low} B cells in peripheral blood of patients with IEI affecting IFNγR-, canonical NF-κB- IL-21R- and CD40 signaling indicated a non-redundant role of these pathways for the differentiation of this B-cell phenotype in vivo.

Conclusions: The identification of IFNγ, IL21 and CD40 for the differentiation of T-bet^{high}CD21^{low} B cells in vivo provides pathways to target this potentially harmful B-cell population in the context of autoimmunity.

Disclosure: No.

Keywords: T-bethighCD21low B cells, IEI, CVID

PD015

SPLENECTOMY FOR THE TREATMENT of A CVID PATIENT WITH REFRACTORY CHRONIC PANCITOPENIA AND HETEROZYGOUS ALLELIC VARIANT IN THE CR2 GENE

POSTER DISPLAY 01: B-CELL BIOLOGY

Jimena Gómez Pérez[1], Hector Balastegui[2], Marisa Di Natale[2], María Mejía[2], Elena Garcia Martinez[2], Eduardo Fernandez Cruz[3], Carmen Rodriguez Sainz[2]
[1]Hospital Universitario Gregorio Marañón, Servicio Inmunología, Madrid, Spain, [2]Hospital General Universitario Gregorio Marañón, Insituto de Investigación biomédica Gregorio Marañón,, Servicio Inmunología, MADRID, Spain, [3]Hospital General Universitario Gregorio Marañón, Insituto de Investigación biomédica Gregorio Marañón,, Servicio Inmunología, Madrid, Spain

Background and Aims: CVID encompasses a heterogeneus set of disorders with clinical and molecular manifestations. We present a patient with CVID with chronic diarrhea with multiple outbreaks with ileocolitis, pancolitis in terminal ileum diagnosis , with severe pancitopenia (anemia, neutropenia, leukopenia and thrombocytopenia), portal hypertension and splenomegaly, with gastric pain and dyspnea. There was poor clinical response to treatments including IVIG, corticosteroids and red blood cells and GM-CSF transfusions . After interdisciplinary (haematology and immunology) consensus surgical intervention with splenectomy was decided.

Methods: This is a case report of a patient with CVID in which has been carried out immunological, haematological, bone marrow puncture and molecular genetic analyses for diagnosis. DNA was isolated and Next Generation Sequencing was performed using screening of 200 genes in relation with the Immunodeficiencies.

Results: Resolution of refractory chronic pancytopenia with significant improvement of the clinical symtoms was observed after splenectomy. Molecular Genetics analysis identified an heterozygous allelic variant in the CR2 gene (NP_001006659.1: p. Arg840Ter).

Conclusions: In this patient with CVID with splenomegaly, refractory chronic pancytopenia and gastrointestinal symptoms, splenectomy was considered as an effective alternative treatment for the standard of care management. Biallelic mutations in CR2 have been associated with CVID specifically group 7. However, detection of one allelic variant in the CR2 gene (p.Arg840Ter) does not allow a definitive molecular diagnosis. Furthermore, due to the absence of studies this variant does not appear to have pathogenic clinical significance, although its presence could be associated with the complex and heterogenous clinical phenotype presented by our patient.

Disclosure: No.

Keywords: IDVC, CR2, Mutation, NGS, SPLENECTOMY, pancytopenia

PD016

INHERITED CD19 DEFICIENCY IMPAIRS SIGNALLING IN PLASMA CELLS.

POSTER DISPLAY 01: B-CELL BIOLOGY

Anoop Mistry[1], Kieran Walker[2], Christopher Watson[2,3], Fatima Nadat[1], Gururaj Arumugakani[1], Clive Carter[1], Gina Doody[2], Sinisa Savic[1,2]
[1]St James's University Hospital, Clinical Immunology And Allergy, Leeds, United Kingdom, [2]University of Leeds, School of Medicine, Leeds, United Kingdom, [3]St. James's University Hospital, Yorkshire And North East Genomic Laboratory Hub, Leeds, United Kingdom

Background and Aims: CD19 is expressed throughout B cell ontogeny and plays a role in propagating signals from the B cell receptor and other receptors such as CXCR4 in mature B cells. Studies of CD19- deficient patients have confirmed its function during the initial stages of B cell activation; however its role in the later stages of B cell differentiation is unclear. Using B cells from a genetically proven CD19-deficient individual, we investigated the role of CD19 in the generation and function of plasma cells using an in vitro differentiation model.

Methods: Flow cytometry was used to characterise the B cell population in the affected patient. Purified B cells from the patient and healthy controls were activated with CD40L, IL-21, IL-2 and anti-Ig, then transferred to different cytokine conditions to induce plasma cell differentiation. Subsequently, the cells were stimulated with CXCL12 to induce signalling through CXCR4. Phosphorylation of downstream proteins including ERK and AKT was assessed by Western blotting.

Results: Flow cytometry confirmed a polyclonal B cell population lacking CD19. CD19-deficient B cells generate phenotypically normal plasma cells with normal levels of CXCR4, however they have an altered response to CXCL12 resulting in a loss of ERK signalling. Additionally, CD19 ligation on normal plasma cells results in AKT phosphorylation.

Conclusions: CD19 is not required for generation of antibody secreting cells but may alter responses of these populations to CXCL12 and direct CD19 engagement, potentially affecting localisation, proliferation, or survival.

Disclosure: No.

Keywords: CD19, antibody deficiency, B cells, plasma cells, CXCR4

PD017

X-LINKED AGAMMAGLOBULINEMIA (XLA) AND PYODERMA GANGRENOSUM (PG)

POSTER DISPLAY 01: B-CELL BIOLOGY

Raquel Letícia Alves[1], Carolina Sanchez Aranda[1], Dirceu Solé[1], Carolinne Troli[1], Mariana Gouveia-Pereira[1], Lara Silva[1], Katherine Silvestre[1], Lais Oliveira[1], Kathleen E Sullivan[2]
[1]Federal University of São Paulo, Division of Allergy, Clinical Immunology And Rheumatology - Department of Pediatrics, São Paulo, Brazil, [2]Children's Hospital of Philadelphia, Division of Allergy And Immunology, Philadelphia, United States of America

Background and Aims: XLA is a primary immunodeficiency (PID) classically characterized by recurrent sinopulmonary infections, agammaglobulinemia, and reduced B cells. While sinopulmonary infections are common in XLA, skin infections are also a significant burden. Indeed, registry data report skin infections including cellulitis and pyoderma in up to 20% of patients We describe the successful treatment of a 36-year-old male with XLA and probable Helicobacter bilis (Hb) skin infection after eight years of countless treatments without adequate response.

Methods: Evaluation of medical charts record of the patient's follow-up for eight years.

Results: A 36 years old, male patient, diagnosed at age 7y with XLA, with multiple hospitalizations for severe and recurrent infections. At the age of 28, he evolved with a difficult-to-heal ulcer in the right lower limb and was diagnosed with PG. The use of multiples agents (such as corticosteroids, methotrexate, cyclosporine, and adalimumab) and several hospitalizations for osteomyelitis and Hemophagocytic lymphohistiocytosis (HLH) were required in the last 8 years until Hb was suspected and the beginning of prolonged treatment with ertapenem plus azithromycin plus levofloxacin was performed to have a significant improvement of the lesion.

Conclusions: Helicobacter and related species are predominantly extracellular bacteria that are typically confined to gastrointestinal mucosal surfaces but in XLA can lead to bacteremia and extensive skin, bone, and joint involvement. The suspicion of different etiologies must be made in all PIDs so that the correct treatment is carried out

Disclosure: No.

Keywords: Helicobacter bilis, pyoderma gangrenosum, X-linked agamaglobulinemia, primary immunodeficiency

PD018

ALLERGIC PHENOTYPE AND FOLLOW-UP of CHILDREN AND ADOLESCENTS WITH SELECTIVE IGA DEFICIENCY: AN ITALIAN MONOCENTRIC STUDY

POSTER DISPLAY 01: B-CELL BIOLOGY

Bianca Laura Cinicola[1], Anna Maria Zicari[1], Cinzia Milito[2], Martina Capponi[1], Giulia Brindisi[1], Isabella Quinti[3], Federica Pulvirenti[3]
[1]Sapienza University of Rome, Department of Maternal Infantile And Urological Sciences, Rome, Italy, [2]Sapienza University of Rome, Department of Molecular Medicine, Rome, Italy, [3]Sapienza University of Rome, Regional Reference Centre For Primary Immune Deficiencies, Azienda Ospedaliera Universitaria Policlinico Umberto I, Roma, Italy

Background and Aims: Although it is widely accepted that Selective IgA Deficiency (SIgAD) is associated with allergy, prevalence and pathogenesis of allergic disorders have not yet been defined. We described the prevalence of allergy in pediatric SIgAD subjects and we characterized infective, autoimmune and immunological phenotypes of atopic SIgAD patients.

Methods: Data from pediatric SIgAD patients were collected yearly for a 14-years period at the Pediatric-Immunology Center of Sapienza University of Rome.

Results: Sixty-seven subjects (median age at last FU 9 years) were included, 91% having an absolute IgA deficiency. Allergy was diagnosed in 34% of patients during FU, with a mean age at allergy diagnosis of 7±4 years. A positive family history for allergy was identified in 57%; 25% SIgAD patients had asthma, 33% rhinitis, 18% atopic dermatitis and 7% food allergy, with 33% having more than one allergic manifestation. The most common allergic sensitivities were dust mites, followed by grasses and olive trees. Allergic SIgAD subjects showed lower levels of neutrophils and lymphocytes than non-allergic patients, but they did not differ for rate and severity of infections nor for autoimmunity. Fifty-one percent of participants had at least a non-protective titre for common vaccinations. Patients with asthma were more likely to have non-protective anti-PCP13 titre than those without asthma, suggesting a more profound B-cell impairment in this subgroup.

Conclusions: Allergic manifestations are common in SIgAD, requiring adequate management to prevent chronic complications and improve quality of life. Vaccine booster dose may be required earlier than in the general population.

Disclosure: No.

PD019

CHARACTERIZATION of CLINICAL AND IMMUNOLOGICAL FEATURES of PATIENTS WITH ANTIBODIES DEFICIENCY SECONDARY TO DIFFERENT CAUSES.

POSTER DISPLAY 01: B-CELL BIOLOGY

Emma Coppola, Emilia Cirillo, Elisabetta Toriello, Antonio De Rosa, Loredana Palamaro, Francesca Cillo, Roberta Romano, Claudio Pignata, Giuliana Giardino
University of Naples "Federico II", Translational Medical Science, Napoli, Italy

Background and Aims: Secondary antibodies deficiency (SAD) usually is an adverse effect of many immunosuppressive drugs or may occur in the context of malignancies or protein-losing state.

Methods: In this study, we described features of patients affected with SAD, defined as the presence of serum IgG levels lower than 5.5 g/L in at least 2 separate evaluations, with or without low IgA or IgM.

Results: 8 patients affected with SAD are in follow-up to our Center. Three patients have hypogammaglobulinemia secondary to protein-losing state, 4 after exposure to rituximab, 1 after exposure to cyclophosphamide. Due to the absence of infections and the slight reduction in IgG levels, four patients do not need IgRT. Among patients exposed to rituximab, one achieved spontaneously normal Ig levels after 8 years of IgRT; two patients still require IgRT, respectively 7 and 6 years after exposure to rituximab. All three patients present with persistent Hyper IgM, which arose a few years after exposure to rituximab and during IgRT. One patient was exposed to 3 cycles of R-CHOP in utero. In one patient with protein-losing state secondary to Fontan operation hypogammaglobulinemia did not respond to IgRT and resolved after cardiac transplant. Four patients have an immunophenotype B similar to patients with CVID, with a reduced percentage of marginal zone and/or switched memory and/or an increase in low CD21 CD38-B cells.

Conclusions: Although SAD are more common than primary antibody deficiency more studies are needed to define the clinical importance of this disorder and treatment outcomes.

Disclosure: No.

Keywords: hypogammaglobulinemia, B-immunophenotype, IgRT, Secondary antibodies deficiency, ruxolitinib, protein-losing state

PD020

IL-7 RECEPTOR SIGNALING DRIVES HUMAN B-CELL PRECURSOR DIFFERENTIATION AND EXPANSION.

POSTER DISPLAY 01: B-CELL BIOLOGY

Fabian Kaiser[1], Iga Janowska[2], Melanie De Gier[3], Roberta Menafra[4], Jakov Korzhenevich[2], Ingrid Pico-Knijnenburg[3], Indu Khatri[5], Ansgar Schulz[6], Taco Kuijpers[7], Arjan Lankester[8], Lukas Konstantinidis[9], Miriam Erlacher[10], Susan Kloet[4], Pauline Van Schouwenburg[3], Marta Rizzi[2], Mirjam Van Der Burg[3]
[1]Erasmus MC, Department of Immunology, Rotterdam, Netherlands, [2]University Medical Center Freiburg, University of Freiburg, Department of Rheumatology And Clinical Immunology, Freiburg, Germany, [3]Leiden University Medical Center, Laboratory For Pediatric Immunology, Leiden, Netherlands, [4]Leiden University Medical Center, Leiden Genome Technology Center, Leiden, Netherlands, [5]Leiden University Medical Center, Department of Immunology, Leiden, Netherlands, [6]Pediatric Immunology, Rheumatology and Stem Cell Transplantation, Ulm University Hospital, Department of Pediatrics And Adolescent Medicine, Pediatric Immunology, Ulm, Germany, [7]Amsterdam UMC, Department of Pediatric Immunology, Rheumatology And Infectious Disease, Amsterdam, Netherlands, [8]Leiden University Medical Center, Department of Pediatrics, Stem Cell Transplantation Program, Leiden, Netherlands, [9]University of Freiburg, Department of Orthopedics And Trauma Surgery, Freiburg, Germany, [10]University of Freiburg, Department of Pediatrics And Adolescent Medicine, Freiburg, Germany

Background and Aims: Whereas mice deficient in IL-7 or the IL-7 receptor (IL-7R) have a complete block in B-cell differentiation, IL-7Rα-deficient SCID patients present with near-normal peripheral blood B-cell counts. Consequently, human B lymphopoiesis has been thought to remain largely unaffected by the lack of IL-7R signaling. We therefore sought to perform an in-depth analysis of the role of the IL-7R in human B-cell development.

Methods: We combined single-cell RNA sequencing and flow cytometric analysis of bone marrow samples of IL-7Rα-deficient patients and *in vitro* differentiation of human B-cell progenitors to study the role of the IL-7R across all stages of human B lymphopoiesis.

Results: IL-7 enhances *EBF1* and *PAX5* expression in early human B-cell progenitors and induces a strong proliferative burst. Consequently, IL-7Rα-deficient SCID patients show a less diverse IgH repertoire. Moreover, IL-7 induces *BACH2* expression during B-lymphoid specification, which may be the missing link that connects the IL-7R to *EBF1* and *PAX5*. Finally, in contrast to mouse B-cell development, IL-7 does not affect survival of early progenitors and only has a minor effect on the proliferation of pre-BII large cells, which may explain the discrepancy in B cell numbers between IL-7Rα-deficient mice and patients.

Conclusions: We hereby prove a crucial role for IL-7R signaling in specifying the B-lymphoid fate and expanding the early progenitor pool in humans. Our work unveils unknown discrepancies and similarities between mice and men and raises important concerns regarding the immunocompetence of IL7Rα-deficient SCID patients with autologous B-cells after hematopoietic stem cell transplantation.

Disclosure: No.

Keywords: IL-7, IL-7Rα, Human immunology, B-cell development, B cells, SCID

PD021

THE EFFECTS of INTRA UTERINE EXPOSURE TO IMMUNOMODULATING CHEMOTHERAPY ON THE DEVELOPING IMMUNE SYSTEM of THE INFANT

POSTER DISPLAY 01: B-CELL BIOLOGY

Jantien Wieringa[1], Mirjam Esser[2], Joyce Van Beers[2], Jan Damoiseaux[2], Gertjan Driessen[2]
[1]Haaglanden Medical Center, Paediatrics, The Hague, Netherlands, [2]Maastricht University Medical Center, Paediatrics, maastricht, Netherlands

Background and Aims: Treatment with immunomodulating chemotherapy during pregnancy might affect the developing immune system of the infant.

Methods: We describe 3 infants exposed to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) during pregnancy because of maternal B-cell lymphoma.

Results: Last infusions of R-CHOP were administered at gestational age 35 (infant 1), 34 (infant 2) and 33 weeks (infant 3). All infants were born in gestational week 36. Rituximab concentrations were 22 mcg/ml (infant1), 0.8 mcg/ml (infant 2) and 0.2 mcg/ml (infant 3) measured 1,2 and 3 months after birth respectively. Infant 3 was also exposed to infliximab because of maternal Crohn's disease, resulting in infliximab concentration of 0.5 mcg/ml at 3 months of age. In all infants IgG was decreased at 6 months. Severe (transient) B cell-lymphopenia early in life occurred in infant 1 and 2: B cells measured in first 2 months were absent but recovered within 6 months. Infant 2 was also neutropenic during these months. Leukocytes were normal in infant 3 at 3 months, but response to 10-valent pneumococcal conjugate vaccine 1 month after primary series was <0.35 mcg/ml for 4 of 5 measured serotypes. Response to vaccinations in other infants was not measured. Infant 1 and 2 received cotrimoxazole prophylaxis and infant 2 also received immunoglobulins once. No abnormal infections occurred during follow up in first year of life.

Conclusions: Chemotherapy with R-CHOP during pregnancy might affect the developing immune system of the infant, resulting in (transient) B cell lymphopenia, neutropenia, hypogammaglobulinemia and decreased response to vaccinations. Immune monitoring of exposed infants seems warranted.

Disclosure: No.

Keywords: B cells, pregnancy, immune system development, Neonate, chemotherapy

PD022

CHARACTERISATION of IMMUNE DEFECT IN COMMON VARIABLE IMMUNODEFICIENCY BY COMBINING ANTI-SPIKE ANTIBODIES AND SPECIFIC-MEMORY B-CELLS RESPONSE TO BNT162B2 IMMUNISATION

POSTER DISPLAY 01: B-CELL BIOLOGY

Federica Pulvirenti[1], Eva Piano Mortari[2], Sara Terreri[2], Cinzia Milito[3], Stefano Di Cecca[4], Andrea Palladino[5], Bianca Laura Cinicola[6,7], Eleonora Sculco[8], Giulia Di Napoli[3], Concetta Quintarelli[4], Rita Carsetti[4], Isabella Quinti[8]
[1]Regional Reference Centre for Primary Immune Deficiencies, Azienda Ospedaliera Universitaria Policlinico Umberto I, Rome, Italy, Regional Reference Centre For Primary Immune Deficiencies, Azienda Ospedaliera Universitaria Policlinico Umberto I, Rome, Italy, Roma, Italy, [2]Bambino Gesù Children's Hospital, IRCCS,, B Cell Unit, Immunology Research Area,, ROMA, Italy, [3]Sapienza University of Rome, Molecular Medicine, ROMA, Italy, [4]Bambino Gesù Children Hospital, IRCCS,, Department Onco-haematology, And Cell And Gene Therapy, ROMA, Italy, [5]Sapienza University of Rome, Dpt of Molecular Medicine, ROMA, Italy, [6]Sapienza University of Rome, Pediatric Immunology And Allergology, Rome, Italy, [7]Sapienza University of Rome, Department of Maternal Infantile And Urological Sciences, Rome, Italy, [8]Sapienza University of Rome, Molecular Medicine, Rome, Italy

Background and Aims: Immunization of CVID patients against SARS-CoV-2 allows investigation of the defective mechanisms of immune responses to a novel antigen. Heterogeneity of post-immunization antibodies reflects the variability of CVID phenotype and might represent only an epiphenomenon of a more complex immune failure.

Methods: Longitudinal study on 47 CVID adults naive to SARS-CoV-2 immunized with three-doses of mRNA-BNT162b2 vaccine. Patients were grouped by combination of serum anti-Spike-IgG and Spike-specific memory B-cells (MBCs) with low(S+) and high(S++) affinity. After stimulation(CytoStim), CD40L expression and citokines production by CD4+T-cells were assessed. Six-months later, uninfected participants were immunized by the fourth-dose.

Results: Four groups were identified: group-1 (14 patients, anti-S1-IgG levels, S+and S++MBCs, RBD-specific-MBC) with unaffected B-cell phenotype; group-2 (7 patients, anti-S1-IgG, S+MBCs) with reduced switched-MBCs; group-3 (9 patients, anti-S1-IgG) with reduced IgM- and switched-MBCs; group-4 (17 patients, undetectable anti-S1-IgG/Spike-specific MBCs) with CD19+B-cells reduction and absent MBCs. Groups-3 and-4 displayed higher incidence of pulmonary and autoimmune disorders. During follow-up, 12 participants were infected (50% from group-4). Six-months later, anti-S1-IgG antibodies were still detectable in responders. After the fourth-dose (25 patients), anti-S1-IgG levels were boostered in group-1, remaining undetectable in group-4. Only group-1 showed S++MBCs. RBD-specific-MBCs increased after the fourth-dose in groups-1 and-2, mostly IgM-isotype in group-2. Following stimulation, T-cell activation was defective in groups-2 and-3.

Conclusions: Combining specific antibodies and B-cells after immunization by mRNA-BNT162b2 differentiates patients in those with: 1) conserved germinal-center reaction and (possibile) defective plasma-cell survival (group-1); 2) combined B/T-defect (group-2 and-3, with group-3 having perturbated low-affinity IgM-type cells generation); 3) defective mature B-cells survival (group-4).

Disclosure: No.

Keywords: COVID-19, specific B-cell, combined immunodeficiency, Common variable immunodeficiency, classification, mRNA BNT162b2 vaccine

PD023

HUMAN CARMIL2 DEFICIENCY UNDERLIES A BROADER IMMUNOLOGICAL AND CLINICAL PHENOTYPE THAN CD28 DEFICIENCY: AN INTERNATIONAL STUDY of A COHORT of 89 PATIENTS

POSTER DISPLAY 02: T-CELL BIOLOGY

Romain Lévy[1], Florian Gothe[2], Carmil2 Working Group[1], Carmil2 Consortium[1], Christoph Klein[3], Jean-Laurent Casanova[4], Fabian Hauck[3], Vivien Beziat[1]
[1]University of Paris, Laboratory of Human Genetics of Infectious Diseases, Paris, France, [2]Dr. von Hauner Children's Hospital, Department of Pediatrics, Munich, Germany, [3]Dr. von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-Universität München, Department of Pediatrics, Munich, Germany, [4]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, New York, United States of America

Background and Aims: CARMIL2 is an essential scaffolding protein for CD28 costimulation in T cells. CARMIL2 deficiency causes a combined immunodeficiency, predisposing to numerous infections, whereas CD28 deficiency selectively impairs immunity to papillomaviruses, challenging our understanding of the role of CARMIL2. Patients with CARMIL2 or CD28 deficiency have defective T-cell CD28 signaling, but their immunological and clinical phenotypes have been determined from only small numbers of cases.

Methods: We undertook an in-depth characterization of the genetic, immunological, and clinical features of CARMIL2 deficiency in an international cohort of 89 patients.

Results: We show that only one of three CARMIL2 isoforms is produced and functional across leukocyte subsets. Tested mutant *CARMIL2* alleles from 89 patients impair canonical NF-kB but not AP-1 and NFAT activation in T cells stimulated via CD28. Like CD28-deficient patients, CARMIL2-deficient patients display recalcitrant warts and low blood counts of $CD4^+$, $CD8^+$ memoryT cells and $CD4^+$ T_{REGs}. Unlike CD28-deficient patients, they have low counts of NK cells and memory B cells, and their antibody responses are weak. CARMIL2 deficiency is fully penetrant by the age of 10, and is characterized by numerous viral, bactrial and fungal infections, EBV^+ smooth-muscle tumors, and mucocutaneous inflammatory lesions, including inflammatory bowel disease. Finally, we found that patients with somatic reversions of a mutant allele in $CD4^+$ T cells have milder phenotypes.

Conclusions: The phenotypic description of CARMIL2 deficiency, and dissection of CD28 signaling in patients cells, has highlighted the existence of a role for CARMIL2 extending beyond CD28 signaling in T cells, as a pleiotropic molecule orchestrating immune responses.

Disclosure: No.

Keywords: Inborn error of immunity (IEI), T cell biology, combined immunodeficiency, Genetics, CD28 signaling, NF-kappa B

PD024

EFFECT of EARLY THYMECTOMY ON LATER HEALTH

POSTER DISPLAY 02: T-CELL BIOLOGY

Rea Rantanen[1,2], Minna Honkila[1,2], Hanna-Riikka Kämä[2], Merja Kallio[1,2,3], Tytti Pokka[1,2], Jaana Pihkala[3], Otto Rahkonen[3], Ilkka Mattila[4], Merja Helminen[5], Santtu Heinonen[6,7], Eliisa Kekäläinen[8], Terhi Tapiainen[1,2]
[1]Oulu University Hospital, Department of Paediatrics And Adolescent Medicine, Oulu, Finland, [2]University of Oulu, Pedego Research Unit And Medical Research Centre Oulu, Oulu, Finland, [3]New Children's Hospital Helsinki University Hospital, Department of Pediatric Cardiology, Helsinki, Finland, [4]New Children's Hospital, Helsinki University Hospital, Department of Pediatric Surgery, Helsinki, Finland, [5]Tampere University Hospital, Department of Pediatrics, Tampere, Finland, [6]New Children's Hospital Helsinki University Hospital, Department of Pediatric, Helsinki, Finland, [7]University of Helsinki, Pediatric Research Center, Helsinki, Finland, [8]University of Helsinki, Translational Immunology Research Program, Helsinki, Finland

Background and Aims: Congenital heart defects (CHD) often require treatment with open-heart surgery in neonatal period or early infancy. In most CHD operations, the thymus is partially or totally removed. Early thymectomy has been associated with an increased risk of autoimmune diseases, cancer, and infectious diseases in small patient series. In the present case-control study, we set out to investigate the impact of thymectomy on later health in children aged 1-3, 5-7, and 13-15 years.

Methods: We sent electronic questionnaires to children identified from the Pediatric Cardiac Surgery Database (Helsinki, Finland). Control participants were retrieved from the Digital and Population Data Services Agency and matched for sex, age ja hospital district. In logistic regression analysis, adjusted odds ratios (ORs) for predefined outcomes were calculated.

Results: After excluding children with persistent severe cardiac or respiratory problems after CHD surgery, there were 207 cases and 1403 controls in the study. Children with early thymectomy had an increased risk for recurrent hospitalizations due to infections (aOR 7.9, 95% confidence interval [CI] 4.0-15.6), pneumonia (aOR 3.7, 95% CI 2.3-5.8), asthma (aOR 2.4, 95% CI 1.5-3.9), and wheezing (aOR 2.0, 95% CI 1.5-2.8). There were no statistically significant differences between cases and controls in the occurrence of otitis media, sinusitis, eczema, or autoimmune and autoinflammatory diseases in this study population.

Conclusions: In this case-control study, early thymectomy was markedly associated with an increased risk of common infections and respiratory diseases, such as recurrent hospitalizations due to infections, pneumonia, asthma, and wheezing.

Disclosure: No.

Keywords: Thymectomy, Case-control study, Congenital heart defect, infections, Respiratory diseases

PD025

PERSISTENT T LYMPHOPENIA AFTER CARDIAC SURGERY: LONG-TERM FOLLOW-UP WITH DETAILED CLINICAL AND IMMUNOLOGICAL EVALUATION

POSTER DISPLAY 02: T-CELL BIOLOGY

Tuba Karakurt[1], Royala Babayeva[2], Sevgi Bilgic Eltan[2], Cansu Melek Ayhan[3], Busra Aysu Alibas[3], Mehmet Cihangir Catak[2], Alper Bulutoglu[2], Elif Karakoc-Aydıner[2], Ahmet Ozen[2], Safa Baris[2]
[1]Istanbul Medeniyet University, Pediatric Allergy And Immunology, Kadıköy/Istanbul, Turkey, [2]Marmara University, Pediatric Allergy And Immunology, Istanbul, Turkey, [3]Marmara University, Faculty of Medicine, Istanbul, Turkey

Background and Aims: The thymus is one of the main sites responsible for T-cell lymphopoiesis in fetal and early postnatal life. Early removal of the thymus during corrective cardiac surgery(CCS) can impair the development of immune system, especially the T-cell component. Long-term effects of early thymectomy were scarcely evaluated. Herein, we evaluated the consequences of early thymectomy on the immune system of the patients underwent CCS.

Methods: Twelve patients who had thymectomy during CCS in the first year of life were included. Clinical features with immunological evaluation including immunglobulin (Ig) levels, antibody responses, and extensive lymphocyte subpopulations were assessed with a long-term follow-up.

Results: The mean age of the patients was 98.3±72.4 months with a post-operation follow-up period of 94.2 ±74.1months. At least one Ig value was low for age in 58.3% of the patients (IgG: n=5, IgA: n=3, IgM: n=5). Anti-Hbs titers were available in all patients with 75% positivity. Decreased CD3,CD4,CD8,CD19, and CD16+56 counts were observed in 66%, 66%, 50%,16%, and 16% of patients, respectively. The percentages of patients with both decreased naive CD4 and recent thymic emigrant cell were 75%. A significant correlation between the absolute lymphocyte counts and age was observed (r=-0.73,p=0,009). Three (25%) patients had severe infections requiring hospitalization during the follow-up (pneumonia: n=2, diarrhea: n=1). T-cell proliferation was evaluated in three patients and found to be normal.

Conclusions: The history of major cardiac surgery should be considered in patients presenting with T-cell lymphopenia. The lymphocyte count tends to improve with age, and serious infection is rare despite ongoing T-cell lymphopenia.(TUBITAK-318S202)

Disclosure: No.

Keywords: cardiac surgery, child, T Lymphopenia

PD026

MUTATIONS ASSOCIATED WITH CARTILAGE-HAIR HYPOPLASIA IMPAIR RIBOSOME SYNTHESIS

POSTER DISPLAY 02: T-CELL BIOLOGY

Nic Robertson[1], Vadim Shchepachev[1], David Wright[2], Tomasz Turowski[1], Christos Spanos[1], Aleksandra Helwak[1], Rose Zamoyska[2], David Tollervey[1]
[1]University of Edinburgh, Wellcome Centre For Cell Biology, Edinburgh, United Kingdom, [2]University of Edinburgh, Ashworth Laboratories, Edinburgh, United Kingdom

Background and Aims: Cartilage-hair hypoplasia (CHH) is characterised by immune dysfunction together with skeletal, hair and gastrointestinal abnormalities. CHH results from biallelic mutations in the non-coding RNA RMRP, the core of the RNA-protein complex RNase MRP. In other eukaryotes RNase MRP processes the pre-ribosomal RNA (pre-rRNA) and CRISPR-mediated disruption of RMRP in a human cell line caused pre-rRNA accumulation and growth arrest. Lymphocytes from CHH patients showed reduced proliferation in response to stimulation and increased activation-induced cell death. We aimed to determine whether disease-linked mutations cause this phenotype through a ribosome synthesis defect.

Methods: Recently developed CRISPR-based techniques were used to non-specifically mutate RMRP in primary mouse T cells, and generate human cell lines with the most common CHH-associated mutation (A71=>G) in RMRP). Pre-rRNA processing and rRNA abundance were assessed by Northern Blotting, qPCR and flow cytometry. The RNA-bound proteome of mutant cells was mapped by Total RNA-bound Protein Purification (TRAPP), a novel technique based on UV-crosslinking and mass-spectrometry of RNA-associated proteins.

Results: T cells with disrupted RMRP were viable but had reduced proliferation and impaired pre-rRNA processing. CHH patient fibroblasts and cell lines with the A71=>G mutation showed similar RNA processing defects with accumulation of 41S pre-rRNA, leading to reduced total ribosomal RNA and reduced intact ribosomes per cell. The A71=>G mutation also destabilised the association of RMRP RNA with interacting proteins.

Conclusions: We conclude that RMRP mutations cause disease by inhibiting ribosome synthesis, and provide methods to assess the efficacy of novel treatments for CHH in cellular models.

Disclosure: No.

Keywords: Cartilage-Hair Hypoplasia, RMRP, ribosomopathy

PD027

COMBINED IMMUNODEFICIENCY ASSOCIATED WITH NOVEL HOMOZYGOUS DNMT3B MUTATION

POSTER DISPLAY 02: T-CELL BIOLOGY

Samia Rekaya[1], Najla Mekki[2], Ahmed Ayari[3], Monia Ben Khaled[1], Afef Rais[2], Beya Largueche[4], Monia Ouedrni[1], Imen Ben-Mustapha[4], Mohamed-Ridha Barbouche[2]
[1]Bone MarrowTransplant Center, Tunis, Department of Pediatrics: Immunology, Hematology And Stem Cell Transplantation, Tunis, Tunisia, [2]Institut Pasteur de Tunis, Laboratory of Transmission, Control And Immunobiology of Infections (lr11ipt02), Tunis, Tunisia, [3]Children's Hospital Béchir Hamza, Tunis, Tunisia, Pediatric Intensive Care, Tunis, Tunisia, [4]Institut Pasteur de Tunis, Immunology, Tunis, Tunisia

Background and Aims: Immunodeficiency, centromeric instability and facial anomalies syndrome type1 (ICF-1) is a rare inborn error of immunity due to biallelic mutations in DNMT3B gene. Immune disease consists mainly of humoral immunodeficiency. However T-cell dysfunction and severe combined immununodeficiecny phenotype had been also reported.

Methods: Herein, we report novel homozygous DNMT3B mutation in Tunisian patient presenting in early infancy with combined immunodeficiency (CID).

Results: A 2 month-old girl born to first-degree consanguineous parents presented with hypoxic bilateral pleuropneumonia. Microbiological analysis found E.coli and Pneumocystis Jirovecci in bronchoalveolar fluid, and Candida Tropicalis in pleural fluid. At this time, complete blood count, immunoglobulin levels and NBT-test were normal. Immunophenotyping showed normal T and B but decreased NK lymphocytes. T-cell proliferation in response to mitogen and antigen was reduced. Three months later, she developped CMV infection complicated with macrophage activation syndrome and disseminated BCGitis. NGS screening was performed and confirmed a novel homozygous DNMT3B mutation (p.Gly407Ser). A reevaluation of the patient at 8 months revealed discreet facial anomalies with hypertelorism and flat nasal bridge. Moreover, immunophenotyping revealed a decline of lymphocyte count (3040cells/µl), CD4+ T-cell lymphopenia (19.9%) and a decrease in recent emigrants Tcells (33%) indicating poor thymic output and suggesting that the detectable T cells, which are mainly CD45RO+CD4 T-cells , are most likely of maternal origin. A normal numbers of circulating B lymphocytes associated to a lacks memory cells was also confirmed.

Conclusions: This description expands the clinical and immunological spectrum of immunodeficiency in ICF-1 and highlights that this disease should be managed as CID.

Disclosure: No.

Keyword: DNMT3B, NGS, ICF syndrome, T-cell Immunodeficiency

PD028

NOVEL CDC42 VARIANT ASSOCIATED WITH SCID-LIKE THYMIC OUTPUT, DECREASED IL-7R SIGNALING, DECREASED T CELL SURVIVAL AND NARROWED TCR REPERTOIRE

POSTER DISPLAY 02: T-CELL BIOLOGY

Kristian Assing[1], Sofie Jørgensen[2], Katrine Sandgaard[3], Marie Hansen[4], Mikkel Petersen[5], Ulla Hartling[6], Christian Nielsen[1], Marianne Jakobsen[1], Eleanor Watt[7], Stuart Adams[7], Qin Hao[8], Christina Fagerberg[8], Trine Mogensen[9]
[1]Odense University Hospital, Department of Clinical Immunology, Odense C, Denmark, [2]Aarhus University (AU), Department of Biomedicine, Aarhus, Denmark, [3]Aarhus University Hospital, Department of Paediatrics And Adolescent Medicine, Aarhus, Denmark, [4]Statens Serum Institut, Department For Congenital Disorders, Copenhagen, Denmark, [5]Aarhus University Hospital, Department of Clinical Immunology, Aarhus, Denmark, [6]Odense University Hospital, Department of Paediatrics, Odense C, Denmark, [7]University College London, Great Ormond Street Hospital, London, United Kingdom, [8]Odense University Hospital, Department of Genetics, Odense C, Denmark, [9]Aarhus University, Department of Biomedicine, Aarhus C, Denmark

Background and Aims: CDC42 affects a plethora of cellular functions. Reduced newborn thymic output, secondary to a human CDC42 variant, has not been reported.

Methods: Whole exome and genome sequencing was performed. We ascertained thymic output (signal joint T cell Receptor Excision Circles (sjTRECS), recent thymic emigrants, complementary determining region (CDR) 3 diversity), kappa-deleting recombination ECS, IL-7Rα surface expression and signaling, T cell proliferation and survival, innate immune sensing and NK-cell cytotoxicity in (P(atient)1) and her daughter (P2), harboring the same novel heterozygous CDC42 missense variant, but presenting with discrepant immuno-phenotypes.

Results: A novel heterozygous CDC42 variant (p.Lys16Glu) was detected in P1 and P2, P1 being a mosaic. P1's infectious history was characterized by early onset acral warts, upper and lower mucosal infections, lately dominated by HPV driven vaginal carcinogenesis. At birth (historic sample), P1 displayed normal sjTRECS levels (1742 copies/10^5 cells) which, at the age of 29 years, were nearly absent. P2 was born with SCID-like sjTRECS (< 50 copies/10^5 cells) levels, reduced RTE fractions and severe CD4+ and CD8+ lymphopenia. Their KRECS levels were normal. Surface IL-7Rα expression was decreased on CD8+ T cells (P1 + P2) and on CD4+ T cells (P2). Consistent with reduced IL-7Rα expression, reduced pSTAT5 expression, in response to IL-7, as well as increased T cell death characterized both patients. Both patients displayed markedly reduced CDR3 TCR diversity and cluster formation.

Conclusions: This is the first report documenting severely compromised thymic function, narrowed CDR3 TCR repertoire, decreased IL-7Rα expression and signaling in relation to a novel, N-terminal, heterozygous CDC42 variant.

Disclosure: No.

Keyword: CDC42, sjTRECS, CDR3, IL-7R, STAT5, cell death

PD029

COMBINED IMMUNODEFICIENCY DUE TO JAK3 MUTATION ASSOCIATED WITH REFRACTORY CMV INFECTION AND BCG-OSİS

POSTER DISPLAY 02: T-CELL BIOLOGY

Ayşe Aygün[1], Ezgi Topyildiz[2], Neslihan Karaca[3], Guzide Aksu[4], Necil Kutukculer[4]
[1]Ege university, Faculty of Medicine, Pediatric, izmir, Turkey, [2]Ege University, Depatment of Pediatric Allergy And Immunology, IZMIR, Turkey, [3]Ege University, Faculty of Medicine, Department of Pediatrics, Izmir, Turkey, [4]Ege University Faculty of Medicine, Department of Pediatrics, Izmir, Turkey

Background and Aims: Hypomorphic mutations in genes causing severe combined immunodeficiency(SCID) can cause combined immunodeficiency(CID) with residual Tcell function,late clinical presentation,autoimmunity,skin manifestations,lymphoproliferation and malignancy.

Methods: A15-month-old girl presented with frequent infections since newborn period.She was born as the dizygotic twin sister,to second-degree consanguineous healthy parents.She had recurrent sinopulmonary infections,diarrhea and CMV viremia since 3 months of age.CD3+CD4+Tcell lymphopenia and heterozygous JAK3 mutation had been observed at another hospital.She was referred for further immunologic investigation.Physical examination findings on admission.were high IgM,low IgG and IgA levels,normal/low CD3+ Tcell counts,undetectable CD3+CD4+T helper cells, elevated CD3+CD8+TCR-gamma/delta levels and low In vitro Tcell proliferative response were the pathologic laboratory findings. CMV-DNA copy was extremely high.With the knowledge that homozygous JAK3 mutations cause SCID and good clinical condition for 6 months with normal development,without any infections requiring hospitalization, the decision for HSCT was postponed.Immunologic and molecular genetic analyses were performed in her twin haploidentical sibling in order to exclude silent CID in the potential donor.She was found to carry the same heterozygous JAK3 mutation.Unfortunately,the patient began to have recurrent diarrhea,failure to thrive,bronchopneumonitis since 2 years of age.She had multiple skin abscesses on arms and abdomen.MycobacteriumBovis was isolated from abscess.

Results: She died due to sepsis and multi-organ failure.Re-analysis of WES was compatible with a homozygous mutation in JAK3 gene(p.Arg402Cys),that has not yet been described as disease-causing to date.

Conclusions: This case is presented to emphasize the CID due to JAK3 defect in patients with low/normal T cell counts,resistant CMV infection and BCG-osis.Early diagnosis and prompt HSCT is crucial for survival of these patients.

Disclosure: No.

Keywords: #scıd, cmv viremia, BCGosis, jak3, child, HSCT

PD030

ANALYSIS of CIRCULATING MIRNAS TO IDENTIFY PHENOTYPIC VARIABILITY IN ATAXIA TELANGIECTASIA PATIENTS

POSTER DISPLAY 02: T-CELL BIOLOGY

Emilia Cirillo[1], Giuliana Giardino[2], Elisabetta Toriello[3], Antonio De Rosa[3], Annarosa Soresina[4], Raffaele Badolato[5], Rosa Dellepiane[6], Patrizia Bertolini[7], Davide Montin[8], Francesca Conti[9], Antonietta Tarallo[10], Giancarlo Parenti[11], Claudio Pignata[2]
[1]University of Naples "Federico II", Translational Medical Science, Naples, Italy, [2]University of Naples "Federico II", Translational Medical Science, Napoli, Italy, [3]University of Naples, Translational Medical Science, Naples, Italy, [4]Pediatric Immunology Unit, Dpt of Pediatrics, University of Brescia,, Asst-spedali Civili Di Brescia, Brescia, Brescia, Italy, [5]Pediatrics Clinic and "A. Nocivelli" Institute for Molecular Medicine, Department of Clinical And Experimental Sciences, University of Brescia, Asst- Spedali Civili of Brescia, Brescia, Italy, [6]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlnico, Pediatric Department, Milano, Italy, [7]AOU Parma, Materno Infantile, Parma, Italy, [8]Ospedale Infantile “Regina Margherita", Pediatria Ad Indirizzo Infettivologico, Torino, Italy, [9]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Pediatric Unit, Bologna, Italy, [10]Telethon Institute of Genetics and Medicine, Tigem, Pozzuoli, Italy, [11]University of Naples "Federico II", Translational Medical Sciences, Napoli, Italy

Background and Aims: Ataxia Telangiectasia (AT) is a rare disorder characterized by cerebellar neurodegeneration, telangiectasia, immunodeficiency, cancer susceptibility. microRNAs (miRNAs) are short RNAs involved in post-transcriptional gene regulation, differentially expressed also in specific brain regions. There is evidence suggesting a role of miRNA in the ATM regulation. Aim of this study is to investigate the differential expression of miRNAs (DEmiRNA) in PBMC of AT patients

Methods: miRNA profiling was obtained from PBMC from 11 AT (4 males, age range 6-41 years) and 9 healthy subjects. Two couples of siblings were also included. DIANA-miRPath was employed to collect predicted gene targets of all significant DEmiRNAs and to characterize associated biological pathways. A correlation with phenotype and genotype has been performed.

Results: 9 patients were Caucasian, 2 of other ethnicity. Six patients had bi-allelic ATM truncating mutations. All the subjects had gait ataxia and 5 were wheelchair confined. Four patients had decreased proliferative response to PHA. Six miRNA were significantly differentially expressed in AT patients compared to control: miR365a-5p, miR3131, miR4771, miR375-3p, miR30a-3p, miR342-3p. A total of 31 KEGG pathways were significantly enriched (FDR< 0.05) including the hippo signaling pathway, prion diseases, p53 signaling pathways and various cancer-associated pathways. Mir342-3p, a tumor suppressor miRNA localized to 14q32, had a variable expression among patients.

Conclusions: miRNA profiling may reveal new molecular mechanisms potentially interfering in the pathophysiology or in the natural history of AT.

Disclosure: No.

Keywords: miRNA, T cell immunodeficiency, cancer, Ataxia Telangiectasia

PD031

PD-L1 IS EXPRESSED ON HUMAN ACTIVATED NAIVE EFFECTOR CD4+ T CELLS. REGULATION BY DENDRITIC CELLS AND REGULATORY CD4+ T CELLS

POSTER DISPLAY 02: T-CELL BIOLOGY

Fabienne Mazerolles, Frédéric Rieux-Laucat
1. Institut National de la Santé et de la Recherche Médicale, Mixed Research Unit 1163, Laboratory of Immunogenetics of Paediatric Autoimmunity- Necker Enfants Malades Hospital, PARIS, France

Background and Aims: The T cell expression of various co-signalling receptors from the CD28 immunoglobulin superfamily (Inducible T cell co-stimulator (ICOS), Programmed cell death 1(PD-1), cytotoxic T lymphocyte associated protein 4, B and T lymphocyte attenuator (BTLA) or from the tumour necrosis factor receptor superfamily (glucocorticoid-induced TNFR family related, 4-1BB and CD27), is essential for T cell responses regulation. Other receptors (such as T cell immunoglobulin and mucin domain-containing protein 3, T cell immunoglobulin and T cell immunoglobulin and ITIM domain (TIGIT), and lymphocyte activation gene 3) are also involved in this regulation. Disturbance of the balance between activating and inhibitory signals can induce autoimmunity.

Methods: We have developed an in vitro assay to simultaneously assess the function of naive $CD4^+$ effector T cells (TEFFs), dendritic cells (DCs) and regulatory T cells (TREGs) and the expression of co-signalling receptors. By running the assay on cells from healthy adult, we investigated the regulation of activated T cell proliferation and phenotypes.

Results: We observed that TEFFs activated by DCs mainly expressed BTLA and PD-1, whereas activated TREGs mainly expressed TIGIT and CD27. Strikingly, we observed that programmed death-ligand 1 (PD-L1) was significantly expressed on both activated TEFFs and TREGs. Moreover, high PD-L1 expression on activated TEFFs was correlated with a higher proliferation. In parallel to the TREG-mediated suppression of TEFF proliferation, we observed the specific modulation of the surface expression of PD-L1 on activated TEFFs.

Conclusions: Our results suggest that the regulation of T cell proliferation is correlated with the specific expression of PD-L1 on activated TEFFs.

Disclosure: No.

Keywords: Treg suppression, activated naïve CD4+ T cells, PD-L1, human, T cell proliferation

PD032

PRIMARY IMMUNE REGULATORY DISORDERS (PIRDS) THAT AMPLIFY TCR SIGNALING SHARE PATTERNS of T CELL EXHAUSTION

POSTER DISPLAY 02: T-CELL BIOLOGY

Peyton Conrey[1], Jose Campos[1], Samir Sayed[1], Andrea Mauracher[1], Diego Espinoza[2], Alana Mcsween[2], Kelly Rome[1], Clemence Queirault[1], Soma Jyonouchi[1], Neil Romberg[1], Jolan Walter[3], Helen Su[4], Jennifer Leiding[5], Megan Cooper[6], Suzanne Macfarland[7], Melanie Ruffner[1], Will Bailis[1], Jocelyn Farmer[8], V. Koneti Rao[9], Sarah Henrickson[1]
[1]Children's Hospital of Philadelphia, Division of Allergy And Immunology, Department of Pediatrics, Philadelphia, United States of America, [2]University of Pennsylvania, Perelman School of Medicine, Philadelphia, United States of America, [3]Johns Hopkins All Children's Hospital, St. Petersburg, Division of Allergy/immunology, Department of Pediatrics, St.Petersburg, United States of America, [4]National Institute of Health, Human Immunological Diseases, Bethesda, United States of America, [5]Johns Hopkins, Immunology, St. Petersburg, United States of America, [6]Washington University in St. Louis, Department of Pediatrics, Division of Rheumatology/immunology, St. Louis, United States of America, [7]Children's Hospital of Philadelphia, Division of Oncology, Philadelphia, United States of America, [8]Beth Israel and Lahey Health, Department of Medicine, Boston, United States of America, [9]National Institutes of Health, National Institute of Allergy And Infectious Diseases, Bethesda, United States of America

Background and Aims: Primary Immune Regulatory Disorders (PIRDs) are a complex subset of Inborn Errors of Immunity (IEI) that are characterized by immune dysregulation and are challenging to treat. Given that there are many ultra-rare PIRDs, it will not be feasible to design a targeted therapy for each disorder. An alternate strategy for precision medicine in PIRDs is to identify shared aspects of T cell dysfunction and strategies to target them. We have focused our studies on four PIRDs that amplify T cell receptor (TCR) signaling. Our cohort of patients includes activated PI3 kinase delta syndrome (APDS), PTEN-deficiency, [MS1] CTLA-4 haploinsufficiency and RAS-associated leukoproliferative disease (RALD).

Methods: We performed high-dimensional immune profiling via CyTOF as well as immunometabolic and mitochondrial function testing with 33 PIRD patients and a large group of age-matched healthy controls. We have also used CRISPR/Cas9 to edit CTLA-4 in healthy control CD8 T cells (CD8T) towards creating a model of CTLA-4 haploinsufficiency for perturbation studies.

Results: Across our cohort, have identified varied alterations in CD8T immunophenotype that are consistent with T cell exhaustion (e.g., altered T cell differentiation, increased levels of activation markers, inhibitory receptors and transcription factors including PD-1, CD39, TIGIT and TOX). More specifically, we have found significantly increased PD-1+CD39+ and TOX expression in CD8 T cells in APDS and RALD. Furthermore, cytokine and proliferation assays demonstrated reduced CD8 T cell function.

Conclusions: We have identified potentially targetable pathways to modulate CD8T function in PIRDs. We are developing in-vitro assays for trials of pathway perturbation in primary and gene edited CD8T.

Disclosure: No.

Keywords: Inborn errors of immunity, Activated PI3 Kinase Syndrome, RAS-associated leukoproliferative disease, PTEN-deficiency, CTLA-4 haploinsufficiency, exhaustion

PD033

P.Y153X CD247 VARIANT IS STABLE IN IMMORTALIZED T CELLS AND FORMS CD247 HETERODIMERS

POSTER DISPLAY 02: T-CELL BIOLOGY

Rebeca F Megino[1], Ana V Marin[1], Daniel Chacon-Arguedas[1], Alejandro C Briones[1], Elena García-Martínez[2], Elena Seoane-Reula[2], Carmen Rodríguez-Sainz[2], José R Regueiro[1]
[1]Complutense University of Madrid and 12 de Octubre Health Research Institute (imas12), Immunology, Ophthalomology And Ent, Madrid, Spain, [2]Gregorio Marañón Health Research Institute, Immunology, Madrid, Spain

Background and Aims: The T-cell receptor (TCR) consists of a variable heterodimer, two invariant CD3 heterodimers and a single invariant homodimer (TCRζ/CD247). CD247 is essential for TCR expression and signaling through its three ITAMs (immunoreceptor tyrosine-based activation motifs). Homozygous null mutations in *CD247* are associated with primary immunodeficiency, but carriers (+/–) show no clinical features. Such cases help to understand human TCR biology. We studied an 8-year-old female with chronic refractory immune thrombocytopenia that inherited a hitherto undescribed heterozygous mutation in *CD247* (c.459C>A, p.Y153X) predicted to truncate the third ITAM. Our aim was to stablish a cell model to recapitulate p.Y153X carrier T cells and analyze if it may affect TCR expression, structure and/or function with pathogenic relevance.

Methods: PBMC were immortalized using HTLV-1. Extra and intracellular TCR/CD3/CD247 phenotype was performed and compared between immortalized and primary CD4+ T cells by flow cytometry. Western blot was used to analyze CD247 proteins.

Results: HTLV-1 T-cell lines fully recapitulated the CD247 phenotype of p.Y153X carrier primary T cells, showing normal surface TCR levels, in contrast to +/– T cells. Western blot analyses showed a normal-sized CD247 protein (14.5 kDa), but also a smaller 14.3 kDa band, likely p.Y153X, giving rise to three CD247 dimer forms: two dominant dimers (a normal homodimer and a normal/p.Y153X heterodimer) and a minor p.Y153X homodimer.

Conclusions: We have thus developed a reliable cell model to further study TCR assembly and function and shown that p.Y153X is stable and may form frequent variant surface TCR ensembles that could be involved in the patient`s pathology.

Disclosure: No.

Keywords: CD247, CD3z, TCR, T cell receptor, Cell lines

PD034

MUTATIONS IN CARMIL2 ARE ASSOCIATED WITH PARTIAL T CELL DEFECTS AND INFECTION WITH MYCOBACTERIUM MICROTI

POSTER DISPLAY 02: T-CELL BIOLOGY

Ben Warne[1], Hoi Ping Mok[1], Rainer Doffinger[2], Nicole Gossan[3], Daniel Brown[4], Francis Scott[5], Timothy Sadler[5], Ania Manson[2], Dinakantha Kumararatne[2], Lalita Ramakrishnan[2], Effrossyni Gkrania-Klotsas[1]
[1]Cambridge University Hospitals, Infectious Diseases, Cambridge, United Kingdom, [2]Cambridge University Hospitals, Clinical Immunology, Cambridge, United Kingdom, [3]Manchester University NHS Foundation Trust, North West Genomics Laboratory Hub, Manchester, United Kingdom, [4]Cambridge University Hospitals, Neurosurgery, Cambridge, United Kingdom, [5]Cambridge University Hospitals, Radiology, Cambridge, United Kingdom

Background and Aims: A 26-year-old man presented with a scalp lesion and subcutaneous collection. Imaging revealed skull osteomyelitis and abscess/phlegmon in the extradural space. The phlegmon progressed on interval imaging with intradural extension and cerebral oedema, requiring excision of surrounding bony and dural margins. The infecting organism was found to be *Mycobacterium microti*, a member of the *Mycobacterium tuberculosis* complex that is rarely pathogenic in humans. His past medical history was notable for failure to thrive in infancy, recurrent skin infections, colitis, food allergies, asthma, eczema, renal calculi and sialectasis of the parotid glands. Immunodeficiency was suspected.

Methods: Functional immunological assays and genome sequencing of the patient were undertaken.

Results: Cytokine studies revealed significantly reduced IFN gamma, IL2, IL17 and IL10 in response to polyclonal T cell stimulation, in particular to PHA. T cell spectrotype, B cell phenotype and vaccine responses were normal. Whole genome sequencing revealed distinct variants in each copy of the CARMIL2 gene: NM_001013838.1:c.1544dup p.(Leu515PhefsTer16), a frameshift mutation classified as pathogenic and NM_001013838.1:c.1869C>A p.(Asp623Glu), a variant located in an evolutionarily constrained region previously found in a homozygous state in a patient with inflammatory bowel disease. A diagnosis of immunodeficiency 58 (OMIM 610859) was made. The patient is being treated with antimycobacterial agents and repeat debridement.

Conclusions: This patient, a compound-heterozygote for distinct CARMIL2 variants that are likely to be pathogenic, acquired an infection by a poorly pathogenic mycobacterium. CARMIL2 mutations should be considered as causes for Mendelian susceptibility to mycobacterial disease (MSMD).

Disclosure: No.

Keywords: T cell dysfunction, CARMIL2, Mendelian susceptibility to mycobacterial disease, Immunodeficiency 58

PD035

BED-TO-BENCH PATIENT-DERIVED T LYMPHOCYTE DEFICIENCY CELL MODELS

POSTER DISPLAY 02: T-CELL BIOLOGY

Daniel Chacon-Arguedas, Rebeca F Megino, Ana V Marin, José R Regueiro
Complutense University of Madrid and 12 de Octubre Health Research Institute (imas12), Immunology, Ophthalomology And Ent, Madrid, Spain

Background and Aims: Inborn errors of immunity due to T Cell defects are rare and clinically severe, causing a fast deterioration of the patient with fatal consequences. Hematopoietic Stem Cell Transplantation is the best treatment, but once performed, valuable biological material to study the physiopathology of the defect is lost. Our aim was to establish cell models of congenital T-cell immunodeficiency patients: $CD247^{-/-}$ and $CD247^{+/-}$ (Marin AV, *et al*, J Allergy Clin Immunol. 2017 Jan;139(1):347-349.e8), $CD3D^{\Delta Ex2/\Delta Ex2}$ (Gil J *et al*, J Clin Invest. 2011 Oct;121(10):3872-6).

Methods: To this end, PBMC were co-cultured with HTLV-1-producing γ-ray-irradiated MT2 cells in presence of IL-2 and PHA-L. Cells were kept in culture for at least 1 month and then phenotyped for CD4, TCRαβ and CD3. Functional studies included CD69/CD137 induction and CD3/TCRαβ dow-regulation after CD3 engagement.

Results: We obtained stable cell lines from all the patients, including $CD247^{+/-}$ revertant T-cells from a $CD247^{-/-}$ patient. All lines were $CD4^{+}$, they proliferate in the presence of IL-2, and they recapitulated the T-cell phenotype and function reported for the patient which they were derived: $CD3^{-}$ $TCR\alpha\beta^{-}$ phenotype with poor CD69/CD137 induction for $CD247^{-/-}$ and $CD3D^{\Delta Ex2/\Delta Ex2}$ T-cells, and $CD3^{int}$ $TCR\alpha\beta^{int}$ phenotype for $CD247^{+/-}$ T-cells with moderate CD3-induced function relative to a normal control.

Conclusions: In summary, T-cell lines resembling the phenotypical and functional status of congenital T-cell immunodeficiency patients can be obtained using HTLV-1 as a valuable tool and models to performed in-deep studies of T-cell and TCR physiopathology.

Disclosure: No.

Keywords: T-cell, cell model, Inborn errors of immunity, T-cell physiopathology, disease model

PD036

SKIN MANIFESTATIONS IN ADULTS WITH CHRONIC GRANULOMATOUS DISEASE (CGD) IN THE UNITED KINGDOM

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Luiza Campos[1], Carla Henríquez[2], Bodo Grimbacher[3], David Lowe[1], George Meligonis[4], Catherine Orteu[5], Siobhan Burns[1]
[1]UCL, Institute of Immunity And Transplantation, London, United Kingdom, [2]Albert-Ludwigs-University of Freiburg, Center For Chronic Immunodeficiency, Freiburg, Germany, [3]Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany, [4]Royal Free Hospital, Histopathology Department, London, United Kingdom, [5]Royal Free Hospital, Dermatology Department, London, United Kingdom

Background and Aims: Although skin is commonly affected in CGD, cutaneous manifestations of the disease are poorly documented and often misdiagnosed. Our aim was to characterize skin manifestations in a large cohort of uncorrected adult CGD patients and provide guidance for clinicians treating these patients.

Methods: Clinical records of adult CGD patients cared for at the Royal Free Hospital were assessed. Patients transitioned to adult services (>16years) with no prior corrective hematopoietic stem cell transplantation or gene therapy were included. Medical photographs of skin lesions were examined and classified by an experienced dermatologist. Histology was reviewed in an MDT including the pathologist, immunology clinicians and dermatologist.

Results: 35 patients had skin manifestations, representing 59% of our CGD adult cohort. 83% had 2 or more types of skin lesions, which were classified as: (i) CGD-related pustular eruptions (acneiform folliculitis, papulonodular pustular eruptions, micropapular pustular eruptions), (ii) abscesses and furuncules (iii) hidradenitis suppurativa, (iv) facial erythema (seborrheic dermatitis, rosacea, mucocutaneous lupus), (v)orofacial granulomatosis and (vi) eczema. The most frequent manifestations were pustular eruptions, present in 80% of the patients. Skin abscesses occurred in areas with background folliculitis. Seborrheic dermatitis (SD) affected 43% of the patients. Rosacea and cutaneous lupus represented each 11% of the skin manifestations. Rosacea usually overlapped with SD. 3 patients had orofacial granulomatosis. 60% of the biopsies showed granulomas and were all negative in stains for pathogens.

Conclusions: Skin disease is common in adults with CGD and can be classified into discreet subgroups, requiring specific management. Specialist dermatology input is important for diagnosis and management.

Disclosure: No.

Keywords: Chronic Granulomatous Disease, skin manifestations, cutaneous lesions, CGD

PD037

IDENTIFICATION of POTENTIAL CORE FUNCTIONS IN HUMAN IMMUNE RESPONSES of GENES WITH PREVIOUSLY UNKNOWN FUNCTION

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Emil Vorsteveld[1,2], Simone Kersten[1,2], Caspar Van Der Made[1,2,3], Charlotte Kaffa[4], Marloes Steehouwer[2], Mihai Netea[1,3], Alexander Hoischen[1,2,3]
[1]Radboud University Medical Center, Internal Medicine, Nijmegen, Netherlands, [2]Radboud University Medical Center, Human Genetics, Nijmegen, Netherlands, [3]Radboud University Medical Center, Internal Medicine, Radboud Center For Infectious Diseases (rci), Nijmegen, Netherlands, [4]Radboud University Medical Center, Center For Molecular And Biomolecular Informatics, Nijmegen, Netherlands

Background and Aims: Inborn errors of immunity (IEI) is a group of heterogeneous genetic disorders of the immune system. Exome and genome sequencing leads to a diagnosis in 15-30% of IEI cases, indicating a potential for improvement, in part through the identification of novel genes with a role in the immune system and, in turn, in IEIs. We aimed to identify potential core genes in the human innate immune response using RNA sequencing.

Methods: We applied QuantSeq 3' mRNA sequencing of peripheral blood mononuclear cells (PBMCs) from 5 healthy donors stimulated in vitro with LPS, S. Aureus, PolyIC and C. Albicans for 4 and 24 hours to mimic early and late innate immune responses to gram-negative and gram-positive bacteria, viruses and fungi, respectively.

Results: Overlapping genes differentially expressed in response to all four stimuli allowed for the identification of genes that have a potential core functions in innate immunity, which include four uncharacterized "Corf" and "KIAA" genes; KIAA0040, C11orf21, C1orf122 and C15orf48. However, the latter has been recently found to be implicated in the regulation of inflammation and immunity.

Conclusions: These results indicate the potential for the characterization of the innate immune response, which provides candidate genes that may play a role in the pathogenesis of IEIs. We will reanalyse the genetic variants in these uncharacterized genes in exomes of IEI patients in our in-house database, potentially contributing to the growing number of genes implicated in IEIs and for the diagnosis of patients using previously missed disease-causing variation.

Disclosure: No.

Keywords: Transcriptomics, Innate Immunity, Genetics

PD038

CHARACTERIZATION of A NOVEL HETEROZYGOUS TICAM1/TRIF MUTATION IN A SINGLE FAMILY

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Dorit Verhoeven[1], Ira Sabli[2], Stephanie Hodeib[2], Mirkomol Mirzarakhimov[2], Machiel Jansen[3], Ester Van Leeuwen[3], Marc Hilhorst[4], Godelieve De Bree[4], Vanessa Sancho-Shimizu[2], Taco Kuijpers[1]
[1]Amsterdam UMC, Department of Pediatric Immunology, Rheumatology And Infectious Disease, Amsterdam, Netherlands, [2]Imperial College London, Department of Paediatric Infectious Diseases & Virology, London, United Kingdom, [3]Amsterdam UMC, Department of Experimental Immunology, Amsterdam, Netherlands, [4]Amsterdam UMC, Department of Internal Medicine, Amsterdam, Netherlands

Background and Aims: Toll/IL-1R (TIR) domain-containing adaptor inducing IFN-β (TRIF) is a cytosolic adaptor, facilitating signaling of Toll-like receptors (TLRs) 3/4. TRIF mediates signaling cascades activating downstream transcription factors NFκB, AP-1 and IRF3/7, which results in the production of type I interferons (IFNs) and pro-inflammatory cytokines. Mutations in TICAM1/TRIF have been linked to an increased predisposition to developing Herpes Simplex virus (HSV) encephalitis (HSE). This study describes a new kindred with four family members harboring a novel mutation in the TICAM1/TRIF gene with variable clinical presentation. The index case was a female patient evaluated for recurrent HSV-2 meningeal infections starting from the age of 20.

Methods: DNA sequencing was conducted and identified a heterozygous mutation (c.1285G>T, p.(Glu429*)) causing a stop codon in the TICAM1/TRIF gene. Variant impact on the TLR3-signaling pathway was assessed.

Results: Incomplete clinical penetrance in this family was evident. The genetically affected grandmother suffers from a currently unexplained small fiber neuropathy but never developed HSE, while being seropositive for HSV-IgG. Index patient dermal fibroblasts showed an impaired production and release of IFN-β and IFN-λ1 upon TLR3-agonist poly(I:C) and TLR4-agonist LPS stimulation. An IFN-β luciferase reporter assay showed inability of the TRIF mutant to induce any activity in contrast to WT TRIF. Moreover, patient monocytes showed residual but reduced phosphorylation of IRF3 and NFκB-p65 upon poly(I:C) stimulation, but normal IFN responses measured by pSTAT1 and CD169 upregulation.

Conclusions: These data identifies TRIF deficiency as the etiology of adult-onset recurrent HSV-2 meningitis, indicating that TRIF is important for the control of cerebral HSV-2 infection.

Disclosure: No.

Keywords: Toll like receptor 3 (TLR3), Type I interferons (IFNs), TICAM1/TRIF, Herpes simplex virus-2 (HSV-2), HSV-2 meningitis, TRIF deficiency

PD039

SEEKING ILC'S TRUE COLOURS - PANEL DESIGN FOR MULTIPARAMETRIC ANALYSIS of HUMAN INNATE LYMPHOID CELLS USING SPECTRAL FLOW CYTOMETRY

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Sarah Benezech[1,2], Thierry Walzer[2], Alexandre Belot[2,3]
[1]Institut d'Hematologie et Oncologie Pediatrique, Paediatric Hematology And Immunology, LYON, France, [2]Centre International de Recherche en Infectiologie, Inserm U1111, Lyon, France, [3]Hospices Civils de Lyon, Hfme, Rheumatology Department, Bron, France

Background and Aims: Innate lymphoid cells (ILCs) are major components of innate immune response. Shifts in phenotypes of human ILCs subsets among the 5 described to date (i.e. Natural Killer (NK) Cells, ILCs 1, 2, 3 and Lymphoid Tissue Inducer Cells) have been depicted in various inflammatory and dysimmune conditions. However, studies are still limited due to the absence of clear phenotype for human ILCs 1 and overall plasticity of ILCs. Here we present a 39 parameter, 35-colour full spectrum flow cytometry panel dedicated to in-depth analysis of circulating ILCs subsets in cryopreserved human peripheral blood mononuclear cells (PBMCs), and including an integrated cytometric interferon signature.

Methods: Design and optimization of this panel was performed on Cytek®Aurora-5L, on cryopreserved PBMCs samples from healthy controls and pediatric patients presenting with dysregulated type I/II IFN signaling.

Results: In addition to an extensive characterization of NK cells maturation, activation, and exhaustion profile, classical supervised analysis allowed a precise and reliable discrimination of circulating ILCs 1, 2 and 3 in healthy controls as well as in pathological conditions. Cytometric IFN signature was reliably correlated with the IFN signature as assessed by gold standard technique with gene expression (NanoString nCounter). Unsupervised analysis was able to highlight major phenotypic trends of ILCs through the course of diverse immune conditions.

Conclusions: First implementation of this panel will be dedicated to explore the impact of chronic interferon signaling on ILCs phenotype and function, and conducted on a series of pediatric patients presenting with interferon-signaling dysregulation associated diseases.

Disclosure: No.

Keywords: flow cytometry, Innate Lymphoid Cells, Natural Killers Cells, Interferonopathies

PD040

ABNORMAL NK CELL DIFFERENTIATION IN A DEF6 DEFICIENT PATIENT

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Giovanna Perinetti Casoni[1], Tessa Campbell[1], Donatella Galgano[2], Marie Meeths[3], Peter Priftakis[4], Yenan Bryceson[1]
[1]Karolinska Institutet, Medh (herm), Huddinge, Sweden, [2]Instituto Nazionale di Genetica Molecolare “Enrica e Romeo Invernizzi", Ingm, Milano, Italy, [3]Karolinska Institutet, Department of Women's And Children's Health, Stockholm, Sweden, [4]Karolinska University Hospital, Astrid Lindgren Children’s Hospital, Stockholm, Sweden

Background and Aims: Autosomal recessive mutations in DEF6, encoding a small GTPase activating protein, have recently been associated with autoimmunity and increased susceptibility to severe herpes virus infections. Recurrent herpes virus infections are a hallmark of NK cell deficiencies, but their phenotype and function has not been extensively studied in DEF6 deficiency. We assessed the NK cell phenotype of one patient with DEF6 deficiency. In blood, the patient displayed an unusually high frequency of immature $CD56^{bright}$ NK cells, whereas the frequency of terminally differentiated $CD56^{dim}CD16^{+}CD57^{+/-}$ NK cells was reduced. Therefore, we decided to study the role of DEF6 in NK cell function and differentiation.

Methods: By flow cytometry-based assays, we studied cell proliferation, adhesion and IL-15 uptake in wild type and DEF6 knock-out primary human NK cells. We are now investigating other pathways by RNA-sequencing in DEF6 knock-out human NK cells.

Results: In healthy individuals, DEF6 protein expression increased throughout NK cell differentiation. Knock-out of DEF6 in human NK cells did not impair IL-15 mediated proliferation. Nor did DEF6 knock-out interfere with NK cell adhesion.

Conclusions: Our findings suggest a role for DEF6 in the regulation of NK cell differentiation that contributes to the susceptibility of patients to herpes virus infections.

Disclosure: No.

Keywords: Cell Differentiation, natural killer, IEI

PD041

NEUTROPHIL FUNCTION AND ADAPTIVE IMMUNE SYSTEM ABNORMALITIES IN LAD I AND LAD III DEFICIENT PATIENTS

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Inga Sakovich[1], Ekaterina Polyakova[1], Olga Pashchenko[2], Sevan Iritsian[3], Anna Hilfanova[4], Anastasiia Bondarenko[4], Oksana Boyarchyk[5], Svetlana Vakhlyarskaya[6], Ludmila Gankovskaya[2], Tatjana Prokofjeva[7], Mikhail Belevtsev[1], Alla Volokha[4], Dariia Zabara[8], Aleksandra Kupchinskaya[1], Yulia Mareika[1], Nina Minakovskaya[1], Irina Kondratenko[6], Olga Aleinikova[1], Svetlana Sharapova[1]
[1]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Research Department, Borovlyany, Belarus, [2]Pirogov Russian National Research Medical University, Immunology Department, Moscow, Russian Federation, [3]National Institute of Health, Department of Haematology And Transfusion Medicine, Yerevan, Armenia, [4]Shupyk National Medical Academy for Postgraduate Education, Department of Pediatric Infectious Diseases And Pediatric Immunology, Kyiv, Ukraine, [5]I.Horbachevsky Ternopil National Medical University, Department of Children's Diseases And Pediatric Surgery, Ternopil, Ukraine, [6]Russian Children's Clinical Hospital of Pirogov Russian National Research Medical University, Clinical Immunology And Rheumatology Department, Moscow, Russian Federation, [7]Children's Clinical University Hospital, Pediatric Clinic, Riga, Latvia, [8]National Academy of Medical Sciences of Ukraine, Institute of Pediatrics, Obstetrics And Gynecology Named After Academician O.m. Lukyanova, Kyiv, Ukraine

Background and Aims: Leucocyte adhesion deficiency is rare autosome-recessive disorder, characterized impaired leucocyte migration and severe life-threating infections. LAD-deficiency is usually fatal; few patients survive to adulthood without HSCT.

Methods: We present evaluation of neutrophil function (adhesion molecules expression, migration, respiratory burst) and lymphocytes subsets in 10 patients with genetically-confirmed LAD-I(n=7) and LAD-III(n=3).

Results: LAD-I-cohort enrolls patients in the age from 12d-21yrs at the moment of investigation. 3/7 with complete CD18-deficiency underwent HSCT and/or died in the first years of life, therefore Immunological tests were restricted and included standard lymphocytes subsets evaluation, revealed only decreased CD4+-T-cells percentage (p=0.049). Cohort with partial CD18-deficiency(9-21yrs) includes patients: with CD18-brigh lymphocytes subset (n=2), with “weak” CD18-expression on all leucocytes (n=2). In this cohort neutrophil migration was partially preserved (up to 50% of normal); 2pt have “hyperactivated” neutrophil phenotype (↓CD62L and ↑CD35-expression) and enhanced “respiratory burst” to fMLP (>90%). Partial-CD18-deficient patients have decreased percentage of Naïve-CD4+ T-cells(p=0.0085), RTE(p=0.0001) and Tregs(p=0.0247) compared to HC. Both switched and non-switched B-memory cells were variable: from normal-to-elevated (n=2) to decreased-to-absent (n=2). Also CD21low(p<0.0001, p=0.0068) and CD21lowCD38low(p=0.0077, p=0.038) B-cells percentage and absolute number were elevated. LAD-III deficient cohort includes 3 patients from 2 families (3-6yrs, 1pt-died, 2pts- HSCT). In this cohort predominantly B-cells lymphocytosis (50-60%of lymph, >12000cells/μL) was noted. Almost all B-cells were B1(CD5+, >80%of B-cells).

Conclusions: Patients with partial LAD-deficiency have sings of immunodysregulation, such as decreased naïve CD4+-T-cells, Tregs, elevated CD21low and CD21lowCD38low B-cells and neutrophils hyperactivation, that can result to increased risks of autoimmune and autoinflammatory complications.

Disclosure: No.

Keywords: Leucocyte adhesion deficiency, immunodysregulation, neutrophil function, B-cells

PD042

P2Y12 IS A NOVEL DRUGGABLE TARGET FOR BLOCKING MACROPHAGE-MYOFIBROBLAST TRANSITION DRIVEN CANCER-ASSOCIATED FIBROBLAST FORMATION IN LUNG CARCINOMA

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Max Kam-Kwan Chan[1], Chiu Tsun Philip Tang[1], Ka-Fai To[1], Hui-Yao Lan[2], Patrick Ming-Kuen Tang1[1]
[1]The Chinese University of Hong Kong, Department of Anatomical And Cellular Pathology, Hong Kong, Hong Kong PRC, [2]The Chinese University of Hong Kong, Department of Medicine And Therapeutics, Li Ka Shing Institute of Health Sciences,, Hong Kong, Hong Kong PRC

Background and Aims: Macrophage-MyofibrlbalstMyofibroblast Transition (MMT) is a newly discovered Smad3-dependent mechanism for directly promoting the generatingdirect generation of protumoral cancer-associated fibroblasts (CAF) in thefrom tumor microenvironment via a macrophage Smad3 dependent manner, better-associated macrophages (TAM). Better understanding of its regulatory mechanism would uncover theraputic targetnovel therapeutic targets for developing its precision medicationmedicine against CAF-driven non-small-cell lung carcinoma (NSCLC)

Methods: By conducting high -resolution single-cell RNA-sequencing with bone marrow -derived macrophages (BMDM), we identified P2Y12 as a novel Smad3 direct target gene in the cells undergoing TGF-β-driven MMT in vitro.

Results: We found that macrophage P2Y12 level significantly correlated to the CAF abandanceabundance and associated with thepoorer overall survival of NSCLC patients. Genetic silencing of macrophage P2Y12 markedly suppressed MMT-driven myofibroblast formation and protumoral effectors in vitro and in vivo. Encouragingly, pharmaceutical inhibition of P2Y12 with FDA-approved P2Y12 inhibitor Clopidogrel effectively blocked MMT and associated-driven CAF formation and cancer progression in mice bearing sygeneicsyngeneic lung carcinoma LLC as well as human NSCLC xenograft in vivo.

Conclusions: Thus, we successfully identified macrophage P2Y12 as a druggable target for presielyprecisely targeting MMT-driven protumoral CAF formation in lung carcinoma.

Disclosure: No.

Keywords: immunity, cancer, P2Y12, Macrophage-Myofibroblast Transition, Tumor microenvironment

PD043

ASSESSMENT of THE IN VITRO IMMUNOMODULATORY CAPACITY of INTRAVENOUS IMMUNOGLOBULIN USING A NEW DEVELOPED AND VALIDATED METHOD

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Alexandra Serra[1], Carolina Romero[2], Elisabeth Calderón[3], Núria Marzo[1], Jose Maria Diez[2], Berta Pons[1], Maite Lopez[1], Salvador Grancha[1]
[1]Grifols, Research And Development, Barcelona, Spain, [2]Grifols, Immunotherapies Unit, Bioscience R&d, Scientific Innovation Office, Barcelona, Spain, [3]Grifols, Scientific And Medical Affairs, Barcelona, Spain

Background and Aims: The immunomodulatory and anti-inflammatory effects of intravenous immunoglobulins (IVIG) are associated with the modulation of pro-inflammatory cytokines. AIM: to assess an in vitro cell culture assay to measure the immunomodulatory capacity of the IVIG.

Methods: Peripheral blood mononuclear cells (PBMCs) were stimulated with stimuli (phorbol 12-myristate-13-acetate and ionomycin [PMA/iono], lipopolysaccharide [LPS]) for 4 h, followed by incubation with IVIG (5-25 mg/mL) at different times (24 h and 48 h). IL-6 and TNF-α cytokine levels were determined by ELISA and cell viability by flow cytometry. Experimental conditions which yielded the highest and most reproducible cytokine inhibition were validated by measuring sensitivity, specificity, precision, accuracy, linearity, and range.

Results: IVIG markedly inhibited LPS-stimulated IL-6 secretion (5 and 20 mg/mL, 56% and 87% reduction) and PMA/iono-stimulated TNF-α secretion (20 mg/mL, 52% reduction). No differences in cytokine levels were observed at different incubation times. Higher IVIG concentrations significantly correlated with reduced cytokine levels (IL-6, r=0.990, P=0.010; TNF-α, r=0.994, P=0.006), without decreasing cell viability (IL-6, r=0.196, P=0.804; TNF-α, r=0.085; P=0.915). The assay was validated measuring IL-6 secretion in IVIG-treated PBMCs (20 mg/mL, 24h), with excellent performance: sensitivity (100%), specificity (100%), intra-assay and inter-assay precision (coefficient of variation 4.78% and 4.97%, respectively), accuracy (recovery, 96.67%), linearity ($R^2 \geq 0.9923$) and range (0-800 pg/mL).

Conclusions: IVIG markedly inhibited LPS-stimulated IL-6 secretion without decreasing cell viability, demonstrating the immunomodulatory capacity of IVIG. A robust and reproducible method has been successfully developed and validated.

Disclosure: The authors of the study are full-time employees of Grifols, a manufacturer of intravenous immunoglobulins

Keywords: immunomodulatory, intravenous immunoglobulins, interleukin-6, cytokines

PD044

VERY LATE-ONSET CHRONIC GRANULOMATOUS DISEASE: FACT OR ARTIFACT?

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Jose Marcos Cunha[1], Raphael Roubach[1], Maria Clara Galhardo[2], Marise Mattos[1,2]
[1]Federal University of Rio de Janeiro, Internal Medicine, Rio de Janeiro, Brazil, [2]INI/FIOCRUZ, Infectious Diseases, Rio de Janeiro, Brazil

Background and Aims: An 87-year-old male patient, with no previous history of relevant infections until age 85, was referred for investigation after an unusual recurrence of cutaneous infections: i) pyogenic granuloma with osteomyelitis of the right thumb, ii) paronychia in the right hallux, and iii) extensive locoregional reaction to COVID19 vaccine (Pfizer) in the right arm, with isolation of Burkholderia gladioli, Candida albicans plus Stenotrophomonas maltophilia and Apiotrichum montevideense, respectively. He also had pleural effusion associated with granulomatous pleuritis, with isolation of Burkholderia cepacia. There was suture dehiscence at the pleural biopsy site. Additionally, he had septic shock associated with toe intertrigo with isolation of Serratia marcescens and Fusarium solani. All infections improved slowly after proper antimicrobial treatment.

Methods: After an extensive and inconclusive laboratory workup, neutrophil superoxide production was investigated by flow cytometry using dihydrorhodamine (DHR) test.

Results: Neutropenia and antibody deficiencies were ruled out. DHR test showed a complete lack of oxidative burst in patient's neutrophils, with negligible fluorescence shift, in contrast to marked fluorescence increase in both healthy donor and age-matched control. This profile is consistent with X-linked CGD. Continuous prophylaxis with sulfamethoxazole/trimethoprim was started after diagnosis.

Conclusions: This report emphasizes the importance of recognizing unusual clinical manifestations and their respective causative pathogens should prompt the investigation of functional phagocyte defects regardless of patients' age. Clonal hematopoiesis is a possible mechanism to explain the phenotype reported herein. Molecular diagnosis is essential to better define this diagnosis.

Disclosure: No.

Keywords: Chronic Granulomatous Disease, skin infections, vaccine adverse event, elderly

PD045

PRIMARY IMMUNODEFICIENCY IN COMBINATION WITH FALLOT TETRALOGY AND THROMBOCYTOPENIA IN A PATIENT WITH JACOBSEN SYNDROME; CASE REPORT

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Öner Özdemir, Ümmügülsüm Dikici
Sakarya University Medical Faculty, Pediatric Allergy And Immunology, Sakarya, Turkey

Background and Aims: Jacobsen syndrome (JS) is characterized by growth and psychomotor retardation, facial dysmorphism, multiple congenital abnormalities, and thrombocytopenia. Here, we present a patient with JS with primary immunodeficiency and multiple abnormalities.

Methods: Case presentation: A 2-year-old female patient was consulted with the pediatric immunology due to multiple hospitalizations due to frequent infections. The patient had been undergone thru surgery for tetralogy of Fallot when she was 4-month-old and had persistent thrombocytopenia. Physical examination revealed mental and growth retardation, trigonocephaly, upward palpebral fissures, operation scar on the sternum, and a 2-3/6 systolic murmur.

Results: Hemogram showed WBC was 5.550/mm3, neutrophil 3.740/mm3, lymphocyte 1.480/mm3, platelet 73.000/mm3. In the past laboratory evaluations, thrombocytopenia and lymphopenia were persisted as well. Immunologically IgG 573 mg/dL, IgA 32 mg/dL, IgM 33 mg/dL, CD3: 42%, CD4: 17.6%, CD8: 23%, CD19: 26.7% , CD16 24.2%, anti-A: 1/8 positive and Anti-HBs was 23.71. Intravenous immunoglobulin (IVIG) replacement therapy was started at 0.5 g/kg once a month. Clinical benefit was seen in the patient with IVIG treatment. Genetic screening was compatible with Jacobsen syndrome.

Conclusions: Jacobsen syndrome is caused by a terminal deletion on the long arm of chromosome 11 and has an estimated prevalence of 1 in 100.000 newborns. Clinical manifestations are diverse and are frequently associated with Paris Trousseau syndrome, which is characterized by thrombocytopenia and platelet dysfunction. In addition, antibody deficiency is a common finding in patients with JS.

Disclosure: No.

Keyword: Jacobsen Syndrome, congenital heart disease, primary immunodeficiency, Paris- Trousseau Syndrome

PD046

NEUROCOGNITIVE EVALUATION of PATIENTS WITH DI GEORGE SYNDROME

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Zuhal Karali[1], Sukru Cekic[1], Yasin Karali[1], Sara Sebnem Kilic[2]
[1]Uludag University Faculty of Medicine, Pediatric Immunology And Allergy, Bursa, Turkey, [2]Uludag University, Faculty of Medicine, Pediatric Immunology, Bursa, Turkey

Background and Aims: We aimed to evaluate the clinical, laboratory, radiological, and neuropsychological findings of our patients diagnosed with Di George Syndrome (DGS) in this study.

Methods: Patients with DGS between June 2001-March 2022 were included in the study. Clinical and laboratory data were evaluated retrospectively. Neuropsychological tests were applied to the patients to evaluate their neurocognitive findings.

Results: Fifty-two patients (28 male and 24 female) were included in our study. Thirteen of the patients died in the follow-up. The median age was 10 years 7 months (2 months- 49 years 5 months) and the median age at diagnosis was 5 years and 4 months (1 month- 48 years 1 month) of the patients. Among 37 patients, who have been followed up, 27 (72.9%) had cardiac pathologies, 15 had hypoparathyroidism. Thirteen (35.1%) patients developed an autoimmune disease. Two patients had cancer (Non-Hodkin lymphoma and mycosis fungoides). Bilateral conduction deceleration in the anterior visual pathways in 6 (20%) of 30 patients was determined by the VEP (Visual Evoked Potentials). The auditory brainstem evoked potential test (BAEP) showed sensorineural hearing loss in 11 out of 30 patients. Cranial MRI disclosed developmental brain abnormalities in 20 out of 25 patients. Impairments were noted in executive functions, expressive language, verbal memory in twenty patients who were neuropsychologically assessed. Immunological investigation 54% of patients had low IgM levels, 51.3% of patients had an absolute CD3 count <1500/mm3.

Conclusions: Awareness of the potential for underlying neurologic disorders is key to anticipatory guidance, optimization of therapies, and maximizing life quality.

Disclosure: No.

Keywords: Neuropsychological tests, Di George syndrome, Neurocognitive

PD047

AN X-CGD PATIENT WITH AGGREGATIBACTER APHROPHILUS CERVICAL LYMPHADENITIS COMPLICATED WITH LEMIERRE SYNDROME

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Tiphaine Arlabosse[1], Margherita Plebani[2], Tom Stoelers[3], Isshak Mrabet Deraoui[3], Raffaele Renella[4], Michaël Hofer[1], Fabio Candotti[5], Katerina Theodoropoulou[1]
[1]Pediatric Immuno-Rheumatology of Western Switzerland, Service of Pediatrics, Department Women-Mother-Child, Chuv, Lausanne, Switzerland, [2]Pediatric Infectiology Unit, Service of Pediatrics, Department Women-Mother-Child, Chuv, Lausanne, Switzerland, [3]Department of pediatrics, Rhne, Neuchâtel, Switzerland, [4]Pediatric Hematology-Oncology Unit, Service of Pediatrics, Department Women-Mother-Child, Chuv, Lausanne, Switzerland, [5]Division of Immunology and Allergy, Chuv, Lausanne, Switzerland

Background and Aims: Patients with chronic granulomatous disease (CGD) are highly susceptible to infections by fungi and catalase-positive bacterial strains. We report on a 10-year-old boy with X-CGD hospitalized for an episode of Lemierre syndrome complicating a cervical lymphadenitis caused by Aggregatibacter aphrophilus, a commensal bacterium of the upper respiratory tract and a rather unexpected pathogen in CGD due to its catalase-negative property. Notably, Aggregatibacter aphrophilus has never been described in association with Lemierre syndrome.

Methods: Case report.

Results: The second child of non-consanguineous parents, the patient has a family history positive for Crohn's Disease, cutaneous lupus and rosacea in the mother, as well as recurrent oral aphtosis and rosacea in the sister. His medical history was remarkable for abscessed cervical lymphadenitis at age 8 and necrotic pneumonia at age 9. The most recent event was characterized by fever, tender cervical adenopathy, trismus and chest pain. CT scan revealed suppurated cervical lymphadenitis, segmental internal jugular vein thrombosis, and multiple pulmonary nodules compatible with septic emboli, indicating Lemierre syndrome. Cervicotomy and drainage were performed and intravenous antibiotics were initiated. Catalase-negative, facultative anaerobic Aggregatibacter aphrophilius was identified and confirmed by metagenomic analysis. No fusobacterium species were identified. The outcome was favorable. Immunological workup revealed a severely reduced dihydrorhodamine (DHR) oxidation suggestive of CGD. The mother and sister showed biphasic DHR oxidation patterns compatible with an X-linked genetic transmission. Mutation analysis is ongoing.

Conclusions: Patients with CGD can suffer from life threatening infections by catalase-negative bacteria, such as Aggregatibacter aphrophilius that can lead to Lemierre syndrome.

Disclosure: No.

Keywords: Chronic Granulomatous Disease, CGD, Aggregatibacter aphrophilius, Lemierre syndrome

PD048

A DIAGNOSIS of VERY EARLY-ONSET of CHRONIC GRANULOMATOUS DISEASE (CGD) IN A NEONATE

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Theodora Papastamatiou[1,2], Sofia Tantou[2], Kassandra Tataropoulou[3], Kelly Syggelou[3], Eirini Eleutheriou[3], Marianna Tzanoudaki[2], Maria Kanariou[4], Manolis Liatsis[2], Nikos Spyridis[3]
[1]Aglaia Kiriakou Hospital, 2nd Department of Pediatrics of The National And Kapodistrian University of Athens, ATHENS, Greece, [2]"Aghia Sophia" Children's Hospital, Dept. of Immunology & Histocompatibility, AΘHNA, Greece, [3]Aglaia Kiriakou Hospital, 2nd Department of Pediatrics of The National And Kapodistrian University of Athens, AΘHNA, Greece, [4]IASO CHILDRENS HOSPITAL, 1st Pediatric Dpt, AΘHNA, Greece

Background and Aims: Presentation of Chronic Granulomatous Disease (CGD) may be easily overlooked in neonatal period. CGD is characterized by recurrent life-threatening bacterial and fungal infections with a high mortality rate.

Methods: A 12-day-old male infant was referred to our hospital, due to a three day history of rash. On admission, he was febrile with well demarcated pustular lesions around the genital area and crusted pustular lesion on the face. Other clinical symptoms included conjunctivitis with purulent discharge, dactylitis in the right foot and cellulitis in the dorsum and planum of left and right foot, respectively. Ultrasonography revealed abscesses under the cellulitis site. He was initially treated with IV vancomycin due to severity of lesions. Bacterial culture of the nares was positive for MRSA, whereas cultures from blood, skin lesions and pus grew Serratia marcescens. Following antibiogram, meropenem was added. Fever subsided on day 2, and abscesses reduced in size. CGD was suspected and DHR test was performed that came up pathological.

Results: The neonate had a normal recovery following 2 weeks of therapy and discharged home on prophylactic cotrimoxazole and itraconazome. Two days following discharge, he represented with new abscesses and he was treated again with IV antibiotics. He was also given IFN gamma and was planned for hematopoietic cell transplantation (HCT).

Conclusions: CGD disease is rarely seen in neonates, however neonates with multiple abscesses, especially when caused by unusual pathogens such as Serratia marcescens, should raise the suspicion for underlying immunodeficiency, like CGD. Prompt diagnosis and treatment with broad spectrum antibiotics are crucial.

Disclosure: No.

Keywords: Chronic Granulomatous Disease (CGD), Neonate

PD049

ADULT SIBLINGS WITH INBORN ERROR of IMMUNITY CAUSED BY TYK2 DEFICIENCY

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Boris Karanovic[1], Marko Baresic[1], Fran Borovecki[2], Igor Aurer[3], Josipa Matesevac[2], Branimir Anic[1]
[1]University Hospital Center Zagreb, Division of Clinical Immunology And Rheumatology, Department of Internal Medicine, Zagreb, Croatia, [2]University Hospital Center Zagreb, Department For Functional Genomics, Center For Translational And Clinical Research, Zagreb, Croatia, [3]University Hospital Center Zagreb, Division of Hematology, Department of Internal Medicine, Zagreb, Croatia

Background and Aims: TYK2 deficiency is a rare disorder characterized by recurrent mycobacterial and viral infections that can be associated with hyper IgE syndrome. Only 18 cases with this condition have been described so far.

Methods: A 31-year-old male patient with a history of respiratory infections since the age of 1 month, asthma and recurrent pneumonia complicated by acute respiratory distress syndrome (ARDS) requiring mechanical ventilation was examined at our outpatient clinic. A year later he developed EBV-encoded RNA (EBER) negative primary mediastinal B-cell lymphoma (PMBCL), that was successfully treated with chemotherapy. The patient's sister (age 20) was also referred to our outpatient clinic due to recurrent infections starting at the age of 1 month (umbilical granuloma) and a history of unspecified dermatitis, asthma, gingivostomatitis, herpes zoster, mononucleosis and recurrent herpes virus infections. Patients denied consanguinity and underwent screening for systemic autoimmune disorders and primary immunodeficiencies.

Results: Initial laboratory testing of both patients excluded antibody, complement and cellular deficiency, but both had mildly elevated IgE levels. The female patient also had mild eosinophilia, basophilia and mildly elevated IgG4 levels. Targeted next generation sequencing of both patients revealed a homozygous 2-bp deletion in the TYK2 gene, c.1177_1178delGT, resulting in frameshift and premature protein termination (p.Val393GInfsTer98).

Conclusions: We present a case of siblings with TYK2 mutation whose clinical course is different regarding the frequency and severity of infections. The brother's disease was complicated by the development of PMBCL. TYK2 deficiency is a rare disorder whose treatment modalities are challenging.

Disclosure: No.

Keywords: TYK2 deficiency, siblings, Lymphoma, NGS

PD050

A CASE of STAT-1 GAIN of FUNCTION MASQUERADING AS AUTOIMMUNE DISEASE

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Maria Cunha, Inês Sousa, Tiago Marques
Centro Hospitalar Universitário Lisboa Norte, Infectious Diseases, Lisboa, Portugal

Background and Aims: We present the case of a pregnant 30-year-old Caucasian woman who was admitted to the Department of Infectious Diseases of the Santa Maria Hospital in Lisbon, Portugal, following a diagnosis of streptococcal cerebral abscess. The patient's medical history was relevant for recurrent pulmonary infections during childhood as well as a history of oral and genital aphthous ulcers which had motivated an autoimmune screening, positive for ANAs and anti-dsDNA, with a negative pathergy test and HLA B51 haplotype. During hospitalization, the presence of vaginal as well as oral candidiasis was noted, in addition to an exuberant dermatophytosis on both feet; the patient also exhibited significant vulvar dystrophy compatible with Bowenoid papulosis, with histological documentation of in situ spinocellular carcinoma (positive for HPV 16 and 18). Imaging studies also revealed bronchiectasis, which later yielded Pseudomonas aeruginosa.

Methods: After exclusion of HIV infection and demonstration of a normal lymphocyte count and immunoglobulin profile, the patient was investigated for an underlying primary immunodeficiency associated with chronic mucocutaneous candidiasis. A Th-17 deficiency was identified through flow cytometry, suggesting a STAT-1 gain-of-function mutation. A genetic study was performed, leading to the identification of a heterozygous STAT-1 gene variant c.1957G >A, p(Val 653 lle).

Results: Following treatment of infectious complications, the fetus vas delivered through cesarean section. The patient was thereafter discharged to be followed-up by a multidisciplinary team involving experts in Infectious Diseases, Immunology and Gynecology.

Conclusions: This case exemplifies the need to consider differential diagnosis of primary immunodeficiencies when considering the possibility of an autoimmune disease.

Disclosure: No.

PD051

A CASE of CHRONIC GRANULOMATOUS DISEASE WITH DISSEMINATED INFECTION DUE TO PHAEOACREMONIUM PARASITICUM TREATED WITH VORICONAZOLE

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Maria Cunha, Tiago Marques, Inês Sousa
Centro Hospitalar Universitário Lisboa Norte, Infectious Diseases, Lisboa, Portugal

Background and Aims: We present the case of a 26-year-old Caucasian man with a relevant clinical history of chronic granulomatous disease associated with a NADPH oxidase mutation (p22-phox), resulting in several infectious complications such as neonatal BCG lymphadenitis and recurrent invasive salmonellosis, who was chronically medicated with cotrimoxazole, itraconazole, and gamma-interferon. The patient also suffered from a protein losing enteropathy and granulomatous colitis, for which he was under corticosteroid treatment with 10mg of prednisolone.

Methods: The patient presented to an Infectious Diseases appointment following a 1-month period of lower left limb pain, headache, bilateral axillary adenopathies and night sweats. A whole-body CT scan demonstrated pyomyositis of the left tibialis anterior muscle, in addition to de novo hepatic lesions that were interpreted as abscesses. Cranial imaging performed after identification of a fronto-parietal ulcer revealed erosive osteomyelitis of the coronal suture with a surrounding soft-tissue abscess that extended into the dura-mater.

Results: The patient was submitted to muscle and lymph node biopsies, both yielding Phaeoacremonium parasiticum. Following fungal identification while on itraconazole prophylaxis, the patient was promptly started on voriconazole, which has been well tolerated for over a year, with clear symptom relief and frank regression of both skin lesions and lymph node enlargement.

Conclusions: This represents a rare case of extensive phaeohyphomycosis secondary to Phaeoacremonium parasiticum in a patient with chronic granulomatous disease successfully treated with long-term voriconazole.

Disclosure: No.

PD052

INFECTIONS WITH REPEATED SUPPURATION THINK ABOUT PRIMARY IMMUNODEFICIENCY: CASE REPORT

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Fatiha Boukandoura[1], Ourida Gacem[2], Nacera Hammadouche[3], Kahina Ouahbi[1], Hanifa Benmekhlouf[4], Mohamed.Samir Ladj[5]
[1]Alger, University of Medecine Algiers, Algeria, Eph Birtraria, Algiers, Algeria, [2]university of algiers - faculty of medecine, Department of Pediatric Djillali Belkhenchir Hospital Algiers Algeria, ALGER, Algeria, [3]university of algiers - faculty of medecine, Eph Djilali Belkhenchir (ex Birtraria), ALGER, Algeria, [4]Alger, University of Medecine Algiers, Algeria, Eph Birtraria, ELBIAR, Algeria, [5]Alger, University of Medecine Algiers, Algeria, Eph Birtraria, [sélection de la municipalité de naissance], Algeria

Background and Aims: we describe the case of patient who presented with recurrent abscess episodes leading to the diagnosis of Chronic Granulomatous Disease (CGD)

Methods: This case of a 06 month old boy who was referred to Birtraria Children's Hospital care for perianal abscess.

Results: The patient had a particular personal health history of recurrent abscesses requiring several hospitalizations and with a significant family medical history of maternal cousin’s deaths (severe sepsis). During his hospitalization he showed signs of a severe infectious syndrome with fever (39°C), oral aphthosis, abnormal abscesses of the lymphatic ganglia and two anal fistulas with a remarkable perianal abscess. Laboratory testing revealed hyperleukocytosis, increased erythrocyte sedimentation rate positive protein C reactive. Immunologic studies showed hyper-gammaglobulin, the lymphocyte subpopulations T CD3/CD4 and CD3/CD8 were normal. Microbiological studies were carried out where the existence of Aspergillus and in in the biopsy of lymphatic ganglia multi-resistant staphylococcus epidermidis was found. The patient’s further exploration found a positive Tetrazolium Nitro Blue (NBT) test twice one month apart; the diagnosis of CGD is confirmed by genetic studies which showed an X-linked form (CYBB gene mutation). The treatment includes the use of potent antimicrobial. He received a continuous chemoprophylaxis with trimethoprime-sulfamethoxasole and VFEND. During a course of hospitalization we observed clinical improvement.

Conclusions: The isolation of particular opportunistic infections such as Aspergillus should prompt a diagnostic approach for CGD. the prognosis improved considerably with antibacterial and antifungal prophylaxie, most patients live well into adulthood

Disclosure: No.

Keyword: recurrent infections; Primary immunodeficiency; chronic granulomatous disease

PD053

IMPAIRED TOLEROGENIC DENDRITIC CELLS QUALITIES AS A CAUSE of AUTOIMMUNE COMPLICATIONS IN PATIENTS WITH STAT1-GAIN-OF-FUNCTION MUTATIONS

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Zuzana Parackova, Marketa Bloomfield, Irena Zentsova, Anna Sediva
Faculty Hospital in Motol, Department of Immunology, Prague, Czech Republic

Background and Aims: STAT1 GOF is the most common cause of inherited syndromic chronic mucocutaneous candidiasis (CMC), a persistent or recurrent infection with Candida species due to skewed STAT1/STAT3 signalling and consequently Th1/Th17 disbalance. However, STAT1 GOF mutations are often associated with autoimmune complications (hypothyroidism, T1D, SLE). To date, only limited knowledge exists regarding the mechanisms underlying autoimmune complications in patients with STAT1 GOF. Our aim was to study whether STAT1/STAT3 signalling disbalance in dendritic cells might be the underlying cause of such development of autoreactive features.
Methods

Methods: Monocyte-derived DCs were generated from adhered monocytes cultivated in the presence of IL-4 and GM-CSF for 6 days. Subsequently, functional studies and RNA seq were performed.

Results: The DC subpopulations in patients with STAT1 GOF mutations were skewed. We observed fewer plasmacytoid and CD16- myeloid DC (mDC), but higher numbers of CD16+ mDCs. The phenotype and cytokine productions of both patients' conventional (cDCs) and tolerogenic (tDCs) dendritic cells differed substantially from healthy controls, particularly in the increased pro-inflammatory profile. Additionally, the patient cDCs induced higher numbers of IFNγ-producing T lymphocytes, while the patients' tDC failed to induce regulatory T cells (FoxP3+CD25+CD4+).

Conclusions: Our data revealed impaired functions of conventional and tolerogenic dendritic cells of STAT1 GOF patients, suggesting their role in autoimmune complications.

Disclosure: No.

Keywords: Autoimmunity, STAT1 GOF, tolerogenic dendritic cells, dendritic cells

PD054

AN ELF4 HYPOMORPHIC VARIANT RESULTS IN NATURAL KILLER CELL DEFICIENCY

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Sandra Andrea Salinas[1], Emily Mace[2], Matilde Conte[2], Chun Park[3], Yu Li[2], Joshua Sepulveda[4], Sanjana Mahapatra[5], Emily Moore[2], Evelyn Hernandez[2], Ivan Chinn[5], Abigail Reed[2], Barclay Lee[2], Alexander Frumovitz[5], Richard Gibbs[6], Jennifer Posey[6], Lisa Forbes Satter[5], Akaluck Thatayatikom[7], Eric Allenspach[8], Theodore Wensel[4], Carl Allen[1], James Lupski[6], Daniel Lacorazza[3], Jordan Orange[2]
[1]Baylor College of Medicine, Texas Children's Cancer Center, Department of Pediatrics, Houston, United States of America, [2]Vagelos College of Physicians and Surgeons, Columbia University, New York City, United States of America, [3]Baylor College of Medicine, Department of Pathology & Immunology, Houston, United States of America, [4]Baylor College of Medicine, Department of Biochemistry, Houston, United States of America, [5]Baylor College of Medicine, William T. Shearer Center for Human Immunobiology, Department of Pediatrics, Houston, United States of America, [6]Baylor College of Medicine, Department of Molecular And Human Genetics, Houston, United States of America, [7]University of Florida, Shands Children's Hospital, Division of Pediatric Allergy, Immunology, And Rheumatology, Gainesville, United States of America, [8]Seattle Children's Research Institute, Center For Immunity And Immunotherapies, Seattle, United States of America

Background and Aims: Natural Killer cell deficiency (NKD) is an IEI in which the major clinically relevant immunologic abnormality affects NK cell number, maturity, or function. An individual with recurrent viral infection and NKD was found to have an X-linked damaging variant in *ELF4*.

Methods: The effect of the *ELF4* variant on protein expression, localization, and function was evaluated using proband's derived cells and an overexpression system. Its effect upon human NK cell maturation was evaluated via an in vitro system using the proband's progenitor cells. NK cell development and biology were further characterized using a bone marrow chimera mouse model.

Results: The proband's ELF4 variant disrupts DNA binding, reducing transcriptional activation of NK cell relevant target genes, thus selectively impairing ELF4 function. Corroborating previous ELF4 deficient murine models, the expression of the proband's ELF4 variant disrupted NK cell development, maturation, and perforin expression. Similarly, the proband sample had decreased NK cell frequency, with diminished perforin and an increase in immature subsets; additionally corroborated by decreased yields of mature NK cells from the in vitro NK cell maturation system.

Conclusions: We established the identified variant to be hypomorphic and to drive a specific NK cell phenotype, determining ELF4 as necessary for normal NK cell development, terminal maturation, and function. Through the characterization of the NK cells of the proband, expression of the proband's variant in *Elf4*$^{-/-}$ mouse hematopoietic precursor cells, and a human in vitro NK cell maturation model, we established this particular *ELF4* variant as a novel cause of NKD.

Disclosure: No.

Keywords: NK cells, NK cell deficiency, cytotoxicity, Viral infection

PD055

LUNG-BRAIN AXIS: METABOLOMICS AND PATHOLOGICAL CHANGES IN LUNGS AND BRAIN of RESPIRATORY SYNCYTIAL VIRUS INFECTED MICE

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Ousman Bajinka
University of The Gambia, Medical School, Banjul, Gambia

Background and Aims: The lung-brain-axis is an emerging area of study that got its basis from the gut-brain-axis biological pathway. This study aimed to investigate the role of metabolites in the RSV-associated neurologic syndromes as well as to further dissect the molecular mechanisms at the basis of RSV-induced long-term immune disorders.

Methods: Material and Methods: After establishing the mice model, the samples were sent to Wuhan GeneCreate Biological Engineering Co., Ltd for metabolomics analysis. In addition, Hematoxylin-eosin staining, indirect immunofluorescence (IFA) and RT-qPCR were also carried out to establish the pathological changes

Results: RSV infection promoted epithelial shedding and infiltration of inflammatory cells. Also, RSV immunofluorescence and titres were significantly increased. Moreover, IL-1, IL-6 and TNF-αwere also significantly increased after RSV infection and the cell structure of hippocampal CA1 area was loose and disordered. Inflammatory cytokines IL-6 and IL-1βexpression in the brain also increased however, TNF-αexpression showed no differences among the control and RSV group.We observed an increased expression of IBA-1 and decreased NeuN neuronal. In addition, RSV mRNA expression levels were also increased and15 metabolites were found upregulated in the RSV group including nerve-injuring metabolite glutaric acid, hydroxyglutaric acid and Spermine. Finally, α-Estradiol increased significantly while normorphine decreased significantly at day 7 of infection among the RSV group.

Conclusions: Conclusion: This study established a mouse model for the metabolomics model, and utilised hematoxylin-eosin staining, IFA and RT-qPCR to establish the pathological changes. It reported epithelial shedding and infiltration of inflammatory cells post RSV infection, along with RSV immunofluorescence and increased titres.

Disclosure: No.

Keyword: Lung brain axis, metagenomics, metabolomics, RSV infection, neurons

PD056

PYODERMA GANGRENOSUM COMPLICATING PSEUDOMONAS INFECTION IN A PATIENT WITH MYD88 DEFICIENCY

POSTER DISPLAY 03: BIOLOGY of INNATE IMMUNITY

Intisar Abdelhakam[1], Ruth Radcliffe[2], Arthur Price[2]
[1]University Hospital of Leicester, Immunology, Leicester, United Kingdom, [2]University Hospitals Leicester, Immunology, Leicester, United Kingdom

Background and Aims: Myeloid Differentiation factor (MyD) 88 is known to impairs Toll-like receptor and interleukin-1 receptor-mediated immunity. MyD88-deficient patients present with a narrow predisposition to pyogenic bacterial infections mainly during the first 10 years of life, however, it is usually invasive and life-threatening. Most non-invasive Bacterial Infections in MyD88-deficient patients affect the skin and the upper respiratory tract sites where necrotizing infections are particularly common

Methods: Here we report the appearance of pyoderma gangrenosum as a presenting feature associated with pseudomonal bacteremia in a patient with MyD88 deficiency. The patient is a 7-month old girl of non-consanguineous healthy parents from Latvian Roma Gipsy community. She presented with disseminated pseudomonal infection including bilateral otitis media and retropharyngeal abscess. Concurrently, a necrotic lesion appeared at her right calf with a typical picture of pyoderma gangrenosum. Notably her CRP was elevated during the acute infection.

Results: Here intial testing showed impaired CD62 ligand shedding. She was subsequently genetically diagnosed with Autosomal recessive Myeloid Differentiation factor (MyD) 88 deficiency using the NHS clinically available gene panel.

Conclusions: The association between pyoderma gangrenosum and pseudomonal infection is well known, but, it has hitherto not been described in MyD88 deficiency. **References:** Clinical features and outcome of patients with IRAK-4 and MyD88 deficiency. Capucine Picard et all, Medicine (Baltimore). 2010 Nov;89(6):403-425. Pyogenic bacterial infections in humans with MyD88 deficiency. Horst von Bernuth et all. Science. 2008 Aug 1;321(5889):691-6. Infectious Diseases in Patients with IRAK-4, MyD88, NEMO, or IκBα Deficiency. Capucine Picard et all, ." Clinical microbiology reviews 24.3 (2011): 490-497.

Disclosure: No.

Keywords: pyoderma gangrenosum, immunodeficiency, MyD88 deficiency

PD057

SUBTLE DIFFERENCES DUE TO IMMUNE DYSREGULATION IN SOLUBLE SURFACE MARKERS AND CELL COUNTS IN COMMON VARIABLE IMMUNE DEFICIENCY

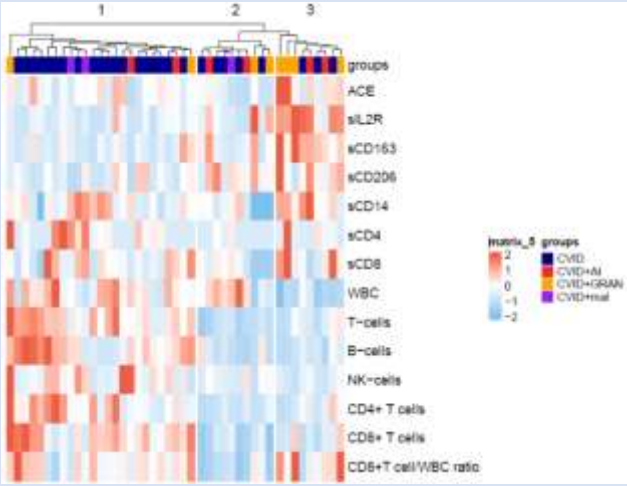
POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Astrid Van Stigt
Erasmus university Medical Center, Department of Immunology, Laboratory Medical Immunology, Rotterdam, Netherlands

Background and Aims: CVID is a primary antibody deficiency with heterogeneous clinical phenotype, characterized by decreased levels of immunoglobulin (Ig) G and/or IgA and/or IgM, impaired response to immunization and recurrent infections. +68% of CVID patients have additional noninfectious complications (NIC). NIC result from immune dysregulation, and are associated with increased mortality. 2 clinical phenotypes are seperated:
- CVID patients with recurrent infections only (CVID IO)
- CVID patients with additional immune dysregulated complications (CVID+NIC) Research questions
1) Are there differences in soluble surface markers and cell numbers of CVID IO, CVID+NIC, and HC?
2) What drives these differences in CVID patients, suggesting differences in immune compartment involvement?

Methods: Retrospective single center analysis on CVID IO n = 27, CVID with NIC (CVID+AI n = 6; CVID+gran n = 8;CVID+mal n = 3). ELISA on first collected serum: sIL-2R, sCD4, sCD8, sCD163, sCD206, sCD14, ACE. Flow cytometry analysis on blood: white blood cell, T-cell, CD4+ and CD8+, B-cell, NK-cell.

Results:



PCA and heatmap showed majority of CVID IO patients clustered together. For CVID+AI and CVID+gran, more heterogeneous populations were observed. ACE, sIL-2R and sCD163 appeared important drivers. Spearman correlation profiles showed CVID+gran and CVID+AI were relatively similar. Similarities existed between the subgroups, but CVID IO showed a different profile as compared to CVID+NIC.

Conclusions: - Differences in soluble surface markers and cell numbers can be observed between CVID IO en CVID+NIC subgroups
- The macrophage biomarkers sCD163 and sCD206 seemed more informative and also to correlate more strongly with sIL-2R as did sCD4 and sCD8 or T-cell numbers.

Disclosure: No.

Keyword: CVID, infections, noninfectious complications, immune dysregulation

PD058

RARE – OR NON-LANGERHANS CELL – HISTIOCYTOSES: THE GERMAN COLLECTION AND CONSULTATION SERVICE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Carl Friedrich Classen
University Childrens Hospital Rostock, Pediatric Oncology And Palliative Care, Rostock, Germany

Background and Aims: Non-Langerhans cell histiocytoses (non-LCH) include malignant and benign, localized or diffuse diseases. In pediatrics, the most frequent are juvenile xanthogranulomatosis (JXG) and Rosai-Dorfman disease (RDD) followed by Erdheim-Chester disease (ECD), and malignant histiocytoses. Recently, molecular genetic alterations, particularly in the ras-raf kinase pathway, were identified.

Methods: In 2012, the German registry and consultation study for non-LCH - part of the International Rare Histiocytic Disease Registry - was initiated. Ninety-two patients were reported (36/50 female/male, 6 unknown; aged 0-4 years:40; 5-9:14; 10-14:10; 15-19:12; 20-39:5; >39:10).

Results: 6 patients died (aged: 1, 10, 42, 42, 51, 54 years); the others lost to follow-up (lfu). Among 34 JXG patients (all survivors or lfu), 2 had localized, 4 generalized skin involvement, 2 bone, 5 CNS, 2 eye, 3 deep soft tissue, 2 skin/liver involvement, 2 mediastinal/tracheal compression, 2 intrathoracal extension. 5 patients received steroids/polychemotherapy. Two ECD patients were lfu. Among 16 RDD patients (all survivors or lfu), 9 had cervical lymphadenopathy (1 received steroids), 6 had extended disease (2 meningeal, 1 mediastinal/tracheal compression, 2 bone, 1 liver/lungs; 5 received steroids/polychemotherapy). Five had histiocytic sarcoma (2 died; one survived after polychemotherapy/BMT). One patient had Langerhans cell sarcoma (survivor after polychemotherapy), 1 had H syndrome. Non-LCH was undefined in 27 (4 deaths after different treatments). Three patients with ALK positive undefined non-LCH received molecular therapies. Complete genetic workup was only performed in a subgroup of patients.

Conclusions: Rare histiocytoses represent a very heterogeneous disease spectrum. Appropriate consultation depends on international prospective data collection, which should be further propagated.

Disclosure: No.

Keywords: Histiocytosis, Non-Langerhans, Xanthogranuloma

PD059

AUTOIMMUNITY, T-LARGE GRANLUAR LYMPHOCYTES (T-LGL) AND SWITCHED MEMORY B CELLS (SMB) IN COMMON VARIABLE IMMUNODEFICIENCY (CVID)

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Patrick Bez, Beatrice Piazza, Riccardo Scarpa, Marcello Rattazzi, Carlo Agostini, Francesco Cinetto
University of Padua, Department of Medicine, Treviso, Italy

Background and Aims: CVID is the most common symptomatic immunodeficiency among adults and clinical manifestations include not only infectious risk, but also autoimmune disorders. The aim of the study was to evaluate the prevalence of autoimmunity and their clinical associations in CVID patients.

Methods: We conducted a retrospective study in a population of 137 CVID patients followed up in our Centre. We used Fisher exact test and unpaired t student to evaluate associations, with p considered significant when <0.05.

Results: 71 patients (52%) had at least one autoimmune manifestation, including: autoimmune cytopenia (AC) in 20 (15%) patients, in particular 18 autoimmune thrombocytopenia, 5 hemolytic anemia, 2 autoimmune neutropenia; GLILD in 23 (17%); organ-specific autoimmunity in 35 (26%), in particular 11 psoriasis, 7 vitiligo, 11 autoimmune thyroiditis, 7 autoimmune gastritis, 3 lichen ruber planus, 1 type one diabetes, 1 Miller-Fisher Syndrome; autoimmune entheropathy in 18 (13%), in particular 8 IBD-like, 9 celiac-like entheropathy, and 1 lymphocytic colitis; two patients have connective tissue disease. Autoimmunity represented CVID onset in 25/71 patients (35%). No correlations between autoimmunity and other complications could be established. We compared the immunephenotyping in autoimmunity versus non-autoimmunity patients and found a higher T -LGL percentage (19.5% ± 1.8 vs 14.0% ± 1.6, p=0.025), especially in AC and GLILD subgroups, and a lower smB percentage (5.0± 0.8 vs 8.3 ± 1.2, p=0.020).

Conclusions: Autoimmunity manifestations in CVID patients are highly frequent and often the first sign of disease. Higher T-LGL and lower smB percentage are associated with autoimmunity. Further studies are needed to confirm these observations.

Disclosure: No.

Keywords: CVID, Autoimmunity, B cells, T-LGL

PD060

LEUCINE-RICH REPEAT-CONTAINING PROTEIN 8A IS ESSENTIAL FOR T CELL-DRIVEN ACUTE GRAFT VERSUS HOST DISEASE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Megan Elkins[1], Faris Jaber[2], Abdallah Beano[2], Wayne Bainter[1], Yousef Badran[3], Janet Chou[1]
[1]Boston Children's Hospital, Immunology, boston, United States of America, [2]Icahn School of Medicine at Mount Sinai, Internal Medicine, New York, United States of America, [3]Massachusetts General Hospital, Internal Medicine, Boston, United States of America

Background and Aims: Leucine-Rich Repeat-Containing Protein 8A (LRRC8A) is a transmembrane protein important for early T cell development and regulation of osmotic stress. We previously showed that a complete knockout of LRRC8A impairs thymocyte development at the double negative 2 to double negative 3 stages. Here, we aimed to identify the role of LRRC8A in mature T cell function and to determine the biologic relevance of LRRC8A in T cell-driven diseases.

Methods: We created a Cd4CreLrrc8a$^{fl/fl}$ mouse model in which LRRC8A is conditionally deleted at the very late double negative 4 stage of thymocyte development. To determine the function of LRRC8A in T cell function, we used in vitroassays of T cell activation and metabolism as well as a mouse model of acute graft versus host disease (GVHD).

Results: We found that LRRC8A is dispensable for T cell development after the double negative 4 stage of thymocyte development. LRRC8A is not needed for the activation of CD4$^+$ T cells by professional antigen-presenting cells. However, CD4$^+$ T cells with conditional deletion of LRRC8A had defective activation by non-professional antigen-presenting cells, demonstrated by reduced survival, proliferation, cytokine production, and metabolic function. Notably, selective deletion of LRRC8A in donor CD4$^+$ T cells reduces mortality and attenuates gastrointestinal inflammation in a major histocompatibility class II-mismatched mouse model of acute GVHD.

Conclusions: These findings demonstrate that LRRC8A is essential for the activation of CD4$^+$ T cells by non-professional antigen presenting cells and identify a novel role for LRRC8A in CD4$^+$ T cell mediated acute GVHD.

Disclosure: No.

Keywords: Leucine-Rich Repeat-Containing Protein 8A (LRRC8A), acute graft versus host disease (GVHD)

PD061

NEW INSIGHTS INTO IKBKB- GOF-DISEASE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Julia Körholz[1], Nina-Christine Knopf[1], Franziska Taube[2], Clemens Kastl[1], Leonora Pietzsch[1], Joachim Roesler[1], Catharina Schuetz[1]
[1]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Pediatric Immunology, Dresden, Germany, [2]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Internal Medicine, Dresden, Germany

Background and Aims: Heterozygous IKBKB variants associated with gain of function (GOF) cause combined T- and B-cell deficiencies (Cardinez et al. 2018). We describe two patients with variants in IKBKB and distinct phenotypes. Patient A is a 16 year-old female who presented with recurrent skin infections, respiratory tract infections, signs of chronical sinusitis and chronic non-malignant lymphoproliferation. Patient B is a 48 year-old male who suffered from recurrent episodes of pansinusitis, chronic otitis media and multiple pneumonias resulting in bronchiectases and prompting lobar resection.

Methods: Cystosolic and intranuclear protein expression and phosphorylation were measured by Western Blot. Patients were characterized immunophenotypically and functionally.

Results: Patient A harbours the well-described variant c.607G>A (p.Val203Ile, heterozygous) in IKBKB. For patient B the novel variant c.368T>C (p.Leu123Pro, heterozygous) was found. Patient A has combined immunodeficiency because of severely impaired T- and B-cells and a spectrum of auto-antibodies. Patient B has a CVID-like phenotype with absent class-switch, but no evidence of T-cellular abnormalities. Compared to healthy controls, p65-phosphorylation in the nuclear and cytosolic compartment was prolonged and IkBa-phosphorylation was enhanced indicative of an activated NFkB-signaling.

Conclusions: IKBKB- GOF may also present as CVID without T-cellular abnormalities. In order to capture the various phenotypes, identification of additional patients will be instructive.

Disclosure: No.

Keywords: NFkB signaling, Phenotypes, IKBKB-GOF variants, CVID

PD062

DYSIMMUNE COMPLICATIONS of COMMON VARIABLE IMMUNODEFICIENCY IN A MULTICENTER SPANISH-BASED COHORT

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Marta Dafne Cabanero-Navalon[1], Víctor García Bustos[1], María Núñez Beltrán[1], Lourdes Mateu[2], Xavier Solanich Moreno[3], Juan Luís Carrillo[4], Ángel Robles Marhuenda[5], Francesc Puchades[6], Ana Pelaez Ballesta[7], Nuria Osle[8], Miguel Ángel Torralba[9], Ana María Bielsa[10], Jorge Diego Gil[11], Nutia Tornador[12], Guillem Pascual Castellanos[12], Rosario Sánchez[13], José Manuel Barragán[14], Andrés González[15], José Luis Patier[16], Daniel López Wolf[17], Antonia Mora Rufete[18], Alba Cánovas[18], Pedro Moral Moral[1]
[1]University and Politechnic Hospital La Fe, Internal Medicine, Valencia, Spain, [2]Hospital Universitari Germans Trias i Pujol, Internal Medicine, Badalona, Spain, [3]Hospital Universitari de Bellvitge, Adult Primary Immunodeficiency Unit, L'Hospitalet de Llobregat, Spain, [4]Hospital Universitario Virgen de la Victoria, Internal Medicine, Málaga, Spain, [5]Hospital Universitario La Paz, Internal Medicine, Madrid, Spain, [6]Hospital General de Valencia, Internal Medicine, Valencia, Spain, [7]Hospital Universitario Rafael Méndez, Internal Medicine, Lorca, Spain, [8]Hospital de Cruces, Internal Medicine, Barakaldo, Spain, [9]Hospital Clínico Universitario Lozano Blesa, Internal Medicine, Valencia, Spain, [10]Hospital Miguel Servet, Internal Medicine, Zaragoza, Spain, [11]Hospital Universitario 12 de Octubre, Internal Medicine, Madrid, Spain, [12]Hospital General de Castellón, Internal Medicine, Castellón, Spain, [13]Hospital General de Alicante, Internal Medicine, Alicante, Spain, [14]Complejo Asistencial de Ávila, Internal Medicine, Ávila, Spain, [15]Hospital Universitario Santiago Ramón y Cajal, Internal Medicine, Madrid, Spain, [16]Hospital Universitario Santiago Ramón Y Cajal, Internal Medicine, Madrid, Spain, [17]Hospital de Alcorcón, Internal Medicine, Madrid, Spain, [18]Hospital Universitario de Elche, Internal Medicine, Valencia, Spain

Background and Aims: Common variable immunodeficiency (CVID) is a clinically heterogeneous primary immunodeficiency (PID) characterized both by infectious and non-infectious complications. Since the introduction of immunoglobulin replacement therapy, the main causes of morbidity and mortality have suffered an epidemiological shift towards autoimmune disorders. This study aimed to characterize the clinical profile of dysimmune complications in Mediterranean CVID patients.

Methods: Two-hundred and fifty patients with CVID were included in a multicenter Spanish-based cohort leaded by the Working Group of Minority Diseases of the Spanish Society of Internal Medicine (GTEM-SEMI). Epidemiological, clinical, and comorbidity-related parameters were registered with emphasis in autoimmune disorders.

Results: The mean age of the population was 54 years, and 121 patients were male. Immune cytopenias were registered in 33.73%, with Evan's syndrome accounting for most (14.3%). Lymphadenopathies were present in 88 patients, in which granulomatosis and benign lymphoproliferation were the main histological traits (44.45% and 65.91%). Eighty-two and 47 patients showed splenomegaly and hepatomegaly, respectively. Atrophic gastritis (27.36%) and immune enteropathy were relatively common, with diagnosed inflammatory bowel disease in 15.38% patients, celiac disease in 3.73%, villous atrophy in 27.1%, malabsorption in 15.45%, and eosinophilic or lymphocytic colitis in 9.47% and 18.39% of patients. Systemic autoimmune diseases were more frequent than in general population, with 2.81% suffering type 1 diabetes, 2.41% ankylosing spondylitis, 2% sarcoidosis, 0.80% systemic lupus erythematosus 0.40% rheumatic polymyalgia and 0.80% vasculitis disorders, among others.

Conclusions: Immune dysregulation in PID entails a higher risk of systemic autoimmune disorders requiring prompt diagnosis and tailored treatment.

Disclosure: No.

Keywords: Common variable immunodeficiency, Immune Dysregulation, multicenter study, Autoimmunity

PD063

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN COMMON VARIABLE IMMUNODEFICIENCY: IMPACT of B CELL IMPAIRMENT.

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Francesco Cinetto[1], Riccardo Scarpa[1], Alessandro Dell'Edera[2], Alessandro Bressan[1,2], Anna Spada[1], Marcello Rattazzi[1], Chiara Nardin[1], Elisabetta Faggin[1]
[1]Rare Disease Referral Center, Internal Medicine 1, Ca Foncello Hospital, ULSS2 Marca Trevigiana, Treviso, Italy., Department of Medicine-dimed, University of Padova, Padua, Italy., padova, Italy, [2]University of Padua, Department of Medicine, Treviso, Italy

Background and Aims: Although the immune system is involved in vascular disorders, the actual role of B cells in atherosclerotic cardiovascular disease (ASCVD) remains unclear. CVID, due to the impaired B cell function, may represent a pathological condition suitable for studying the role of B cells in ASCVD.

Methods: We investigated the prevalence of cardiovascular risk factors and subclinical ASCVD in a cohort of CVID patients, grouped according to clinical phenotype. Vascular structural and functional investigation was performed by SphygmoCor(R) XCEL instrument.

Results: We enrolled 55 males and 67 females (mean age 50.9±14.4). No differences in age, sex, BMI, waist circumference were detected between “infection only” and complicated phenotype. Complicated patients showed increased CRP and more often required steroids (p=0.017) and immunosuppressants (p<0.001). Surprisingly, they presented lower total cholesterol (182±36vs204±41mg/dl, p=0.009) and LDL cholesterol (112±33vs129±42mg/dl, p=0.04), as well as lower fasting glucose (89±14vs98±17mg/dl, p=0.011) and glycosylated haemoglobin levels (33±4vs 38±6mmol/mol, p<0.001) compared to uncomplicated cohort. Complicated patients also presented higher levels of CD21lo B cells (10.8% vs 6.8%), and large granular lymphocytes (26.0% vs 14.4%; p<0,001) and significantly reduced levels of switched-memory B cells (4.0%, vs 7.8%; p=0,043). Flow mediated dilation (FMD) and intima media thickness (IMT) were not different between groups in a sub-cohort of 45 patients.

Conclusions: Our data suggest that clinical phenotypes of CVID may be associated with different cardiovascular risk profiles, possibly based on different underlying immunological features.

Disclosure: No.

Keywords: CVID, B cells impairment, Immune Dysregulation, Cardiovascular disease

PD064

EVALUATING THE USE of RUXOLITINIB TO TREAT STAT1 GAIN of FUNCTION DRIVEN PRIMARY IMMUNODEFICIENCY

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Joe Mcdowell[1], Alex Mckenna[2], Siobhan Burns[2], Emma Morris[2]
[1]UCL, Infection And Immunity, London, United Kingdom, [2]University College London, Division of Infection And Immunity, London, United Kingdom

Background and Aims: In response to interferons, signal-transducer-and-activator-of-transcription 1 (STAT1) becomes phosphorylated by Janus Kinases (JAKs) promoting the transcription of gene programmes that promote antimicrobial defence. To date, hundreds of patients harbouring mutations in STAT1 termed gain of function (GOF) have been described worldwide, comprising a diverse primary immunodeficiency which includes vulnerability to infection, autoimmunity and cancer. A common hallmark of STAT1 GOF is raised pSTAT1 levels which provided a rationale for using JAK inhibitors in the clinic to prevent pSTAT1 mediated gene transcription. However, treatment with the JAK1/2 inhibitor Ruxolitinib does not lead to widespread amelioration of symptoms in patients.

Methods: To explain this lack of response we transduced U3A cells ($STAT1^{-/-}$) with WT or common gain of function mutations. STAT1 phosphorylation and gene expression dynamics were assessed by flow cytometry and nanoluciferase reporter assays, respectively.

Results: In line with previous studies [1,2], we demonstrate that in cells expressing STAT1 GOF mutations STAT1 phosphorylation and gene expression is raised at baseline and upon stimulation with interferons compared to cells expressing WT STAT1. Treatment with Ruxolitinib decreased cellular levels of pSTAT1 at baseline and in response to interferons across all cell types. However, although Ruxolitinib potently inhibited gene transcription in WT expressing cells, it was ineffective in their mutant counterparts.

Conclusions: Despite the ability of Ruxolitinib to inhibit STAT1 phosphorylation in GOF mutant expressing cells, it failed to bring gene expression down to within the range of WT. This provides evidence of pSTAT1-independent gene transcription as a novel mode of drug-resistant pathogenesis.

Disclosure: No.

Keywords: STAT1, gain-of-function, ruxolitinib

PD065

EXPLORING THE ROLE of DNA METHYLATION IN THE PATHOGENESIS of PAD

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Manfred Anim, Natalia Dubrowinskaja, Georgios Sogkas, Torsten Witte, Faranaz Atschekzei
Hannover Medical School, Rheumatology And Immunology, Hannover, Germany

Background and Aims: CVID is the most common symptomatic PID in adults, characterized by B-cell abnormalities and inadequate antibody response. Autoimmunity in CVID often manifests with autoimmune cytopenias. CVID patients with non-infectious complications are at a significantly greater risk of morbidity and mortality than those without autoimmunity. Several monogenic defects have been identified in CVID. However, only a part of CVID pathogenesis can be explained by genetic; it is evident that other additional factors are involved in disease onset and progression. We aim to define the epigenetic mechanism contributing to autoimmunity in CVID patients.

Methods: Applying the Infinium Methylation EPIC array, we examined the DNA methylation in sorted CD19+ B- and CD4+ T cells of CVID patients groups (ITP, infection-only) and healthy controls. The software R, GSEA and GO were used for data analysis. In order to validate our results, pyrosequencing was used.

Results: The analysis resulted in 208 top gene candidates or sequences with significantly different methylated DMRs.The candidate genes/sequences included genes of importance to the immune system or genes that encode for transcriptional control and execution elements. Furthermore, differences in the CpG methylation of large chromosome segments (DMBs) were determined, requiring further analysis.

Conclusions: Our current results indicate a role of epigenetic aberration in CVID with autoimmunity. They may identify relevant DNA methylation changes in immune cells that could explain the manifestation of autoimmunity in these patients. Coming experiments should investigate whether it may be possible to use such epigenetic changes as a marker to identify autoimmunity before the onset of irreversible damage.

Disclosure: No.

Keywords: Inborn errors of immunity, Epigenetic, DNA methylation, Autoimmunity, CVID, ITP

PD066

CASE STUDY: A NOVEL CXCR4 P.SER346PROFS*12 VARIANT IN A CHILD WITH WHIM SYNDROME

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Katarina Zmajkovicova[1], Sumit Pawar[2], Ivana Wiest[3], Jacob Bledsoe[4], Christoph Geier[5,6], Sabine Maier-Munsa[1], Melis Yilmaz[7,8], Peter Newburger[9], Arthur Taveras[10], Jolan Walter[7,8,11], Mirta Cavieres[12]
[1]X4 Pharmaceuticals (Austria) GmbH, Discovery, Vienna, Austria, [2]Formerly of X4 Pharmaceuticals, Discovery, Vienna, Austria, [3]X4 Pharmaceuticals (Austria) GmbH, Research And Development, Vienna, Austria, [4]Boston Children's Hospital, Department of Pathology, Boston, United States of America, [5]University Medical Center Freiburg, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [6]University Medical Center Freiburg, Department of Rheumatology And Clinical Immunology, Freiburg, Germany, [7]University of South Florida Morsani College of Medicine, Division of Allergy And Immunology, Departments of Pediatrics And Medicine, Tampa, United States of America, [8]Johns Hopkins All Children's Hospital, Division of Allergy And Immunology, Department of Pediatrics, St Petersburg, United States of America, [9]UMass Chan Medical School, Departments of Pediatrics And Molecular, Cell, And Cancer Biology, Worcester, United States of America, [10]X4 Pharmaceuticals, Inc., Research And Development, Boston, United States of America, [11]Massachusetts General Hospital for Children, Division of Allergy And Immunology, Boston, United States of America, [12]Dr. Luis Calvo Mackenna Children’s Hospital, Hematology Unit, Santiago, Chile

Background and Aims: Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) syndrome is a rare, autosomal-dominant primary immunodeficiency associated with increased susceptibility to recurrent bacterial infections and human papillomaviruses. Nearly all WHIM cases have been linked causally to heterozygous gain-of-function mutations in the CXCR4 C-terminus that result in increased receptor signaling. We report a case of a female presenting with symptoms of WHIM since age 3 years and harboring a novel CXCR4 mutation.

Methods: A female aged 8 years with prior diagnosis of autoimmune neutropenia presented with history of persistent severe neutropenia, leukopenia, recurrent infections, myelokathexis, and no warts since age 3 years. The patient was assessed for mutations associated with congenital neutropenia. Immune cell phenotypes and immunoglobulin G (IgG) levels were assessed at different ages.

Results: No mutations were detected in ELANE, HAX-1, G6PC3, or JAGN 1 genes. IgG levels were 690-831 mg/dL. Review of medical history revealed previously undiagnosed neutrophil hypersegmentation and connection of nuclear lobes with fine chromatin filaments consistent with myelokathexis. Genetic testing identified a novel heterozygous CXCR4 variant: c.893_1034dup (p.Ser346Profs*12). In vitro analysis of patient peripheral blood mononuclear cells and recombinant CXCR4-negative K562 cells expressing Ser346Profs*12 showed impaired CXCL12-induced receptor internalization and enhanced chemotaxis, typical hallmarks of $CXCR4^{WHIM}$ mutations. Acute treatment with filgrastim (G-CSF) led to marked improvement in leukocyte and absolute neutrophil counts.

Conclusions: This case allowed for identification of the most distal C-terminal CXCR4 variant observed to date in a patient clinically confirmed with WHIM, with a truncation of only the last 7 amino acids.

Disclosure: Katarina Zmajkovicova is a current employee and has equity ownership of X4 Pharmaceuticals.

Keywords: CXCR4, variant, immunodeficiency, genetic disorders, immune disorder, WHIM syndrome

PD067

ABERRANT T-BET EXPRESSION IN PATIENTS WITH SUSPECTED MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE IN SOUTH AFRICA

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Ansia Van Coller[1], Brigitte Glanzmann[2], Marlo Möller[2], Craig Kinnear[2], Monika Esser[3], Richard Glashoff[1]
[1]Stellenbosch University, Pathology, Cape Town, South Africa, [2]Stellenbosch University, Biomedical Sciences, Cape Town, South Africa, [3]Stellenbosch University, Paediatric Rheumatology, Cape Town, South Africa

Background and Aims: The transcription factor T-bet has various important roles in innate and adaptive immunity. T-bet is also integral to the Mendelian Susceptibility to Mycobacterial Disease (MSMD)-associated IL-12-IFN-γ pathway and could represent a potential proxy marker for immune dysfunction in individuals with MSMD. The aim of this study was to investigate T-bet expression in South African patients with clinically suspected MSMD and to compare this expression to other functional readouts of the IL-12-IFN-γ immune pathway.

Methods: Peripheral blood mononuclear cells were isolated from 11 healthy controls and 23 suspected MSMD patients, i.e., presenting with severe, persistent, unusual and/or recurrent mycobacterial/TB infections. Multiple flow cytometry-based assays were used to assess T-bet expression in various immune cell subsets along with IL-12/IFN-γ receptor expression and pSTAT1/pSTAT4 signalling. Induced IL-12 and IFN-γ production was assessed through Luminex analysis.

Results: All suspected MSMD patients had aberrant T-bet expression in >33% of the immune cell subsets assessed. Reduced T-bet expression in CD16+ lymphocytes (particularly NK cells) and monocytes was the most prominent phenotype observed. Additionally, T-bet expression correlated significantly to IL-12 and IFN-γ receptor expression and signalling. Most notably, patients with reduced T-bet expression in all NK cells also had reduced IL-12 signalling and IL-12 production in response to IFN-γ stimulation.

Conclusions: The suspected MSMD patients had aberrant T-bet expression compared to the controls, which correlated with dysfunction in the IL-12-IFN-γ pathway. This indicates that T-bet is a promising proxy marker for immune dysfunction relating to MSMD/TB susceptibility and could be used to earmark patients for further genetic investigations.

Disclosure: No.

Keywords: MSMD, TB, T-bet, IL-12, IFN-γ

PD068

INBORN ERRORS of IMMUNITY (IEI) IN PEDIATRIC HEMATOLOGY DEPARTMENTS: TIME TO INCREASE DIAGNOSTIC AWARENESS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Giorgio Costagliola[1], Filippo Consonni[2], Francesco Pegoraro[3], Margherita Nardi[1], Laura Luti[1], Rita Consolini[4], Ebe Schiavo[5], Beatrice Martini[5], Maria Luisa Coniglio[6], Elena Sieni[6], Marinella Veltroni[6], Gabriella Casazza[1], Claudio Favre[6], Eleonora Gambineri[5]
[1]University hospital of Pisa, Division of Pediatric Oncology/hematology, Pisa, Italy, [2]University of Florence, Department of Health Sciences, Florence, Italy, [3]University of Florence, Department of Health Sciences, Firenze, Italy, [4]Section of Clinical and Laboratory Immunology, Division of Pediatrics, University of Pisa, Pisa, Italy, [5]University of Florence, Department of Neurosciences, Psychology, Drug Research And Child Health (neurofarba), Florence, Italy, [6]Meyer Children's Hospital, Centre of Excellence, Division of Pediatric Oncology/hematology, Florence, Italy

Background and Aims: IEI may display kaleidoscopic clinical presentations. Herein wefocused on children who manifested with hematological features (cytopenias, lymphoproliferation, eosinophilia,leukemia/lymphoma susceptibility, hemophagocytic lymphohistiocytosis) as a first sign of IEI.

Methods: We retrospectively collected data from children (<18 years of age) who presented between 2010-2022 with hematological symptoms at two Italian pediatric hematology units and were eventually diagnosed with an IEI.

Results: Thirty-two patients were included. The diagnosed IEI were heterogeneous, and comprehended Predominantly antibody deficiencies (Six Common Variable ImmunoDeficiency, 1 activated PI3K-delta syndrome, 1 TACI and 1 TRNT1 deficiencies), Combined immunodeficiencies (1 IKAROS and 1RAG1 deficiencies), Syndromic IEI (1 Wiskott-Aldrich, 1 X-linked thrombocytopenia, 1 Kabuki, 1 Hebo deficiency), and Immunedysregulatory disorders (6 ALPS, 2 STAT3-GOF, 1 IPEX, 3 familial HLH, 2 X-linked lymphoproliferative syndromes). Defects of phagocytes (2 GATA2 deficiency) and Bone marrow failure syndromes (1 RTEL1 deficiency) were also observed. At presentation, 18 patients showed cytopenia (3 bilinear, 1 trilinear), 12 benign lymphoproliferation, 5 HLH, 2 malignancies (lymphoma, acute myeloid leukemia), 2 myelodysplasia, and 1 eosinophilia. 10/32 patients (31%) had a positive family historyand 8/32 (25%) showed other signs of immunedysregulation.

Conclusions: A wide array of IEI could initially present with hematological involvement. Though single entities are rare, the cumulative number of patients with IEI who are firstly addressed to hematology units is clinically relevant, highlighting the need to increase the diagnostic awareness of IEI among pediatric hematologists. Positive family history and concurrent signs of immunedysregulation are key elements to raise diagnostic suspicion.

Disclosure: No.

Keywords: Hemophagocytic Lymphohistiocytosis, Cancer predisposing syndromes, LYMPHOPROLIFERATION, Pediatric hematology, cytopenia, Immune Dysregulation

PD069

MHV68 INFECTION CAUSES A DISTINCT LUNG PHENOTYPE IN ITK-/- DEFICIENT MICE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Ciro Novaes Rosa Lino[1], Zhe Lu[1], Christiane Knobbe-Thomsen[2], Ingo Drexler[3], Aleksandra Pandyra[1], Arndt Borkhardt[1], Sujal Ghosh[1]
[1]Center of Child and Adolescent Health, Medical Faculty, Heinrich Heine University, Department of Pediatric Oncology, Hematology And Clinical Immunology, Düsseldorf, Germany, [2]Medical Faculty, Heinrich Heine University Düsseldorf, Department of Neuropathology, Duesseldorf, Germany, [3]Medical Faculty, Heinrich Heine University Düsseldorf, Institute of Virology, Duesseldorf, Germany

Background and Aims: Inducible T-cell kinase (ITK) deficient patients present with EBV (Epstein-Barr Virus) lymphoproliferative disease, hemophagocytic lymphohistiocytosis and hypogammaglobulinemia. Unlike in classical cytotoxicity defects, e.g. perforin deficiency, a murine model with a distinct clinical phenotype upon viral infection, resembling the human counterpart, has not been established. We chose to characterize the infection of itk-/- deficient mice with murine gammaherpesvirus 68 (MHV-68), which is the closest analogue of EBV.

Methods: Itk-/- mice were infected with MHV-68 intranasally (n=61), uninfected itk-/- mice and infected B6 mice (n=60) served as a control. Mice were analyzed after a period of 1, 2, 4, 8, 12 and 24 weeks. Lymphocyte subsets were analyzed by flow cytometry on spleen, lymph node, liver, lung tissue and broncheoalveolar lavage. Spleen, liver and spleen were analyzed by immunohistochemistry.

Results: Itk-/- mice show a distinct immunological phenotype (increased CD8 T cells, effector T cells, TCRVbeta4 cells, decreased naïve T cells and CD4 T cells). Furthermore we observe tissue infiltration in the lungs of itk-/- mice, a feature, which is also observed in ITK deficient patients. BAL analyses suggest an significantly increased T cell activity 12 weeks after infection compared to infected wild-type mice.

Conclusions: After viral infection we observe distinct immunological and clinical features, which suggest that MHV-68 infection in the itk-/- murine setting resembles partly the human phenotype with patients presenting with characteristic lung infiltrates. Further studies to investigate if therapeutic approaches are able to ameliorate the phenotype with e.g. adoptive T cell transfer are warranted to gain more insight.

Disclosure: No.

Keywords: ITK deficiency, EBV, LYMPHOPROLIFERATION, combined immunodeficiency, Immune Dysregulation

PD070

CARDIOVASCULAR COMORBIDITY IN COMMON VARIABLE IMMUNODEFICIENCY: DATA FROM A MULTICENTRE SPANISH COHORT

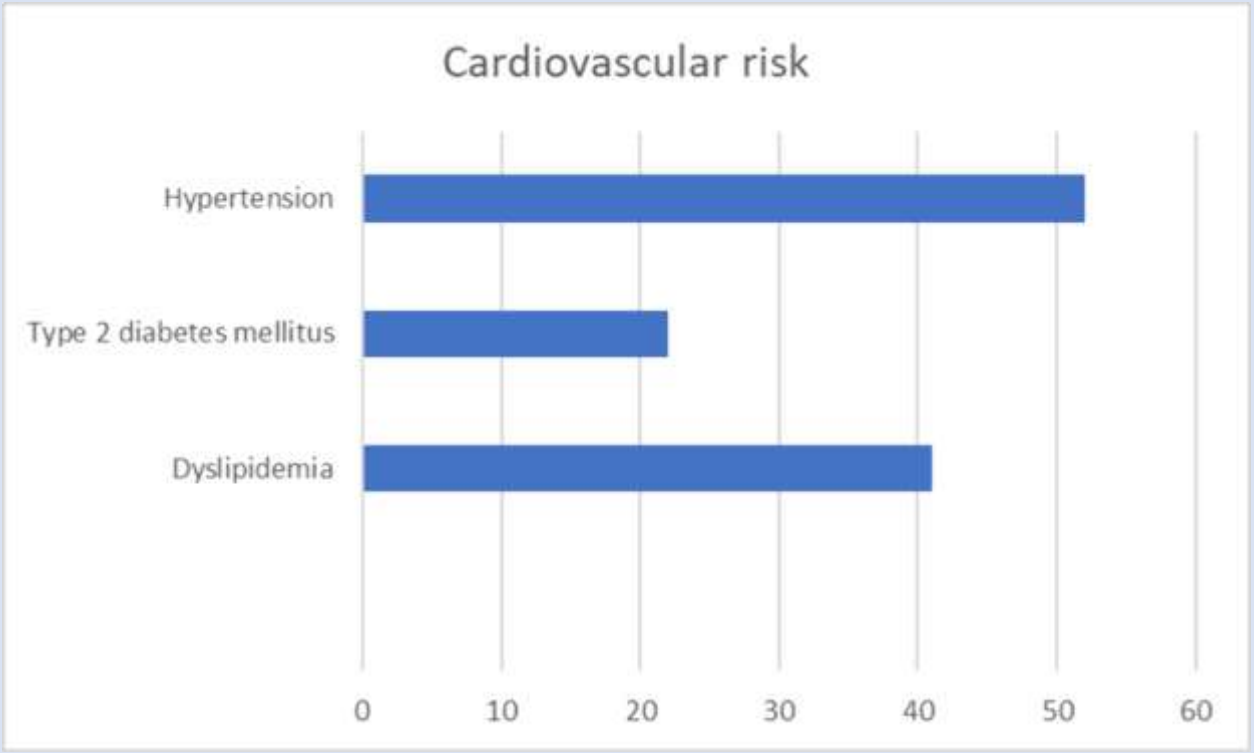
POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Marta Dafne Cabanero-Navalon[1], Víctor García Bustos[1], María Núñez Beltrán[1], Lourdes Mateu[2], Xavier Solanich Moreno[3], Juan Luís Carrillo[4], Ángel Robles Marhuenda[5], Francesc Puchades[6], Ana Pelaez Ballesta[7], Nuria Osle[8], Miguel Ángel Torralba[9], Ana María Bielsa[10], Jorge Diego Gil[11], Nutia Tornador[12], Guillem Pascual Castellanos[12], Rosario Sánchez[13], José Manuel Barragán[14], Andrés González[15], José Luis Patier[16], Daniel López Wolf[17], Antonia Mora Rufete[18], Alba Cánovas[18], Pedro Moral Moral[1]
[1]University and Politechnic Hospital La Fe, Internal Medicine, Valencia, Spain, [2]Hospital Universitari Germans Trias i Pujol, Internal Medicine, Badalona, Spain, [3]Hospital Universitari de Bellvitge, Internal Medicine, L'Hospitalet de Llobregat, Spain, [4]Hospital Universitario Virgen de la Victoria, Internal Medicine, Málaga, Spain, [5]Hospital Universitario La Paz, Internal Medicine, Madrid, Spain, [6]Hospital General de Valencia, Internal Medicine, Valencia, Spain, [7]Hospital Universitario Rafael Méndez, Internal Medicine, Lorca, Spain, [8]Hospital de Cruces, Internal Medicine, Barakaldo, Spain, [9]Hospital Clínico Universitario Lozano Blesa, Internal Medicine, Valencia, Spain, [10]Hospital Miguel Servet, Internal Medicine, Zaragoza, Spain, [11]Hospital Universitario 12 de Octubre, Internal Medicine, Madrid, Spain, [12]Hospital General de Castellón, Internal Medicine, Castellón, Spain, [13]Hospital General de Alicante, Internal Medicine, Alicante, Spain, [14]Complejo Asistencial de Ávila, Internal Medicine, Ávila, Spain, [15]Hospital Universitario Santiago Ramón y Cajal, Internal Medicine, Madrid, Spain, [16]Hospital Universitario Santiago Ramón Y Cajal, Internal Medicine, Madrid, Spain, [17]Hospital de Alcorcón, Internal Medicine, Madrid, Spain, [18]Hospital Universitario de Elche, Internal Medicine, Valencia, Spain

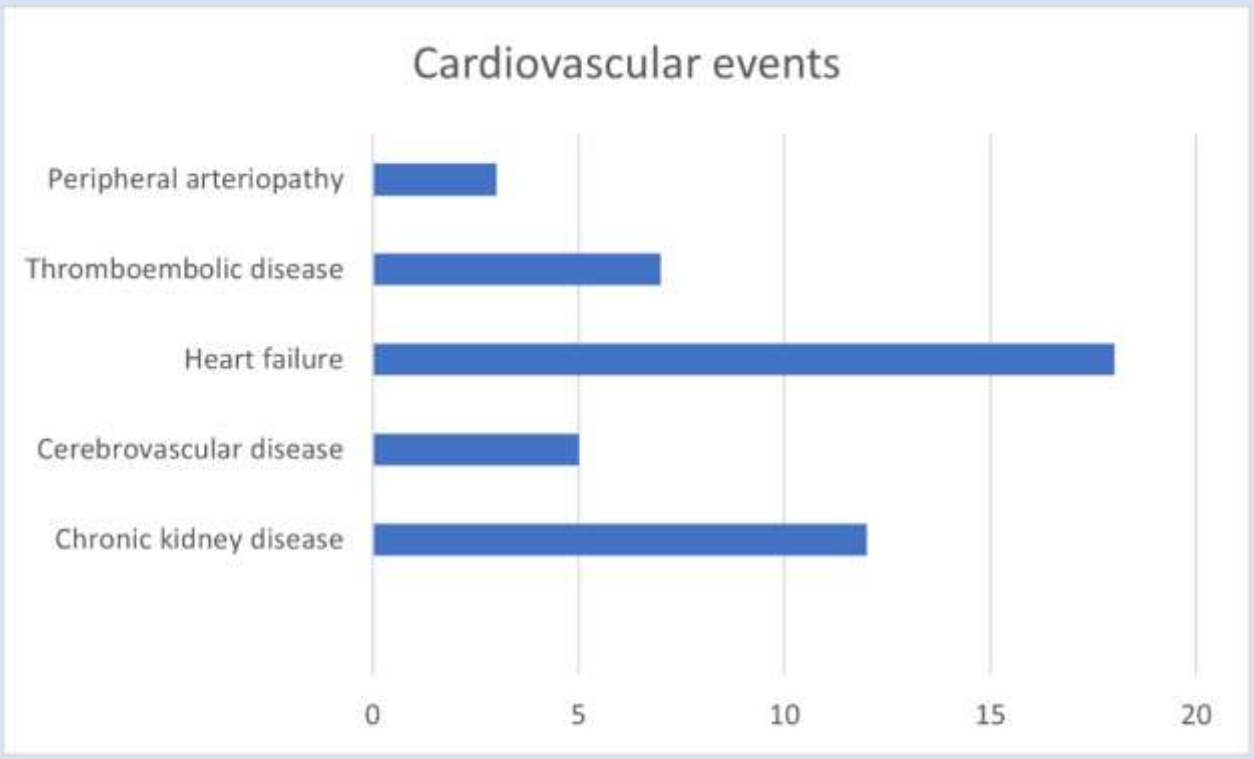
Background and Aims: Non-infectious complications in patients with common variable immunodeficiency (CVID) have emerged as a great clinical challenge. Chronic inflammation has been related with increased risk of cardiovascular events. Thus, the aim of this study was to determine whether there is an increased risk of cardiovascular disease and a higher number of cardiovascular events in patients with CVID.

Methods: Two hundred and fifty patients diagnosed with CVID were included in the Spanish registry of CVID developed by the Minority Disease Working Group of the Spanish Society of Internal Medicine (GTEM SEMI). Demographic parameters, survival data, infectious complications and non-infectious comorbidities such as cardiovascular events were collected. Statistical analysis was made with R version 4.0.0.

Results: The mean age of CVID patients was 54 years. Forty-eight percent of the patients were male. The prevalence of cardiovascular risk factors such as hypertension, dyslipidemia and type 2 diabetes mellitus was higher than in common population; namely 20.88%, 16.65% and 8.84%, respectively (Fig.1). When analysing cardiovascular events, remarkably, 7.23% suffered heart failure, almost 7-fold than common population aged over 40 years old (Fig.2). Additionally, chronic kidney disease, cerebrovascular disease and peripheral arteriopathy were present in 4.82%, 2% and 1.20%, respectively. Figure



1 Figure



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Conclusions: A higher cardiovascular risk exists in CVID patients. In addition, cardiovascular events in CVID patients were more frequently documented than in common population. Further studies are needed to determine the etiology of these findings. Bibliography: DOI: 10.3389/fimmu.2020.00149 DOI: 10.1159/000435818

Disclosure: No.

Keywords: Common variable immunodeficiency, cardiovascular risk, non-infectious complications

PD071

TRANSCRIPTOME-, PROTEOME- AND CHROMATIN ACCESSIBILITY ANALYSIS IN NAIVE B CELLS of PATIENTS HARBORING THE C104R MUTATION IN TACI

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Neftali Ramirez[1,2], Sara Posadas-Cantera[1,2], Niko Langer[2], Andrés Caballero-Oyteza[1,2], Michele Proietti[1,2,3,4], Bärbel Keller[2,5], Fangwen Zhao[6], Matteo Pecoraro[7], Herman Eibel[2,5], Klaus Warnatz[2,5], Esteban Ballestar[8,9], Christoph Bock[6,10], Roger Geiger[7,11], Claudia Bossen[2], Bodo Grimbacher[1,2,4,12,13]
[1]Institute for Immunodeficiency, University Medical Center Freiburg, Freiburg im Breisgau, Germany, [2]Center for Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg, Germany, [3]Department of Rheumatology and Clinical Immunology, Hannover Medical University, Hannover, Germany, [4]Resolving Infection Susceptibility (RESIST) – Cluster of Excellence 2155, Hanover Medical School, Satellite Center Freiburg, Freiburg, Germany, [5]Department of Rheumatology and Clinical Immunology, University Medical Center Freiburg, Freiburg, Germany, [6]CeMM, Research Center For Molecular Medicine of The Austrian Academy of Sciences, Vienna, Austria, [7]Institute for Research in Biomedicine, Università Della Svizzera Italiana, Bellinzona, Switzerland, [8]Epigenetics and Immune Disease Group, Josep Carreras Research Institute (ijc),08916 Badalona, Barcelona, Spain, [9]Chromatin and Disease Group, Cancer Epigenetics and Biology Programme (PEBC), Bellvitge Biomedical Research Institute (idibell), Barcelona, Spain, [10]Institute of Artificial Intelligence and Decision Support, Center For Medical Statistics, Informatics, And Intelligent Systems, Vienna, Austria, [11]Institute of Oncology Research, Università Della Svizzera Italiana, Bellinzona, Switzerland, [12]DZIF – German Center for Infection Research, Satellite Center Freiburg, Germany, Freiburg, Germany, [13]Center for Integrative Biological signaling Studies (CIBSS), University of Freiburg, Freiburg, Germany

Background and Aims: Common variable immunodeficiency (CVID) is the most prevalent symptomatic primary immunodeficiency in humans. 10% of CVID patients carry heterozygous mutations in the tumor necrosis factor receptor superfamily member 13B gene (TNFRSF13B), encoding TACI. Mutations in TNFRSF13B alone may not be sufficient for the development of CVID, as 1% of the healthy population carry these mutations. The common hypothesis is that TACI mutations are not fully penetrant and additional factors contribute to the development of CVID.

Methods: We investigated the perturbations of transcription factor binding and the transcriptome profiles in unstimulated and CD40L/IL21-stimulated naïve B cells from CVID patients harboring the C104R mutation in TNFRSF13B, and compared them to their healthy relatives with the same mutation. In addition, the proteome of stimulated naïve B cells was investigated. For functional validation, intracellular protein concentrations were measured by flow cytometry.

Results: Our analysis revealed 8% less accessible chromatin in unstimulated naïve B cells and 25 % less accessible chromatin in class-switched memory B cells from affected and unaffected TACI mutation carriers compared to healthy donors. The most enriched transcription factor binding motifs in TACI mutation carriers involved ETS, IRF and NF-kB transcription factor family members. Validation experiments supported dysregulations in the NF-kB and MAPK pathways. In steady state, naïve B cells had increased cell death pathways and reduced cell metabolism pathways; while after stimulation, enhanced immune responses and decreased cell survival was detected.

Conclusions: Using a multi-omics approach, our findings provide valuable insights into the impaired biology of naïve B cells from TACI mutation carriers.

Disclosure: No.

Keywords: ATAC-seq, Proteomics, TACI, CVID, naive B cells, RNA-seq

PD072

RITUXIMAB TREATMENT FOR AUTOIMMUNE ENCEPHALITIS of IMMUNE DYSREGULATION, POLYENDOCRINOPATHY X-LINKED SYNDROME: CASE REPORT

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Van Anh Nguyen Thi
National Children Hospital, Allergy - Immunology - Rheumatology, Hanoi, Viet Nam

Background and Aims: IPEX syndrome is a rare hemizygous disorder that presents most commonly in early infancy and is characterized by severe enteropathy, chronic dermatitis, early-onset type I diabetes mellitus, hypoparathyroidism. Autoimmune encephalitis is another rare complication that could be severe if not treated with appropriate immunosuppressive agents and HSCT. Aims: Describe the successful treatment of autoimmune encephalitis by Rituximab for IPEX patient

Methods: Case report

Results: We report an 8-year-old boy admitted at the age of 7.5 with seizure and behavior disorder. In history, he had atopic dermatitis and hypothyroidism, recurrent URTI, and no history of IBD. CSF revealed AMPA antibody (+). Cranial MRI: hippocampal brain damage. Autoimmune encephalitis was confirmed and treated with bolus corticosteroid, 2 doses of IVIG, Mycophenolate Mofetil, antiepileptic drugs, but he did not improve. After 6 months, he got severe diabetes with positive Anti – TG and anti – TPO. Analyzing the PID Panel gene find a pathogenic variant, c.1150G>A (p.Ala384Thr) in FOXP3. The patient's mother is a carrier, and his sister is not. We use Rituximab 375mg/m2/dose x 4 doses every 1 week. After the second dose of Rituximab, the CD20 count was=0 cells/ml. After 4th dose, convulsions and memory improved, and he could calculate. After 6 months, blood sugar improved and insulin dose gradually decreased, skin lesson is better. His condition improved well in perception, calculation, and cycling, with no convulsions no behavioral disturbances. Currently we are planning for a HSCT by an HLA-matched sibling donor.

Conclusions: Rituximab is effective in treatment for autoimmune encephalitis in IPEX syndrome

Disclosure: No.

Keywords: RITUXIMAB, Autoimmune encephalitis, treatment, IPEX syndrome, FOXP3, AMPA antibody

PD073

A NOVEL FAMILIAL CASE of TNFAIP3 MUTATION CAUSES LYMPHOPENIA AND AN AUTOINFLAMMATORY DISORDER RESPONSIVE TO ANAKINRA

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Laura Dotta[1], Lucia Savaré[2], Marco Cattalini[2], Vassilios Lougaris[3,4], Silvia Clara Giliani[5], Raffaele Badolato[4]
[1]ASST Spedali Civili di Brescia, Pediatrics, Brescia, Italy, [2]University of Brescia, Clinica Pediatrica, Brescia, Italy, [3]University of Brescia, ASST Spedali Civili of Brescia, Pediatrics Clinic, Department of Clinical And Experimental Sciences, Brescia, Italy, [4]Pediatrics Clinic and "A. Nocivelli" Institute for Molecular Medicine, Department of Clinical And Experimental Sciences, University of Brescia, Asst- Spedali Civili of Brescia, Brescia, Italy, [5]Institute for Molecular Medicine A. Nocivelli, Department of Molecular And Translational Medicine, University of Brescia, brescia, Italy

Background and Aims: TNFAIP3 encodes for A20 protein, a negative regulator of NF-kB and IFNγ signaling. Heterozygous loss-of-function mutations cause early-onset autoinflammatory diseases, variably associated with immunodeficiency. We report a novel familial TNFAIP3 mutation that associates to heterogeneous phenotypes.

Methods: We collected clinical data and performed genetic and immunological studies.

Results: A 12-year-old male patient presented high fever, associated with hepatosplenomegaly, lymphadenopathy, erythematous maculopapular rash, and pancytopenia (WBC 1200 cell/uL; Hb 10 g/dL; PLTs 61000/uL). He had a previous history of type 1 diabetes that onset at the age of 5 years, autoimmune thyroiditis, chronic urticaria and lymphopenia (ALC 570 cell/μL). Extended investigation of infectious diseases tested negative, and he was treated with immunoglobulins (2g/kg), with resolution of fever and increase of blood counts. Afterwards, he developed two coronary artery aneurysms that rapidly resolved with steroid treatment. Then, he relapsed with fever, rash, and splenomegaly that responded to immunoglobulins, and the IL-1R inhibitor anakinra was started. Next Generation Sequencing identified a novel heterozygous variant the c.219delC:p.Q74Rfs*21 in the TNFAIP3 gene. The same mutation was found in his mother who presented autoimmune thyroiditis, chronic urticaria, without recurrent fever, nor lymphopenia, with high proportion of $CD19^{high}CD21^{low}$ B cells. On anakinra, the proband has no recurrent fever, but has lymphopenia (CD4 152 cell/uL) with a reduction of memory B cells.

Conclusions: We report two familial cases of novel TNFAIP3 mutation: the clinical heterogeneity in the immunological manifestations may affect the morbidity. The role of the mutation in the lymphopenia requires further investigation.

Disclosure: No.

Keywords: A20 haploinsufficiency, TNFAIP3, Autoinflammatory Disease, lymphopenia

PD074

CLINICAL CHARACTERISTICS AND RESPONSE TO ABATACEPT TREATMENT IN A GROUP of PATIENTS WITH LRBA AND CTLA4 DEFICIENCIES (A.K.A T-REGOPATHIES)

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Darya Bogdanova[1], Daria Yukhacheva[2], Anna Roppelt[2], Alexandra Laberko[2], Zoya Nesterenko[3], Vasiliy Burlakov[2], Anna Khoreva[4], Elena Deripapa[2], Anna Mukhina[2], Irina Abramova[2], Oxana Shvets[2], Dmitry Pershin[2], Victoria Vedmedskaya[5], Galina Tereshchenko[6], Maxim Alexenko[7], Elena Raykina[7], Amina Kieva[7], Alexey Pshonkin[1], Anna Shcherbina[2], Yulia Rodina[2]
[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation, Short-term Treatment Department, Moscow, Russian Federation, [2]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [3]National Medical Research Center of Pediatric Hematology, Oncology and Immunology named after Dmitry Rogachev, Moscow, Immunology, Moscow, Russian Federation, [4]Dmitriy Rogachev National Center for Pediatric Hematology, Oncology, and Immunology, Moscow, Russian Federation, Immunology, Moscow, Russian Federation, [5]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Laboratory of Transplantation Immunology And Immunotherapy of Hemoblastoses, Moscow, Russian Federation, [6]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Radiology, Moscow, Russian Federation, [7]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Laboratory of Molecular Biology, Moscow, Russian Federation

Background and Aims: T-regopathies are combined primary immunodeficiencies characterized by immune dysregulation, leading to autoimmune, infectious and oncological manifestations.

Methods: We retrospectively analyzed 18 patients with CTLA4 haploinsufficiency (CHAI) and 3 with LRBA deficiency (LATAEI), all genetically confirmed. The severity of the disease was assessed using the Immune Deficiency and Dysregulation Activity (IDDA) score.

Results: The median age of the disease onset was 25.5 months (0 - 177 months). The most frequent clinical manifestations included autoimmune cytopenias (17/21), interstitial lymphocytic lung disease (16/21), lymphoproliferation (15/21), inflammatory bowel disease (11/21), skin/mucous lesions (9/21), endocrinopathy (7/21), arthritis (4/21). 15/21 patients had moderate decrease of CD3+ (mean 1.161±0.747 cell/ul) and CD19+ (mean 0.262±0.279 cell/ul) lymphocytes, and profound reduction of switched B-cells (mean 0.020 ±0.030 cell/ul). Immunosuppressive therapy with glucocorticosteroids, mycophenolate mofetil, rituximab, sirolimus did not lead to complete symptoms remission in any patients. 15 patients were switched to abatacept and were assessed after at least 12 months of treatment (median 19.7 months (range 12–72)). In 11 patients treated with abatacept at an average dose of 18.6mg/kg every 2 weeks, IDDA score decreased from a mean of 11.8 ±1.8 to 3.4 ±2.0 points ($p<0.001$). In 4 patients treated with abatacept at an average dose of 11 mg/kg every 4 weeks, IDDA score decreased from a mean of 11.8 ±2.6 to 5.5 ±1.5 points ($p=0.074$).

Conclusions: Patients with T-regopathies have diverse autoimmune symptoms. Abatacept, especially at higher doses is a promising treatment for patients with LRBA and CTLA4 deficiencies.

Disclosure: No.

Keyword: CTLA4 haploinsufficiency, LRBA deficiency, immune dysregulation, Abatacept, IDDA score

PD075

CLINICAL AND IMMUNOLOGICAL EFFECTS of RUXOLITINIB IN STAT3 GAIN-OF-FUNCTION PATIENTS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Royala Babayeva[1], Mehmet Cihangir Catak[1], Demet Hafizoglu[2], Nalan Yakici[3], Fatih Celmeli[4], Alper Bulutoglu[1], Sevgi Bilgic Eltan[1], Dilek Baser[1], Elif Karakoc-Aydıner[1], Ahmet Ozen[1], Safa Baris[1]
[1]Marmara University, Pediatric Allergy And Immunology, Istanbul, Turkey, [2]Dortcelik Pediatric Hospital, Pediatric Allergy And Immunology, Bursa, Turkey, [3]KARADENİZ TECHNİCAL UNİVERSİTY, Pediatric Allergy And Immunology, TRABZON, Turkey, [4]University of Health Sciences, Pediatric Allergy And Immunology, Istanbul, Turkey

Background and Aims: STAT3 GOF germline mutations have been described recently and pose to early-onset multiorgan dysfunction, autoimmune disorders, lymphoproliferation, susceptibility to infection, and growth failure. Janus kinase inhibitors can control the disease activity; however, the efficacy of this targeted drug has not been precisely evaluated. Herein we prospectively evaluated the effect of ruxolitinib in STAT3 GOF patients.

Methods: We included 4 patients who were evaluated every 3 months for long-term clinical and immunological responses of ruxolitinib. Extensive lymphocyte subpopulations, circulating T follicular helper (cT_{FH}), and regulatory T cells, were determined by flow cytometry.

Results: The mean age of the patients was 14.7±2.0 years with a follow-up period of 15 months. Ruxolitinib was started for lymphoproliferation (n=4), autoimmune cytopenia (n=3), and FTT (n=2) with doses as 15-20 mg/m^2/twice a day. After one year of treatment, four patients demonstrated complete control of LP and autoimmune cytopenias and achieved statistically better quality of life scores. FTT in 2 patients was not improved. There were no serious side effects. Baseline decreased T, B and NK cell counts were observed in 30%, 8%, 30% of patients, respectively. Ruxolitinib did not change T, B, NK cell counts during the follow-up. High cT_{FH} cell frequencies were observed in all patients at baseline, partially reversed on treatment. At baseline, the percentages of regulatory T cell ($CD4^+CD25^+FOXP3^+$) were comparable between patients and controls. Interestingly, elevation in Treg cells were observed in all patients with ruxolitinib. TUBITAK (318S202).

Conclusions: Long-term ruxolitinib therapy is effective and safe in patients with STAT3 GOF mutations.

Disclosure: No.

Keywords: ruxolitinib, STAT3 GOF, Immune Dysregulation, Targeted therapy

PD076

A DIFFERENTIAL ROLE FOR STK4/MST1 IN RESTING AND PROLIFERATING T CELLS.

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Rafah Mackeh, Asha Elmi, Nourhen Agrebi, Tracy Augustine, Mohamed Alsabbagh, Amel Hassan, Bernice Lo
Sidra Medicine, Research - Human Genetics, Doha, Qatar

Background and Aims: STK4 is the mammalian homolog of Hippo, which regulates proliferation and apoptosis in Drosophila. In the canonical pathway, STK4 activation leads to the degradative phosphorylation of YAP transcription factor, which leads to a proliferation arrest. Although STK4 mediates a pro-apoptotic role in non-immune cells, the human cases of STK4 deficiency revealed a non-canonical function of STK4 in mediating the survival of T cells. We have recently reported a homozygous nonsense mutation in STK4 identified in a pediatric patient leading to a complete loss of protein expression. Here we describe extended investigations into the functional consequences of STK4 deficiency differentially in resting and proliferating T cells.

Methods: We combined cell and molecular approaches (Western Blot, qRT-PCR and Flow Cytometry) to address the consequences of STK4 deficiency on various cell mechanisms.

Results: Similar to the previously reported cases of human STK4 deficiency, patient's peripheral T cells undergo a high level of apoptosis. Patient's memory T cells are increased while naïve T cells are below normal range. However, unlike any previously reported cases, the patient's T cells exhibit much stronger proliferation in response to TCR stimulation. Among the targets of STK4, phosphorylation of the tumor suppressor MOB1 was completely impaired, suggesting that the faster proliferation observed was due to the loss of MOB1's inhibitory role on cell cycle.

Conclusions: We present a case of STK4 deficiency with an accelerated TCR-induced T cell proliferation, where we investigated the differential role of Hippo pathway in naive and resting T cells.

Disclosure: No.

Keyword: SKT4, MST1, Immunodeficiency, Hippo pathway, MOB1.

PD077

IMPLEMENTATION of A FUNCTIONAL IL-10R MEDIATED CYTOKINE INHIBITION ASSAY IN CLINICAL PRACTICE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Marianna Tzanoudaki[1], Maria Rogalidou[2], Maria Tsouprou[3], Konstantinos Zachos[3], Sofia Tantou[1], Rediona Kane[1], Virginia Polaki[1], Alexandra Papadopoulou[2], Manolis Liatsis[1]
[1]"Aghia Sophia" Children's Hospital, Dept. of Immunology & Histocompatibility, Athens, Greece, [2]"Aghia Sophia" Children's Hospital, Division of Gastroenterology And Hepatology, First Department of Pediatrics, University of Athens, Athens, Greece, [3]"Aghia Sophia" Children's Hospital, First Department of Pediatrics, Athens, Greece

Background and Aims: Timely diagnosis of IL-10R deficiency has been facilitated by NGS. However, as its sensitivity and availability are questioned, simple functional tests are needed. We therefore evaluated a simple cytokine inhibition assay in children with Inflammatory Bowel Disease (IBD).

Methods: Heparinized whole blood from 28 IBD patients (median age 3 years) and 28 healthy controls was incubated overnight in Complete Media, either unstimulated ("Unst") or LPS (1μg/mL) stimulated without IL-10 ("LPS") or LPS stimulated after 45 min pre-incubation with IL-10 ("IL-10inc") (10ng/mL, 20ng/mL, 30ng/mL or 40ng/mL). Concentrations of IL-10, IL-6, and TNFα in the supernatant were assessed by cytometric bead assay. Reduction of cytokine production after IL-10 incubation was calculated as (LPS-IL10inc)*100/(LPS-Unst), using the respective concentrations in the supernatant.

Results: IL-6 median reduction in controls was 53%, 79% 83% and 88% (for 10ng/mL, 20ng/mL, 30ng/mL and 40ng/mL IL-10 respectively). TNFα respective median reduction was 80%, 86%, 88% and 95%. Most IBD patients had comparable results (63%, 84% 91% and 95% for IL-6 and 76%, 80%, 86% and 93% for TNFα). In two patients with very early-onset IBD (2 months, 4 years old) IL-6 decreases were extremely small (3 and 4% in maximal IL-10 concentrations), whereas increases of 5% and 8% were observed for TNFα. These results facilitated timely IL-10R diagnosis in the EO-IBD infant and were compatible with IL10R Sanger Sequencing of the toddler with initially negative WES.

Conclusions: The above functional IL-10R assay is easily applicable and provides readily interpretable and clinically consistent results, which could compensate for unavailable or false negative WES.

Disclosure: No.

Keywords: IL10-R deficiency, Functional assay, IBD

PD078

DEMOGRAPHIC, CLINICAL, AND IMMUNOLOGICAL FEATURES IN COMBINED IMMUNODEFICIENCY PATIENTS WITH AND WITHOUT PULMONARY COMPLICATIONS: A RETROSPECTIVE MULTICENTER STUDY FROM IRAN

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Ghamartaj Khanbabaee[1], Matin Pourghasem[1], Mahnaz Jamee[2], Zahra Chavoshzadeh[2], Narges Eslami[2], Mitra Khalili[3]
[1]Shahid Beheshti University of Medical Scienses, Pediatric Pulmonology, Tehran, Iran, [2]Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Immunology And Allergy Department, Tehran, Iran, [3]Shahid Beheshti University of Medical Scienses, Radiology, Tehran, Iran

Background and Aims: Combined immunodeficiency (CID) is a heterogeneous group of inborn errors of immunity (IEIs), characterized by profound defects in the development and function of both B and T cells.The non-infectious complications and immunologic profile in patients with CID may help identify patients who are more prone to the development of respiratory complications and therefore require periodic pulmonary evaluations for risk assessment purposes.

Methods: This retrospective study was performed on patients with established diagnosis of CID registered between 2009 and 2020.Patients were divided into two groups based on the development of pulmonary complications, and their demographic, clinical, and laboratory characteristics were compared.

Results: 146 patients were enrolled in the study and divided into two groups of patients with (n=88) and without (n=58) pulmonary complications. Patients with pulmonary complications presented the disease's symptoms earlier compared to patients without pulmonary involvement. In patients with pulmonary complications, oral candidiasis, failure to thrive, and otitis media, had higher frequency while in the other group, anemia, autoimmunity, rheumatologic disorders, and skin lesions. HRCTs available in 54.5% of patients with pulmonary complications, were compatible with pneumonia (39.8%), bronchiectasis (12.5%), pulmonary nodules (3.4%), atelectasis (1.1%), interstitial lung disease (1.1%), and pneumothorax (1.1%). Patients with pulmonary complications had lower number of T CD4+ but higher levels of CD8+ cells compared to patients without pulmonary complications (p=0.012 and p=0.005, respectively).

Conclusions: The results of our study showed that respiratory disorders are of great importance in CID patients and require early periodic monitoring by respiratory tests and HRCT imaging to avoid irreversible injuries.

Disclosure: No.

Keywords: combined immunodeficiency, pulmonary complications, primary immunodeficiency, Inborn errors of immunity

PD079

LYMPHOCYTE PROLIFERATION ASSAY BY FLOW-CYTOMETRY: OUR EXPERIENCE FROM CHANDIGARH, NORTH INDIA

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Sumit Goel[1], Vignesh Pandiarajan[2], Rashmi Rikhi[3], Saniya Sharma[4], Amit Rawat[5], Surjit Singh[5]
[1]PGIMER, CHANDIGARH, INDIA, Pediatrics, CHANDIGARH, India, [2]Postgraduate Institute of Medical Education and Research, Department of Pediatrics, Advanced Pediatrics Centre, Chandigarh, India, [3]Post graduate Institute of Medical Education and Research, Pediatrics, Chandigarh, India, [4]Postgraduate Institute of Medical Education and Research, Pediatric Allergy And Immunology, Chandigarh, India, [5]Postgraduate Institute of Medical Education and Research, Pediatrics, Chandigarh, India

Background and Aims: Primary immunodeficiency diseases (PID) are a diverse group of disorders that affect various components of the immune system resulting in diverse clinical manifestations.

Methods: Lymphocyte proliferation assay was assessed by using the Carboxyfluorescein succinimidyl ester (CFSE) dye dilution method. Briefly, peripheral blood mononuclear cells were isolated by the Ficoll gradient centrifugation method and stained with CFSE. Stained cells were seeded in a tissue culture plate under various conditions including without any stimulation and stimulation with phytohaemagglutinin-P and CD3/CD28 beads. These cells were cultured for 6 days in a CO_2 incubator and acquired through a flow-cytometer followed by analysis by Kaluza software.

Results: Over the last 1 year, 17 patients were analyzed for lymphocyte proliferation. Out of these, 6 had reduced proliferation; 7 had normal proliferation and 4 had equivocal proliferation. Out of the 6 patients, 2 (patients 1 and 6) had features of nail dystrophy, alopecia & reduced CD3/CD4 T cells. While one had compound heterozygous variants in FOXN1, the other had a single heterozygous variant in FOXN1. One (patient 2) had features of early-onset inflammatory bowel disease & CD4 lymphopenia. Another patient (patient 3) had features of combined immunodeficiency, eczema & extensive molluscum contagiosum infection. This patient had a novel homozygous splice site variant in CARMIL2. One (patient 4) had features of disseminated cytomegalovirus infection, cryptosporidial diarrhea, and CD4 lymphopenia. One (patient 5) had unexplained encephalopathy and persistent lymphopenia. Next-generation sequencing showed a novel homozygous missense variant in RAG1.

Conclusions: Lymphocyte proliferation assay by flow-cytometry serves as a quick and effective way of confirming underlying combined immunodeficiency, especially in cases where novel variants in PID genes are encountered.

Disclosure: No.

Keywords: CD3/CD28 beads, Primary immunodeficiency diseases (PID), Lymphocyte proliferation assay, CFSE, Phytohaemagglutinin-P (PHA-P)

PD080

PUSTULAR PSORIASIS AS CLINICAL PRESENTATION IN A BOY WITH X- LINKED INHIBITOR of APOPTOSIS (XIAP) MUTATION: A CASE REPORT

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Alejandra King, Javiera Berho, Gabriela Romero, Katherine Aranguiz, Camila Valdes
Hospital Luis Calvo Mackenna, Immunology, SANTIAGO, Chile

Background and Aims: XIAP deficiency is an inborn error of immunity caused by mutations in XIAP/BIRC4. The disease is characterized by recurrent hemophagocytic lymphohistiocytosis, inflammatory bowel disease, hypogammaglobulinemia, severe and/or recurrent infections, splenomegaly, and cytopenias. Dermatological findings are very uncommon. Until now, there is not report of pustular psoriasis as a manifestation in XIAP[1].

Methods: Clinical case presenation

Results: One year-old male who at 3 months presented papulosquamous exanthema predominantly on face treated with antibiotics and antivirals with partial response. Patient progressed to erythroderma plus fever, adenopathies, nodular lesions in spleen, diarrhea and wet cough. Biopsy of skin lesions: pustular psoriasis. No consanguinity or family history of immunodeficiency. He evolved with persistent fever and elevated inflammatory markers without response to broad-spectrum antibiotics. All cultures were negative. He developed multifactorial severe anemia. Bone marrow aspiration was negative for leukemia. He had normal T, B and NK cell counts, immunoglobulins, and abnormal lymphocyte proliferation to PHA (24%). He received subcutaneous anakinra 1mg/kg/day with decrease of all inflammatory markers, no fever and resolution of skin lesions in a few days. INVITAE panel reported a hemizygous pathogenic variant in XIAP c.755dup (p.Asn252Lysfs*15).

Conclusions: CONCLUSIONS Until now, there is no report of pustular psoriasis as a manifestation of XIAP deficiency. This would be the first case. Like the absence of XIAP promotes inflammasome activation interleukin-1 receptor antagonist could be an option. The only curative treatment option for XIAP deficiency is allogeneic HSCT.
REFERENCES [1] Mudde ACA, Booth C and Marsh RA (2021) Evolution of Our Understanding of XIAP Deficiency. Front. Pediatr.

Disclosure: No.

Keywords: XIAP, anakinra, IMMUNODISREGULATION, PUSTULAR PSORIASIS

PD081

NEUROLOGICAL INVOLVEMENT IN PRIMARY IMMUNODEFICIENCIES

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Sara Sebnem Kilic, Hulya Kose
Uludag University, Faculty of Medicine, Pediatric Immunology, Bursa, Turkey

Background and Aims: The nervous system may be affected in primary immune deficiency (PID) syndromes through infectious, autoimmune, neoplastic mechanisms, or as a primary feature of the syndrome. The aim of this study is to reveal the neurological manifestations in patients with PID.

Methods: A retrospective analysis was evaluated of patients with PID by the department of Pediatric Immunology between January 2015 and January 2021. Hundred-seven patients who had neurological complaints were included in the study. Neurological findings were classified as primary, secondary, or coincidental.

Results: The female/male ratio was 48/57, the median age: 11 years (min=1 max=60), the median follow-up time was 72 months (min=7, max=240). The most common findings were; cognitive delay (n=62, 59%), epilepsy (n=23, 24.8%) and ataxia (n=20, 18%) respectively. Cranial MRI was abnormal in 80.4% (n=78) of the patients. Primary involvement was detected in 52% (n=48,5), secondary involvement was found in 20.8% (n=20), and structural or anatomical variants were founded in 16.7% (n=16) of the patients. Intracranial pathologies were grouped based on the anatomical location of MRI findings in the gray matter (n=6, 6.3%), the white matter (n=27, 28.4%), the pituitary gland (n=3, 3.2%), hydrocephalus (n=5, 5,3%), cerebral atrophy (n=21, 22.3%), cerebellar atrophy (n=33, 30%), and intracranial hemorrhage (n=3, 3%).The most common clinical findings were; cognitive delay (n=62, 59%), epilepsy (n=23, 22%) and ataxia (n=20, 18%) respectively

Conclusions: The neurologic presentation may constitute the initial manifestation in certain types of PID. Early recognition and treatment are important to prevent or reduce future irreversible neurological damage.

Disclosure: No.

Keyword: Primary immunodeficiency, neurologic involvement

PD082

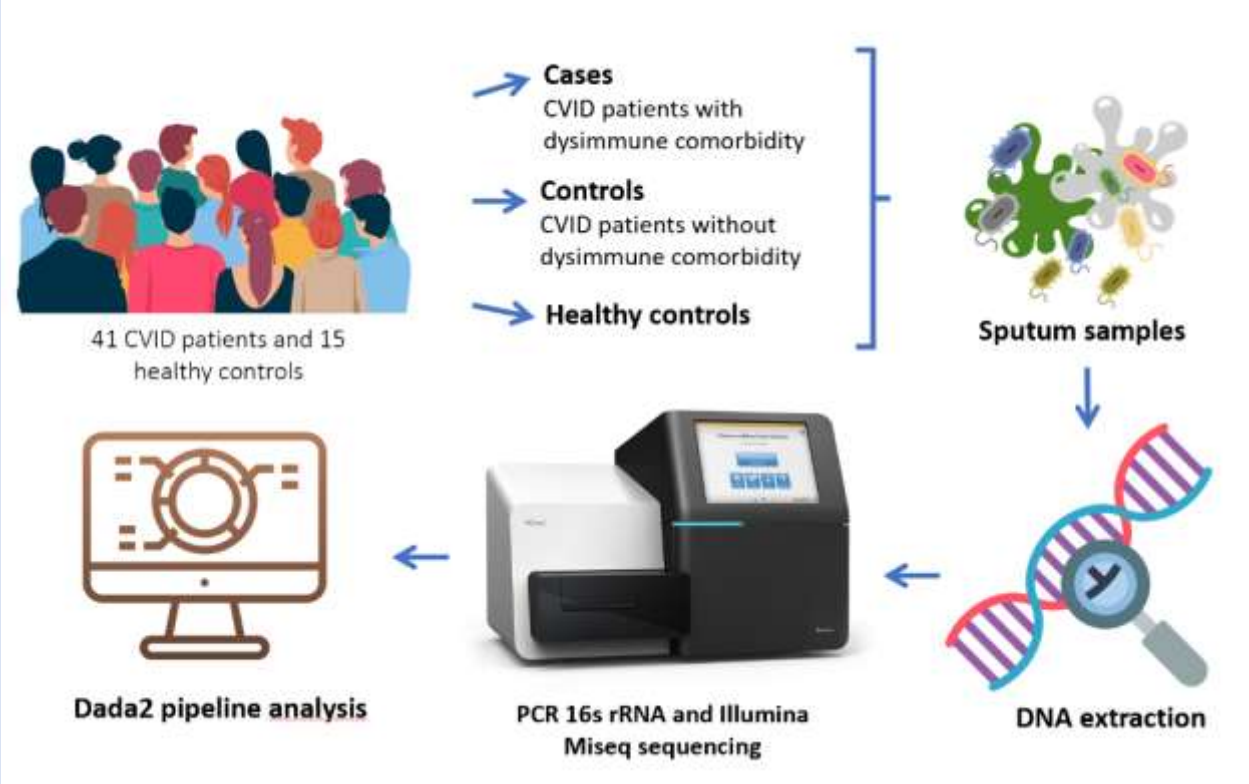
DIFFERENTIAL ANALYSIS of LUNG MICROBIOME IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

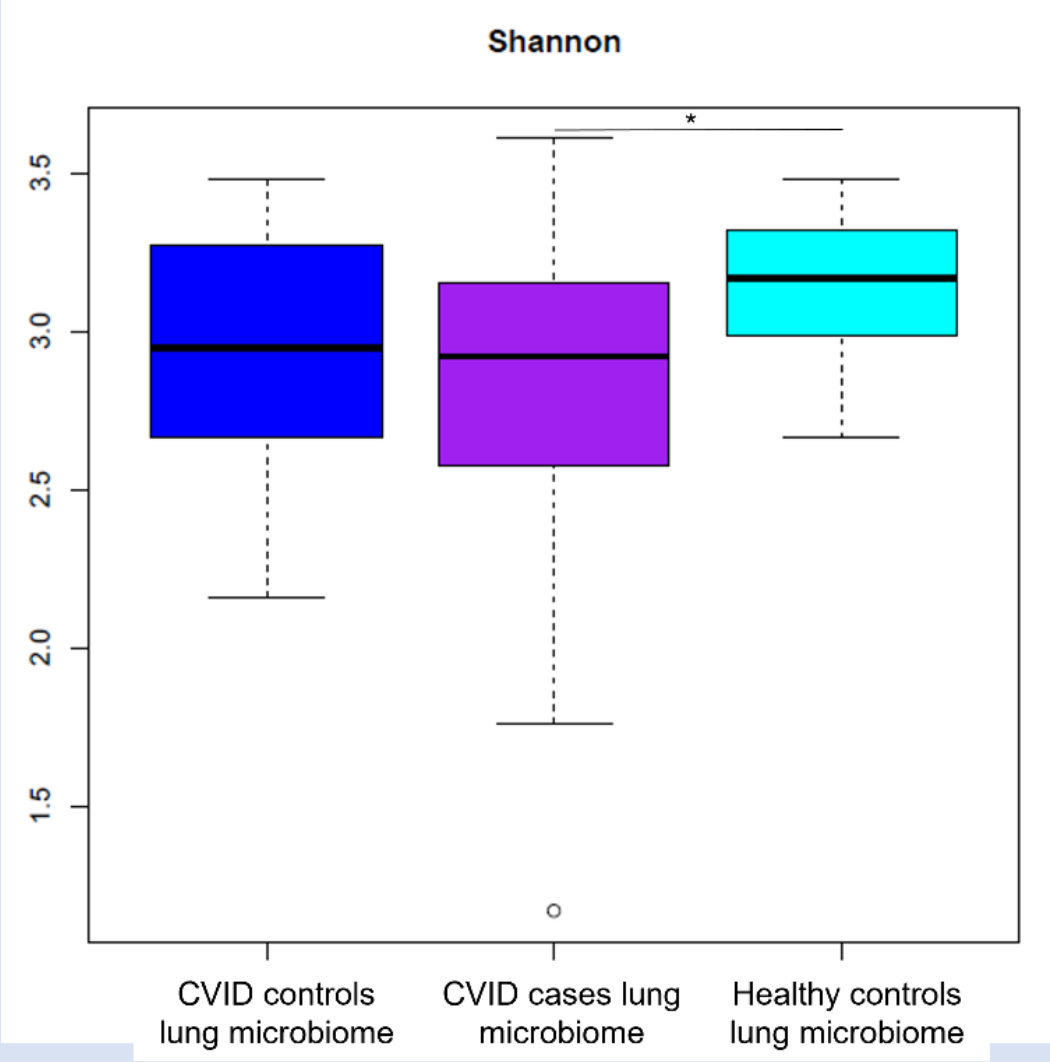
Marta Dafne Cabanero-Navalon[1], Víctor García Bustos[1], Miguel Cardá Diéguez[2], Carlos Puig Navarro[1], Nelly Catalán Cáceres[3], Sandra García Esteban[2], María Núñez Beltrán[1], Miguel Salavert Lletí[1], Pedro Moral Moral[1], Alejandro Mira Obrador[2]
[1]University and Politechnic Hospital La Fe, Internal Medicine, Valencia, Spain, [2]FISABIO Foundation, Oral Microbiome Laboratory, VALENCIA, Spain, [3]University and Politechnic Hospital La Fe, Allergology, Valencia, Spain

Background and Aims: To perform a differential analysis of lung microbiome in patients with common variable immunodeficiency (CVID) with dysimmune disorders (cases), CVID patients who only suffered infections (controls) and healthy controls.

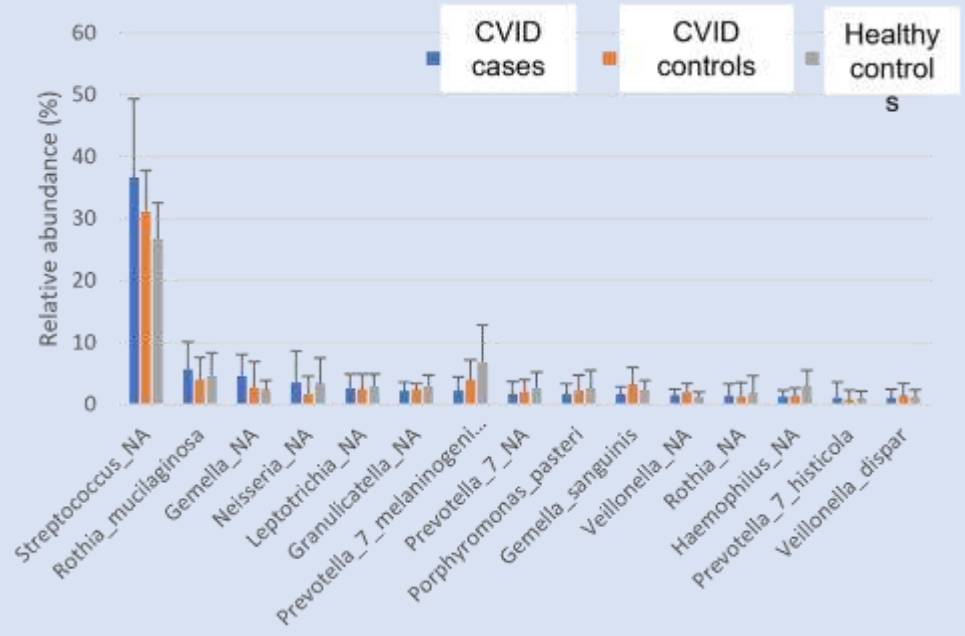
Methods: Sputum samples were collected from 41 patients diagnosed of CVID followed in a primary immunodeficiencies referral unit. Cases (25) were defined as CVID with polyclonal lymphocytic infiltration, autoimmune or autoinflammatory diseases, non-infectious enteropathy and/or tumours. Controls (16) only presented infectious comorbidity. Fifteen healthy double controls were randomly selected. After DNA extraction, V3-V4 hypervariable regions were amplified with rRNA 16s universal primers. Illumina Miseq was used for gene sequencing. Sequences were quality-filtered and end-trimming for eliminating final base pair was conducted. They were transferred to Dada2 pipeline analysis obtaining genus and species taxonomy (Amplicon Sequence Variants or ASVs) (Fig. 1).



Results: Shannon biodiversity index statistically differed in the lung microbiome composition among CVID cases and healthy double controls ($p<0.05$). No statistically significant differences were found in the lung microbiota of CVID cases and controls, or among CVID controls and healthy controls (Fig.2) The lung microbiome composition of 5 patients with granulomatous lymphocytic interstitial lung disease (GLILD) was also analysed and compared with CVID cases, with no statistical significance. Streptococcus spp. was the most frequent genus found in the three groups, but its relative abundance was higher in CVID cases (Fig. 3) Figure 2 Figure


Shannon
*
3.5
3.0
2.5
2.0
1.5
CVID controls lung microbiome
CVID cases lung microbiome
Healthy controls lung microbiome

3


CVID cases
CVID controls
Healthy controls
Relative abundance (%)
60
50
40
30
20
10
0
Streptococcus_NA
Rothia_mucilaginosa
Gemella_NA
Neisseria_NA
Leptotrichia_NA
Granulicatella_NA
Prevotella_7_melaninogeni...
Prevotella_7_NA
Porphyromonas_pasteri
Gemella_sanguinis
Veillonella_NA
Rothia_NA
Haemophilus_NA
Prevotella_7_histicola
Veillonella_dispar

Conclusions: In conclusion, our findings suggest a potential role of the lung microbiome, never analysed until date, in the pathophysiology of the dysimmune disorders associated to CVID. Bibliography: doi:10.1007/s10875-018-0574-z

Disclosure: No.

Keywords: granulomatous lymphocytic interstitial lung disease, microbiota, lung microbiome, Common variable immunodeficiency

PD083

DETECTION AND EVOLUTIONARY DYNAMICS of SOMATIC VARIANTS CAUSING ALPS IN PERIPHERAL BLOOD SAMPLES WITH HIGH AND LOW DOUBLE-NEGATIVE ALPHA-BETA T CELL COUNTS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Laura Batlle-Masó[1], Clara Franco Jarava[2], Marina Garcia-Prat[1], Alba Parra-Martínez[1], Aina Aguiló-Cucurull[2], Pablo Velasco[3], Maria Antolin[4], Andrea Martín-Nalda[1], Jacques Rivière[1], M Martinez-Gallo[2], Pere Soler-Palacin[1], Roger Colobran[2,4]
[1]Vall d'Hebron University Hospital, Pediatric Infectious Diseases And Immunodeficiencies Unit, Barcelona, Spain, [2]Vall d'Hebron Barcelona Hospital Campus, Immunology Division, Barcelona, Spain, [3]Hospital Universitari Vall d'Hebron, Department of Pediatric Hematology And Oncology, Barcelona, Spain, [4]Vall d'Hebron Barcelona Hospital Campus, Clinical And Molecular Genetics, Barcelona, Spain

Background and Aims: Somatic pathogenic variants at the FAS gene underly up to 20% of ALPS cases. These variants are restricted to double-negative alpha-beta T cells (DNT) which are elevated in ALPS patients but normalized under immunosuppressive treatment. Therefore, the identification of these somatic variants is a major challenge in patients under treatment and can delay the molecular diagnosis.

Methods: Here, we present a patient with early-onset ALPS in whom we identified a somatic pathogenic insertion (FAS:c.718_719insGTCG). For that, we used Sanger and deep amplicon sequencing (DAS) in CD3+ cells and peripheral blood. Moreover, we studied samples before and during the treatment with Sirolimus (across five years) to explore the detection limits of the technique and study the evolutionary dynamics of the somatic event.

Results: The variant was first discovered in CD3+ enriched samples (RosetteSep™) by Sanger sequencing but was not detected in peripheral blood (7.4% DNT cells). However, using DAS, it was found in blood and CD3+ cells, even in low DNT counts (0.89%). In that scenario, we demonstrated that the variant allele frequency was doubled in CD3+ enriched samples (1.6% CD3+, 0.68% blood) and that there was an excellent correlation between DNT counts and the frequency of the variant (Pearson's R: 0.98).

Conclusions: Our results evidence that somatic variation is more likely to be detected on CD3+ enriched cells and pre-treatment samples but it can also be discovered in peripheral blood of patients under treatment. This highlights the success of sorting-free sequencing experiments and the importance of somatic studies in previously unsolved ALPS cases.

Disclosure: No.

Keywords: ALPS, Genetics, Somatic Variants

PD084

EFFICACY of IVIG IN PATIENTS WITH PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME (PANS)

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Isaac Melamed
ImmunoE, Immunology, Centennial, United States of America

Background and Aims: Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is a clinical diagnosis in children with severe, acute manifestation of neuropsychiatric symptoms, including obsessive-compulsive disorder and tics, triggered by infectious agents. Previously, in a clinical trial in 21 participants, multiple, consecutive infusions of intravenous immunoglobulin (IVIG) was effective in ameliorating psychiatric symptoms. To further explore the hypothesis of postinfectious autoimmunity and immune dysregulation in PANS, 10 additional participants with PANS were evaluated.

Methods: The primary endpoint was the change in monocyte activation levels in PANS from baseline to post-infusion 6 (6 infusions at 3 week intervals of IVIG [Octagam 5%]). Additional endpoints were changes in psychological evaluation scores (Children's Yale-Brown Obsessive Compulsive Scale [CY-BOCS] and the Yale Global Tic Severity Score [YGTSS]) from baseline to post-infusion.

Results: Ten male participants with moderate to severe PANS were enrolled based on severity of baseline symptoms. The mean age was 12.4 years (range 6 to 16 years). Preliminary monocyte analysis has shown downregulation of all inflammatory monocytes correlating to clinical psychological response. Clinical evaluations demonstrated statistically significant improvement, similar to the previous study, resulting in overall reduction in CYBOCS (-64.83%, $p<0.001$)and YGTSS (79.18%, $p<0.001$) scores.

Conclusions: Combined data from both studies (31 PANS participants) emphasize that PANS is an autoimmune disease and IVIG has an immune-modulatory impact. Further analysis will clarify the role of IVIG in this disease.

Disclosure: Dr. Melamed received an independent grant from Octopharma for the study of PANS.

Keywords: Autoimmunity, PANS

PD085

MOLECULAR SIGNATURES INDICATING INTERFERON SIGNALING DYSREGULATION AND ESTIMATION of THE IMPACT of EX VIVO JANUS KINASE INHIBITION IN DOWN SYNDROME

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Pilar Blanco Lobo[1], Paloma Guisado Hernández[1], Beatriz De Felipe[1], Anna Mensa Vilaró[2], Juan Ignacio Aróstegui[2], Peter Olbrich[1], Olaf Neth[1]
[1]Hospital Universitario Virgen del Rocío, Institute of Biomedicine of Seville (IBIS)/ Universidad de Sevilla/CSIC, Red de Investigación Traslacional en Infectología Pediátrica RITIP, Pediatric Infectious Diseases, Rheumatology And Immunology Unit., Sevilla, Spain, [2]Hospital Clínic, Immunology Department, Barcelona, Spain

Background and Aims: Some individuals with Trisomy 21 (T21) show clinical manifestations and cellular phenotypes similar to those reported for STAT1-GOF mutations such as immune dysregulation and increased infection susceptibility. Subsequently, an at least partially, shared pathophysiologic mechanisms have been proposed. We therefore aimed to explore the effect of ex vivo JAK inhibition.

Methods: Determination by flow cytometry of Interferon (IFN)-alpha/IFN-gamma receptors(R) expression on monocytes obtained from 2 individuals with T21. Total (n-terminus) and phosphorylated STAT1 (pSTAT1) levels were determined on monocytes obtained from patients with T21 (n=3), STAT1 GOF (n=3) and one T21 patient carrying a STAT1-GOF mutation. The IFN signature was evaluated using the NanoString® nCounter® Element platform.

Results: Higher IFN-αR2 and IFN-γR2 levels were observed in T21 compared to healthy controls (HC). Similar to STAT1-GOF, individuals with T21 had higher basal STAT1 (mean: T21 326 vs. HC 286 MFI) and pSTAT1 levels after IFN-gamma stimulation (mean: T21 3302 vs. HC 1942) were higher in T21 individuals when compared to HC. Similarly, STAT1-GOF and DS individuals also shared higher expression of genes associated with the IFN pathway, such as CXCL10 or CXCL9. Baricitinib was effective in modulating STAT1 phosphorylation in a T21 individual in the recommended dose range (2mg/24h dose of oral Baricitinib achieves peak plasma concentration of~50nM) following a similar pattern compared to a STAT1-GOF patient.

Conclusions: We here show an overlap of IFN mediated immune dysregulation between T21 and STAT1 GOF and provide preliminary data suggesting JAK inhibition as a targeted therapeutic strategy for a subgroup of individuals with T21.

Disclosure: No.

Keywords: Down Syndrome, Trisomy 21, JAK INHIBITION, Baricitinib, IFN signaling

PD086

FULL-LENGTH FOXP3 PRECEDES EXPRESSION of OTHER ISOFORMS IN HUMAN THYMOCYTES AND NAIVE T CELLS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Reiner Mailer
University Medical Center Hamburg-Eppendorf, Institute of Clinical Chemistry, Hamburg, Germany

Background and Aims: The transcription factor FOXP3 is indispensable for regulatory T (Treg) cells demonstrated by the development of immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) in patients with impaired FOXP3 functions. In humans, alternative splicing of FOXP3 generates isoforms that lack coding exon 2, exon 7 or both. Isoforms lacking exon 7 (e.g., FOXP3Δ2Δ7) fail to induce a suppressive phenotype and promote Th17 differentiation, whereas the isoform lacking exon 2 (FOXP3Δ2) supports Treg-cell functions in cooperation with full-length FOXP3. However, IPEX mutations within exon 2, that restrict functional protein expression to the FOXP3Δ2 isoform, indicate that FOXP3Δ2 alone is insufficient to facilitate Treg-cell development.

Methods: We investigated FOXP3 isoform expression in human thymocytes and in stimulated naïve CD4+ T cells using real-time PCR, immunoblots and FACS analysis.

Results: We found that thymocytes predominantly express full-length FOXP3 and that the presence of FOXP3Δ2 is greatly diminished compared to Treg cells from peripheral blood. Moreover, full-length FOXP3 precedes FOXP3Δ2 induction upon T-cell antigen receptor stimulation in naïve CD4+FOXP3- T cells.

Conclusions: FOXP3 induction leads to the initial generation of full-length FOXP3, whereas isoform expression with alternatively spliced FOXP3 exon 2 is delayed. These results provide a rationale for the increased full-length FOXP3 isoform ratio in chronic diseases and help to understand why unaffected FOXP3Δ2 isoform expression fails to prevent IPEX in patients with FOXP3 exon 2 mutations.

Disclosure: No.

Keywords: IPEX, alternative splicing, FOXP3 isoforms, Treg cells

PD087

FEATURES of IMMUNE DYSREGULATION IN PRIMARY IMMUNODEFICIENCY PATIENTS AT SOBA UNIVERSITY HOSPITAL, KHARTOUM –SUDAN

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Rayan Goda[1], Ahmed Seri[1], Nahla Erwa[2]
[1]Soba University Hospital, Immunology And Allergy Unit, Khartoum, Sudan, [2]University of Khartoum, Faculty of Medicine - Department of Medical Microbiology, Khartoum, Sudan

Background and Aims: We reviewed all patients with primary immunodeficiency diseases (PID) that presented to the immunology clinic at our hospital for features of immune dysregulation. Aim: To describe the clinical manifestations and basic immunological findings in Sudanese patients with features of immune dysregulation. Additionally, we looked into how these findings affected their management and outcome.

Methods: Retrospective analysis of all patients referred with PID looking for features of immune dysregulation: autoimmunity, allergy, lymphoproliferation and cytopenias.

Results: Total number of patients with suspected PID was 120 patients. Sixteen patients had features suggestive of immune dysregulation in the form of autoimmunity evident as autoimmune cytopenia, endocrinopathies, lymphoproliferation, inflammatory bowel disease, enteropathy, arthropathy and allergy. Most reported allergic features included eczema and food allergy. Half of the patients had altered immune phenotypes with low immunoglobulin levels; either IgG or IgA (5 patients), increased IgE was noted in 4 patients. Four patients (25%) had low CD4 helper T cells, increased double-negative T (DNT) cells were seen in 4 patients and one patient had low CD4+CD25+FOXP3+ T cells. Management proved difficult due to recurrent infections, medication side effects or refractory disease. Almost half of the patients were lost to follow up, with 3 deceased patients.

Conclusions: Immune dysregulation in patients with PIDs is poorly identified and hence under reported in Sudan and Africa. Inter-clinic collaboration is recommended to identify more patients, with the provision of better diagnostic and therapeutic modalities including targeted therapy and specific genetic diagnosis.

Disclosure: No.

Keywords: Primary Immunodeficiency Diseases, Immune Dysregulation, allergy, Autoimmunity, LYMPHOPROLIFERATION

PD088

PERFORIN-INDEPENDENT CYTOTOXICITY ENHANCED BY CYTOKINE COMPLEXES

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Tommaso Marchetti[1], Diana Tintor[2], Samantha Milanesi[2], Stefano Vavassori[2], Onur Boyman[3], Jana Pachlopnik Schmid[4]
[1]University Children's Hospital Zurich, Immunology, Zürich, Switzerland, [2]University Children's Hospital Zurich, Immunology, Zurich, Switzerland, [3]University Hospital Zurich, Immunology, Zurich, Switzerland, [4]University of Zurich, Pediatric Immunology, Zurich, Switzerland

Background and Aims: The biological activity of interleukin-2 can be modulated by complexing with anti-cytokine monoclonal antibodies. Some cytokine complexes containing interleukin-2 (IL-2cx) preferentially stimulate effector cells, such as natural killer cells and cytotoxic T lymphocytes, whereas other IL-2cx selectively activate regulatory T cells. In the setting of experimental hemophagocytic lymphohistiocytosis (HLH), it has been shown that treatment with certain IL-2cx results in premature death of perforin (Prf)-deficient animals, despite restoring the relative lack in regulatory T cells, which occurs during HLH. We hypothesize that a specific stimulation of effector cells by IL-2cx might promote Prf-independent killing and be beneficial during HLH.

Methods: In the setting of experimental hemophagocytic lymphohistiocytosis (HLH), we investigated the effect of a specific stimulation of effector cells by IL-2cx.

Results: When using specific IL-2cx, we observed a reduction in spleen size in LCMV-infected Prf-deficient mice. Blood values of white blood cells and hemoglobin also improved in IL-2cx-treated animals. CD8 T cell numbers in both LCMV-infected WT and Prf-deficient mice decreased under IL-2cx treatment. Furthermore, lower viral loads were measured in IL-2cx-treated WT and HLH mice, when compared with untreated mice.

Conclusions: Thus, we have set the prerequisites to test the biological activity of IL-2cx in experimental HLH and to investigate whether IL-2cx could skew the cytotoxic machinery towards Prf-independent alternative killing, improving immune homeostasis in experimental HLH.

Disclosure: No.

Keywords: Hemophagocytic Lymphohistiocytosis (HLH), mouse model, cytokines, targeted treatment

PD089

TREATMENT of AN HLH-MIMIC DISEASE BASED ON HAVCR2 VARIANTS WITH ABSENT TIM-3 EXPRESSION

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Samantha Tromp[1,2], Marijn Gillissen[3], Sophie Bernelot Moens[3], Ester Van Leeuwen[2], Machiel Jansen[2], Lianne Koens[4], Caroline Rutten[3], Taco Kuijpers[1,2]
[1]Amsterdam UMC location University of Amsterdam, Department of Pediatric Immunology, Rheumatology And Infectious Diseases, Amsterdam, Netherlands, [2]Amsterdam UMC, Department of Experimental Immunology, Amsterdam, Netherlands, [3]Amsterdam UMC location University of Amsterdam, Department of Hematology, Amsterdam, Netherlands, [4]Amsterdam UMC location University of Amsterdam, Department of Pathology, Amsterdam, Netherlands

Background and Aims: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease characterized by uncontrolled immune activation and tissue damage. We describe a 30-year-old male patient with no medical history, presenting with prolonged fever, hepatosplenomegaly, ascites, increased ferritin and LDH reminiscent of HLH, but normal cell counts and a complete lack of HLH-associated cytopenia.

Methods: WES was performed to identify underlying immunogenetic defects. Extensive immunophenotyping and NK-cell function tests were performed.

Results: Besides T- and B-cell lymphopenia, NK-cell numbers were normal but their function impaired. PET-CT showed FDG-avid mesenteric lesions, apart from hepatosplenomegaly. Biopsies revealed prominent omentum infiltration by lymphocytes and signs of hemophagocytosis in liver and bone marrow. Having excluded autoimmunity, infectious causes and malignancy, routine HLH gene panel analysis was negative. More extensive gene analysis with an IEI gene panel and subsequent studies revealed compound heterozygosity for two variants in HAVCR2, resulting in absent T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) expression. Upon treatment, the patient fully recovered, laboratory findings and his NK-cell function normalized.

Conclusions: The patient was diagnosed with complete TIM-3 deficiency causing prominent hyperinflammation in the absence of any underlying condition including malignancy. The immune activation syndrome was treated with etoposide and dexamethasone according to the HLH-94 protocol. Once the TIM-3 variants became evident, treatment with immunosuppressive agents (cyclosporine and prednisolone) was continued instead of extended chemotherapy combined with allo-HSCT. To date, one year later, after cautious withdrawal of prednisolone, the patient is in complete remission with low dose cyclosporine as the only immune suppression.

Disclosure: No.

Keywords: HAVCR2, T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), Hemophagocytic Lymphohistiocytosis (HLH), HLH-mimic disease, Dysregulated immune activation or proliferation (DIAP), Inborn error of immunity (IEI)

PD090

FUNCTIONAL ASSESSMENT of IMMUNOLOGICAL RESPONSE IN TWO PATIENTS WITH IL-10RA MUTATION PRESENTING WITH EARLY-ONSET INFLAMMATORY BOWEL DISEASE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Rayan Goda[1], Raffaele Badolato[2], Mauro Giacomelli[2,3], Laura Dotta[4], Elena Soncini[5], Fulvio Porta[6]
[1]University of Brescia, Clinical And Experimental Sciences, Brescia, Italy, [2]Pediatrics Clinic and "A. Nocivelli" Institute for Molecular Medicine, Department of Clinical And Experimental Sciences, University of Brescia, Asst- Spedali Civili of Brescia, Brescia, Italy, [3]ASST Spedali Civili of Brescia, Department of Microbiology And Virology, Brescia, Italy, [4]ASST Spedali Civili di Brescia, Pediatrics, Brescia, Italy, [5]Children's Hospital, Spedali Civili, Brescia, Italy,, Oncohematology And Bone Marrow Transplant (bmt) Unit, Brescia, Italy, [6]Children's Hospital, Spedali Civili, Brescia, Italy, Oncohematology And Bone Marrow Transplant (bmt) Unit, Brescia, Italy

Background and Aims: Immune dysregulation with colitis is classified as an inborn error of immunity (IEI). We describe two patients who presented with IBD-like clinical features with different mutations in IL-10RA and MEFV genes. The aim was to study the patients' clinical, and immunological features including cytokine expression, signalling, levels and response to treatment.

Methods: IL-10R expression, pro-inflammatory and regulatory cytokines' expression and levels, and STAT3 phosphorylation were investigated under different conditions in comparison to age and sex-matched healthy controls via flow cytometry and Real Time-PCR.

Results: Patient 1 had significantly decreased but not absent expression of IL-10RA. However, IL-10 induced STAT3 phosphorylation in both monocytes and lymphocytes was absent. IL-10 producing type-1 regulatory T cells were higher in the patient's unstimulated cells in comparison to HC. The patient's PBMCs and CD4 T cells showed increased expression of FOXP3, CTLA4, HELIOS, ICOS, IL-10, IL-1, IL-17, and IL-23 in comparison to HC. Plasma cytokine levels measured at different time intervals were variable but generally lower in patient-1 than in patient-2 and HC, especially IL-17A, IFN-ɣ, IL-1β and IL-18. Ruxolitinib-treated patient-1-derived cell lines showed decreased IL-10 production but not when treated with Anakinra. IL-10 and Anakinra stimulated PBMCs also showed decreased expression of IFN-ɣ mRNA by RT-PCR, in comparison to reduced IL-6 and IL-1b mRNA expression in stimulated HC. Patient 2 stimulated PBMCs had higher TNF levels in comparison to patient-1 and HC.

Conclusions: This study demonstrates the immunological processes and the possible therapeutic approaches in two patients presenting with features consistent with IBD-like disease.

Disclosure: No.

Keywords: Inborn errors of immunity, IL-10, IL-10R deficiency, Monogenic IBD

PD091

CLINICAL, IMMUNOLOGICAL, AND GENETIC FEATURES of A MEXICAN COHORT of PATIENTS WITH DOCK8 DEFICIENCY.

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Eduardo Liquidano-Perez[1], Gibert Maza-Ramos[2], Tania Barragan Arévalo[3], Saúl Lugo Reyes[1], Sara Espinosa Padilla[1], Juan Carlos Bustamante Ogando[1], Marimar Saéz-De-Ocariz[4], Gilberto Ramirez Ristori[5], Tamara Staines-Boone[6], Edna Venegas-Montoya[6], Nideshda Ramirez-Uribe[7], Francisco Rivas Larrauri[8], Marco Yamazaki-Nakashimada[8], Selma Scheffler-Mendoza[8], Maria Edith González Serrano[1]
[1]National Institute of Pediatrics, Primary Immunodeficiency Research Unit, Mexico City, Mexico, [2]Medica Sur, Dermatology, Mexico City, Mexico, [3]Institute of Ophthalmology “Conde de Valenciana”, Genetics, Mexico City, Mexico, [4]National Institute of Pediatrics, Dermatology, Mexico City, Mexico, [5]National Institute of Pediatrics, Pathology, Mexico City, Mexico, [6]UMAE-25 IMSS, Immunology, Monterrey, Mexico, [7]National Institute of Pediatrics, Stem Cell Transplant, Mexico City, Mexico, [8]National Institute of Pediatrics, Immunology, Mexico City, Mexico

Background and Aims: DOCK8 deficiency (DOCK8-Def) is an inborn immunity error (IEI) resulting from deletions in the DOCK8 gene. DOCK8-Def hallmarks are high IgE levels, T and B cells defect, propensity to develop eczema, recurrent cutaneous viral infections, allergy, autoimmunity, inflammation, and cancer. Unlike other Hyper-IgE syndromes the disease is usually more aggressive. Hence the curative treatment is with Hematopoietic stem cell transplantation. We aimed to describe the clinical, immunological, and genetic characteristics of a DOCK8-Def cohort at the Instituto Nacional Pediatria Immunodeficiency Research Unit (IRU-INP).

Methods: We obtained information from the records registered with a DOCK8-Def in the IRU-INP's database. Descriptive analysis was carried out.

Results: We found ten patients in seven families: 2 consanguineous, 4 had inbreeding, and 4 had a history of IEI. The median age at diagnosis was 88.7 months (4-141.6). Infectious, allergic, and autoimmune characteristics are shown in Table. We found rare symptoms such as pyramidal syndrome, partial paralysis of the right third pair, and pelvic mononeuropathy. One patient developed stage 3 lymphomatoid granulomatosis. We obtained a functional diagnosis in 8 patients using flow cytometry and a genetic diagnosis in 9. The immunological parameters were: high eosinophils (50%), low CD3 (30%), low CD4 (40%), low CD8 (20%), low CD19 (30%), low CD56 (20%); immunoglobulins high IgE (80%), low IgM (40%).

ID	Sex	Gene variant	DOCK8 expression	Clinical course	Infections	Allergy	Autoimmunity
F1.P1	Male	c.760delC	Low	Dead	Sinopulmonary: AOM, mastoiditis, pneumonia, bronchiolitis, lung abscess, pulmonary aspergillosis Cutaneous: Eczema herpeticum, EBV, impetigo, scabies, HPV, EBV, cellulitis Systemic: urinary candidiasis, sepsis	Atopic eczema Asthma	Sclerosing cholangitis Leukocytoclastic vasculitis Autoimmune hepatitis
F1.P2	Male	c.760delC	Low	Alive	Sinopulmonary: Pharyngitis, AOM, Sinusitis, Pneumonia, Bronchitis Cutaneous: Herpetic gingivostomatitis, HPV, chicken pox, impetigo, odontogenic abscess	Atopic eczema Allergic rhinitis Asthma	None
F1.P3	Female	c.760delC	Low	Alive	Sinopulmonary: Pharyngitis, Sinusitis, AOM, Pneumonia, Bronchitis, Pulmonary candidiasis, Pulmonary aspergillosis Cutaneous: Chicken pox, herpetic keratitis, HPV, cellulitis, right plantar abscess	Atopic eczema Allergic rhinitis Asthma	None
F2.P1	Male	Intron 3-26	Not done	Dead	Sinopulmonary: Pharyngitis, Pneumonia Cutaneous: herpetic gingivostomatitis, chickenpox, herpetic keratitis, HPV, cellulitis, pneumonia Gastrointestinal: *Giardia lamblia, Cryptosporidium parvum, Blastomycstis hominis* Systemic: Sepsis	Atopic eczema	Autoimmune hepatitis Leukocytoclastic vasculitis Inflammatory bowel disease
F2.P2	Female	Intron 3-26	Not done	Dead	Sinopulmonary: Pharyngitis, Sinusitis, AOM, Pneumonia, Pulmonary Aspergillosis Cutaneous: Eczema herpeticum, chickenpox, herpetic keratitis, HPV Gastrointestinal: Giardia lamblia Systemic: Encephalitis	Atopic eczema	Autoimmune hepatitis Leukocytoclastic vasculitis UC, acute pancreatitis
F3.P1	Female	Not done	Absent	LFU	Sinopulmonary: Pharyngitis, Sinusitis, Mastoiditis, Pneumonia Cutaneous: Herpetic gingivostomatitis, Eczema herpeticum, HPV, cellulitis Systemic: Sepsis	Food allergy Atopic eczema	Anemia hemolytic
F4.P1	Female	Exon 4-26	Absent	Dead	Sinopulmonary: Pharyngitis, AOM, AOE, Sinusitis, Pneumonia Cutaneous: Eczema herpeticum, varicella, HPV, varicella, onychomycosis, herpetic keratitis, EBV, candida Gastrointestinal: Giardia lamblia, Cryptosporidium parvum, Salmonella, Rotavirus	Food allergy Atopic eczema Allergic Rhinitis Asthma Anafilaxis	Sclerosing cholangitis
F5.P1	Female	Exon 12-14 / Exon11	Absent	Dead	Sinopulmonary: Pharyngitis, AOM, AOE, Pneumonia, Bronchiolitis, Pneumonia Cutaneous: Chicken pox, impetigo, cellulitis	Food allergy Atopic eczema Asthma	Autoimmune nephropathy Leukocytoclastic vasculitis Takayasu vasculitis
F6.P1	Male	Intron 14-26	Absent	Alive	Sinopulmonary: Pharyngitis, AOM, Pneumonia, Bronchiolitis Cutaneous: HPV, genital candidiasis	Food allergy Atopic eczema	
F7P 1	Female	c.4163del	Absent	Alive	Sinopulmonary: Pharyngitis, Sinusitis, AOM, OAS, Mastoiditis, Pneumonia, Pulmonary candidiasis Cutaneous: HPV Gastrointestinal: *Entamoeba histolytica* Systemic: osteomyelitis	Food Allergy Atopic eczema	

AOM, Acute otitis media. LFU, lost follow-up. AOE, Acute otitis externa.

Conclusions: The DOCK8-Def clinical manifestations are as broad as the functions of the DOCK8 protein in the body. Therefore, the evaluation of DOCK8 expression by flow cytometry is an affordable, adequate and quick diagnostic test, as good as the genetic diagnosis.

Disclosure: No.

Keywords: Hyper-IgE, DOCK8, combined immunodeficiency, eccema, lymphopenia

PD092

DISSEMINATED NOCARDIOSIS AND ANTI-GM-CSF ANTIBODIES.

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Lorenzo Salvati[1], Boaz Palterer[1], Nicoletta Di Lauria[1,2], Annarita Botta[1,2], Camilla Tozzetti[3], Manuela Capone[1], Filomena Ferrentino[3], Chiara Naldi[3], Giovanni Ascione[3], Laura Maggi[1], Alessio Mazzoni[1], Giulia Lamacchia[1], Anna Vanni[1], Barbara Brugnoli[1], Ilaria Campo[4], Francesco Liotta[1,5], Lorenzo Cosmi[1,5], Alessandro Bartoloni[1,2], Francesco Annunziato[1,6], Paola Parronchi[1,5]
[1]University of Florence, Department of Experimental And Clinical Medicine, Firenze, Italy, [2]Careggi University Hospital, Florence, Italy, Infectious And Tropical Diseases Unit, Firenze, Italy, [3]Internal Medicine Unit 3, Careggi University Hospital, Florence, Italy, [4]Internal Medicine and Infectious Diseases Department, IRCCS Policlinico San Matteo Foundation, Pneumology Unit, Pavia, Italy, [5]Careggi University Hospital, Immunolgy And Cell Therapy Unit, Firenze, Italy, [6]Careggi University Hospital, Flow Cytometry Diagnostic Center And Immunotherapy, Firenze, Italy

Background and Aims: Infections that are unusually severe or caused by opportunistic pathogens are a hallmark of primary immunodeficiency (PID). Recently, anti-cytokine autoantibodies (ACA) have emerged as the cause of some of these infections, determining acquired immunodeficiency and behaving like PID phenocopies. Nocardia spp. are Gram-positive bacteria that can cause disseminated infection in immunocompromised patients. However, several cases occur in apparently immunocompetent hosts. Anti-GM-CSF autoantibodies have been detected in patients with autoimmune pulmonary alveolar proteinosis (PAP), disseminated nocardiosis or cryptococcosis (particularly Cryptococcus gattii infection). We report an apparently immunocompetent individual presenting with disseminated nocardiosis.

Methods: Flow cytometry was used to measure lymphocyte populations. Anti-GM-CSF autoantibodies were measured with ELISA.

Results: A 55-year-old otherwise healthy woman presented with disseminated nocardiosis with cerebral and pulmonary abscesses. There was no family history of infections or autoimmunity. She received BCG vaccination without complications. She had leukopenia and lymphopenia with normal T and B cell subsets, mild hypogammaglobulinemia, indeterminate TB-IGRA test, negative HIV test, normal DHR test and reduced IFN-γ production after mitogen stimulation. Serum anti-GM-CSF autoantibodies were increased (57 mcg/ml, normal ≤3). She had no clinical or instrumental signs of PAP. Trimethoprim-sulfamethoxazole and imipenem were administered, with progressive improvement.

Conclusions: We identified anti-GM-CSF autoantibodies as the cause of disseminated nocardiosis in a previously healthy and apparently immunocompetent adult. This case emphasizes the importance of including ACA in the differential diagnosis of PID, especially in previously healthy adults. Recognition of anti-GM-CSF autoantibodies warrants careful screening for PAP. Currently there are no specific treatment or prophylaxis recommendations for anti-GM-CSF autoantibodies-related infections.

Disclosure: No.

Keywords: anti-cytokine autoantibodies, anti-GM-CSF autoantibodies, disseminated nocardiosis, PID phenocopies, apparently immunocompetent adult

PD093

FADD DEFICIENCY MAY IMPAIR FAS-MEDIATED APOPTOSIS IN THE ABSENCE of AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS) BIOMARKERS: A RARE, EXPANDING PHENOTYPE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Filippo Consonni[1], Elena Procopio[2], Annalisa Vetro[3], Giada Giovannini[4], Ebe Schiavo[5], Beatrice Martini[5], Stefano Meletti[4], Renzo Guerrini[5], Eleonora Gambineri[5]
[1]University of Florence, Department of Health Sciences, Firenze, Italy, [2]Meyer Children's Hospital, Florence, Italy, Metabolic And Muscular Unit, Florence, Italy, [3]Meyer Children's Hospital, University of Florence, Pediatric Neurology, Neurogenetics And Neurobiology Unit And Laboratories, Florence, Italy, [4]Center for Neuroscience and Neurotechnology, University of Modena and Reggio Emilia, Department of Biomedical, Metabolic, And Neural Science, Modena, Italy, [5]University of Florence, Department of Neurosciences, Psychology, Drug Research And Child Health (neurofarba), Florence, Italy

Background and Aims: FAS-associated protein with death domain (FADD) deficiency is a rare autosomal recessive disorder due to a disruption of the extrinsic apoptosis pathway and characterized by ALPS-like lymphoproliferation, recurrent encephalitis, cerebral atrophy, liver steatosis and cardiac abnormalities.

Methods: We report a 17 years-old female who came to our attention for three recurrent episodes of encephalitis requiring intensive care. In one case a concomitant EBV infection was detected. All events resolved after treatment with Levetiracetam, steroids and intravenous immunoglobulins. Past clinical history revealed recurrent pneumonias and upper respiratory infections, eczema, and mild liver steatosis despite normal BMI. Her older brother displayed a similar episode of encephalopathy and a specific learning disorder.

Results: Whole exome sequencing in the patient and her brother revealed a homozygous p.C105R mutation in FADD, formerly described as pathogenic in a compound heterozygous individual. Immunological workup showed normal levels of ALPS biomarkers (TCRαβ+ double negative T cells, vitamin B12, IL-10), oppositely to other reported cases of FADD deficiency. FAS-mediated apoptosis assay on PBMCs showed a significant increase – compared to control – in the percentage of surviving cells after both low ($p=0.012$) and high ($p<0.001$) concentrations of anti-FAS stimulating antibodies (Apo1-3).

Conclusions: These findings imply that an impairment of the extrinsic apoptosis pathway is not sufficient to generate ALPS biomarkers and that homozygous p.C105R may be a hypomorphic genotype of FADD deficiency. Moreover, the patient developed mild COVID-19 during follow-up, despite FADD's importance in type I Interferon response. These elements expand the phenotype of FADD deficiency, demonstrating that it may present variable expressivity.

Disclosure: No.

Keywords: FADD deficiency, Autoimmune lymphoproliferative syndrome, primary immune regulatory disorders, FAS-mediated apoptosis, encephalitis, Whole Exome Sequencing

PD094

DEVELOPMENT of LYMPHOMATOID GRANULOMATOSIS IN DEFICIENCY of ADENOSINE DEAMINASE 2 WITH UNCONTROLLED EBV INFECTION

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Logan Gardner[1,2], Lachlin Vaughan[3], Stuart Tangye[4,5], Mingwei Lin[2,4,6]
[1]University of Queensland, Faculty of Medicine, Brisbane, Australia, [2]Westmead Hospital, Department of Immunology, Westmead, Australia, [3]Westmead Hospital, Department of Haematology, Westmead, Australia, [4]Garvan Institute of Medical Research, Clinical Immunogenomics Research Consortium of Australasia, Sydney, Australia, [5]Garvan Medical Research Institute, Immunology, Darlinghurst, Australia, [6]Faculty of Medicine, University of Sydney, Sydney, Australia

Background and Aims: Deficiency of Adenosine Deaminase 2 (DADA2) typically presents with vasculopathy similar to polyarteritis nodosa and occasionally autoimmunity and immunodeficiency. While overt cellular immune deficiency is not recognised, susceptibility to Epstein Barr Virus (EBV) has been reported. Prolonged EBV viraemia can predispose to haematological malignancy including the rare variant Lymphomatoid Granulomatosis (LG). We present the first case of LG in DADA2.

Methods: NOT APPLICABLE

Results: A 38-year-old woman initially presented for assessment of recurrent sinopulmonary infections and was given a provisional diagnosis of Common Variable Immunodeficiency based on low immunoglobulins, low switched memory B cells and an absent response to pneumococcal vaccination. Genetic studies demonstrated a pathogenic homozygous mutation in ADA2 consistent with DADA2. Her family history included a consanguineous Lebanese background, a male sibling with similar infections and a female sibling deceased at age 6 years secondary to leukaemia. The patient developed intermittent immune dysregulation with cytopenias, hepatitis, alopecia, inflammatory arthropathy, Raynauds phenomenon and multiorgan granulomatous disease. There was no radiological or clinical evidence of a medium vessel vasculitis. After six years of immunoglobulin replacement monotherapy, the patient developed recurrent fevers, weight loss and progressive lymphadenopathy in the setting of normal IgG levels and a lack of sinopulmonary infections. Persistent EBV viraemia was identified with a viral load of 127,500 copies/mL and a histological diagnosis of Lymphomatoid Granulomatosis was made.

Conclusions: DADA2 is a heterogenous disorder with the full spectrum of clinical phenotypes yet to be established. These patients are at risk of chronic EBV viraemia and the subsequent risk of haematological malignancy.

Disclosure: No.

Keywords: DADA2, Lymphomatoid Granulomatosis, EBV, CVID

PD095

DONOR-DERIVED TIM-3 DEFICIENCY UNDERLYING POST-TRANSPLANT INFLAMMATORY BOWEL DISEASE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Adrian Baldrich[1], Dominic Althaus[2], Jan Niess[2], Benedikt Meyer[1], Thomas Menter[3], Alexander Navarini[4], Petr Hruz[2], Mike Recher[1]
[1]University Hospital Basel, Department of Biomedicine, Basel, Switzerland, [2]University Hospital Basel, Department of Gastroenterology, Basel, Switzerland, [3]University Hospital Basel, Institute of Pathology, Basel, Switzerland, [4]University Hospital Basel, Department of Dermatology, Basel, Switzerland

Background and Aims: The immune system is regulated by immune checkpoint proteins like T cell immunoglobulin and mucin domain 3 (TIM-3). Germline loss-of-function mutations in TIM-3 have been linked with systemic immune activation and subcutaneous T cell lymphoma. Non-germline genetically determined TIM-3 deficiency has not been described so far.

Methods: Saliva, blood and skin samples of an index patient were examined by whole exome sequencing and by TIM-3 targeted Sanger sequencing. Freshly isolated peripheral T cells of healthy donors and the patient were stimulated with PHA and IL-2 and TIM-3 expression was analyzed by flow cytometry. TIM-3 expression of the whole intestinal tract of the patient vs. controls was analyzed in situ by immune-histology.

Results: A patient with severe Crohn's disease occurring following stem cell transplant was found to carry a heterozygous pathogenic I97M missense mutation in HAVCR2 encoding TIM-3 in donor-derived hematopoietic but not in skin-derived cells. TIM-3 expression following in vitro stimulation of donor derived T cells was almost completely absent while CD25 upregulation was intact. Immune-histology of the intestinal tract of the patient revealed that TIM-3 expression was virtually absent in inflamed and also in non-inflamed intestinal tract of the patient.

Conclusions: The patient had been apparently engrafted with stem cells carrying a disease-causing mutation I97M in TIM-3 causing nearly absent TIM-3 expression following activation in vitro but also in the intestinal tract in vivo. This is to our knowledge the first report of hematopoietic cell-restricted TIM-3 mutation/deficiency associated with severe post-transplant inflammatory bowel disease.

Disclosure: No.

Keywords: Colon, Inflammation, TIM-3, primary immunodeficiency, Transplantation

PD096

TRACHEAL DIVERTICULUM IN DNSTAT3 HYPER IGE SYNDROME

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Amanda Urban[1], Ahmed Hamimi[2], Susan Roy[3], Jean Ulrick[4], Christine Lafeer[4], Ahmed Gharib[2], Alexandra Freeman[4]
[1]Leidos Biomedical Research in support of NIAID, Niaid - Lcim, Bethesda, United States of America, [2]National Institute of Diabetes and Digestive and Kidney Diseases, Biomedical And Metabolic Imaging Branch, Bethesda, United States of America, [3]National Institutes of Health, Clinical Center Nursing Department, Bethesda, United States of America, [4]National Institute of Allergy and Infectious Diseases, Laboratory of Clinical Immunology And Microbiology, Bethesda, United States of America

Background and Aims: Hyper IgE Syndrome caused by dominant negative mutations in STAT3 (STAT3DN) is a rare primary immunodeficiency characterized by sinopulmonary infections, eczema, and vascular and musculoskeletal changes. Pulmonary infections can be complicated by aberrant healing, leading to parenchymal damage and increasingly difficult to increase infections. A pediatric DNSTAT3 patient presented with a mediastinal abscess that grew Strep intermedius. She was noted to have a tracheal diverticulum which was thought to be the sources of this infection as bacteria could be sequestered in the diverticulum. The aim of this project is to identify the frequency of tracheal diverticula in DNSTAT3 patients.

Methods: CT Chest images and radiology reports were retrospectively reviewed for 151 patients.

Results: A tracheal diverticulum was identified in 30 patients (19.8%), 16 male and 14 female, ranging in age from 7 to 71 years with 85 women and 65 men. 17 of those 30 patients were also noted to have bronchiectasis and pneumatoceles.

Conclusions: Tracheal diverticula range from about 4-8% in the general population and are typically incidental findings. Tracheal diverticula are reported in some chronic lung conditions, and in Cystic Fibrosis where they have been found in about 28% of patients. Tracheal diverticula appear to be similarly increased in STAT3DN, and further increase the risk of infection in this population. They should be considered a possible etiology of infection if a mediastinal infection is found, particularly when the infection is from oral flora. Further study is needed to assess their role in pulmonary infections and function, and what treatment options are possible.

Disclosure: No.

Keyword: DNSTAT3, tracheal diverticula

PD097

ROLE of STAT3 GAIN-OF-FUNCTION VARIANT IN THE DEVELOPMENT AND TREATMENT of CYSTOID MACULAR EDEMA

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Z.Z Zhou[1,2,3], Kornvalee Meesilpavikkai[4], Mirthe Lourens[1,2,3], Nattiya Hirankarn[4], Hanna Ijspeert[1,2], Virgil Dalm[1,2,3], Saskia Rombach[1,2], Alberta Thiadens[5], Tom Missotten[5], Willem Dik[1,2], P.M Van Hagen[1,2,3]
[1]Erasmus MC, University Medical Center, Academic Center For Rare Immunological Diseases (ridc), Rotterdam, Netherlands, [2]Erasmus Medical Center, Immunology, Rotterdam, Netherlands, [3]Erasmus MC, University Medical Center, Department of Internal Medicine, Division of Clinical Immunology, Rotterdam, Netherlands, [4]Chulalongkorn University, Center of Excellence In Immunology And Immune-mediated Diseases, Department of Microbiology, Faculty of Medicine, Bangkok, Thailand, [5]The Rotterdam Eye Hospital, The Rotterdam Eye Hospital, Rotterdam, Netherlands

Background and Aims: We identified two family members with a novel heterozygous gain of function (GOF) variant in STAT3 (p.[L387R]). Both patients presented with hypogammaglobinemia, recurrent infections, lymphoproliferation and cystoid macula edema (CME). CME has not been described in STAT3 patients, and is a major complication in a variety of retinal diseases. The current treatments for CME are limited. Recently, limited reports showed successful anti-IL-6 receptor treatment of CME. However, the pharmacological basis of anti-IL-6 are yet unknown. In this study we aimed to study how (hyper)activation of the IL-6 pathway leads to CME.

Methods: STAT3 WT and STAT3-L387R variants were overexpressed in human retinal cell lines. Expression of STAT3 protein, phosphorylated STAT3 (pSTAT3), and negative regulator SOCS3 after IFN-α stimulation was measured by flow cytometry, Western Blot and RT-PCR. Stat3-L386R mice was generated by CRISPR-Cas9 editing.

Results: Retinal cell lines overexpressing STAT3 WT and STAT3-L387R were established. STAT3-GOF phenotype was confirmed by higher expression of pSTAT3 and SOCS3 after IFN-α stimulation. Stat3-L386R heterozygous mice are in breeding. No homozygous mice survived to birth, suggesting that $L387R^{+/+}$ mice might be embryotic lethal. Some of the heterozygous Stat3-L386R mice had ocular abnormalities.

Conclusions: The STAT3-L386R variant might play a role in the development of CME. Currently, functional assays are performed to determine the effect of STAT3 GOF on the function of the retinal cells. These STAT3 GOF cell lines could be used as a model to test the efficacy of anti-IL-6 therapy and other currently available drugs that targets IL6-STAT3 pathway.

Disclosure: No.

Keywords: anti-IL6 pathway therapies, eye disease, macular edema, STAT3 GOF

PD098

STAT3 GOF SYNDROME WITH HYPOGAMMAGLOBULINEMIA, LYMPHOPROLIFERATION AND RECURRENT INFECTION PHENOTYPE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Bernadett Hon-Balla[1], Judit Kállai[2], Árpád Lányi[2], Zoltán Nyul[3], György Balázs[4], László Maródi[5], Melinda Erdős[5]
[1]Semmelweis University, Faculty of Medicine, Department of Dermatology, Venereology And Dermatooncology, Budapest, Hungary, [2]University of Debrecen, Faculty of Medicine, Department of Immunology, Debrecen, Hungary, [3]University of Pécs, Faculty of Medicine, Department of Pediatrics, Pécs, Hungary, [4]Heim Pál National Institute of Paediatrics, Center For Pediatric Mri And Ct, Budapest, Hungary, [5]Semmelweis University, Faculty of Medicine, Department of Dermatology, Venereology And Dermatooncology, Primary Immunodeficiency Clinical Unit And Laboratory, Budapest, Hungary

Background and Aims: STAT3 GOF syndrome is an early-onset monogenic inborn error of immunity characterized by multi-organ autoimmunity, growth failure and lymphoproliferation. The most frequent autoimmune manifestations are cytopenia, enteropathy, interstitial lung disease, thyroiditis, type I diabetes, and arthritis. Autoimmune disorders appear sequentially with very early-onset endocrinopathies and gastrointestinal diseases. We present a unique clinical phenotype of STAT3 GOF syndrome dominated by infections, lymphoproliferation and severe hypogammaglobulinemia but lacking early-onset and multi-organ autoimmunity.

Methods: Serum immunoglobulins and lymphocyte subsets were measured by routine laboratory assays. Mutational analysis was performed using the BigDye Terminator Cycle sequencing kit and an ABI PRISM 3130 Genetic Analyzer.

Results: The patient presented with recurrent respiratory infections, generalized lymphadenomegaly, hepatosplenomegaly and short stature. Later he had loose stools and swelling of the ankles and knees. Laboratory tests showed severe hypogammaglobulinemia and $CD4^+$ T lymphopenia. Sanger sequencing revealed a c.508G>C, p.D170H STAT3 variant. Chest HRCT showed mild bronchiectasis with non-fibrosing alveolar-interstitial disease and maldevelopment of the first ribs. The patient was put on monthly IVIG therapy. From late childhood the family neglected medical follow up. The patient died at the age of 22 due to heart failure. The last lung HRCT showed progression in inflammatory airway disease without fibrosis or progression in alveolar-interstitial involvement.

Conclusions: Our observation suggests that patients with STAT3 GOF syndrome may lack early-onset autoimmune manifestations or present only mild and/or delayed-onset autoimmunity. Thus, patients with hypogammaglobulinemia, lymphoproliferation and recurrent infection phenotype should be screened for STAT3 variants, even if autoimmune manifestations are missing.

Disclosure: No.

Keywords: primary immunodeficiency, Autoimmunity, hypogammaglobulinemia, STAT3

PD099

CLINICAL CHARACTERISTICS AND OUTCOMES of 10 CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A FIVE-YEAR SINGLE-CENTER EXPERIENCE FROM ROMANIA

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Andreea Ioan, Alexis Virgil Cochino, Oana Maria Farkas
National Institute for Mother and Child Alessandrescu Rusescu, Immunology, Bucharest, Romania

Background and Aims: Hemophagocytic lymphohistiocytosis (HLH) is a rare clinical entity with severe hyperferritinemic hyperinflammatory immune response and high mortality rates. We report clinical and laboratory findings along with outcome analysis in a series of primary and secondary pediatric HLH cases.

Methods: We reviewed medical records of patients hospitalized between 2015 and 2021 diagnosed with HLH according to the Histiocyte Society HLH-2004 diagnostic criteria. We evaluated the total number of HLH episodes and identified triggers, genetic defects and treatment responses.

Results: A total number of 16 events fulfilling criteria for HLH syndrome were identified in 10 patients, with a mortality rate of 12%. Genetic analysis was confirmatory for familial HLH (fHL5) in one patient and for primary HLH in two patients (Griscelli type 2, Chediak-Higashi). Four patients had secondary HLH, three of whom were triggered by infection and responsive to dexamethasone alone and one triggered by early-onset IBD. One patient with likely immune dysregulation disease, in spite of negative genetic analysis and normal functional lymphocyte testing, had five recurrent MAS-HLH episodes while on sequential treatment with methotrexate, tocilizumab and/or anakinra. All patients required induction treatment for HLH remission, including those with infection-associated HLH

Conclusions: Infection-associated HLH is higher in our cohort than in other series. An already defined gene defect was identified in four patients, while two more have possible causative mutations. HLH secondary to rheumatic diseases was encountered in two patients, one of them having the highest relapse rate (5 episodes to date).

Disclosure: No.

Keywords: Hemophagocytic lymphohistiocytosi, macrophage activation syndrome, familial HLH, secondary HLH, recurrent MAS

PD100

FAMILY HISTORY of IMMUNE DYSREGULATION IN A GREEK COHORT of PATIENTS WITH PAEDIATRIC-ONSET COMMON VARIABLE IMMUNODEFICIENCY DISORDERS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Antonios Gkantaras[1], Konstantina Charisi[1], Eleni Papadimitriou[1], Anna Taparkou[1], Androniki Kapousouzi[2], Vasiliki Sgouropoulou[1], Matthaios Speletas[2], Evangelia Farmaki[1]
[1]Aristotle University of Thessaloniki, Paediatric Immunology And Rheumatology Referral Center, 1st Department of Paediatrics, Thessaloniki, Greece, [2]University of Thessaly, School of Health Sciences, Faculty of Medicine, Department of Immunology And Histocompatibility, Larissa, Greece

Background and Aims: The vast majority of Common Variable Immunodeficiency (CVID) cases are sporadic. However, an increased risk of autoimmunity and malignancy has been reported in family members of CVID patients. Herein, we aimed to determine the prevalence of family history of primary immunodeficiency disorder, autoimmunity and malignancy in a Greek cohort of patients with established diagnosis of paediatric-onset CVID.

Methods: All patients (n=51) and their caregivers were interviewed, using a detailed, 20-page, structured questionnaire at diagnosis and after 24 and 48 months, to collect information about history of infections, autoimmunity and malignancy. Molecular analysis of the TACI gene was performed by PCR in 48/51 patients.

Results: The rate of parental consanguinity was 5.9% (n=3). There were 9 familial cases (17.6%): 3 with an affected first-degree relative (FDR), 6 with at least one affected second-degree relative. In addition, 3 cases reported a FDR with selective IgA deficiency (n=1) and unclassified hypogammaglobulinemia (n=2). Family history of autoimmunity and malignancy was reported in 21 (41.2%) and 22 cases (43.1%), respectively. Hematologic malignancies were the most frequently reported neoplasms among family members (8/22;36.4%). There was no correlation between family history of immune dysregulation and clinical phenotypes (p=0.731) or presence of TACI mutations (p=1.000).

Conclusions: Despite the low consanguinity rate, the high prevalence of family history of immune dysregulation in our CVID cohort suggests complex polygenic model of inheritance, with polygenic overlap and shared genetic susceptibility loci between CVID and autoimmunity/tumorigenesis. Family history of autoimmune conditions and/or hematologic malignancies should raise suspicion of underlying CVID disorders.

Disclosure: No.

Keywords: Common variable immunodeficiency, Immune Dysregulation, Autoimmunity, Malignancy, TACI, Familial CVID

PD101

TOWARDS BETTER UNDERSTANDING of HUMAN LRBA DEFICIENCY SYNDROME

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Shahrzad Bakhtiar[1], Emilia Salzmann Manrique[1], Celia Kaffenberger[1], Sabine Donhauser[1], Leon Lueck[1], Julia Fekadu[1], Ralf Schubert[2], Peter Bader[1], Sabine Huenecke[1]
[1]University Hospital Frankfurt, Division For Stem Cell Transplantation, Immunology And Intensive Care Medicine, Department For Children And Adolescents Medicine, Frankfurt am Main, Germany, [2]University Hospital Frankfurt, Devision For Allergy, Pneumatology And Cf, Frankfurt am Main, Germany

Background and Aims: LRBA deficient patients suffer from multi-organ immune dysregulation. The dysfunctionality of LRBA causes a lack of CTLA-4 on Treg. Consequently, there is an increase of T follicular helper cells (Tfh) with an impact on B cell maturation and function.

Methods: Peripheral B-cells subsets with focus on regulatory B cells (Breg) of genetically confirmed LRBA-deficient patients (n=6) were compared to an age matched healthy control cohort (N=48) and to non-LRBA patients (N=13) suffering from an inborn error of immunity (IEI) with immune dysregulation. Flow cytometry based longitudinal data including Breg and regulatroy T cells subsets (Treg) were collected from the LRBA cohort while patients received bi-weekly abatacept. Three LRBA deficient patients received allogeneic stem cell transplantation. Furthermore, the LRBA interactome was analysed in a B cell model.

Results: Compared to the non-LRBA IEI group and healthy controls, LRBA-patients showed significantly lower switched memory B-cells (P=0.031), a lack of adequate B10 expansion (P=0.031), as well as a tendency towards increased circulating CD21 ^{low} B-cells (P=0.063). Treatment with abatacept resulted in an effective decrease in CD21^{low} B-cells over time (P=0.021). During abatacept treatment there was also a significant increase in natural Treg (P=0.003), while decreasing levels of induced and memory Treg (P= 0.059 and P= 0.145, respectively) were observed.

Conclusions: The knowledge of Breg as well as the development of Breg and Treg subsets during abatacept treatment in LRBA patients paired with the interactome analysis in a B and Treg cell model adds to the current understanding of human LRBA deficiency and might provide novel therapeutic aspects.

Disclosure: No.

Keywords: B reg, T reg, LRBA, Abatacept, Immune Dysregulation

PD102

CASE REPORT: MORE THAN AN ALPS PHENOTYPE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Maria Tejada, Andrea Gómez Raccio, Daniela Di Giovanni, Maria Gaillard, Ana García, Agostina Llarens, María Caldirola, María Martínez, Agustin Bernacchia, Analia Seminario, Patricia Carabajal
Hospital de Niños Ricardo Gutiérrez, Immunology Unit, Ciudad Autonoma de Buenos Aires, Argentina

Background and Aims: Ten eleven translocation methylcytosine dioxygenase 2 (TET2) is a regulator of gene expression, highly expressed in hematopoietic stem cells, and crucial in epigenetic modification of the mammalian genome and DNA demethylation. Homozygous germline TET2 impairment can lead to ALPS phenotype, myeloproliferation, and lymphomagenesis.

Methods: To report a patient with clinical and laboratory findings of ALPS-like with a nonsense variant in heterozygosis at TET2.

Results: An Argentinean 10 years old female, born from non-consanguineous parents. At 8 years old she has been diagnosed with autoinflammatory syndrome: prolonged fever, myalgia, periorbital edema, and non-infectious, non-malignant lymphoproliferation with inflammatory parameters in the laboratory. Bone marrow biopsy (BMB): normal. Immunology profile: normal immunoglobulins, protein response, complement, auto-antibodies, and lymphocyte population. She received corticoid with partial response. Later, she continued with lymphoproliferation and fasciitis. Laboratory findings: increased inflammatory parameters with elevated cytokines (predominantly IL-6 at plasma), DNT CD3+ TCRαβ+ CD4–CD8– 14%, normal B12 vitamin dosage, decreased total B memory cells. BMB: myeloid hyperplasia with myelodysplastic focal changes. Nowadays she presents severe headaches with a presumptive diagnosis of vasculitis of central nervous system; cyclophosphamide was initiated. An heterozygous non-sense variant, probably pathogenic, in TET2 gene was found: NM_001127208.3: c.3709C>T (p.Arg1237*) by NGS, not found at parents segregation.

Conclusions: TET2 heterozygous variant has not enough evidence at the moment to be described as pathogenic, but this could explain the clinic features and laboratory findings in the patient. DNA methylation assay would be useful to support the diagnosis. HSCT could be an option for treatment.

Disclosure: No.

Keywords: TET2, Immune Dysregulation, Inborn errors of immunity, AUTOINFLAMMATORYN DISORDERS, Myeloproliferation, ALPS-Like

PD103

IMPROVE UNDERSTANDING of STAPHYLOCOCCUS AUREUS INFECTION IN STAT3-HYPER IGE SYNDROME

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Renate Effner[1,2], Daniele De Donato[1,2], Theresa Mittweg[1,2], Goran Abdurrahman[3], Anica Lechner[1,2], Murthy Darisipudi[3], Gihanna Galindez[4,5], Matthias Reiger[2,6], Thomas Volz[7], Reinhard Hoffmann[8], Tim Kacprowski[4,5], Andreas Wollenberg[9,10], Beate Hagl[1,2], Alexander Mellmann[11], Barbara Bröker[3], Vera Schwierzeck[11], Ellen Renner[1,2,12]
[1]Translational Immunology in Environmental Medicine, School of Medicine, Technical University of Munich, Munich, Germany, [2]Institute of Environmental Medicine, Helmholtz Zentrum München, German Research Center For Environmental Health, Neuherberg, Germany, [3]Institute of Immunology, University Medicine Greifswald, Greifswald, Germany, [4]Division Data Science in Biomedicine, Peter L. Reichertz Institute For Medical Informatics of Tu Braunschweig And Hannover Medical School, Braunschweig, Germany, [5]Braunschweig Integrated Centre of Systems Biology (BRICS), Tu Braunschweig, Braunschweig, Germany, [6]Department of Environmental Medicine, Faculty of Medicine, University of Augsburg, Augsburg, Germany, [7]Department of Dermatology and Allergology, School of Medicine, Technical University of Munich, Munich, Germany, [8]Institute for Laboratory Medicine and Microbiology, University Hospital Augsburg, Augsburg, Germany, [9]Department of Dermatology and Allergy, Ludwig Maximilan University, Munich, Germany, [10]Department of Dermatology, Vrije Universiteit Brussel, Universitair Ziekenhuis Brussel, Brussels, Belgium, [11]Institute of Hygiene, University Hospital Muenster, Muenster, Germany, [12]Department of Pediatrics, Klinikum Rechts Der Isar, School of Medicine, Technical University of Munich, Munich, Germany

Background and Aims: STAT3-hyper IgE syndrome (STAT3-HIES), an inborn error of immunity caused by monogenic defects in the STAT3 gene, is associated with increased susceptibility to Staphylococcus aureus (S. aureus) infections on mucocutaneous body sites. STAT3-dependent impairment of T helper type 17 (Th17) immunity is one major factor for defective microbial response. Here, we assess S. aureus-host interactions and link it to Th17 immunity in STAT3-HIES.

Methods: We characterized S. aureus strains isolated from STAT3-HIES patients by whole genome sequencing, multi-locus sequence and protein A typing to determine presence of resistance and virulence genes and to classify isolates. Reactivity of serum IgE, Th cells and keratinocytes to S. aureus-specific serine protease-like proteins (Spls) was assessed. Skin fibroblasts were infected with S. aureus and mRNA sequencing was performed.

Results: Profiling of S. aureus strains matched the molecular epidemiology in Germany. S. aureus strains expressed genes of the immune evasion complex, the spl operon and few enterotoxins. STAT3-HIES patients showed strong IgE serum reactivity, whereas Th17 cytokine profile to Spls was reduced in vitro. In response to Spls, STAT3-HIES keratinocytes showed an innate immune response similar to healthy keratinocytes. S. aureus triggered Th17-associated metabolic pathways were impaired in STAT3-HIES fibroblasts.

Conclusions: The type of S. aureus strain is determined by local epidemiology rather than by STAT3-HIES. Reactivity to S. aureus toxins provides evidence that recurrent infections are due to imbalanced adaptive immunity rather than an intrinsic STAT3 signaling defect in epithelial cells. Regulation of metabolic pathways might have the potential to restore imbalanced adaptive immunity.

Disclosure: No.

Keywords: Staphylococcus aureus, TH17 immunity, STAT3-HIES

PD104

DEVELOPMENT of A REPORTER-BASED ASSAY TO QUANTIFY NHEJ/HR RATIO IN PRIMARY T-CELLS USING TRANSIENT TRANSFECTION

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Yasaman Shamshirgaran[1], Ola Hammarsten[2], Pegah Johansson[3]
[1]Sahlgrenska University Hospital, Department of Clinical Chemistry, Göteborg, Sweden, [2]Sahlgrenska University Hospital, Laboratory of Clinical Chemistry, Göteborg, Sweden, [3]Sahlgrenska University Hospital, Clinical Chemistry, Gothenburg, Sweden

Background and Aims: DNA repair deficiency disorder is a type of rare inherited disease result from mutations in genes involved in DNA repair. Patients with DNA repair deficiency in double-strand breaks also present with severe immune deficiency and are hypersensitive to some cancer treatments such as radiotherapy. There is no clinical assay to detect the functional ability of patient cells to repair double-strand breaks. We hypothesize that quantification of DNA repair efficiency in patient cells may predict patient sensitivity to treatment. Our aim is to establish an assay to quantify the two pathways involved in double-strand breaks, namely NHEJ and HR.

Methods: We develop an assay to quantify NHEJ and HR by transient transfection of a reporter transgene into primary T-cells. The transgenes have been designed to express the reporter gene upon repaired via either NHEJ or HR. Using fluorescent constructs allow for quantification of the active repair pathways at individual DNA breaks by flow-cytometry. The number of GFP positive cells counted by flow cytometry provides quantitative measure of NHEJ or HR efficiency.

Results: While we have a variation in NHEJ and HR among patients. Our preliminary data show that using an inhibitor of NHEJ kinase (DNA-PK), reduced NHEJ in primary T-cells while inhibition of the protein involved in HR, ATM inhibitor, reduced HR in the cells.

Conclusions: The assay can be used to evaluate the DNA repair deficiency in cells from immunodeficient patients with variants in DNA repair genes of unknown significance.

Disclosure: No.

Keywords: DNA-PK inhibitor, ATM inhibitor, DNA repair deficiency, NHEJ/HR, Primary T- cell, Double strand break

PD105

HSCT IN CGD PATIENTS: NOT ALWAYS AN EASY TREATMENT

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Marta Comini[1], Elena Soncini[2], Federica Bolda[1], Stefano Rossi[2], Giulia Baresi[2], Alessandra Beghin[1], Vassilios Lougaris[3], Annarosa Soresina[4], Arnalda Lanfranchi[1], Fulvio Porta[2]
[1]ASST Spedali Civili di Brescia, Stem Cell Laboratory, Section of Hematology And Blood Coagulation, Clinical Chemistry Laboratory, Diagnostic Department, Brescia, Italy, [2]Children's Hospital, Spedali Civili, Brescia, Italy, Oncohematology And Bone Marrow Transplant (bmt) Unit, Brescia, Italy, [3]University of Brescia, ASST Spedali Civili of Brescia, Pediatrics Clinic, Department of Clinical And Experimental Sciences, Brescia, Italy, [4]Pediatrics Clinic, Asst Spedali Civili Di Brescia, University of Brescia, Brescia, Italy

Background and Aims: Chronic granulomatous disease(CGD) is an inborn error of immunity characterized by mutations in genes encoding proteins involved in the NADPH oxidase complex. Lack of radical species production compromise the neutrophil-killing mechanism. Because of this, patients present with increased susceptibility to bacterial and fungal infections and chronic inflammatory manifestations. HSCT is a curative option even if is associated with significant risks for morbidity and death. The most difficult challenge has been conditioning regimen and timing for HSCT.

Methods: We started HSCT in CGD patients in 1990. Nowadays, 21 patients were transplanted.

Results: We performed 26 HSCT(and 4 boost), 21 of 26 after using myeloablative conditioning regimen. The source was BM in 13 cases, PBSC in 10 and cord blood in 3 patients. 14 HSCT involved MUD, 9 HLA-identical familiar donors and 3 haploidentical donors. Unfortunately, 6 patients died due overwhelming infections. GvHD complications were negligible in MUD since we applied a method with CD34+ selection and controlled T cell add-back. Chimerism analysis post HSCT showed 17 patients with total donor chimerism, 3 patients with mixed chimerism and only 1 patient with autologous reconstitution.

Conclusions: HSCT for CGD patients is an indication. Our experience demonstrates that HSCT is successful if performed at younger age and in absence of a severe history of infectious disease. We are now privileging myeloablative regimens to avoid risk of mixed chimerism that can lead to lose the graft. Moreover, minimize the time from diagnosis to transplant is the goal, so that haploidentical transplant in some setting can be the option.

Disclosure: No.

Keywords: CGD, HSCT IN CGD

PD106

AUTOLOGOUS RECONSTITUTION of T-CELLS WITH COMPLETE NON-T-CELL DONOR CHIMERISM AFTER BONE MARROW TRANSPLANTATION IN A PATIENT WITH APDS1

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Lisa Debler, Manfred Hönig, Ansgar Schulz, Ingrid Furlan, Kerstin Felgentreff, Eva Jacobsen, Klaus Debatin
University Medical Center Ulm, Germany, Department of Pediatrics And Adolescent Medicine, Ulm, Germany

Background and Aims: Patients with activated PI3K-delta syndrome (APDS) can be cured by hematopoetic stem cell transplantation.

Methods: We report on a 21-year-old female patient with a PIK3CD-GOF variant presenting with recurrent respiratory tract infections, bronchiectasis, chronic lymphadenopathy and autoimmune mesangial proliferative and membranous glomerulonephritis with stage 3 chronic kidney disease (CKD) who received a bone marrow transplant after busulfan-based myeloablative conditioning from her HLA-ident sister. GvHD prophylaxis included alemtuzumab, sirolimus and MMF. No signs of a/cGvHD were observed.

Results: A lineage-specific chimerism three months after HSCT revealed a nearly complete autologous reconstitution of T-cells with a complete donor chimerism of other cell lineages. Lymphocyte phenotyping showed poor immunological reconstitution of T-cells with inverse CD4+/CD8+ ratio and absence of naïve T-cells. Furthermore, the pre-existing CKD deteriorated after HSCT. Peripheral donor T-cell engraftment could not be improved by reduction of immunosuppressive therapy and donor lymphocyte infusion.

Conclusions: This unusual constellation of autologous T-cell reconstitution could be explained by a selective advantage of autologous T-cells in this disease and has not been previously reported. Despite of myeloid engraftment the patient cannot be considered cured from APDS and will need immunosuppression to avoid further organ damage.

Disclosure: No.

Keywords: Bone Marrow Transplantation, activated PI3K delta syndrome

PD107

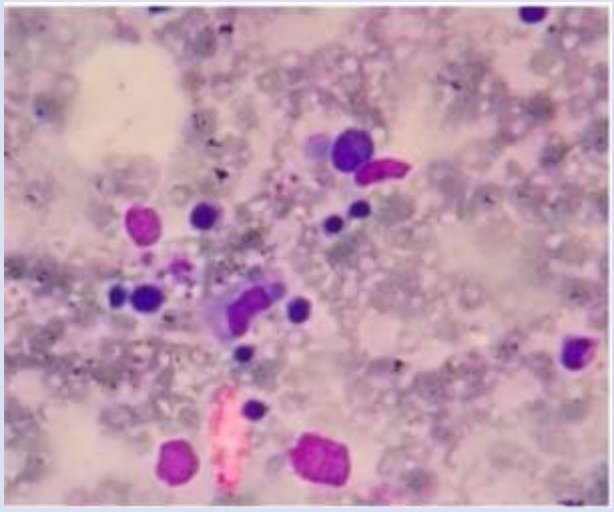
LYSO-SPHINGOMYELIN-509 INCREASED IN GRISCELLI SYNDROME TYPE 2

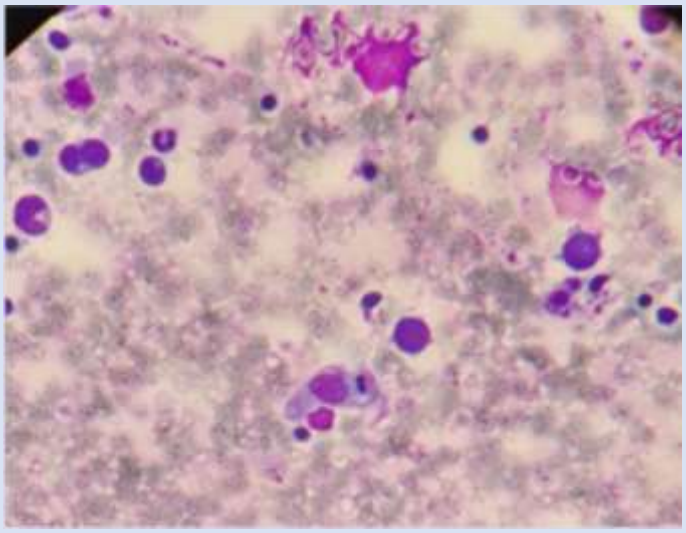
POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Lara Antonini[1], Irene D'Alba[1], Lucia Santoro[2], Barbara Bruschi[1], Simona Gobbi[1], Valeria Petroni[1], Alberto Burlina[3], Paola Coccia[1]
[1]AOU - Ospedali Riuniti, Paediatric Onco-haematology, Ancona, Italy, [2]AOU - Azienda Ospedali Riuniti Salesi Children Hospital, Paediatric, Ancona, Italy, [3]Azienda Ospedaliera di Padova -Università di Padova, Uoc Malattie Metaboliche Ereditarie, Padova, Italy

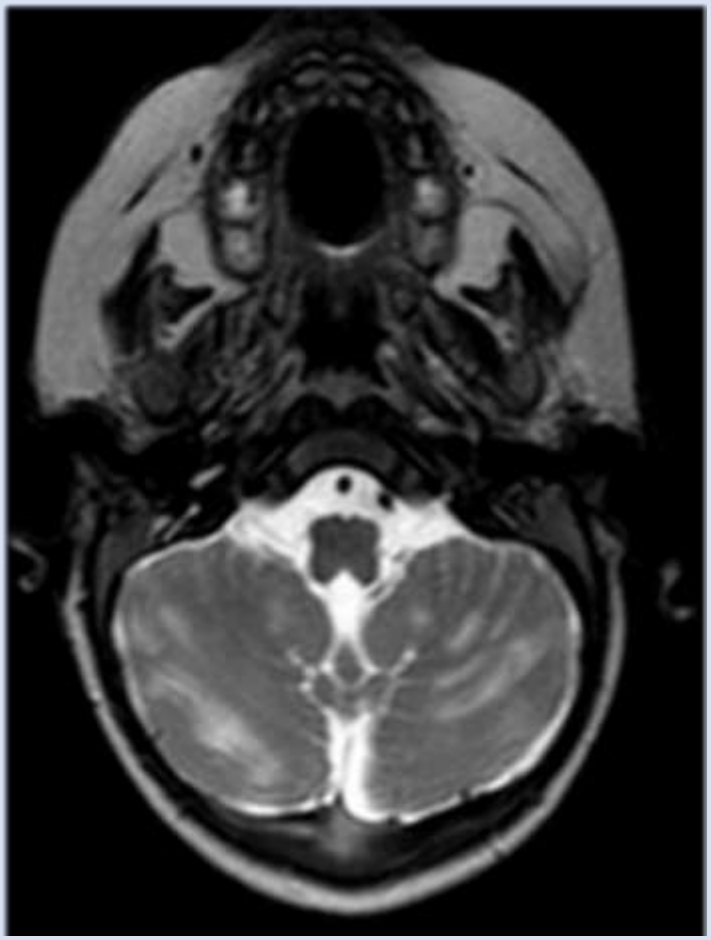
Background and Aims: Haemophagocytic Lymphohistiocytosis (HLH) is a potentially life-threatening disorder with immune dysregulation, non-specific presentation, which can be primary or secondary to other underlying diseases.

Methods: A 7-months-old infant with a few days' history of fever and vomiting. Consanguineous parents of Algerian origin and relatives' early deaths in the paternal line. On examination: dehydration, respiratory distress, hepatosplenomegaly and silver blond hair and eyebrows. Blood tests: pancytopenia, hypertriglyceridemia, hypercholesterolemia, impaired liver function, increased pro-inflammatory markers (ERS, CRP, sCD25). Haemophagocytosis on bone marrow aspirate.

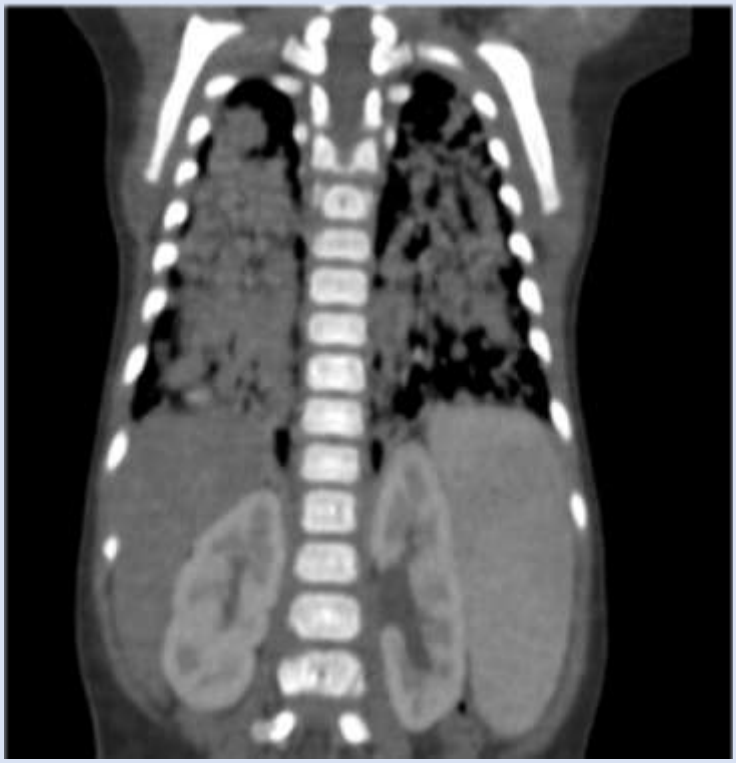


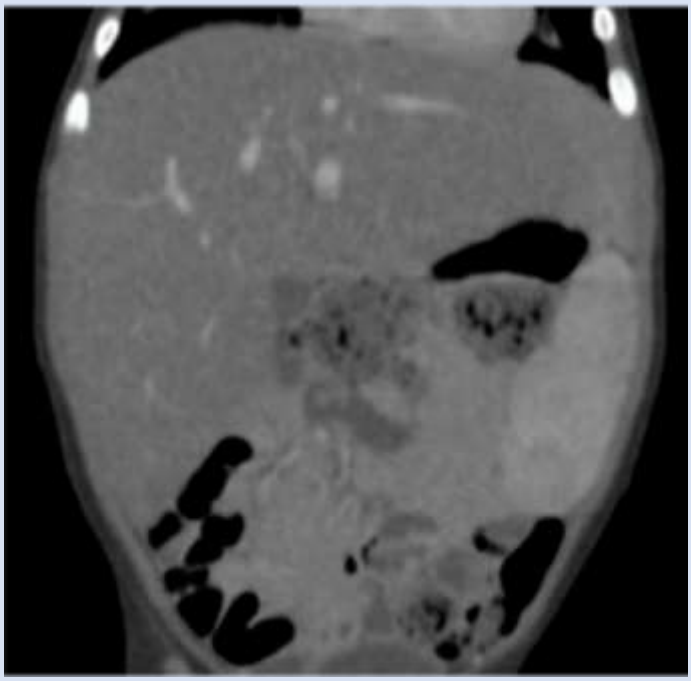


Brain MRI: multifocal bilateral abnormalities on T2-weighted imaging involving brainstem and cerebellar hemispheres.

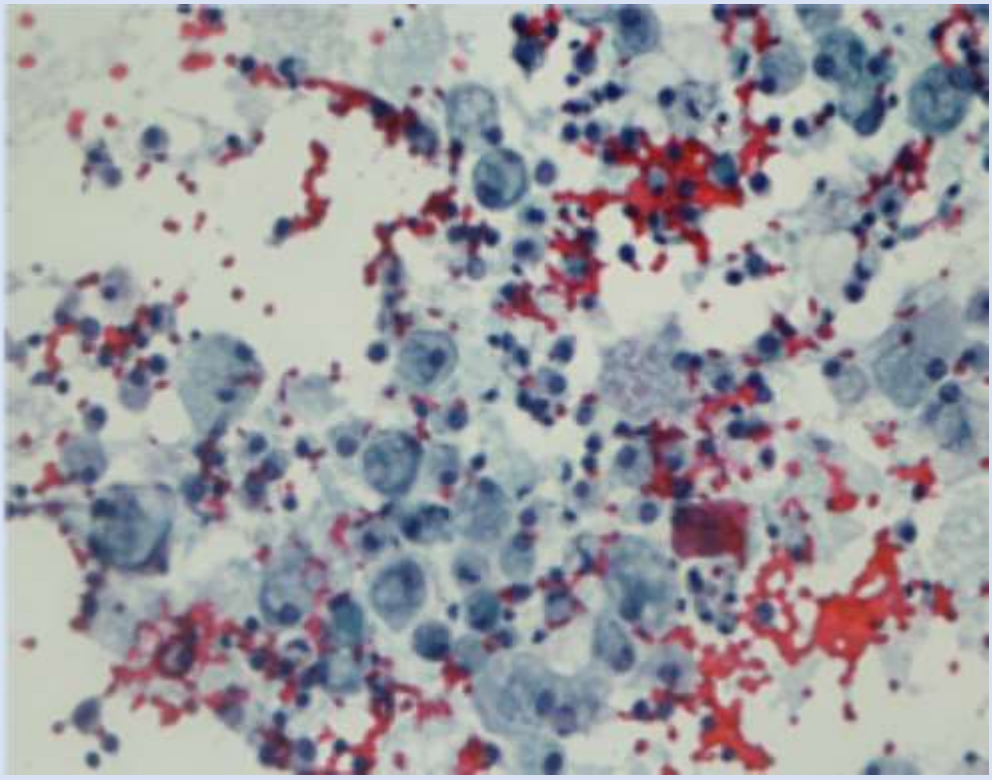


Thoraco-abdominal CT-scan: multiple bilateral pulmonary infiltrates and severe hepatosplenomegaly.





BAL and liver biopsy: foamy macrophages and massive hepatic steatosis respectively.



Metabolic tests showed elevated levels of lyso-sphingomyelin-509 (882.56 nMol/L).

Results: He was started on Miglustat (100 mg/day). In the suspicion of a secondary HLH due to lysosomal storage disorder, he received dexamethasone and etoposide, but molecular investigation for Niemann Pick C disease resulted negative. Immunological tests showed hypogammaglobulinemia and moderate granule release abnormalities on flowcytometry studies. Molecular analysis of Rab27a gene showed homozygous variant c.148_149delAGinsC, pArg50GInfs33 suggesting a diagnose of Griscelli syndrome type 2 (GS2). He underwent to Hematopoietic Stem Cell Transplant.

Conclusions: GS2 is an autosomal recessive disorder with partial albinism and immunodeficiency due to defects in lysosomal trafficking. To our knowledge this is the first case reported of GS2 with elevated lyso-sphingomyelin-509, a highly specific (91%) and sensitive (100%) biomarker for Niemann-Pick C disease type 1 (NPC1). Altered molecular trafficking can explain this finding? Further studies are needed.

Disclosure: No.

Keywords: Griscelli syndrome type 2 (GS2), Haemophagocytic Lymphohistiocytosis (HLH), Lyso-sphingomyelin-509

PD108

A NOVEL STAT3 GAIN-OF-FUNCTION MUTATION IN FATAL INFANCY-ONSET INTERSTITIAL LUNG DISEASE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Mengyue Deng[1], Yue Li[1], Yulu Li[1], Xiaolan Mao[1], Han Ke[2], Weiling Liang[3], Xiaoguang Lei[2], Yu Lung Lau[3,4], Huawei Mao[5]
[1]Children's Hospital of Chongqing Medical University, Department of Pediatric Research Institute, Chongqing, China, [2]Peking University, Beijing National Laboratory For Molecular Sciences, Key Laboratory of Bioorganic Chemistry And Molecular Engineering of Ministry of Education, Department of Chemical Biology, College of Chemistry And Molecular Engineering, Beijing, China, [3]the University of Hong Kong-Shenzhen Hospital, Department of Pediatrics, Shenzhen, China, [4]the University of Hong Kong, Department of Paediatrics & Adolescent Medicine, Hong Kong, China, [5]Beijing Children's Hospital, Capital Medical University, Department of Immunology, Beijing, China

Background and Aims: Signal transducer and activator of transcription 3 (STAT3) gain-of-function (GOF) mutations cause early-onset immune dysregulation syndrome. In this study, we reported a patient presented with fatal infantile ILD caused by STAT3 mutation and then reviews related literature, aiming to expand the clinical spectrum and provide evidence to guide clinical diagnosis and treatment.

Methods: The STAT3 phosphorylation in PBMCs of the patient and healthy controls were measured using flow cytometry. The phosphorylation of mutant STAT3 was detected by western blot. In addition, transcriptional activity was detected using a dual-luciferase reporter assay.

Results: This patient presented with fatal infancy-onset ILD, along with recurrent diarrhea and infection. Next-generation sequencing identified a heterozygous mutation in STAT3 (c.989C>G, p.P330R), which has not been reported before. This mutation caused a much higher activation of STAT3 than the wild-type control under the steady state or interleukin 6 stimulation. In addition, the T helper 17 cell level in the patient was significantly higher than that in normal controls. Apart from JAK inhibitors, we also provided experimental evidence of a STAT3 selective inhibitor (Stattic) effectively suppressing the activation of mutant STAT3 in vitro.

Conclusions: In this study, we identified a novel STAT3 GOF mutation and expanded the clinical spectrum of STAT3 GOF syndrome. STAT3 GOF mutation appears as a new etiology of ILD and should be considered in patients with early-onset ILDs. The specific STAT3 inhibitor would be an appealing option for the targeted treatment.

Disclosure: No.

Keywords: STAT3, autoimmune disease, Gain-of-function mutation, Interstitial disease, STAT3 inhibitor, JAK inhibitor

PD109

WHOLE BLOOD TCR VB21.3 STAINING AS A DIAGNOSTIC TEST FOR MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN: A PROOF-OF-CONCEPT STUDY

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Levi Hoste[1,2], Jef Willems[3], Evelyn Dhont[3], Petra Schelstraete[1], Joke Dehoorne[4], Kristof Vandekerckhove[5], Alexandre Belot[6,7], Brigitte Bader-Meunier[8,9,10], Christophe Malcus[6], Simon Tavernier[2,11], Filomeen Haerynck[1,2]
[1]Ghent University Hospital, Department of Internal Medicine And Pediatrics, Division of Pediatric Pulmonology, Infectious Diseases And Inborn Errors of Immunity, Ghent, Belgium, [2]Ghent University, Primary Immune Deficiency Research Laboratory, Department of Internal Diseases And Pediatrics, Centre For Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis And Research Centre, Gent, Belgium, [3]Ghent University Hospital, Pediatric Intensive Care, Gent, Belgium, [4]Ghent University Hospital, Department of Pediatric Rheumatology, Ghent, Belgium, [5]Ghent University Hospital, Department of Pediatric Cardiology, Ghent, Belgium, [6]Centre International de Recherche en Infectiologie, Inserm U1111, Lyon, France, [7]Hospices Civils de Lyon, Hfme, Rheumatology Department, Bron, France, [8]Necker Hospital for Sick Children, Pediatric Immunology, Hematology And Rheumatology Unit, Paris, France, [9]Paris Cité University, Imagine Institute, Paris, France, [10]Laboratory of Immunogenetics of Pediatric Autoimmunity, Inserm U1163; Necker Hospital For Sick Children, Paris, France, [11]Ghent University Hospital, Department of Internal Medicine, Ghent, Belgium

Background and Aims: Multisystem inflammatory syndrome in children (MIS-C) is a rare inflammatory condition, occurring 1-2 months after SARS-CoV-2 infection in children. The clinical features of MIS-C are nonspecific. Since early treatment is of prognostic value, clinicians are faced with the challenge to recognize patients timely. However, lacking a specific test, diagnosing MIS-C remains largely based on clinical expertise. Enrichment of Vβ21.3+ T-cell receptors is a frequent finding in MIS-C. We aimed to assess the value of whole blood (WB) Vβ21.3 staining as a diagnostic test for MIS-C.

Methods: EDTA blood was obtained in healthy controls (HCs) and patients fulfilling the WHO MIS-C case definition (before immunomodulatory treatment). WB was stained, lysed and fixed within 2h of sampling. By flow cytometry, the relative frequency of Vβ21.3+ T-cells (CD3/CD4/CD8) was assessed as well as activation markers (HLA-DR).

Results: Four patients and five HCs were included. The Vβ21.3+ T-cell proportions were increased in one case (3.6-5.6% of T-cells), a 12yo girl presenting typical MIS-C and responding rapidly with first-line treatment. Although all other patients fulfilled the MIS-C case definition at inclusion, their further disease course led to alternative diagnoses, including Streptococcus pyogenes sepsis, haemophagocytic lymphohistiocytosis and metabolic cardiomyopathy. These non-MIS-C patients and HCs showed only 1.0-2.6% Vβ21.3+ T-cells. Additionally, in MIS-C 37.7% of Vβ21.3+ lymphocytes were HLA-DR+, while only 0.1-11% in HCs and non-MIS-C patients.

Conclusions: We provide proof-of-concept that Vβ21.3 staining can be used as a rapid diagnostic test to distinguish MIS-C from other inflammatory diseases. Its sensitivity and specificity should be assessed in larger prospective studies.

Disclosure: No.

Keywords: MIS-C, COVID-19, T cell receptor, superantigen

PD110

T-CELL ABERRANCIES IN CVID CORRELATE WITH PRO-INFLAMMATORY MONOCYTE GENE EXPRESSION, AND ARE AGGRAVATED IN THE PRESENCE of AUTOIMMUNE COMPLICATIONS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Olivia Manusama[1], Hemmo Drexhage[1], Annemarie Wijkhuijs[1], Rogier Van Wijck[2], Martin Van Hagen[3], Virgil Dalm[4]
[1]Erasmus University Medical Center Rotterdam, Immunology, Rotterdam, Netherlands, [2]Erasmus University Medical Center Rotterdam, Pathology, Division of Bioinformatics, Rotterdam, Netherlands, [3]Erasmus University Medical Center Rotterdam, Internal Medicine, Rotterdam, Netherlands, [4]Erasmus MC, University Medical Center Rotterdam, Academic Center For Rare Immunological Diseases (ridc), Rotterdam, Netherlands, Netherlands

Background and Aims: Background: Autoimmunity is a great cause of morbidity and mortality in Common Variable Immune Deficiency (CVID). Both monocyte and T-cell aberrancies have been described in CVID and may contribute to the development of autoimmunity. Aim: To characterize T-cell aberrancies and inflammatory monocyte gene expression profile in CVID patients with autoimmune complications.

Methods: From frozen peripheral blood mononuclear cells (PBMC) from adult CVID patients with autoimmune complications (CVID-A) (N=14), we carried out a monocyte gene expression analysis and measured various T (helper) cell subsets. We compared outcomes to those of CVID patients without autoimmune complications (CVID-0) (N=32) and sex-/age-matched healthy controls (HCs) (N=87).

Results: Compared to HCs, CVID-A patients had significantly reduced numbers of $CD4^+$ T cells, Tregs, Th2 cells and naïve $CD4^+$ T cells and significantly increased numbers of $CD8^+$ memory T cells. These aberrancies were more outspoken in CVID-A patients than in CVID-0 patients. Monocytes of CVID-A patients showed a stronger expression profile of the pro-inflammatory genes IL1B, BCL2A1, MXD1, ADM, MAFF and DUSP2, compared to monocytes of CVID-0 patients and HCs. These pro-inflammatory genes were moderately to strongly correlated to especially naïve $CD4^+$ T cells, but also to Tregs and $CD45RO^-$ T cells.

Conclusions: T-cell aberrancies in CVID patients include a naïve $CD4^+$ cytopenia and signs of premature immunosenescence, correlating with a pro-inflammatory monocyte profile in CVID patients. Both T-cell and monocyte compartment seem to be more affected in CVID patients with autoimmune complications, indicative of their synergistic contribution to autoimmunity in CVID.

Disclosure: No.

Keywords: Immunosenescence, common variable immune deficiency, Monocyte activation, T cell aberrancy, Autoimmune complications

PD111

STAT3-CONFUSION-OF-FUNCTION: BEYOND THE LOSS AND GAIN DUALISM.

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Lorenzo Lodi[1,2], Laura Eva Faletti[3], Maria Elena Maccari[3], Filippo Consonni[2], Miriam Gross[3], Ilaria Pagnini[4], Silvia Ricci[2], Maximilian Heeg[3], Gabriele Simonini[4], Chiara Azzari[1,2], Stephan Ehl[3]
[1]Meyer Children's Hospital, Pediatric Immunology Unit, Firenze, Italy, [2]University of Florence, Department of Health Sciences, Firenze, Italy, [3]University of Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency, Medical Center, Freiburg, Germany, [4]Meyer Children's Hospital, Pediatric Rheumatology Unit, Firenze, Italy

Background and Aims: Germline mutations of signal transducer and activator of transcription 3 (STAT3) are responsible for two distinct human diseases: autosomal-dominant hyper-immunoglobulin E syndrome (AD-HIES) caused by STAT3 loss-of-function (STAT3-LOF) mutations and STAT3 gain-of-function (STAT3-GOF) disease. So far, these entities have been regarded as antithetic, with AD-HIES mainly associated with characteristic infections and a connective tissue phenotype and STAT3-GOF characterized by lymphoproliferation and poly-autoimmunity. The R335W substitution in the DNA binding domain of STAT3 was initially described in 2 patients with typical AD-HIES, but paradoxically, recent functional analysis demonstrated a GOF effect of this variant. We describe a patient with Sjögren syndrome and features of AD-HIES with this mutation and further characterize its molecular consequences.

Methods: We provide a clinical and immunological description of the patient. We studied STAT phosphorylation in primary patient cells and used A4 cells transfected with the patient allele to study phosphorylation kinetics, transcriptional activity and target-gene induction.

Results: The hybrid clinical features of the patient were associated with normal Th17 cells. We observed enhanced and prolonged STAT3 phosphorylation, an increased STAT3 driven luciferase reporter activity upon interleukin-6 stimulation, but reduced IL-6 induced SOCS3 production.

Conclusions: The germline R335W-STAT3 variant displays a mixed behavior in vitro that mainly shows gain-of-function, but also loss-of-function features. This is matched by an ambiguous clinical and immunological phenotype which dismantles the classical antithetic dualism of gain- versus loss-of-function. Germline STAT3 mutation related-disease represents a pathological spectrum with the p.R335W mutation locating midway between the two extremes.

Disclosure: No.

Keywords: STAT3, Hyper-immunoglobulin E syndrome, Sjögren's syndrome, STAT3 loss-of-function, STAT3 gain-of-function, Th17 cells

PD112

EFFICACY AND SAFETY of A SUBCUTANEOUS HUMAN IMMUNOGLOBULIN (20% SCIG - NEWNORM) IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES – DESIGN of A PHASE 3 STUDY

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Roger Kobayashi[1], Jiri Litzman[2], Doris Hinterberger[3], Sonja Hoeller[4]
[1]UCLA School of Medicine Los Angeles, CA/USA, Ucla School of Medicine Los Angeles,, LA, United States of America, [2]St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Department Clinical Immunology And Allergology, Brno, Czech Republic, [3]Octapharma Pharmazeutika Produktionsges.m.b.H., Vienna, Austria, Clinical R&d, Wien, Austria, [4]Octapharma Pharmazeutika Produktionsges.m.b.H., Global Medical & Scientific Affairs, Vienna, Austria

Background and Aims: Patients with primary immunodeficiency diseases (PID) need life-long treatment with immunoglobulins (IG). Reduced systemic side effects, remarkable improvement in the patient's quality of life and treatment compliance drives the need for development of safe and effective subcutaneous human immunoglobulin products.

Methods: This phase 3 study is a prospective, open-label, single-arm, multicentre study with a 52-week efficacy period and pharmacokinetic (PK) substudy conducted globally in 25 study sites. At least 50 patients (aged ≥2 and ≤75 years) diagnosed with PID and on a stable, therapeutic dose of IVIG or SCIG or fSCIG will be enrolled in the study and infused weekly. SCIG dosing will be adjusted by a converting factor of 1.37 to previous IVIG dose and 1:1 dosing to previous SCIG dose and 1.3 dosing to previous fSCIG dosing. The primary objectives are to assess the safety and efficacy of a glycine stabilized 20% SCIG in preventing serious bacterial infections (SBIs) and to confirm that the average total IgG levels with weekly SC dosing are non-inferior to the 3- or 4- weekly IV dosing. The primary efficacy endpoint is the rate of SBIs per person-year on treatment analysed for the 52-week efficacy period. The primary PK endpoint is the average total IgG concentration (C_{av}) on steady-state dosing.

Results: Analysis will be conducted after all patients finalised 52 weekly SC infusions.

Conclusions: This study will evaluate the efficacy, pharmacokinetic and safety of a newly designed glycine stabilized 20% SCIG in PID patients. The 20% SCIG formulation is based on the well-established panzyga® manufacturing process

Disclosure: No.

Keywords: PID, SCIG, IGRT, efficacy, subcutaneous, Immunoglobulin

PD113

ALPS IN A PATIENT WITH FOXP3 MUTATION: A DIAGNOSTIC CHALLENGE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Imen Ben-Mustapha[1], Afef Rais[1], Najla Mekki[1], Monia Ben-Khaled[2], Nourhen Agrebi[1], Faten Fedhila[3], Mohamed-Ridha Barbouche[1]
[1]Institut Pasteur de Tunis, Laboratory of Transmission, Control And Immunobiology of Infections (lr11ipt02), Tunis, Tunisia, [2]Bone Marrow Transplantation Center Tunis, Pediatric Immuno-hematology Unit, Tunis, Tunisia, [3]Children's Hospital, Pediatrics, Tunis, Tunisia

Background and Aims: ALPS and IPEX are two well-characterized inborn errors of immunity with immune dysregulation, considered as two master models of monogenic auto-immune diseases. Thus, with autoimmunity as their primary clinical manifestation, these two entities may show clinical overlap. Traditionally, immunological biomarkers are used to establish an accurate differential diagnosis. Herein, we describe a patient who presented with clinical features and biomarkers fulfilling the diagnostic criteria of ALPS.

Methods: Biological and immunological investigations include complete blood count, serum Ig levels, flow cytometry lymphocyte phenotyping, lymphocyte proliferation tests, ALPS parameters analysis, auto-antibodies screening, Fas gene sequencing and targeted NGS.

Results: Severe apoptotic defect was also shown in the patient's cell lines and PHA-activated peripheral blood lymphocytes. Sanger sequencing of the FAS gene did not reveal any causal mutation. NGS screening revealed a novel deleterious variant located in the N terminal repressor domain of FOXP3 but no mutations in the FAS pathway-related genes. TEMRA cells (terminally differentiated effector memory cells re-expressing CD45RA) and PD1 expression were increased arguing in favor of T-cell exhaustion, which could be induced by unrestrained activation of T effector cells because of Treg deficiency. Moreover, defective FOXP3 observed in the patient could intrinsically induce increased proliferation and resistance to apoptosis in T effector cells.

Conclusions: This observation expands the spectrum of FOXP3 deficiency and underscores the role of NGS in detecting mutations that induce overlapping phenotypes among inborn errors of immunity with immune dysregulation. In addition, these findings suggest a potential link between FOXP3 and FAS pathways.

Disclosure: No.

Keywords: ALPS, NGS, apoptosis, IPEX

PD114

EXTRACORPOREAL PHOTOPHERESIS AND RENAL TRANSPLANT IMMUNE TOLERANCE

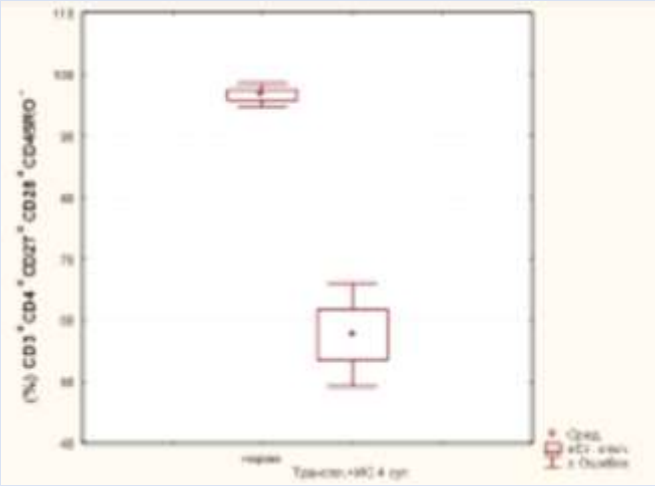
POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

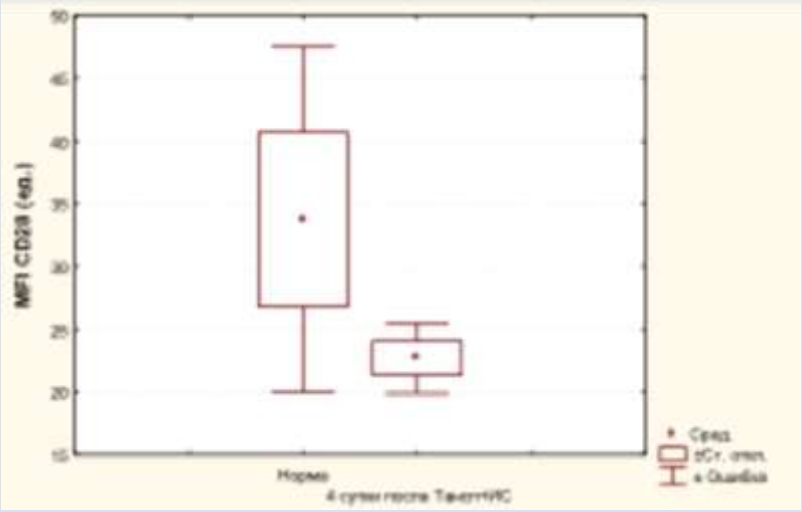
Veronika Fedulkina
Moscow Regional Research and Clinical Institute ("MONIKI"), Surgical Department of Kidney Transplantation, Moscow, Russian Federation

Background and Aims: Extracorporeal photochemotherapy (ECP) is an effective method for the treatment of acute renal transplant rejection [Xipell M. et al., 2021; Augusto JF et al., 2021; Gregorini M. et al., 2021]. The aim was to determine the value of ECP in the immunological parameters of tolerance.

Methods: An open cohort randomized study was conducted with 20 renal allograft recipients received paired kidneys from 10 donors. Patients of the main group, in addition to basic immunosuppression (tacrolimus, mycophenolate mofetil, and prednisolone), received 15 ECP sessions.

Results: Analysis of immunological parameters showed that the number of cells expressing coactivation CD28 molecules was almost 2 times less than normal as a result of immunosuppression on the 4th day. At the same time, the density of their co-expression on naive lymphocytes (MFI) decreased in proportion to their number (r=0.58, p=0.01). 30 days after transplantation there was no significant change in the number of cells expressing coactivation molecules (57.7±18.2% and 52.7±23.2%; p>0.05) and MFI (22.7± 6.0 and 19.6±7.0 E; p>0.05) in the comparison group. In the main group there was a statistically significant decrease in the number of such cells (from 57.7±18.2 to 34.5±11.4%; p<0.05) and MFI (from 22.7±6.0 up to 16.8±5.1 U; p<0.05) (Fig. 1).





Conclusions: ECP is possible to block selectively the second pathway of coactivation of T-helpers and suppressors and can be a valuable addition to the standard immunosuppressive therapy protocol providing the induction of antigen-specific inhibition of effector T-cell functions and the immunological tolerance to donor organ antigens.

Disclosure: No.

Keywords: Renal transplantation, Immune tolerance, Extracorporeal photopheresis, Acute rejection

PD115

IMMUNE DYSREGULATION IN CHILDREN WITH INHERITED BONE MARROW FAILURE SYNDROME AND REFRACTORY CYTOPENIA of CHILDHOOD: PERIPHERAL IMMUNOPHENOTYPING AS POTENTIAL TOOL FOR DIFFERENTIAL DIAGNOSIS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Ebe Schiavo[1], Beatrice Martini[1], Filippo Consonni[2], Francesco Pegoraro[2], Giorgio Costagliola[3], Annalisa Legitimo[4], Maria Luisa Coniglio[5], Margherita Nardi[3], Claudio Favre[5], Marinella Veltroni[5], Eleonora Gambineri[1]
[1]University of Florence, Department of Neurosciences, Psychology, Drug Research And Child Health (neurofarba), Florence, Italy, [2]University of Florence, Department of Health Sciences, Firenze, Italy, [3]University hospital of Pisa, Division of Pediatric Oncology/hematology, Pisa, Italy, [4]Santa Chiara University Hospital, Clinical Immunology Unit, Pisa, Italy, [5]Meyer Children's Hospital, Centre of Excellence, Division of Pediatric Oncology/hematology, Florence, Italy

Background and Aims: Inherited bone marrow failure syndromes (IBMFS) are usually identified when patients develop hematologic complications, such as severe BMF, myelodysplastic syndrome or leukemia. In clinical practice, differential diagnosis with refractory cytopenia of childhood (RCC) or autoimmune cytopenia associated or not with inborn error(s) of immunity may be challenging. To fill this gap, we aim at profiling the immunological landscape associated with pediatric chronic cytopenia(s).

Methods: We enrolled patients presenting with chronic cytopenia (>12 months): isolated autoimmune cytopenia(s) (AIC, N=11); IBMFS (N=12: 4 Diamond-Blackfan; 4 Shwackman-Diamond, 2 Fanconi anemia, 1 Congenital dyskeratosis, 1 RUNX1-deficiency) and RCC (N=6). Peripheral blood immunophenotyping was performed to compare the AIC to IBMFS and RCC group.

Results: Lymphocyte subpopulations analysis revealed lower frequencies of CD4 recent thymic emigrants in IBMFS group ($p=0.020$), CD4 naïve T cells in both IBMFS ($p=0.002$) and RCC ($p=0.041$) patients and CD8 naïve T cells in IBMFS group ($p=0.021$), counterbalanced by a higher frequency of CD4 central memory (CM; $p=0.001$ for IBMFS; $p=0.022$ for RCC) and CD8 CM T cells ($p<0.05$ for IBMFS and RCC). A similar profile was detected in both cohorts for naïve Tregs ($p<0.05$) towards memory Tregs ($p<0.05$).

Conclusions: Strikingly, we observed a T cell immune-dysregulation due to an imbalance towards memory compartment in pediatric patients with RCC and IBMFS. As this scenario is reminiscent of what observed in patients with AIC associated with signs of IEI, further investigations are required to define the pathogenicity of the altered immune homeostasis. Nevertheless, peripheral immunophenotyping is confirmed as screening tool able to facilitate differential diagnosis.

Disclosure: No.

Keywords: Peripheral immunophenotyping, inherited bone marrow failure syndromes, autoimmune cytopenias, Refractory Cytopenia of Childhood, Immune Dysregulation

PD116

NOCARDIA BRAIN ABSCESS AND PULMONARY ASPERGILLOSIS IN AN ADULT PATIENT: DIAGNOSTIC CHALLENGE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Inês Farinha[1], Jacinta Bustamante[2,3,4,5,6,7,8,9,10], Pedro Ferreira[11], Eugénia Ferreira[12], José Serra[12], Ana Todo Bom[1,13], Emília Faria[1]
[1]Coimbra Hospital and University Centre, Immunoallergology Department, Coimbra, Portugal, [2]Paris Cité University, Imagine Institute, Paris, France, [3]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Paris, France, [4]Paris Hospital, Study Center For Primary Immunodeficiencies, Paris, France, [5]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, New York, United States of America, [6]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, New York, United States of America, [7]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1136, Paris, France, [8]Imagine Institute, Paris Cité University, Paris, France, [9]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1163, Paris, France, [10]AP-HP, Study Center For Primary Immunodeficiencies, Necker Hospital For Sick Children, Paris, France, [11]Coimbra Hospital and University Centre, Pneumology Department, Coimbra, Portugal, [12]Coimbra Hospital and University Centre, Infectious Diseases Departement, Coimbra, Portugal, [13]Faculty of Medicine of the University of Coimbra, Allergology, Coimbra, Portugal

Background and Aims: The onset of severe systemic infections in adulthood is rare. Inborn errors of immunity (IEI) must be investigated.

Methods: Case report of a 46-year-old man with clinical course suggestive of IEI.

Results: An otherwise healthy man presented in April 2018 to the emergency department (ED) with headache and Wernicke's aphasia. Brain CT showed left temporal hyperdense lesion with extensive adjacent edema which required drainage. In culture of the drained liquid grew Nocardia abscessus. Previously chest CT demonstrated condensation at right lung and its biopsy showed bronchial invasion with fungal elements from which Aspergillus fumigatus was cultured. In this context, he was evaluated for suspected IEI, the laboratory tests performed was only presented low expression of gamma interferon I receptor in monocytes. The patient was included in a complete exome sequencing program but no relevant clinical mutations were identified, however neutralizing anti–GM-CSF autoantibodies were detected. In December 2019, he presented to the ED with chest pain and hypoxemic respiratory failure. Imaging studies showed extensive pulmonary infiltrates and alveolar proteinosis was diagnosed. He underwent therapeutic lavage and actually is under antimicrobial prophylaxis.

Conclusions: This case report presents an example phenocopy of IEI, a special group of immune deficiency that looks and act like a genetic disease but are not conferred by a specific genotype. An accurate diagnosis is essential for its proper recognition and approach. We need to think broader and be awareness about possible phenocopies of IEI in immunocompetent patients with unusual and/or serious infections.

Disclosure: No.

Keywords: anti–GM-CSF autoantibodies, Phenocopies

PD117

EXOME, TRANSCRIPTOME, EPIGENOME, AND PROTEOME ANALYSES IN B CELLS of PATIENTS WITH NFKB1 IMMUNE DYSREGULATION

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Nadezhda Camacho-Ordonez[1,2,3], Neftali Ramirez[1,2], Sara Posadas-Cantera[1,2], Andrés Caballero-Oyteza[1,2], Manfred Fliegauf[1,2,4], Klaus Warnatz[1,2,5], Christoph Bock[6], Esteban Ballestar[7], Roger Geiger[8,9], Michele Proietti[1,2,10,11], Bodo Grimbacher[1,2,4,5,11,12]
[1]Center for Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg, Germany, [2]Institute for Immunodeficiency, University Medical Center Freiburg, Freiburg im Breisgau, Germany, [3]Faculty of Biology, University of Freiburg, Freiburg, Germany, [4]CIBSS - Centre For Integrative Biological Signalling Studies, University of Freiburg, Freiburg, Germany, [5]Department of Rheumatology and Clinical Immunology, University Medical Center Freiburg, Freiburg, Germany, [6]CeMM, Research Center For Molecular Medicine of The Austrian Academy of Sciences, Vienna, Austria, [7]Epigenetics and Immune Disease Group, Josep Carreras Research Institute (ijc),08916 Badalona, Barcelona, Spain, [8]Institute for Research in Biomedicine, Università Della Svizzera Italiana, Bellinzona, Switzerland, [9]Institute of Oncology Research, Università Della Svizzera Italiana, Bellinzona, Switzerland, [10]Department of Rheumatology and Clinical Immunology, Hannover Medical University, Hannover, Germany, [11]Resolving Infection Susceptibility (RESIST) - Cluster of Excellence 2155 to Hannover Medical School, Satellite Center Freiburg, Freiburg, Germany, [12]German Center for Infection Research (DZFI), Satellite Center Freiburg, Freiburg, Germany

Background and Aims: The transcription factor NF-kB plays a pivotal role in the adaptive immune response. NFKB1 deficiency is the most common genetic etiology of common variable immunodeficiency (CVID). Patients commonly present with impaired terminal B cell differentiation, autoimmunity, and immune dysregulation. NF-kB signaling and target gene expression are expected to be dysregulated in NFKB1 deficient patients.

Methods: Here, we characterized epigenomic, transcriptomic, and proteomic changes in B cells from a cohort of clinically affected and unaffected NFKB1 mutation carriers versus wild-type individuals.

Results: Our analysis identifies transcriptional, chromatin accessibility, DNA methylation and proteomic defects in B cells on different levels. Based on this data, we observed a defective expression of negative regulators of NF-kB signaling in NFKB1 mutation carriers, which may be a key factor for the autoinflammatory phenotype of these patients. Additional analysis pinpointed dysregulation of key players of B cell differentiation and proliferation at different levels.

Conclusions: This study establishes a comprehensive multi-omics map of alterations in B cells in the NF-kB signaling pathway in the context of insufficiency, and provides a valuable resource for clinicians and researchers to further identify molecular pathogenesis and therapeutic opportunities in NFKB1 insufficiency.

Disclosure: No.

Keywords: NFKB1 insufficiency, Proteomics, B cells, RNA-seq, ATAC-seq, DNA methylation

PD118

ADA2 DEFICIENCY MANIFESTING AS SEVERE NEUTROPENIA, RECURRENT FEVER AND LYMPHOPROLIFERATION

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Diana Simão Raimundo[1], Ana Isabel Cordeiro[2], Marta Valente[2], Conceição Neves[2], João Farela Neves[2]
[1]Hospital do Divino Espírito Santo, Pediatrics Department, Ponta Delgada, Portugal, [2]Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central, Primary Immunodeficiencies Unit, Lisbon, Portugal

Background and Aims: Deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive disease associated with mutations in ADA2 gene (formerly CECR1) encoding the enzyme ADA2[1,2]. Although its monogenic etiology, it has highly variable clinical presentations[3].

Methods: A 15-year-old caucasian female, born to non-consanguineous parents, has been presenting monthly episodes of recurrent fever, oral aphthous ulcers, and lymphadenomegaly, lasting one week, since 8 years-old. There were no other symptoms or signs, namely abdominal pain, rash or arthralgia. Since the age of 12 years-old, she also presented recurrent episodes of skin furunculus, paronychia and periodontitis, leading to the diagnosis of severe neutropenia (250 cells/uL). Immunological phenotyping revealed normal T and B cell subsets, as well as normal immunoglobulin levels and vaccine responses. Double-negative alfabeta TCR T cells were not increased and there were no auto-antibodies nor chronic viral infections. Measurement of plasma ADA2 enzymatic activity was found to be nearly absent and a compound heterozygosity in the ADA2 gene (Y453C/R169Q) was identified. Her parents were healthy carriers. After DADA2 diagnosis, hematopoietic stem cell transplantation was declined by the family and infliximab has been started.

Results: With now more than 250 DADA2 patients described, it has been understood that they group in three major phenotypes: vasculopathy (the predominant phenotype), hematologic and hypogammaglobulinemia, but overlapping abnormalities occur [3,4]. Interestingly, Y453C or R169Q are among the most common variants reported [1,5].

Conclusions: This patient presented severe symptomatic neutropenia but also recurrent fever and lymphoproliferation, without vasculopathy, highlighting the highly variable phenotype associated with DADA2 [3,6–10].

Disclosure: No.

Keywords: DADA2, neutropenia, ADA2 DEFICIENCY, LYMPHOPROLIFERATION, Y453C, R169Q

PD119

IMPLICATIONS FOR THE DIAGNOSTIC APPROACH IN PEDIATRIC COMMON VARIABLE IMMUNODEFICIENCY:

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Waiswa Moses
UGANDA DEVELOPMENT AND HEALTH ASSOCIATES, Epidemiologic Surveilllance, IGANGA, Uganda

Background and Aims: Infections and infectious complications are hallmarks of common variable immunodeficiency (CVID) and the leading cause of morbidity and mortality in affected patients at any age. However, the pediatric CVID is no longer perceived as a primary immunodeficiency associated solely with infectious manifestations; autoimmune, allergic, and lymphoproliferative.

Methods: We sought to determine the role of immune dysregulation and frequency of non-infectious sequelae in children affected with CVID. We also aimed at providing an insight into the pathogenesis of non-infectious complications and at delineating the diagnostic approach to pediatric CVID with immune dysregulation.

Results: The most common inflammatory comorbidity was asthma, diagnosed in 21 (53.85%) patients. The second most frequent immune dysregulation group was autoimmune disorders, present in 18 (46.15%) of the children studied with a high rate of autoimmune thyroiditis in as many as 10 (25.64%) of the CVID-affected children. Lymphoproliferation was seen in 14 children (35.90%), and, among them, lymphadenopathy occurred in nine (23.08%) cases and granulomatous lymphocytic interstitial lung disease in seven (17.95%) cases.

Conclusions: The most prominent abnormalities in the B- and T-cell compartment contributing to complex immune deficiency and immune dysregulation phenotypes were seen in the autoimmunity group, showing significant reductions in the switched memory B cell, naive T helper cell, and regulatory T-cell subsets. Herein, we document the previously unreported high rate of immune dysregulation in pediatric CVID as a clinical and diagnostic challenge with the variability of defects in the humoral and cellular immune responses.

Disclosure: No.

Keywords: LYMPHOPROLIFERATION, autoimmunity;, Common variable immunodeficiency, Immune Dysregulation

PD120

PRIMARY IMMUNODEFICIENCY DISORDERS PRESENTING WITH AUTOIMMUNE MANIFESTATIONS IN THE ADULT INTERNAL MEDICINE WARD of A TERTIARY CARE CENTRE IN SOUTH INDIA- A CASE SERIES.

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Harikrishnan Gangadharan[1], Vipin Paul[2], Rahul Peter[2], Anusree Seetha[3], Manisha Madkaikar[4], Josemon George[2]
[1]GOVERNMENT MEDICAL COLLEGE KOTTAYAM, General Medicine, Kottayam, India, [2]GOVERNMENT MEDICAL COLLEGE KOTTAYAM, General Medicine, KOTTAYAM, India, [3]GOVERNMENT MEDICAL COLLEGE KOTTAYAM, Pulmonary Medicine, Kottayam, India, [4]Indian Council of Medical Research (ICMR)- National Institute of Immunohaematology (NIIH), Department of Pediatric Immunology And Leukocyte Biology, MUMBAI, India

Background and Aims: Autoimmunity may be the sole manifestation of primary immunodeficiency disorders in the adult internal medicine ward. We describe a series of 4 patients who were evaluated for various autoimmune features in adult internal medicine ward and were subsequently diagnosed as PID.

Methods: This is a one year hospital medical records based case series study done in patients admitted with autoimmune manifestations and subsequently diagnosed to have PID in the adult internal medicine ward of a tertiary care hospital in South India.

Results: Case 1: 35year old male was admitted with megaloblastic anemia, chronic diarrhea and genu valgum deformity since age of 12 years. Investigations revealed pan hypogammaglobulinemia, low class switched memory B cells, poor vaccine response, autoimmune enteropathy and gastric dysplasia confirming a diagnosis of CVID. Case 2: 18year old female was admitted with DCT + autoimmune hemolytic anemia and leukopenia. Workup showed pan hypogammaglobulinemia with poor vaccine response confirming a diagnosis of CVID. Case 3: 18year- old patient of ataxia telangiectasia was admitted with hyperglycemia. On evaluation, anti- islet cell antibody + type 1 diabetes and selective IgA deficiency was diagnosed. Case 4 : 30year old female with fever, ILD, lymphadenopathy and splenomegaly for 1 year with low IgG, normal Ig M and IgA. Clinical exome sequencing showed a novel variant in LRBA gene leading to diagnosis of LRBA defect-mongeneic CVID.

Conclusions: Autoimmune features may constitute the predominant manifestation of PID patients attending the adult internal medicine ward and a high index of suspicion is needed to make a timely diagnosis.

Disclosure: No.

Keywords: Autoimmunity, PID, CVID

PD121

SEVERE AUTOIMMUNITY TRAITS IN A COLOMBIAN BOY: A NOVEL NRAS MUTATION C.182A>G (P.Q61R) CAUSING RAS-ASSOCIATED AUTOIMMUNE LEUKOPROLIFERATIVE DISEASE (RALD)

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Fabio Vargas Cely[1], Andrés Zea Vera[2]
[1]Universidad del Valle, Immunology And Microbiology, Cali, Colombia, [2]National institute of health, Immunology, Bethesda, United States of America

Background and Aims: Describe a new mutation causing RALD syndrome

Methods: Case report

Results: 1-year-old boy with 10 days of fever, gastrointestinal symptoms associated to multiple lymph-node enlargments, hepato-splenomegaly and poor feeding. Initial evaluation found a malnourished boy with regular general state. First laboratories displayed leucocytosis as mainstay with both marked lymphocytosis (19,500/mm3) and monocytosis (4,300/mm3) but with moderate neutropenia and mild anemia. Tumoral lysis syndrome, hematologic malignancy and chronic infections were negative, but molecular studies in stool revealed concomitant infection by Norovirus, Campilobacter jejuni and Giardia intestinalis, treated accordingly. The finding of abnormal hematologic counts, failure to thrive and severe infection with 3 microorganisms rise the aware for a primary immunodeficiency. Blood immunophenotype revealed increased TCRαβ+CD3+ cells 9,200/mm3 and a remarkably high proportion of double negative T cells (TCRαβ+CD3+CD4-CD8-) 1.8% of total lymphocytes and 3.5% of total CD3+ lymphocytes (normal < 1.5% of total lymphocytes and <2.5% of total CD3+ lymphocytes) . Anemia evaluation evidenced features of autoimmune hemolytic anemia. Serum immunoglobulin levels displayed hypergammaglobulinemia in all immunoglobulins along with impressively high antinuclear antibodies 1:2,560 titers, severe hypocomplementemia (C3: 69 mg/dl and C4: 8 mg/dl), CH50 (<10 U/ml). With those findings where mononuclear cell proliferation with high proportion of double negative T cells, autoimmune serological traits, immune cytopenias and immunodeficiency were together raised the alarm for an autoimmune leukoproliferative disorder. Thus, a whole exome sequencing was done, highlighting a new c.182A>G (p.Q61R) pathogenic NRAS heterozygous mutation in peripheral blood, consistent with RALD syndrome

Conclusions: RALD syndrome must be considered among diagnosis of children with autoimmunity

Disclosure: No.

Keywords: children autoimmunity, NRAS, Inborn errors of immunity

PD122

MANAGEMENT of AUTOIMMUNE ENTEROPATHY AND ENDOCRINOPATHY – SUSCEPTIBILITY TO CHRONIC INFECTIONS SYNDROME

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Ignė Kairienė[1], Jelena Rascon[1], Birute Burnyte[2]
[1]Vilnius University Hospital Santaros Klinikos, Center For Pediatric Oncology And Hematology, Vilnius, Lithuania, [2]Vilnius University, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius, Lithuania

Background and Aims: The STAT1-related Autoimmune Enteropathy and Endocrinopathy-Susceptibility to Chronic Infections Syndrome (AESCIS) is characterized by enteropathy, the impairment of the endocrine and immune system. Due to the extreme rarity (<1/1000000) and non-specific symptoms, diagnostics is challenging. Optimal therapeutic management is unclear

Methods: We describe the clinical course, genetic findings, and treatment approach of a patient with AESCIS

Results: A 3-year-old girl presented with subfebrile fever, pallor, sluggishness, and maculopapular rash. Physical examination revealed mild facial dysmorphic features, fragile hair, poor growth, dystrophic nails, aphthous mucosa, and a distended stomach. No lymphadenopathy, hepatosplenomegaly was apparent. From the 2nd month of her life, she suffered from recurrent skin rash and diarrhea. Laboratory evaluation revealed moderate microcytic normochromic anemia, thrombocytopenia, elevated ESR, IL-6, sCD25, positive ANA, high TTH, low iPTH. Ultrasound examination showed hepatosplenomegaly, ascites, intestinal infiltration. Enterobacter cloacae, ESBL was yielded in the feces. An immune deficiency with autoimmune dysregulation was suspected. Cellular immunity, immune globulin levels, response to vaccines were normal. Inborn errors of metabolism, celiac disease were excluded. Ceftriaxone, amikacin, fluconazole, and L-Tyroxin were initiated. The clinical improvement was achieved within three weeks Exome sequencing revealed previously reported heterozygous pathogenic variant c.1154C>T (p.(Thr385Met) in the STAT1. Currently, the patient is followed up by a multidisciplinary team due to recurrent rash, inconsistent defecation, iron deficiency anemia, autoimmune hepatitis, thyroiditis.

Conclusions: Current treatment options focus on symptomatic relief. There are several reports on the clinical effect of ruxolitinib. Although ruxolitinib is widely used in various inflammatory conditions, it can cause a wide spectrum of side effects

Disclosure: No.

Keywords: Enteropathy, chronic infections, immune deficiency, Autoimmunity

PD123

IGG SUBCLASS DEFICIENCY DUE TO NOVEL HETEROZYGOUS NFKB1 MUTATION REVEALED BY ADULT ONSET of PYODERMA GANGRENOSUM IN TWO SIBLINGS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Najla Mekki[1], Nadia Ghariani-Fetoui[2], Lobna Boussofara[2], Afef Rais[1], Mohamed Denguezli[2], Imen Ben-Mustapha[1], Mohamed-Ridha Barbouche[1]
[1]Institut Pasteur de Tunis, Laboratory of Transmission, Control And Immunobiology of Infections (lr11ipt02), Tunis, Tunisia, [2]Farhat Hached Hospital of Sousse, Tunisia., Dermatology, SOUSSE, Tunisia

Background and Aims: Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis characterized by a rapidly enlarging and necrotic skin ulcers mainly associated with systemic autoimmune and inflammatory disorders. Inborn errors of immunity (IEI) i.e agammaglobulinemia and chronic granulomatous disease and common variable immunodeficiency (CVID) can also be rarely associated with PG demonstrating that immune dysregulation might play an important role in the pathophysiology of this disease.

Methods: Herein, we report two sisters born to non consanguineous parents who present at 49 and 43 years old with severe and giant PG occurring after intramuscular injection and C-section, respectively (P1 and P2).

Results: Immunophenotypic studies of lymphocytes populations, T-cell proliferations, immunoglobulin levels (IgA, IgG and IgM) and NBT test were normal. IgG2 level was decreased in both patients and IgG4 was reduced in P2. Because of the severe clinical phenotype and the absence of HIV, inflammatory or autoimmune disease, IEI was suspected and NGS screening was performed. Interestingly, we confirmed the presence of a novel heterozygous deletion in NFKB1 gene (c879_880del) leading to a premature stop codon (p.Val294Leufs*14). This variation was not reported in 1000G or ExAC databases and was predicted to be pathogen.

Conclusions: Loss-of-function mutations in NFKB1 gene are known to be the most frequent monogenic autosomal dominant cause in CVID. Interistingly, in the present study, both patients had no history of infections, IgG, IgA and IgM levels were normal but IgG subclasses were reduced. Further investigations are needed to explain the underlying mechanism of PG and IgG subclass deficiency in NFKB1 deficient patients.

Disclosure: No.

Keyword: Pyoderma gangrenosum, NGS, NFKB1, IgG subclass deficiency

PD124

DOUBLE NEGATIVE B CELLS EXPANSION IN A PEDIATRIC PATIENT WITH HYPOGAMMAGLOBULINEMIA AND HIGH FAMILIAL PREDISPOSITION TO AUTOIMMUNITY: IS THERE A LINK?

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Martina Colli[1], Gemma Giordano[1], Laura Bruni[1], Elisabetta Magrini[2], Paola Selva[2], Francesca Conti[3], Andrea Pession[3]
[1]Specialty School of Paediatrics - Alma Mater Studiorum, Università di Bologna, Bologna, Italy, Pediatric, Bologna, Italy, [2]Laboratory of immuno-haematology - Laboratorio Unico Metropolitano, Azienda USL, Bologna, Italy, Biology, Bologna, Italy, [3]Pediatric Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, Pediatric, Bologna, Italy

Background and Aims: Primary antibody deficiencies generally underly a B-cells maturation, survival and differentiation disorder. Double negative (DN) B lymphocytes ($CD27^-$ IgD^- IgM^+) role hasn't been clearly defined yet; their expansion has been observed in active neuro-inflammatory diseases, systemic autoimmunity, in elderly and after the influenza and tick-borne encephalitis virus vaccination.

Methods: We describe the case of a five-year-old female, presenting to our department due to the occasional finding of hypogammaglobulinemia. She had no history of recurrent/severe infections and clinical red flags for autoimmune diseases or immune dysregulation phenotypes. Her family's medical history had a striking recurrence of autoimmune diseases (Thyroiditis, Myasthenia Gravis, Guillain Barré, Rheumatoid arthritis, Sclerodermia, Coeliac disease and Psoriasis).

Results: Immunological workup showed low IgG and IgM, normal IgA, a pathological expansion of double negative B subset and a mild reduction of B naïve and T regulatory subsets. The ANA titre was 1:640, and anti-Mi-2 autoantibody were detected. The pathogen-specific antibodies response was adequate, except for hepatitis B virus.

Conclusions: Double negative B cells expansion has never been described as feature of inborn humoral defect however a link with autoimmune diseases was reported in literature. We described a pediatric asymptomatic patient with hypogammaglobulinemia, high ANA and anti-Mi-2 titles and abnormal expansion of DN B. These findings associated with the family background, may reflect a warning sign of primary B cell dysregulation. Functional B lymphocytes assessment, extensive characterization of family's immune system and eventually molecular analysis for primary antibody deficiencies will be performed to unveil the genetic predisposition to an increased autoimmunity risk.

Disclosure: No.

Keywords: Double negative B cells, Anti-Mi-2 antibodies, Autoimmunity, hypogammaglobulinemia

PD125

TREND of DNTS IN ALPS AND ALPS-LIKE DISORDER.

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Priyanka Setia, Neha Jodhwat, Umair Ahmed Bargir, Maya Gupta, Aparna Dalvi, Shweta Shinde, Reetika Malik Yadav, Manisha Madkaikar
Indian Council of Medical Research (ICMR)- National Institute of Immunohaematology (NIIH), Department of Pediatric Immunology And Leukocyte Biology, MUMBAI, India

Background and Aims: Autoimmune lymphoproliferative syndrome (ALPS) is a rare genetic disorder characterized by defective extrinsic apoptotic mechanism.Apoptotic defects lead to lymphoproliferative disease with clinical manifestations including splenomegaly, lymphadenopathy, hypergammaglobulinemia, autoimmune cytopenias and elevated Double negative T cells (DNTs). Improvement in genetic technologies has led to the description of several ALPS-like autoimmune and lymphoproliferative disorders, and are labelled as ALPS-like disorders.We aimed to study the expression pattern of DNTs across both the categories.

Methods: Flow cytometry analysis of DNTs using markers (CD3, CD4,CD8, TCRab, B220,HLA-DR, CD45RA, CD27,CD28,CD38 CD57 and KLRG1) in patients with mutations in FAS(1), FASLG(1),FADD(2),CASP8(1),CASP10(1), LRBA(15), CTLA4(3), STAT3-GOF(2), PIK3CD(5), MAGT1(1),TACI(1), STX11(1), NRAS(1) along with healthy controls (5).

Results: The range of DNTs varied across the categories, it was 0.4-2% in healthy controls, 1-12% in ALPS-like disorders and 0.8-35% in the ALPS category. The immunophenotype of DNTs in healthy control was (CD45RA-CD38-HLA-DR-CD45RA+/-KLRG1+ B220-). DNTs of ALPS(FAS, FASLG and FADD) patients showed co-expression of B220, CD45RA/HLA-DR/CD27 /CD38 and CD57, whereas DNTs of CTLA4, STAT3-GOF and TACI patients showed expansion of CD38+ and CD45RA+ (>30%) (Normal :<12%). LRBA-DNTs co-expressed CD45RA and KLRG1. Interestingly, PIK3CD-DNTs, there was an expansion of CD57+ and KLRG1+, but the % of CD27+ CD45RA+ population on DNTs was decreased (20%) (Normal: 70%). STX11-DNTs showed expansion of the CD45RA- HLADR+ population. The DNT phenotype in CASP8, CASP10, MAGT1, and NRAS was similar to healthy controls.

Conclusions: B220 was better predictor marker for diagnosis of FAS, FASLG and FADD. DNTs expression in ALPS-like category was heterogeneous which could possibly explore the role and functions in different genetic deficiencies.

Disclosure: No.

Keywords: ALPS-Like, ALPS, DNTs, Immune Dysregulation

PD126

GRISCELLI SYNDROME: RARE NEONATAL SYNDROME of HEMOPHAGOCYTOSIS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Kahina Abba[1], Nacera Hamadouche[2], Lamia Amirat[2], Mohamed Chouli[1], Nadia Ayad[1], Saliha Guers[2], Nawel Mansouri[1], Lamia Laboun[2], Mohamed.Samir Ladj[3]
[1]pediatric Djillali Belkhenchir department, Department of Pediatric, Algiers, Algeria, [2]pediatric Djillali Belkhenchir department, Pediatrics, Algiers, Algeria, [3]university of algiers - faculty of medecine, Department of Pediatric Djillali Belkhenchir Hospital Algiers Algeria, ALGER, Algeria

Background and Aims: Griscelli syndrome (GS) is a rare autosomal recessive disorder caused by mutation in the MYO5A (GS1, Elejalde), RAB27A (GS2) or MLPH (GS3) genes. Typical features of all three subtypes of this disease include pigmentary dilution of the hair and skin. Whereas the GS2 patients have severe immunological deficiencies that lead to recurrent infections and hemophagocytic syndrome.

Methods: We report the case of Griscelli syndrome in a 6-day-old female newborn

Results: A 6-day-old female newborn, born of a consanguineous marriage, presents a neonatal hyperbilirubinemia , splenomegaly type 3 with hepatomegaly and a partial albinism. Complete blood cell count revealed pancytopenia, triglycerides 2.18 mg/L , ferritenemia 4777 ng/ ml , and a fibrinogen was 1.67 g/ L. A high level of CD25 2400 U/ ml without deficit in humoral immunity. Bone marrow aspirate chowed a prominent histiocytic infiltrate with extensive hemophagocytosis The peripheral blood smear shows no giant cytoplasmic granules in leukocytes. Microscopic examination of hair shafts reveals uneven clusters of aggregated melanin pigment,accumulated mainly in the medullary area of the shaft. The diagnosis of GS was evoked on; consanguineous family, very light silvery-gray color of the hair and eyebrows, Light microscopy examination of the hair showed large, irregular clumps of pigments characteristic of GS. The molecular biology has not been carried out . The first-line therapy was based in HLH protocol, with a good evolution waiting for bone marrow transplantation.

Conclusions: Griscelli syndrome is a rare genetic disease, with a pejorative prognosis and whose diagnosis must be early to allow better management.

Disclosure: No.

PD127

STAT1 GAIN-OF-FUNCTION MUTATION IDENTIFIED IN A PATIENT PRESENTING WITH CHRONIC MUCOCUTANEOUS CANDIDIASIS ASSOCIATED TO SHORT STATURE, PUBERTY DELAY, AND RETAINED PRIMARY TEETH

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Meriem Ben Ali[1], Roukaya Yaakoubi[1], Najla Mekki[1], Amel Ben Chehida[2], Koon Wing Chan[3], Daniel Leung[3], Yu Lung Lau[3], Imen Ben-Mustapha[1], Mohamed-Ridha Barbouche[1]
[1]Institut Pasteur de Tunis, Immunology, Tunis-belvédère, Tunisia, [2]La Rabta Hospital, Department of Pediatrics, Tunis, Tunisia, [3]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Department of Pediatrics And Adolescent Medicine, Hong Kong, China

Background and Aims: Heterozygous gain-of-function (GOF) mutations in signal transducer and activator of transcription 1 (STAT1) have been identified in patients with autosomal dominant (AD) chronic mucocutaneous candidiasis (CMC) since 2011.

Methods: We report herein a 17-year-old girl with a history of recurrent lung infection leading to bronchiectasis. She has also developed vaginal yeast infection, chronic onychomycosis and oral candidiasis. Her physical examination revealed short stature, puberty delay and retained primary teeth. Laboratory findings showed elevated IgE and eosinophilia. She had a score of 53 points according to the NIH clinical Hyper IgE Syndrome (HIES) scoring system. Therefore the diagnosis of HIES was established at that time.

Results: STAT3 phosphorylation was slightly elevated, and the percentage of TH17 cells was reduced as assessed by flow cytometry. No STAT3 mutations were found in coding exons by targeted Sanger sequencing. A mutation in the DNA-binding domain of STAT1 was detected (c.1053G>T, p. L351F) by whole exome sequencing. This variation was previously identified and validated as pathogenic in patients with AD-CMC.

Conclusions: There are multiple differential diagnoses for STAT3-HIES due to overlapping clinical and immunologic features with other disorders. STAT1 GOF underlies a variety of infectious and autoimmune features. Interestingly, there were no signs of hypothyroidism in this patient until age 17 years. In conclusion, we report a STAT1-GOF mutation in a patient presenting with a HIES clinical phenotype. These features add to the complexity of the phenotype observed in STAT1-GOF disorder and make the diagnosis more challenging.

Disclosure: No.

Keywords: STAT1 GOF, Hyper IgE Syndrome, Differential diagnosis

PD128

EFFICACY AND SAFETY of RAPAMYCIN IN CHILDREN WITH APDS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Carolinne Troli, Raquel Letícia Alves, Lara Silva, Katherine Silvestre, Amanda Sobrinho, Lais Oliveira, Luiza Schimid, Mariana Gouveia-Pereira, Carolina Sanchez Aranda, Dirceu Solé
Federal University of São Paulo, Division of Allergy, Clinical Immunology And Rheumatology - Department of Pediatrics, São Paulo, Brazil

Background and Aims: Mutations in the phosphoinositide 3-kinase (PI3K) genes PIK3CD and PIK3R1 cause a combined immunodeficiency syndrome, referred to as activated PI3Kδ syndrome (APDS). Here, we aim to evaluate the use of rapamycin in patients with APDS.

Methods: Prospective evaluation of five patients using rapamycin in 12 months.

Results: Five patients with APDS aged between 5 and 37 years were followed. Four of the patients are children, two with enteropathy and one with erythema nodosum. The adult has protein loss in the feces and nephropathy. Four with p.E1021K and one with p.E1010A. The proposed dose was 1mg/mm^2/day for children and 4mg daily for adults. All were already using immunoglobulin. After 12 months of rapamycin, the children completely improved from the concomitant conditions. The adult patient still has persistent protein loss, but with weight gain and improved quality of life. There were no rapamycin-related adverse events.

Conclusions: The use of mTOR inhibitors may be an additional therapy for the management of APDS. The use of target traps is assertive and can make a valuable contribution to the control of symptoms. In our experience, the use of rapamycin was safe and effective in our patients, including in children.

Disclosure: No.

Keywords: APDS, phosphoinositide 3-kinase, combined immunodeficiency syndrome, activated PI3Kδ syndrome, mTOR, rapamycin

PD129

SUCCESSFUL TREATMENT WITH MYCOPHENOLATE MOPHETILE of RELAPSING/REFRACTORY IMMUNE THROMBOCYTOPENIA IN FOUR PATIENTS WITH DEL22Q11.2 SYNDROME

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Lucia Pacillo[1,2], Carmela Giancotta[3], Donato Amodio[3], Silvia Di Cesare[1,2], Cristina Cifaldi[2], Beatrice Rivalta[1,2], Emma Concetta Manno[3], Veronica Santilli[3], Giuseppe Palumbo[1,4], Paolo Rossi[1,5], Andrea Finocchi[1,6], Paolo Palma[1,3], Caterina Cancrini[1,2]
[1]Tor Vergata University, Department of Systems Medicine, Rome, Italy, [2]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Research Unit of Primary Immunodeficiencies, Rome, Italy, [3]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Unit of Clinical Immunology And Vaccinology,, Rome, Italy, [4]IRCCS Bambino Gesù Children Hospital, Department of Hematology,, Rome, Italy, [5]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics, Rome, Italy, [6]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Unit of Immune And Infectious Diseases,unit of Clinical Immunology And Vaccinology,, Rome, Italy

Background and Aims: Immune dysregulation could be an important feature in patients with del22q11.2 syndrome, among which immune-mediated cytopenia are the most common, often relapsing and refractory to standard therapies.[1] Defects in T and B cell subsets, as reduction of naïve CD4+T-cells and memory B-cells, increased frequency of circulating T follicular helper (cTfh) cells and reduced Treg cells count have been described in these patients.[2] We aim to find the most suitable targeted therapy to maintain remission of cytopenia.

Methods: Four patients (12-17 years old, male:female 2:2) with del22q11.2 syndrome and relapsing and/or refractory cITP, were started on low dosage Mycophenolate Mophetile(MMF) therapy (medium 350 mg/m^2/die). Complete immunological phenotype (T and Bcells naïve and memory, cTfh, Treg) was analyzed at baseline and 3-, 6- and 9-months post-therapy by multiparametric flow cytometry.

Results: Three patients showed normalization of platelets count. One patient showed poor response due to low compliance. None of them experienced relapses. Two patients manifested also autoimmune neutropenia, that resolved. All patients presented, at baseline, reduced naïve CD4+T-cells and memory B-cells, increased cTfh-cells frequency and reduced Treg-cells count. At 9mo FU we detected a significant reduction (medium 14,6%) of cTfh frequencies (4/4). of note, we detect a reduction of Treg in 2/4 patients.

Conclusions: Immunological alterations could represent prognostic biomarkers of autoimmune diseases and could guide clinicians in choosing targeted therapy. MMF resulted successful in treating cITP in these patients showing good clinical and immunological response without any side effects. A longer follow-up is needed to confirm these data. [1]J Pediatr.2014 Jun;164(6):1475-80 [2]JACI Pract.2019 Sep-Oct;7(7):2369-2376

Disclosure: No.

Keywords: Inborn errors of immunity, Autoimmune cytopenia, del22syndrome, Digeorge Syndrome, mycophenolate mophetile, Immune Dysregulation

PD130

SECONDARY HEMOPHAGOCYTIC SYNDROME DUE TO HODGKIN LYMPHOMA IN A PATIENT WITH CVID

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Patricia O Farrill Romanillos[1], Diana Herrera Sánchez[1], Jonny Ramos Blas[2], Luis Guízar García[3]
[1]Mexican Institute of Social Security, Hospital Especialidades, XXI Medical Center, Allergy And Clinical Immunology, Mexico, Mexico, [2]Mexican Institute of Social Security, Hospital de Especialidades, XXI Medical Center, Hematology, Mexico, Mexico, [3]Mexican Institute of Social Security, Hospital de Especialidades, XXI Medical Center, Internal Medicine, Mexico, Mexico

Background and Aims: Introduction :adquired hemophagocytic syndrome, is the main cause in adults of hemophagocytic lymphohistiocitosis. The main triggers are various infections ducha as viruses, autoimmune disease and malignant tumors. The most Common lymphoma and NK/T cells lymphoma, the latter particulary related to EBV. Objetive to present a case of hemophagocytic syndrome due to Hodgkin Limphoma in a patient with IRF2 defect and CVID.

Methods: we presented a case of CVID and secondary hemophagocytic syndrome.

Results: male of 19 years old, recived a related kidney transplant , for renal fibrosis. At 17 years he presented with high fever, asthenia, hyporexia, diarrhea so he was admited to urgent care.
The diagnosis of EBV infection was made, and laso hemofagocytic syndrome, with splenomegaly, cytopenia with anemia and los platelets, and high levels of ferritin, triglycerides , Liver enzymes and hemophagocytes. He recived treatment with etoposide and ciclosporine with complete remisión.
Exome sequencing was performed and mutation in IRF2 was concluded associated with CVID.
2 years later he presents aguín with high fever, asthenia, hyporexia and diarrhea. He hospitalized and diagnosed Hodgkin Lymphoma of mixes cellularity , asocciated with reinfection by EBV.

Conclusions: Conclusions: lymphoma is a complication presented in patients with CVID. Hemophagocytic syndrome in this group of patients is associated with the malignancy, the patient had also another risk factor for EBV infection, causen by secondary immunosupperssion due to the kidney transplant.

Disclosure: No.

Keyword: Lymphoma, Common variable immunodeficiency, hemophagocytic syndrome, EBV

PD131

NOVEL IL12RB1 VARIANT ASSOCIATED WITH SEVERE TUBERCULOSIS IN A SOUTH AFRICAN FAMILY

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Ansia Van Coller[1], Brigitte Glanzmann[2], Marlo Möller[2], Craig Kinnear[2], Deepthi Abraham[3], Monika Esser[3], Richard Glashoff[1]
[1]Stellenbosch University, Pathology, Cape Town, South Africa, [2]Stellenbosch University, Biomedical Sciences, Cape Town, South Africa, [3]Stellenbosch University, Paediatric Rheumatology, Cape Town, South Africa

Background and Aims: While Mendelian Susceptibility to Mycobacterial Disease (MSMD) is typically associated with weakly pathogenic mycobacteria, it has been reported that these individuals are also prone to develop severe, persistent, unusual, and/or recurrent (SPUR) TB, particularly in TB endemic countries. The aim of this study was to perform genetic sequencing and assessment of immunological phenotypes (relating to the IL-12-IFN-γ cytokine pathways) in a South African family with SPUR TB.

Methods: A 2-year-old South African girl presented with a history of recurrent TB lymphadenitis, pulmonary and spinal TB. Upon further investigation it was found that her siblings, a 7-year-old sister and 9-year-old brother, also had a history of SPUR TB and their father had previously had pulmonary TB. DNA and PBMCs were isolated from the family members and 10 healthy controls. Whole genome sequencing (WGS) was performed and in-house flow cytometry and Luminex-based functional assays were used to assess IL-12 receptor expression and signalling via pSTAT4, and downstream IL-12-induced IFN-γ production.

Results: An IL12RB1 variant (c.911_912del) was identified in all family members - homozygous in the index patient and sister, and heterozygous in the brother and father. Decreased IL-12Rβ1 expression, pSTAT4 signalling and IL-12-induced IFN-γ production was observed in all family members compared to controls, with the defect being more pronounced in the siblings that are homozygous for the IL12RB1 variant.

Conclusions: These findings are supportive of a functional impairment of the IL-12 receptor and downstream immunological pathway and may contribute to susceptibility to SPUR TB in this family.

Disclosure: No.

Keywords: MSMD, TB, IL-12, IL12RB1

PD132

AUTOIMMUNE LOSS of ENTERO-ENDOCRINE CELLS IS A HALLMARK APECED MANIFESTATION THAT RESULTS IN SEVERE MALABSORPTION BUT CAN RECOVER WITH IMMUNE SUPPRESSANTS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Levi Hoste[1,2], Leslie Naesens[2], Sara Van Aken[3], Bruno Lapauw[4], Guy T'Sjoen[4], Charlotte Verroken[4], Nicolette Moes[5], Ruth De Bruyne[5], Tessa Kerre[6], Filomeen Haerynck[1,2]
[1]Ghent University Hospital, Department of Internal Medicine And Pediatrics, Division of Pediatric Pulmonology, Infectious Diseases And Inborn Errors of Immunity, Ghent, Belgium, [2]Ghent University, Primary Immune Deficiency Research Laboratory, Department of Internal Diseases And Pediatrics, Centre For Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis And Research Centre, Gent, Belgium, [3]Ghent University Hospital, Department of Pediatric Endocrinology, Gent, Belgium, [4]Ghent University Hospital, Department of Endocrinology, Gent, Belgium, [5]Ghent University Hospital, Department of Pediatric Gastroenterology And Hepatology, Gent, Belgium, [6]Ghent University Hospital, Department of Hematology, Ghent, Belgium

Background and Aims: Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome (APECED) is a rare immune disorder, caused by autoimmune regulator (AIRE) mutations, leading to defective thymic elimination of autoreactive T lymphocytes. APECED is characterized by variable penetrance of autoimmune diseases including hypoparathyroidism and Addison's disease, and vulnerability for chronic mucocutaneous candidiasis (CMC). Less frequently, APECED is complicated by gastrointestinal manifestations. Chronic diarrhea related to hypoparathyroidism, autoimmune hepatitis, or intestinal fungal infection are most frequently encountered.

Methods: We describe two APECED patients with disease-specific autoimmune enteropathy.

Results: We report on two unrelated APECED patients, a 18yo male (P1) and 23yo female (P2), both harboring a previously described homozygous c967_979 AIRE deletion and presenting hypoparathyroidism and CMC. Normocalcemia was difficult to attain in both patients despite high dose supplementation with calcium and alphacalcidol. In adolescence, both patients presented prolonged, severe enteropathy leading to malabsorption with extensive weight loss and episodes of life-threatening hypocalcemia. Fungal and non-fungal infections, pancreatic insufficieny and celiac disease were excluded. In both patients, routine pathological investigations from gastrointestinal endoscopy showed nonspecific findings. Specific investigations revealed complete absence of serotonin-producing entero-endocrine cells (EECs) in stomach and duodenum. Autoimmune-associated EEC destruction is reported in the presence of anti-tryptophan hydroxylase (TPH) antibodies, which seems APECED-specific. High-dose immunosuppressive therapy (methylprednisolone 64mg/day) resulted in recuperation of malabsorption and better calcium absorption in both patients. Additionally, we documented re-expression of EECs by endoscopy in P2.

Conclusions: APECED can present with severe malabsorption associated with autoimmune-driven destruction of EECs. Only specific pathological investigations might reveal EEC absence. Immunosuppressive treatment can be beneficial.

Disclosure: No.

Keywords: APECED, Enteropathy, auto-antibodies

PD133

AUTOIMMUNE VERNAL KERATOCONJUNCTIVITIS (VKC) MANIFESTING AS A FIRST PRESENTATION IN TWO SIBLINGS WITH LPS-RESPONSIVE BEIGE -LIKE ANCHOR PROTEIN (LRBA) DEFICIENCY

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Khwater Ahmed, Tariq Al Farsi, Nashat Al Sukaiti
The Royal Hospital, Pediatric Allergy And Clinical Immunology, Muscat, Oman

Background and Aims: LPS-responsive beige-like anchor protein (LRBA) deficiency is a severe inborn error of immunity characterized by early childhood autoimmunity, lymphoproliferation and immunodeficiency. There are no detailed reports highlighting the autoimmune ophthalmic involvement in patients with LRBA deficiency. This report aims to describe autoimmune vernal keratoconjunctivitis as an early manifestation of immune dysregulation in patients with LRBA deficiency.

Methods: Here we present a case report of two male siblings aged 7 and 9-year-old who suffered from a severe bilateral eye itchiness, redness and photophobia for the last 5 years. Eye examination showed conjunctival injection, limbal thickening and giant papillae. A clinical ophthalmologic diagnosis of severe allergic form of vernal keratoconjunctivitis has been made. However, no aeroallergen sensitization was identified by skin prick test or immunoCAP/RAST assay. Despite receiving recurrent courses of topical olopatadine, sodium cromoglycate, prednisolone and ciclosporin, no significant improvement was noted.

Results: A novel pathogenic variant as chromosome 4 deletion encompassing exon 1-17 loss of the LRBA gene was identified. Given the severity of ocular disease and to avoid further complications including blindness, a targeted therapy with abatacept at a 4 weekly regime was initiated. Six months later, a significant improvement in eye symptoms was observed. A repeat eye examination revealed minimal conjunctival injection, resolution of limbal thickening and reduction in the sizes of papillae.

Conclusions: This case report highlights the importance of considering monogenic inborn error of immunity with immune dysregulation in patients with early onset autoimmune vernal keratoconjunctivitis. The use of targeted therapy may significantly improve the outcome in such patients.

Disclosure: No.

Keywords: Immune Dysregulation, Vernal Keratoconjunctivitis, LRBA, Abatacept, Children

PD134

LOSS of FUNCTION VARIANT IN IFIH1 PRESENTING WITH INFLAMMATORY BOWEL DISEASE AND DIABETES MELLITUS.

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Fatima Albreiki[1], Marguerite Lawler[2], Billy Bourke[3], Cathy Mcmahon[4], Timothy Ronan Leahy[2,5]
[1]CHI @ Crumlin, Immunology, Dublin, Ireland, [2]Children's Health Ireland at Crumlin, Department of Paediatric Immunology And Infectious Diseases, Dublin, Ireland, [3]CHI @ Crumlin, Gastroenterology, Dublin, Ireland, [4]CHI @ Crumlin, Paediatric Intensive Care, Dublin, Ireland, [5]University of Dublin, Trinity College, Pediatrics, Dublin, Ireland

Background and Aims: Heterozygous loss of function mutations in IFIH1 have recently been associated with very early onset inflammatory bowel disease. We report an additional two cases of IBD within a family (P1 son, P2 father), both patients being heterozygous for a loss of function mutation in IFIH1.

Methods: A retrospective review of the patients' medical records, radiological and laboratory results was undertaken, along with evaluation of the immunological phenotype by functional testing. The molecular basis of disease was established by whole exome sequencing undertaken in a clinical genetics laboratory

Results: P1 developed Type 1 Diabetes Mellitus at the age of 7 years, and treatment recalcitrant ulcerative colitis at the age of 12 years, for which he ultimately needed colectomy. P1 developed a sepsis-like episode post-colectomy that may be related to discontinuation of tofacitinib before the procedure. P2 developed inflammatory bowel disease in the second decade of his life, and remains well on azathioprine monotherapy. P1 demonstrated normal serum immunoglobulins and lymphocyte immunophenotyping. Both P1 and P2 were heterozygous for an IFIH1 variant within an essential splice site, predicted to result in a frameshift, and loss of protein.

Conclusions: Loss of function variants in IFIH1, leading to partial MDA5 deficiency, predispose patients to autoimmunity, albeit with incomplete penetrance. This diagnosis should be considered in cases of familial IBD and/or multisystem autoimmunity.

Disclosure: No.

Keywords: Inflammatory bowel disease, MDA-5, viral sensing, Diabetes mellitus

PD135

A DIAGNOSTIC ODYSSEY IN A FEMALE ADOLESCENT WITH RECURRENT SINOPULMONARY INFECTIONS AND POLYARTHRITIS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Taru Goyal[1], Sathish Loganathan[2], Rakesh Kumar Pilania[3], Ankur Jindal[4], Vignesh Pandiarajan[4], Amit Rawat[4], Surjit Singh[4]
[1]Post Graduate Institute of Medical Education & Research, Allergy & Immunology Unit, Department of Pediatrics, Chandigarh, India, [2]Post Graduate Institute of Medical Education and Research, Chandigarh, Pediatrics, Chandigarh, India, [3]Post Graduate Institute of Medical Education and Research, Pediatrics, Chandigarh, India, [4]Postgraduate Institute of Medical Education and Research, Pediatrics, Chandigarh, India

Background and Aims: Common variable immunodeficiency (CVID) is one of the most prevalent heterogeneous primary immunodeficiency syndromes in children and adults.

Methods: A-18-year-old female second born to non-consanguineously married parents presented with a history of swelling in small joints of both hands and skin rash on the face for the past four months alongwith a significant history of recurrent sinopulmonary infections from five years of age. Empirically treated for tuberculosis on 2 occasions. Chest X-ray showed bronchiectasis in the right middle lobe. Bronchoalveolar lavage once revealed mixed growth of Streptococcus pneumoniae and alpha-hemolytic streptococci while found negative for tuberculosis.

Results: Her symptoms frequency reduced after fourteen years of age.Hemoglobin- (13.5gm/dl,N:12.5-16.0) total leukocyte count- (8.65 $x10^9$/L,N:4.0-19.5 $x10^9$/L) platelet counts (187x 10^9/L, N:150-450 x 10^9/L), Differential counts- N_{64}, L_{25}, M_8 and E_2. Serum immunoglobulin profile revealed hypogammaglobulinemia (IgG- 1.85 g/L, N:6.39-13.49 g/L , IgA- 8.2, N: 7-31.2 g/L , IgM- 1.14, N: 5.6-3.52 g/L). Anti-nuclear antibodies and Rheumatoid factor were negative.A decreased proportion and absolute counts of CD19+ B lymphocytes (0.06%, N:6-23%; counts-1, N:110-570) and normal proportion and absolute counts of CD3+ T lymphocytes (83.57%,N:56-84%; counts- 1821, N:1000-2200), and CD 56+ natural killer cells (16.34%,N:3-22%;counts-356,N:70-480). While, low CD4/CD8 ratio (1.46, N:0.67), reduced proportion of memory CD4+ and CD8+ cells (11%, N:18-38%; 1.3%, N:4-23%) compared to naïve T cells. A whole-exome sequencing revealed homozygous single base pair deletion in exon 5 of the CD 19 gene (c.904delT (p.phe302SerfsTer18)).

Conclusions: Panhypogammaglobulinemia and markedly reduced B cells in a female child are the clues for CD19 deficiency in our patient.

Disclosure: No.

Keywords: Sinopulmonary infections, Common variable immunodeficiency, hypogammaglobulinemia, Whole Exome Sequencing

PD136

IMPACT of THE USE of JAK INHIBITORS ON METABOLIC CONTROL IN PATIENTS WITH INBORN ERRORS of IMMUNITUY AND DIABETES MELLITUS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Roberta Romano[1], Giuliana Giardino[2], Francesca Cillo[1], Elisabetta Toriello[3], Emma Coppola[1], Emilia Cirillo[1], Francesca Di Candia[1], Francesco Maria Rosanio[1], Enza Mozzillo[1], Adriana Franzese[1], Claudio Pignata[1]
[1]University of Naples Federico II, Translational Medical Sciences, Section of Pediatrics, Naples, Italy, [2]University of Naples "Federico II", Translational Medical Science, Napoli, Italy, [3]University of Naples, Translational Medical Science, Naples, Italy

Background and Aims: JAK inhibitors (JAKi) are biological drugs targeting JAK/STAT signaling pathway that has been recently discovered as implicated in some inborn errors of immunity (IEI) characterized by immune dysregulation manifestations. Increased insulin sensitivity induced by these drugs has been hypothesized. Here we describe two patients affected by IEI with Diabetes Mellitus (DM) treated with JAKi and their potential impact on glycometabolic compensation.

Methods: Patient 1 (P1) is a 19-year-old boy with STAT1 Gain of Function, treated with Ruxolitinib, and DM, on insulin pump therapy. Patient 2 (P2) is a 14-year-old boy with an undiagnosed complex syndrome characterized by dysmorphic features, short stature, immune dysregulation with DM on multi-injective insulin regimen and alopecia, treated with Tofacitinib. They both displayed poor metabolic control. In order to analyze the effects of JAKi treatment on the glucose metabolism we evaluated insulin requirement, glycated Hemoglobin (HbA1c) and C-peptide over a two-year period, before and after the treatment. T-student test was used for Statistical analysis.

Results: In P1, insulin requirement and HbA1c were significantly decreased on Ruxolitinib (p 0.015 and p 0.05, respectively) and so did C-peptide; he also showed a remarkable improvement of the infectious and immune dysregulation phenotype suggested by the reduction of aphtous ulcers. By contrast, no relevant change occurred in P2, despite partial effectiveness of JAKi on alopecia.

Conclusions: JAKi may reduce insulin requirement and improve glycometabolic control in patients with IEI and DM as comorbidity. Further data are necessary to investigate this potentially beneficial effect.

Disclosure: No.

Keywords: STAT1 GOF, ruxolitinib, Immune Dysregulation, Diabetes mellitus, Tofacitinib, JAK inhibitors

PD137

THE RELATIONSHIP BETWEEN AUTOIMMUNE DISEASES AND SERUM BASAL IGE LEVELS IN CVID PATIENTS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Ümmügülsüm Yılmaz, Fatih Çölkesen, Mehmet Kılınç, Recep Evcen, Fatma Arzu Akkuş, Tuğba Önalan, Şevket Arslan
Necmettin Erbakan University Meram Medical Faculty, Clinical Immunology And Allergy, Konya, Turkey

Background and Aims: CVID is the most common symptomatic primary immunodeficiency disease characterized by recurrent infections and an increased risk of autoimmune diseases. Our study aims to determine the relationship between basal serum IgE levels and the risk of autoimmune disease development in CVID patients.

Methods: CVID patients followed in Necmettin Erbakan University Meram Medical Faculty Clinical Immunology and Allergy Clinic were included in the study. Laboratory data, autoimmune diseases, serum immunoglobulin values, and demographic data of the patients were obtained from the patient files.

Results: Twenty-three (37.1%) of 62 CVID patients had autoimmune diseases. Serum basal IgE and IgA values of CVID patients with autoimmune disease were significantly lower than those of other CVID patients (p=0.026 and 0.031, respectively). Lower than normal range serum baseline IgE levels in CVID patients have been shown to be an independent risk factor for the development of autoimmune diseases (odds ratio, OR = 3.081, 95% confidence interval, CI 1.222–7.771, p = 0.017).

Conclusions: Lower IgE is often associated with lower IgA, IgG2 and IgG4 in CVID patients. At the same time, the loci of the heavy chains of these immunoglobulins are the most expressed group on the 14th chromosome and the coexistence of their deficiencies suggests an isotype switch defect as in TACI, ICOS, CD40L and BAFFR mutations. Considering serum IgE values in the clinical follow-up of CVID patients may be beneficial in terms of early diagnosis and treatment of autoimmune conditions with a high risk of development in this patient group.

Disclosure: No.

Keywords: IgE, Autoimmunity, CVID

PD138

IS A PID OR A SID? THE TROUBLED DILEMMA

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Mayla Sgrulletti[1,2], Simona Graziani[1], Gigliola Di Matteo[3], Silvia Di Cesare[3], Cristina Cifaldi[4], Elisabetta Del Duca[1], Barbara Kroegler[5], Viviana Moschese[1]
[1]Policlinico Tor Vergata, University of Tor Vergata, Pediatric Immunopathology And Allergology Unit, Rome, Italy, [2]University of Rome Tor Vergata, Phd Program In Immunology, Molecular Medicine And Applied Biotechnology, Rome, Italy, [3]University of Tor Vergata, Department of Systems Medicine, Rome, Italy, [4]Bambino Gesù Children's Hospital, IRCCS, Academic Department of Pediatrics, Immune And Infectious Diseases Division, Research Unit of Primary Immunodeficiencies, Rome, Italy, [5]University of Rome Tor Vergata, Rheumatology Allergology And Clinical Immunology, Department “medicina Dei Sistemi”, Rome, Italy

Background and Aims: Primary Immunodeficiencies (PIDs) include a wide group of inherited defects of the innate and/or adaptive immune system characterized by recurrent/severe infections and/or immune dysregulation, which may represent the only clinical manifestation in 20% of cases. Sine qua non for PID diagnosis is the exclusion of Secondary Immunodeficiencies (SID), including iatrogenic SID. In the last decades standard immunosuppressant and biotechnological treatments have been increasingly used in clinical practice which might in turn unmasked an initial expression of a PID. Thus, dissection of a PID vs a SID is a real challenge.

Methods: A 47-year-old female patient with a diagnosis of Rheumatoid Arthritis and recurrent respiratory and urinary tract infections since early infancy was treated with Rituximab after poor response to several biological Disease-Modifying Anti-rheumatic Drugs (bDMARDs). At that time hypogammaglobulinemia was observed and she was sent for immunology referral.

Results: The immunological work-up revealed impaired antibody response to Pneumococcus vaccine, low sFLC and low Switched and IgM Memory B Cells. Clinical and immunological criteria matched CVID diagnosis. NGS analysis identified a heterozygous variant of uncertain significance (VUS) in the IKBKB gene (OMIM:603258) and functional analysis is in progress. IVIG therapy and antibiotic prophylaxis were started with good infectious control.

Conclusions: A SID might mask a PID. Pre-immune modifying treatment (IMT) screening and long-term post-IMT monitoring are essential to address the hurdles in differential diagnosis between PID and SID. PID patients need a different vigilance for infections, lymphoproliferative diseases and malignancy and genetic characterization is paramount for a targeted and/or semi-targeted therapeutic approach.

Disclosure: No.

Keywords: Immune Dysregulation, Targeted therapy, Iatrogenic effects, primary immunodeficiency, Secondary Immunodeficiency, Autoimmunity

PD139

ICF1 PATIENTS TREATED WITH IVIG, THE IMPORTANCE of EARLY RECOGNITION AND INITIATION of TREATMENT AS SEEN IN TWO CASE STUDIES.

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Or Givol[1], Erez Rechavi[2], Muhammad Mahajnah[3], Raz Somech[2], Adi Klein Kremer[4], Vered Schichter Konfino[1]
[1]Hillel Yaffe Medical Center, Allergy And Immunology Unit, Hedera, Israel, [2]Sheba Medical Center, Pediatrics, Immunology, Ramat Gan, Israel, [3]Hillel Yaffe Medical Center, Pediatric Neurology And Child Development Center, Hedera, Israel, [4]Hillel Yaffe Medical Center, Pediatric, Hedera, Israel

Background and Aims: Immunodeficiency, centromeric region instability, and facial anomalies syndrome (ICF) is a rear, autosomal recessive, inborn error of immunity. In this case report we present two pediatric patients with onset of severe infections around the age of six months. Both were diagnosed with ICF type 1 after whole exome sequencing positive for DNMT3B homozygous loss of function mutations.

Methods: We present both patients outcomes after 2 years from diagnosis.

Results: The first patient was treated with intravenous immunoglobulin (IVIG) from the initial presentation and suffered no further severe infections nor chronic diarrhea. He does suffer from global developmental delay at the age of two and a half years. The second patient was diagnosed only at the age of one year and three months, after the development of severe failure to thrive, chronic diarrhea, severe malnutrition, and severe developmental delay. Initiation of IVIG and prophylactic antibiotic and antifungal therapy did not improve here symptoms for 2 years.

Conclusions: The difference in the two cases emphasize the importance of screening for humoral immunodeficiencies presenting as severe infections around the age of six months, due to the apperent potential of improved prognosis with appropriate therapy, including immunoglobulines substitiution therapy.

Disclosure: No.

Keywords: ICF, Epigenetics, IEI, IVIG

PD140

THYROID CARCINOMA IN TWO PATIENTS WITH ATAXIA-TELANGIECTASIA: RADIOSENSITIVITY AND USE of RADIOIODINE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Beatrice Rivalta[1], Carmela Giancotta[1], Fabrizio Leone[2], Lucia Pacillo[1], Chiara Rossetti[1], Graziamaria Ubertini[3], Armando Grossi[3], Paolo Palma[1], Andrea Finocchi[1], Caterina Cancrini[1]
[1]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Unit of Clinical Immunology And Vaccinology,, Roma, Italy, [2]Policlinico Umberto I, Maternal, Infantile And Urological Sciences Department, Roma, Italy, [3]IRCCS Bambino Gesù Children Hospital, Endocrinology, Rome, Italy

Background and Aims: Ataxia-telangiectasia(AT), caused by biallelic loss-of-function ATM gene mutations, is a condition characterized by cerebellar ataxia, telangiectasia, variable immunodeficiency, and high cancer susceptibility. This is explained by the impaired activity of the ATM kinase, involved in the DNA damage detection, and responsible for increased radiosensitivity and genome instability. The development of thyroid carcinoma is rare in patients with ataxia-telangiectasia. Since childhood, these patients developed leukemia and lymphoma, sometimes related to EBV infection. In older patients, various solid tumors, including carcinomas, melanomas, and sarcomas, are also reported.

Methods: We report the case of two AT patients diagnosed with Thyroid Carcinoma with normal thyroid function, in which radioiodine was used post-thyroidectomy. Pt1 is a 20-years-old girl with a progressive but mild neurological involvement, hypogammaglobulinemia, hyper-IgM, and chronic EBV infection. She was diagnosed with an abdominal dermatofibrosarcoma(10 years-of-age), hepatic adenoma (17-years-of-age), and a papillary Thyroid Carcinoma(pT1N.1a) at 18-years-old. One year after the thyroidectomy, an ultrasound revealed an enlarged supraclavicular lymph-adenomegaly. MRI showed also multiple nodular lesions of the thorax and a hepatic lesion. The radioiodine scintigraphy excluded the presence of metastasis. Pt2 is a 22-year-old girl with a severe neurologic involvement and hypogammaglobulinemia. At 21-years-old, she was diagnosed with an invasive follicular papillary carcinoma(pT1b,pNx). Post-thyroidectomy staging with radioiodine scintigraphy showed residual thyroid tissue. She was treated with postoperative radioiodine therapy.

Results: Radioiodine staging and therapy were well tolerated and effective in our patients.

Conclusions: Periodic investigations as echography or MRI are mandatory in these patients with an high risk for malignancy to obtain an early diagnosis.

Disclosure: No.

Keywords: ataxia-telangiectasia, tumor, solid, radiosensitivity, thyroid, case-report

PD141

NO OBVIOUS ASSOCIATION BETWEEN COMMON INFECTIONS AND DISEASE ONSET OR SEVERITY IN CTLA-4 INSUFFICIENCY

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Mate Krausz[1,2,3], Noriko Mitsuiki[4], Valeria Falcone[5], Maria Kanariou[6], Hanns-Martin Lorenz[7], Jiri Litzman[8], Daniel Wolff[9], Hartmut Hengel[5], Laura Gámez-Díaz[2], Bodo Grimbacher[1,2,10,11,12]
[1]Medical Center – University of Freiburg, Faculty of Medicine, Department of Rheumatology And Clinical Immunology, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [2]University Hospital Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [3]Albert-Ludwigs-University of Freiburg, Faculty of Biology, Freiburg, Germany, [4]Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [5]Medical Center – University of Freiburg, Faculty of Medicine, Institute of Virology, Freiburg, Germany, [6]IASO CHILDRENS HOSPITAL, 1st Pediatric Dpt, AΘHNA, Greece, [7]University of Heidelberg, Division of Rheumatology, Department of Internal Medicine V, Heidelberg, Germany, [8]St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Department Clinical Immunology And Allergology, Brno, Czech Republic, [9]University Hospital Regensburg, Department of Internal Medicine Iii, Regensburg, Germany, [10]DZIF – German Center for Infection Research, Satellite Center Freiburg, Germany, Freiburg, Germany, [11]Albert-Ludwigs University, Freiburg, Cibss – Centre For Integrative Biological Signalling Studies, Freiburg, Germany, [12]RESIST – Cluster of Excellence 2155, Hanover Medical School, Satellite Center Freiburg, Freiburg, Germany

Background and Aims: Heterozygous mutations in CTLA4 lead to an inborn error of immunity characterized by immune dysregulation and immunodeficiency, known as CTLA-4 insufficiency. Cohort studies on CTLA4 mutation carriers showed a reduced penetrance (~70%) and variable disease expressivity, suggesting the presence of modifying factors. It is well studied that infections can trigger autoimmunity in humans, especially with the right genetic predisposition.

Methods: To investigate whether specific infectious agents could be associated with disease onset or severity of CTLA-4 insufficiency, we have examined the humoral immune response in CTLA4 mutation carriers without immunoglobulin replacement against cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus 1/2 (HSV 1/2), parvovirus B19 and Toxopasma gondii – pathogens, for which the seroprevalence in the healthy population is close to 70%, the penetrance of CTLA-4 insufficiency. Additionally, we have measured FcγRIII-activation by EBV-specific antibodies to examine the functional capabilities of immunoglobulins produced by CTLA4 mutation carriers.

Results: We analyzed six affected and seven unaffected CTLA4 mutation carriers. The seroprevalence of affected or unaffected CTLA4 mutation carriers for each pathogen was: EBV (EBNA1) 83% and 86%; CMV-IgG 50% and 57%; parvovirus B19 83% and 83%; HSV-1/2 67% and 100%; Toxoplasma gondii 40% and 14%, respectively. The odds ratio for developing an overt disease did not reach significance for the examined pathogens. Additionally, we show that CTLA-4 patients produce normally functioning EBV-specific antibodies.

Conclusions: Our results show that the investigated pathogens are very unlikely to trigger the disease onset in CTLA-4 insufficient individuals on their own, and their prevalence is not correlated with disease severity.

Disclosure: No.

Keywords: Cytotoxic T-lymphocyte antigen 4 (CTLA4), immunodeficiency, Immune Dysregulation, disease modifier, inborn error of immunity

PD142

COMBINED C1-ESTERASE INHIBITOR DEFICIENCY AND ALPHA-1 ANTITRYPSIN DEFICIENCY: A NEW PLAYER IN NEURO-IMMUNE DISEASE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Isaac Melamed
ImmunoE, Immunology, Centennial, United States of America

Background and Aims: In recent years, a relationship has been established between a post-infectious immune response and neurologic changes, which we describe as Alzheimer's of the Immune System.[1] Previously, we identified immune partners that play a role in immune dysfunction, including mast cell (MC) activation, complement activation due to low levels of C1-esterase inhibitor (C1-INH) and function (C1-INHF), alpha-1 antitrypsin (AAT) deficiency, and decreased toll-like receptor (TLR) -3 signaling. Here we present 3 case reports describing autoimmunity in patients with this form of immune dysfunction.

Methods: Our patients share 3 commonalities: low AAT levels, low C1 INH, and TLR signaling defects. All patients displayed evidence of IgM antibodies to infectious pathogens, including Mycoplasma pneumonia, Epstein Barr virus (EBV), and Borrelia burgdorfer. Neurological symptoms, including brain fog, memory loss, psychiatric symptoms, and gastrointestinal issues, were present. All 3 patients had the AAT phenotype, a genetic mutation linked to AAT deficiency. Treatment with alpha 1-proteinase inhibitor (human) was effective in reducing their neurologic symptoms.

Results: Recent evidence on AAT deficiency, C1-INH deficiency, and TLR signaling indicate that they may play a role in abnormal signaling between infections such as EBV, Lyme disease,. and COVID-19 and neurological presentations. Thus, AAT and/or C1-INH therapy has the potential to advance from replacement therapy to a safe modality for post-infectious inflammatory neuro-immune-related diseases.These therapeutic modalities may add to our treatment arsenal for post-infectious disorders. Further research is needed.

Conclusions: [1]Melamed I. Immunotherapy Open Access. 2016; 2:2.

Disclosure: No.

Keywords: C1-INH deficiency, AAT deficiency, Autoimmunity, COVID-19

PD143

GOOD'S SYNDROME; ABOUT A CASE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Silvia Paulina Ruiz López, Patricia O Farrill Romanillos, Diana Herrera Sánchez
Mexican Institute of Social Security, Hospital Especialidades, XXI Medical Center, Allergy And Clinical Immunology, Mexico, Mexico

Background and Aims: Good's syndrome (SG) is a phenocopy, immunodeficiency that affects B/T cells and can be associated with autoimmunity. Thymoma is a rare neoplasm accounting for 30% of mediastinal tumors in adults. Treatment with thymectomy or cytoreduction, although it is not the treatment for the elimination of immunodeficiency.

Methods: A 62-year-old male with no history of inbreeding, consanguinity, or atopy. Uncomplicated childhood pneumonia. In 2019 chronic diarrhoea, weight loss, anorexia, cough, assessed by an immunologist, requested laboratory reports: IgA: 25mg/dl, IgG 439mg/dl, IgM 26mg/dl, IgG1: 374mg/dl, IgG2: 173mg/dl, IgG3: 40.3mg/dl, CD4: 407/ml, CD8: 268ml, CD3: 713ml. Treatment with IgSC for 3 months. The patient who met IDCV criteria continued IVIg treatment. January 2022, with bronchial symptoms, HRCT data of interstitial lung disease, mediastinal tumor suggestive of Thymoma, and mediastinal lymphadenopathies were requested.

Results: Biopsy confirms diagnosis, and thymectomy is scheduled for May 13, 2022.

Conclusions: GS, characterized by the almost absence of B cells, cytopenias, and thymoma, is rare immunodeficiency that is not initially suspected until incidental finding. Thymomas are classified A, AB, B1, B2, B3, the former benign and the latter associated with cancer. Survival at 5 years is 74% in stage I and 24% in thymic IV cancer. Most in GS turn out to be benign. The prognosis after thymectomy is based on follow-up, use of antibiotics, and replacement of immunoglobulins to reduce infections and increase survival. In conclusion, it is a rare immunodeficiency that requires multidisciplinary management, and the study of each of the subgroups could guide new discoveries of specific therapies.

Disclosure: No.

Keywords: phenocopy, Good's Syndrome, thymoma, immunodeficiency

PD144

SJÖGREN-LIKE SYNDROME, MULTIPLE AUTOIMMUNE DISEASES, THYMOMA AND GENETIC VARIANTS IN AIRE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Jonas Cramer[1], Ruth Fritsch-Stork[2,3], Emma Husar-Memmer[3], David Schoerghofer[4], Goekhan Uyanik[4,5], Jochen Zwerina[3]
[1]Sigmund Freud University Vienna, Medical Faculty, Vienna, Austria, [2]Sigmund Freud University Vienna, Medical Faculty of Rheumatology, Vienna, Austria, [3]Trauma Centre Meidling, Ludwig Boltzmann Institute of Osteology at Hanusch Hospital of Oesterreichische Gesundheitskassa and Allgemeine Unfallversicherungsanstalt, First Medical Department, Vienna, Austria, [4]Hanusch Hospital Vienna, Medical Genetics, Vienna, Austria, [5]Sigmund Freud University Vienna, Medical Faculty of Genetics, Vienna, Austria

Background and Aims: The autoimmune regulator gene (AIRE) is the focal point of developing central immunotolerance. The AIRE gene is located on chromosome 21q22.3 and codes for a transcription regulator protein expressed in the thymus. Pathogenic mutations of AIRE typically present as a monogenetic disorder and cause the autoimmune polyendocrine syndrome type 1 (APS-1), further known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).

Methods: Case report

Results: The 38-year-old male patient was transferred to our clinic for immunoglobuline therapy, from his treating neurologist. His medical history included diabetes mellitus type 1, diagnosed in 1996, followed by Grave's disease in 2000, culminating in a thyroidectomy in 2017. In 2009 he underwent a thymectomy for a thymoma. He had been treated with a series of immunosuppressive therapies including prednisolone, rituximab and mycophenolate, as well as plasmapheresis and immunopheresis for his atypical, seronegative myasthenia gravis. Due to the limited effect of the previous therapeutic regimen a trial with intravenous immunoglobulin had been initiated inducing clinical stabilization.

Conclusions: To our knowledge this is the first report of a patient with thymoma and genetic variant(s) in the AIRE gene displaying several autoimmune diseases. Although clinical similarities between thymoma patients and APS1 are known, a genetic link between these 2 diseases has not yet been described. As rheumatic autoimmunity can be induced by either, rheumatologists should be aware of these potentially underlying causes. An additional point of interest is the lack of autoimmunity in the mother with the same genetic variants, which suggests an additional environmental trigger (e.g. smoking, viral infection) in the patient.

Disclosure: No.

Keywords: APECED, AIRE, novel mutation, APS

PD145

EVALUATION of OUR PATIENTS WITH HYPOGAMMAGLOBULINEMIA DIAGNOSED WITH ATOPIC DERMATITIS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Yasin Karali[1], Sara Sebnem Kilic[2]
[1]Uludag University Faculty of Medicine, Pediatric Immunology And Allergy, Bursa, Turkey, [2]Uludag University, Faculty of Medicine, Pediatric Immunology, Bursa, Turkey

Background and Aims: The aim of our study is to evaluate the clinical and laboratory findings of children with AD diagnosed with hypogammaglobulinemia.

Methods: Electronic files of 1000 patients diagnosed with atopic dermatitis between January 2021 and April 2022 in Bursa Medical Faculty Pediatric Immunology and Allergy Clinic were retrospectively analyzed. Among them, 110 patients whose immunoglobulin values below -2SD for age were included in the study.

Results: The frequency of hypogammaglobulinemia in children with atopic dermatitis was 11%. of the 110 patients included in the study, 72 (65%) were male and 38 (35%) were female. The mean age at presentation was 9.5 months (3-52). According to the SCORing Atopic Dermatitis score of the patients, the severity of eczema was mild in 83 (75,4%) patients and moderate-severe in 27 (24,6%) patients. Food allergy sensitivity was present in 41 (37,2%) of the patients. In laboratory findings; in complete blood count, neutropenia was detected in 25 (22,7%) patients. The mean total IgE level was 98,4 µg/mL (0.26-2102). Mean immunoglobulin levels were, for IgG 354,4 mg/dL (151-609), for IgA 15,3 mg/dL (8-49), and for IgM 47,5 mg/dL (12-169) respectively. As a result of the evaluation of the lymphocyte subgroup of ninety nine patients, it was found to be within the normal range for their age. IgG levels were increased in all 53 patients whose consecutive serum immunoglobulin levels were measured.

Conclusions: We think that the evaluation of immunoglobulin levels in children with atopic dermatitis is quite important in the distinguishment of primary immunodeficiencies and in the follow-up of patients.

Disclosure: No.

Keywords: Atopic dermatitis, hypogammaglobulinemia

PD146

THE INTESTINAL MICROBIOME IN HEALTH AND DISEASE of 150 CHILDREN AND ADOLESCENTS WITH OR WITHOUT PRIMARY IMMUNODEFICIENCY OR AUTOIMMUNITY

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Theresa Greimel[1], Kristin Aldover[2], Andrea Thueringer[3], Georg Singer[4], Markus Seidel[2], Gregor Gorkiewicz[3]
[1]Medical University of Graz, Pediatrics, Graz, Austria, [2]Medical University Graz, Pediatric Hematology-oncology, Graz, Austria, [3]Medical University of Graz, Institute of Pathology, Graz, Austria, [4]Medical University of Graz, Pediatric Surgery, Graz, Austria

Background and Aims: The composition of the human intestinal microbiome is involved in immune homeostasis. Alterations of the microbiome may be associated with inflammation and autoimmunity in otherwise healthy individuals or in patients with inborn errors of immunity (IEI) or secondary immunodeficiency. To date, the variability of the healthy gut microbiome of children and adolescents between 0-18 years of age has not yet been compared in detail with that of pediatric patients with severe immune cytopenia (SIC), an autoimmune disease of the blood, e.g. immune thrombocytopenia, autoimmune hemolytic anemia, or Evans syndrome.

Methods: We collected and analyzed 197 stool samples from children and adolescents with elective surgery or conservative treatment of fractures without inflammatory disease or infections (n=100; age 0-20 years), from inpatients of a pediatric hematology-oncology and stem cell transplantation unit with IEI (n=12) or malignant disease, or with SIC (n=38) as part of the SIC-registry study (sic-reg.org) at multiple time points of their disease course. Microbial community profiling (16S rRNA gene sequencing) was performed and data were analyzed comparatively.

Results: At the time point of abstract submission, analyses are ongoing. Preliminary findings show that the most pronounced deviation from a normal diversity of the intestinal microbiome was detected in patients with IEI and multiple immune modulating therapies. Whether a correlation of immune dysregulation activity with microbiome alteration can be detected remains to be defined.

Conclusions: The intestinal microbiome of children with immune deficiencies shows a great variability which is driven by disease type and therapy related factors.

Disclosure: No.

Keywords: intestinal microbiome, cytopenia, 16S rRNA gene sequencing, immune thrombocytopenia, EVANS SYNDROME, Microbial community profiling

PD147

LIVER DISORDERS IN ADULTS PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Patricia O Farrill Romanillos[1], Diana Herrera Sánchez[1], Rosalba Moreno Alcantar[2], Carlos Paredes Manjarrez[3], Lourdes Arriaga Pizano[4]
[1]Mexican Institute of Social Security, Hospital Especialidades, XXI Medical Center, Allergy And Clinical Immunology, Mexico, Mexico, [2]Mexican Institute of Social Security, Gastroenterology, Mexico, Mexico, [3]Mexican Institute of Social Security, Radiology, Mexico, Mexico, [4]Mexican Institute of Social Security,, Research Unit In Immunology, Mexico, Mexico

Background and Aims: Introduction: Common variable immunodeficiency (CVID) encompasses a heterogeneous group of disorders, characterized by hypogammaglobulinemia.
As part of the complications liver disorders have been reported, presentation ranges between 10-33.8%. Liver damage has been attributed to immune dysregulation.
Objective: To determine the frequency and type of liver abnormalities in adult patients with CVID.

Methods: a cross-sectional, descriptive study was carried out, including patients from the Primary Immunodeficiency Clinic, with a definitive diagnosis of CVID, according to the ESID criteria. Liver function tests were performed: AST, ALT, FA, GGT, DHL. In addition to a liver ultrasound, performed and interpreted by an expert radiologist.

Results: 36 patients with CVID were included, 27 women and 9 men. Median age 30 years, range 20-79 years.
36.1% of the patients, with liver abnormalities, elevated liver enzymes one standard deviation above the normal value for age: AST, ALT and GGT; by ultrasound 3 with hepatic steatosis and 7 hepatomegaly, and nodular regenerative hyperplasia. 6 with portal hypertension, the presence of collateral venous network and esophageal varices were documented.
100% with splenomegaly, immune thrombocytopenia. 80% corresponded to the Freiburg IA phenotype. One patient died of spontaneous bacterial peritonitis.

Conclusions: the presentation of liver damage in CVID, ranges from elevated alkaline phosphatase to nodular regenerative hyperplasia, liver cirrhosis and portal hypertension.
The most common form of presentation of liver damage is nodular regenerative hyperplasia (NRH).
It has been established that it is produced by immune dysregulation. Its detection is important due to the morbidity and mortality implications of these patiente.

Disclosure: No.

Keyword: Liver, inmune disregulation, Common variable immunodeficiencies

PD148

CASE REPORT: RARE SOLID TUMORS IN A PATIENT WITH WISKOTT ALDRICH SYNDROME AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Emma Coppola, Giuliana Giardino, Elisabetta Toriello, Antonio De Rosa, Francesca Cillo, Roberta Romano, Claudio Pignata, Emilia Cirillo
University of Naples "Federico II", Translational Medical Science, Naples, Italy

Background and Aims: Wiskott Aldrich Syndrome (WAS) is an X-linked recessive primary immunodeficiency disorder charcaterized by severe eczema, recurrent infections and micro-thrombocytopenia. Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative therapeutic option for patients with classic form. The risk of developing post-transplant tumors appears to be higher in patients with WAS than in other Inborn errors of immunity (IEIs), but the actual incidence is not well defined due to the scarcity of published data.

Methods: Herein, we describe a 10-years-old patient diagnosed with WAS, treated with HSCT in the first year of life, who subsequently developed two rare solid tumors, hemangioendothelioma kaposiform and desmoid tumor.

Results: The patient received diagnosis of classic WAS at the age of 2 month (Zhu score = 3), confirmed by WAS gene sequencing, which detected the c.37C>T mutation. At 9 months, the patient underwent HSCT from a matched unrelated donor with an adequate immune reconstitution, characterized by normal lymphocyte subpopulations and mitogen proliferation tests. Platelet count significantly increased, but they remained lower than the normal reference limits. A mixed chimerism was also highlighted, with a residual WASP- population (WASP- monocytes 27.3%). At 5 years, he developed a kaposiform hemangioendothelioma. At 11 years, a second abdominal tumor was identified, histologically classified as a desmoid tumor.

Conclusions: Here we describe the first case of a patient with WAS who developed two rare solid tumors after HSCT. The risk of cancer in patients with IEIs is not completely suppressed by the HSCT.

Disclosure: No.

Keywords: HSCT, Wiskott Aldrich syndrome, kaposiform hemangioendothelioma, Inborn errors of immunity, tumor, desmoid tumor

PD149

IMMUNODEFICIENCY IN A PATIENT WITH NOONAN SYNDROME 13; A NOVEL IMMUNO-TOROPATHY?

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Saira Tabassum[1], Ben Molloy[2], Eppie Jones[2], Patrick Buckley[2], Rebecca Amet[3], Anthony Mcelligott[3], Derek Doherty[3], Timothy Ronan Leahy[4]
[1]CHI @ Crumlin, Immunology, Dublin, Ireland, [2]Genuity Science, Genetcs, Dublin, Ireland, [3]University of Dublin, Trinity College, Trinity Translational Medicines Unit, Dublin, Ireland, [4]University of Dublin, Trinity College, Pediatrics, Dublin, Ireland

Background and Aims: We report the case of an 11-year-old girl with immunodeficiency in association with Noonan syndrome 13 caused by an activating mutation in MAPK1.

Methods: The patient (P1) was noted to have failure to thrive, neurodevelopmental delay and facial features (hypertelorism, ptosis, low set posteriorly rotated ears, long philtrum) suggestive for Noonan syndrome. She later developed clinical and immunological features consistent with common variable immunodeficiency, and was commenced with good effect on immunoglobulin replacement therapy. The patient also demonstrated features of an autoimmune enteropathy and responded well to 5-ASA.

Results: P1 was later found to be heterozygous for a de novo mutation (c.238C>T; p.His80Tyr) in MAPK1. Mutations in MAPK1 are morbid for Noonan syndrome 13. To investigate the impact of the MAPK1 mutation on P1's immune cells, we undertook Western Blot on PBMCs isolated from whole blood collected from P1 in comparison to a healthy control and measured the relative expression of phosphorylated AKT (pAKT) and phosphorylated S6 (pS6) in both PBMCs and sorted B cells and T cell compartments. The results demonstrated increased pS6 relative to β-actin and increased pAKT relative to total AKT in PBMCs from P1 relative to a healthy control.

Conclusions: We present a patient with an activating mutations in MAPK1 demonstrating many clinical and immunological features typical of patients with an "immune-TOR-opathy" along with convincing evidence of dysregulation of the mTOR-S6 pathway. Sequencing of MAPK1 should be considered in patients presenting with Noonan syndrome phenotype and features of immunodeficiency/ immunodysregulation.

Disclosure: No.

Keywords: CVID, Noonan Syndrome 13, MAPK1, autoimmune enteropathy

PD150

TOXOPLASMOSIS OCULAR IN GOOD SYNDROME. A CASE REPORT.

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Lucia Peirano.
Hospital Italiano Buenos Aires- CIC BEZRODNIK., Internal Medicine- Immunology., Buenos Aires., Argentina

Background and Aims: An 85-year-old man started in 2007 with blepharitis and uveitis, ocular toxoplasmosis was diagnosed. In 2015, he presented with chronic cough, chest CT scan found a thymoma requiring thymectomy and radiotherapy. Laboratory tests revealed the following 04/21/15: IgG, 412 mg/dL; IgA 14 mg/dL; and IgM 10 mg/dL. IgE less than 1.5 mUi/ml. AutoAb were negative. Two year later he presented ocular toxoplasmosis again, this time more severe presenting retinal detachment and posterior blindness. The following year he presented urinary infection by Klebsiella and inguinal herpes zoster with subsequent neuropathy. In 2019 he had a subarachnoid hemorrhage due to a fall and in 2020 in the context of suprapubic abscess he was referred for our evaluation. Other medical history included 2 pneumonias, bronchitis, bronchiectasis, lower extremity deep vein thrombosis, peripheral vascular disease, myocardial infarction, multiple skin infections and mucocutaneous candidiasis. Laboratory tests were requested and showed the following laboratory tests IgG 286 mg/dL; IgA 10 mg/dL; and IgM, less than 7mg/dL. Flow cytometry revealed virtually undetectable levels of peripheral B cells, normal levels of T cells and CD8 cells, but slightly reduced CD4 levels. Good syndrome was diagnosed, and he was given monthly IVIG at 400 mg/kg.

Methods: Good syndrome.Case report.

Results: Patient with IEI.

Conclusions: The concomitant occurrence of immunodeficiency and thymoma is known as Good syndrome. In contrast to other humoral immune defects, patients with this can develop opportunistic infections, the prognosis appears less favorable.

Disclosure: No.

Keyword: hypogammaglobulinemia, ocular toxoplasmosis, thymoma, Good Syndrome, immunodeficiency.

PD151

A CD122 DEFICIENCY CASE PRESENTED WITH HEMOLYTIC ANEMIA AND LUPUS VULGARIS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Hedieh Haji Khodaverdi Khani[1], Hassan Abolhassani[2], Zahra Chavoshzadeh[3], Fahimeh Abdollahimajd[4], Abdollah Karimi[5], Nasrin Khakbazan Fard[3], Maryam Asarehzadegan[3]
[1]Faculty of Medical Science, Shahed university, Department of Immunology, Tehran, Iran, [2]Karolinska Institute, Division of Clinical Immunology, Department of Biosciences And Nutrition, Stockholm, Sweden, [3]Mofid children hospital, Shahid Beheshti university of Medical Science, Department of Allergy And Clinical Immunology, Tehran, Iran, [4]Shahid Beheshti university, Skin Research Center, Tehran, Iran, [5]Mofid children hospital, Pediatric Infections Research Center, Tehran, Iran

Background and Aims: Primary immune deficiency (PID) disorders are a group of diseases associated with genetic mutations that can affect the immune system. This group of illnesses involved multiple manifestations such as recurrent infections, auto-immunity, immune dysregulation, malignancy, inflammation and allergy. Since the skin has an immunological role against external factors, it may be affected in PID patients. Consequently, we are prepared to introduce a PID patient with lupus vulgaris and a charectrized genetic mutation.

Methods: The patient is a 21-year-old boy with a history of hemolytic anemia and severe ulcerative dermatitis who received broad-spectrum antibiotics several times and became partially remission. His physical exam shows hepatosplenomegaly and nasal cartilage deformity. Regarding that in the skin biopsy a large necrotizing granulomatous inflammation had been reported, the sample was stained by Ziehl Neelsen.

Results: Skin's result showed scattered acid fast bacilli. He was therefore identified as a case of lupus vulgaris and treated with anti-TB drugs. After a while, his dermatitis become better. Based on its Whole Exome Sequencing (WES), a genetic mutation in IL-2Rβ (CD122) (c.1229C>G variant) was identified and confirmed by Sanger sequencing in the patient and his parents. We should mention that his parents are consanguine.

Conclusions: According to our findings, we can conclude that in dermatitis with unusual pictures, we should notice immune deficiencies.

Disclosure: No.

Keywords: Primary Immune deficiency, lupus vulgaris, CD122 deficiency, Immune Dysregulation, dermatitis

PD152

PREMATURE GRAYING of HAIR AS IMMUNODISREGULATION FEATURES ASSOCIATED WITH RAG DEFICIENCY

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Beatrice Rivalta[1,2], Lucia Pacillo[1,2], Cristina Cifaldi[2], Chiara Rossetti[1], Fabrizio Leone[3], Silvia Di Cesare[1], Gigliola Di Matteo[1], Alessandra Simonetti[1,2], Paolo Palma[1,2], Caterina Cancrini[1,2], Andrea Finocchi[1]
[1]Tor Vergata University, Department of Systems Medicine, Rome, Italy, [2]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Roma, Italy, [3]Policlinico Umberto I, Maternal, Infantile And Urological Sciences Department, Roma, Italy

Background and Aims: Hypomorphic RAG mutations are associated with a variable phenotype ranging from SCID,to CVID with a broad spectrum of immunodysregulation manifestations. Failure to control infections,particularly chronic CMV or EBV viremias,may trigger/sustain autoimmunity.

Methods: We describe the case of a 6-years-old girl affected by RAG-deficiency with a CID-G/AI and vitiligo, psoriasis, and premature graying of hair.

Results: She was first admitted at 5-years-old for a CMV and Pseudomonas Alcaligenes pneumonia. She was born from non-consanguineous Romanian parents. She developed dermatitis,allergic rhinitis,iron deficiency anemia in the first year of life,and later severe recurring infections, particularly bronchitis,pneumonia, and chorioretinitis treated in another center. Despite specific treatments, the microbiological analysis of sputum and bronchial washing showed persistent positivity for Pseudomonas Aeruginosa. The chest-CT showed a diffuse bronchial thickening, bronchiectasis, and ground glass/micronodular lesions. Subclinical thyroiditis with increased anti-thyroglobulin antibodies was also found. The WES revealed a homozygous deletion in RAG1 c.256_257del(p.Lys86Valfs*33). This variant was already described as a Founder variant in a cohort of patients from Slavic countries with a variable phenotype(SCID,OS,AS/LS with a domination of B+ phenotype and CID-G/AI), autoimmune manifestations, BCGitis and CMV infection. No patients from Romania were included in this study. We also previously described another patient from Macedonia with this variant, AS, an increase of CD19+cells,CMV,BCGite and severe autoimmune manifestations. Moreover,in the past we treated a SCID-del22q11.2 who developed premature graying of hair after thymus transplantation.

Conclusions: Immunodysregulation manifestations and autoimmunity are frequently associated with hypomorphic RAG mutations. Premature graying of hair and vitiligo,extend the number of immunodysregulation manifestations associated with RAG-deficiency.

Disclosure: No.

Keywords: immunodysregulation, RAG1, Premature graying of hair, RAG deficiency, Autoimmunity, Hypomorphic mutation

PD153

REPORT of A NOVEL VARIANT IN AIRE GENE IN TWO SIBLINGS FROM ARGENTINA

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Agustin Bernacchia[1], Antonella Invernizzi[1], María Caldirola[2], Daniela Di Giovanni[2], Maria Gaillard[2], Andrea Gómez Raccio[2], María Martínez[2], Ana García[2], Maria Esnaola Azcoiti[2], Paula Scaglia[2], Agustin Izquierdo[2], Maria Ropelato[2], Patricia Carabajal[1]
[1]Hospital de Niños Ricardo Gutiérrez, Immunology Unit, Ciudad Autonoma de Buenos Aires, Argentina, [2]Hospital de Niños Ricardo Gutiérrez, Immunology Unit, Palermo, Argentina

Background and Aims: Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), is an autosomal recessive disorder caused by mutations in the autoimmune regulator (AIRE) gene. Mutations in AIRE lead to aberrant thymic self-tolerance mechanisms and loss of thymic deletion of autoreactive T cells.
CASE REPORT
Two siblings born from non-consanguineous parents.
P1: ten year old male with history of chronic mucocutaneous candidiasis (CMC) involving oral mucosa and nails since two years of age. Admitted three times to hospital due to recurrent obstructive bronchitis, febrile seizures and pneumonia. At four years old he was referred to our Immunology Unit. Initial workup: Hyper IgG with normal IgA, IgM, IgE, C3, C4 and negatives autoantibodies. Normal T and B cell subsets with low NK cell count (normal cytotoxicity). Low Th17 ($CD4^+CCR6^+$) cells and citoplasmatic IL-17A. Normal STAT1 phosphorylation.
P2: girl admitted at three years old due to a prolonged intermittent fever syndrome and difficulty in walking, arthralgias and lymphoproliferation. History of COVID-19 pneumonia. Autoimmune vs autoinflammatory disease was suspected. Infections were ruled out. Workup: elevated IgG, IgM, C3 and C4 with normal IgA. Positive autoantibodies with normal lymphocytes subsets.

Methods: Whole Exome Sequencing,

Results: Molecular study: a pathogenic variant NM_000383.4:c.967_979del and a novel variant of uncertain significance NM_000383.4:c.136A>T in AIRE gene in both siblings

Conclusions: We report a novel variant in AIRE in two siblings with different phenotypes. Molecular diagnosis was a helpful tool for diagnose and follow up of the girl with autoinflammatory manifestations and his brother with prevailing CMC as features of APECED

Disclosure: No.

Keywords: AIRE, APECED, siblings, CMC, Mutation, Novel

PD156

LATE DIAGNOSIS of ALPK1 PATHOGENIC VARIANT CAUSING ROSAH SYNDROME

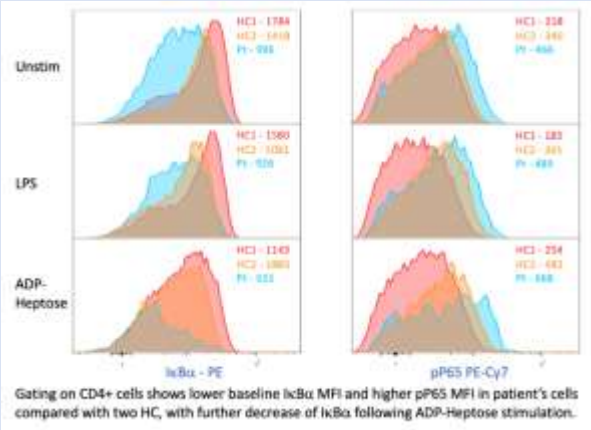
POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Tal Freund, Dikla Adir, Yifat Alcalay, Shira Benor, David Hagin
Tel-Aviv Sourasky Medical Center, Allergy And Clinical Immunology Unit, Tel-Aviv, Israel

Background and Aims: ALPK1 is an intracellular sensor of bacterial sugars, including ADP-Heptose. Dominant gain of function *ALPK1* mutation was first described in 2019 as causing ROSAH autoinflammatory syndrome (retinal dystrophy, optic nerve oedema, splenomegaly, anhidrosis and headache). We aim to describe the major clinical symptom of a ROSAH patient, and functional evaluation of NFκB pathway.

Methods: Genetic evaluation was performed using whole exome sequencing, followed by flow-cytometry evaluation of the NFKB pathway.

Results: A 33 y/o female was referred to our immunology clinic at age 27, due to complex and prolonged medical history, most significant for the following: recurrent fevers since the first year of life, recurrent transient pancytopenia with normal bone-marrow biopsies, severe papilledema since the age of 6, anhidrosis, splenomegaly, and short dental roots and xerostomia. Over the years she was mostly followed for papilledema with treatments including steroids, intra-ocular bevacizumab and acetazolamide, without improvement. Cataract surgery and vitrectomy at age 12 was complicated by retinal detachment and resulted in complete blindness in one eye and legal blindness in the second. Limited PIDD NGS panel in 2018 failed to identify genetic cause, but WES two years later identified a pathogenic p.T237M ALPK1 variant. Upon binding of bacterial metabolites, the bacterial sensor ALPK1 drives NFκB activation. Accordingly, stimulation of patients' PBMCs showed tendency toward increased ADP-Heptose induced IκBα degradation, P65 phosphorylation in CD4+ T-cells.



Gating on CD4+ cells shows lower baseline IκBα MFI and higher pP65 MFI in patient's cells compared with two HC, with further decrease of IκBα following ADP-Heptose stimulation.

Conclusions: Complicated unsolved cases should be evaluated by repeated genetic testing / analysis, as newly described defects could change management. Based on recent report (Kozycki CT. et al), tocilizumab treatment is considered.

Disclosure: No.

Keywords: ROSAH syndrome, IEI, NFkB, Autoinflammatory Disease, ALPK1

PD157

LONG-TERM CLINICAL AND IMMUNOLOGICAL OUTCOME of 12 PATIENTS WITH X-LINKED THROMBOCYTOPENIA: A SINGLE CENTRE EXPERIENCE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Enrico Santangeli[1], Daniele Moratto[2], Elisa Bertoni[3], Annarosa Soresina[4], Luigi Notarangelo[5], Cinzia Mazza[6], Raffaele Badolato[7], Fulvio Porta[8], Silvia Clara Giliani[9], Lucia Dora Notarangelo[10]
[1]Spedali Civili di Brescia, Dipartimento Di Pediatria, Brescia, Italy, [2]Flow Cytometry Laboratory, Diagnostic Department, Asst Spedali Civili, Brescia, Italy, brescia, Italy, [3]Spedali Civili di Brescia, Bone Marrow Transplant Unit 'monica E Luca Folonari', Brescia, Italy, [4]Pediatric Immunology Unit, Dpt of Pediatrics, University of Brescia,, Asst-spedali Civili Di Brescia, Brescia, Brescia, Italy, [5]NIAID, NIH, Laboratory of Clinical Immunology And Microbiology, Division of Intramural Research, Bethesda, United States of America, [6]Medical Genetics Laboratory, Asst-spedali Civili, Brescia, Italy, brescia, Italy, [7]Pediatrics Clinic, Department of Clinical and Experimental Sciences, University of Brescia, Asst Spedali Civili Di Brescia, Brescia, Italy, [8]Children's Hospital, Spedali Civili, Brescia, Italy, Oncohematology And Bone Marrow Transplant (bmt) Unit, Brescia, Italy, [9]Institute for Molecular Medicine A. Nocivelli, Department of Molecular And Translational Medicine, University of Brescia, brescia, Italy, [10]Spedali Civili di Brescia, Direzione Sanitaria, Brescia, Italy

Background and Aims: Mutations in the WASP gene cause a broad spectrum of X-linked disorders spanning from Wiskott-Aldrich syndrome (WAS) to X-linked thrombocytopenia (XLT). While hematopoietic stem-cell transplantation (HSCT) is the elective treatment for patients with WAS, the use of this therapeutic option in XLT patients is under debate.

Methods: We performed a retrospective analysis of clinical and laboratory features of 12 XLT patients from diagnosis onwards.

Results: We examined a cohort of 12 XLT patients, born between 1987 and 2004, who were monitored for an average follow-up period of 18.3 years (range 6-23). They harbor eight different point mutations in the WASP gene, associated to WASP expression ranging from markedly reduced to normal. Thrombocytopenia was a common hallmark of these patients, six of whom underwent splenectomy that in no case brought to a permanent normalization of platelet counts. Analysis of immunological parameters at presentation showed a significant reduction at the level of CD8+ T-cell (6 patients) and B-cell counts (3), while a progressive reduction of the T/NK ratio characterized two patients who received HSC transplantation and gene therapy, respectively. Among major disease complications two cases of autoimmune manifestation were diagnosed. One patient experienced chronic kidney failure, while no malignancies were reported.

Conclusions: Analysis of disease outcome in our cohort indicates that, with careful management of conservative treatments, all the patients could reach adulthood without suffering life-threatening events. However, lifespan persistence and progressive worsening of disease-related manifestations during adulthood suggest that early HSC-based curative treatments should be considered also for patients with XLT.

Disclosure: No.

Keyword: WAS, XLT, HSCT

PD158

MEMORY RESPONSES TO SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 VACCINATION IN PATIENTS WITH HYPER-IMMUNOGLOBULIN E SYNDROMES

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Karrnan Pathmanandavel[1], Geetha Rao[1], Joseph Mackie[1], Tina Nguyen[1], Fabienne Brilot-Turville[2], Stuart Turville[3], Alexandra Freeman[4], Filomeen Haerynck[5], Daniel Suan[6], Cindy Ma[1], Stuart Tangye[1]
[1]The Garvan Institute of Medical Research, Immunology And Immunodeficiency Laboratory, Darlinghurst, Australia, [2]Kids Research Institute, Kids Neuroscience Centre, Westmead, Australia, [3]Kirby Research Institute, Immunovirology And Pathogenesis Program, Kensington, Australia, [4]National Institute of Allergy and Infectious Diseases, Laboratory of Clinical Immunology And Microbiology, Bethesda, United States of America, [5]Ghent University Hospital, Department of Pediatric Pulmonology And Immunology And Pid Research Lab, Ghent, Belgium, [6]Westmead Hospital, Department of Immunology, Westmead, Australia

Background and Aims: Pathogenic variants in genes encoding components of the Signal Transducer and Activator of Transcription 3 (STAT3) signalling pathway cause diverse systemic and immunologic manifestations. In particular, recurrent infections and defects in both cellular and humoral memory have been described in individuals with Hyper IgE Syndrome (HIES) due to dominant negative mutations in *STAT3* or *IL6ST*, or recessive mutations in *DOCK8* or *ZNF341*. We examined the adaptive immune response to vaccination against SARS-CoV-2 in patients with HIES.

Methods: Serial blood and serum samples were collected from 36 HIES patients and 24 healthy donors (HD) receiving SARS-CoV-2 mRNA vaccination. Spike- and Receptor-Binding-Domain (RBD)- specific B cells were measured by flow cytometry. T cell responses to Spike and Nucleocapsid antigens were evaluated by an activation-induced marker assay. SARS-CoV-2 specific antibodies and pseudovirus neutralizing titres were measured from serum.

Results: Consistent with previous findings from our lab, $CD27^+$ memory B cells (MBCs) were markedly reduced in HIES patients compared with HD. Most Spike- and RBD-binding B cells in HIES patients had a phenotype characteristic of atypical ($CD27^-IgG^+$) MBCs, in contrast to the typical ($CD27^+IgG^+$) MBCs observed in HD. Most HIES patients generated CD4 T cell responses to vaccination, whilst only a small proportion produced a comparable CD8 response.

Conclusions: HIES patients develop a humoral response to SARS-CoV-2 vaccination dominated by atypical MBCs. Memory CD4 T cell responses to SARS-CoV-2 were observed more frequently than CD8 responses. Further studies to characterise the functionality of SARS-CoV-2-specific memory subsets in these patients are ongoing.

Disclosure: No.

Keywords: Hyper IgE Syndrome, SARS-CoV-2, STAT3, Vaccination

PD159

CD4 T CELL HELP FOR B CELLS REQUIRES FUNCTIONAL SNARE PROTEIN SYNTAXIN-11

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Sandra Ammann
University Hospital Freiburg, Institute For Immunodeficiency, Freiburg, Germany

Background and Aims: SYNTAXIN-11 (STX11) is a SNARE protein that mediates the fusion of cytotoxic granules with the plasma membrane at the immunological synapse of CD8 T and NK cells. *Stx11*-deficiency is associated with a degranulation defect and impaired lymphocyte cytotoxicity, which causes familial hemophagocytic lymphohistiocytosis type 4 (FHL-4), a hyperinflammatory and life-threatening syndrome. Oberservations in *Stx11*-deficient mice and humans demonstrated hypogammaglobulinemia. We characterized the CD4 T cells and B cells in mice and investigated the function of STX11. To date, a critical function of STX11 in B or CD4 T cells has not been described.

Methods: Immunophenotypings were performed from splenocytes of *Stx11*$^{-/-}$ in comparison to WT or Perforin-deficent mice after LCMV infection. Role of STX11 in CD4 T cells were demonstrated by adoptive WT CD4 T cell transfer into *Stx11*$^{-/-}$ mice, by CD4 T cell depletion experiments,by bone marrow chimera experiments and the obtained *in vivo* results were confirned with a newly established *in vitro* T/B-cell interaction assay.

Results: Our study identified impaired CD4 T helper function of STX11-deficient CD4 T cells, resulting in a secondary B cell defect presented by disturbed germinal center (GC) formation, reduced isotype-class switch and low antibody avidity.

Conclusions: This unexpected function of STX11 in CD4 T cells demonstrates fundamental insights into T-B cell interaction. Additionally thes findings might have cobsequences for the clinical management of FHL-4 patients, since it identifies additional immunological vulnerability to bacterial and viral infections of this particular patient group.

Disclosure: No.

Keywords: T/B cell interaction, Syntaxin 11, FHL-4, Hemophagocytic Lymphohistiocytosis, Secondary B cell defect

PD160

THE EFFECTIVITY AND TOXICITY of STEROIDS AS FIRST LINE TREATMENT FOR GRANULOMATOUS LYMPHOCYTIC INTERSTITIAL LUNG DISEASE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Bas Smits[1], Sigune Goldacker[2], Suranjith Seneviratne[3], Marion Malphettes[4], Hilary Longhurst[5], Omar Mohamed[6], Carla Witt-Rauberger[7], Lucy Leeman[8], Eva Schwaneck[9], Isabelle Raymond[10], Kilifa Meghit[11], Annette Uhlmann[12], Christine Winterhalter[2], Joris Van Montfrans[13], Sarita Workman[14], Claire Fieschi[15], Sonja Boyle[16], Shamin Onyango-Odera[6], Suzanne Price[8], Valerie Aurillac[10], Antje Prasse[17], Ineke Hartmann[18], Jennifer Meerburg[18], Mariette Kemner-Van De Corput[18], Harm Tiddens[18], Bodo Grimbacher[19], Peter Kelleher[20], Smita Patel[21], Anne-Sophie Korganow[22], Jean-Francois Villiard[10], Claire Bethune[23], Hans Tony[9], Hendrik Schulze-Koops[7], Torsten Witte[24], Aarn Huissoon[25], Helen Baxendale[16], Sofia Grigoriadou[26], Eric Oksenhendler[27], Siobhan Burns[28], Klaus Warnatz[29]
[1]UMC Utrecht, Pedriatric Immunology, Utrecht, Netherlands, [2]Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Center For Chronic Immunodeficiency (cci), Freiburg im Breisgau, Germany, [3]Royal Free London NHS Foundation Trust, Department of Immunology, London, United Kingdom, [4]Hôpital Saint Louis, Department of Clinical Immunology, Paris, France, [5]Barts and the London NHS Trust, Immunology, London, United Kingdom, [6]Birmingham Heartlands Hospital, Primary Immunodeficiency Centre, Birmingham, United Kingdom, [7]University of Munich, Medicine Iv, Munich, Germany, [8]University Hospitals Plymouth, Peninsula Immunology And Allergy Service, Plymouth, United Kingdom, [9]University Hospital, Medicine, Wurzburg, Germany, [10]Centre Hospitalier Universitaire of Bordeaux, Internal Medicine, Bordeaux, France, [11]University Hospitals of Strasbourg, Clinical Immunology And Internal Medicine, Strasbourg, France, [12]University Hospital Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [13]University Medical Center Utrecht, Department of Rheumatology & Clinical Immunology, Utrecht, Netherlands, [14]Royal Free Hospital, Clinical Immunology, London, United Kingdom, [15]Saint Louis Hospital, Immuno-hematology, Paris, France, [16]Papworth Hospital, Immunology, Cambridge, United Kingdom, [17]Deutsches Zentrum für Lungenforschung, Respiratory Medicine, Hannover, Germany, [18]Erasmus Medical Center, Department of Pediatric Respiratory Medicine And Department of Radiology, Rotterdam, Netherlands, [19]Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany, [20]Imperial College London, Immunology Section Department of Medicine, London, United Kingdom, [21]University of Oxford, Nihr Brc Oxford Biomedical Research Centre, Oxford, United Kingdom, [22]Tertiary Center for Primary Immunodeficiency, Strasbourg University Hospital, Department of Clinical Immunology And Internal Medicine, National Reference Center For Systemic Autoimmune Diseases (cnr Reso, Strasbourg, France, [23]University Hospitals Plymouth NHS Trust, Immunology And Allergy Service, Plymouth, United Kingdom, [24]Hannover Medical School, Rheumatology And Immunology, Hannover, Germany, [25]University Hospitals Birmingham NHS Foundation Trust, Department of Clinical Immunology, Birmingham, United Kingdom, [26]Barts Health NHS Trust, Department of Immunology, London, United Kingdom, [27]Hopital Saint Louis, Université de Paris Cité, Clinical Immunology, Paris, France, [28]UCL, Institute of Immunity And Transplantation, London, United Kingdom, [29]Medical Center - University of Freiburg, Rheumatology And Clincal Immunology, Freiburg, Germany

Background and Aims: Granulomatous and lymphocytic interstitial lung disease (gl-ILD) is a major cause of morbidity and mortality among patients with common variable immunodeficiency. Corticosteroids are propagated as first-line treatment for gl-ILD, but evidence for its efficacy is lacking. Our aim was to analyze the effect of high dose corticosteroids (>0.5mg/kg) on gl-ILD, measured by high-resolution computed tomography (HRCT) scans and/or pulmonary function test (PFT) results.

Methods: Patients who had received high dose corticosteroids and who underwent repeated HRCT scanning or PFTs during the retrospective and/or prospective phase of the STILPAD study (n=42) were included in the analysis. Patients who had not received immunosuppressive treatment were selected as controls (n=24). HRCT scans were blinded, randomized and scored using the Hartman score. Differences between the baseline and follow up HRCT scan and PFT results were analyzed.

Results: Treatment with high dose corticosteroids significantly improved HRCT scan scores and forced vital capacity ($p<0.01$). Carbon monoxide diffusion capacity significantly improved in both groups. 16/25 patients, for whom further follow-up data was available, achieved a long-term, maintenance therapy independent remission. All patients with relapse were re-treated with corticosteroids, but only 2/9 responded. Corticosteroid treatment was not associated with more infections, however three opportunistic infections were observed among the corticosteroid group and none among the untreated group.

Conclusions: Induction therapy with high dose corticosteroids improved the HRCT scans and PFT of patients with gl-ILD and achieved long-term remission in the majority of patients. It was not associated with major side-effects.

Disclosure: No.

Keywords: gl-ILD, CVID, observational trial, corticosteroids, Hartmann Score, pulmonary function tests

PD161

EARLY CHILDHOOD LYMPHOCYTE COUNTS IN THE PREDICTION of CLINICAL COURSE IN CARTILAGE-HAIR HYPOPLASIA – A LONGITUDINAL STUDY of 32 PATIENTS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Eetu Pello[1], Leena Kainulainen[2], Paula Klemetti[3], Mervi Taskinen[4], Outi Mäkitie[3], Svetlana Vakkilainen[3]
[1]University of Helsinki, Research Program For Clinical And Molecular Metabolism, Helsinki, Finland, [2]Turku University Hospital, Dept. of Peadiatrics And Adolescents, Turku, Finland, [3]University of Helsinki and Helsinki University Hospital, Children's Hospital And Pediatric Research Center, Helsinki, Finland, [4]Helsinki University Hospital and University of Helsinki, Pediatric Hematology-oncology, Children And Adolescents, Helsinki, Finland

Background and Aims: Cartilage-hair hypoplasia (CHH) is a metaphyseal chondrodysplasia with variable immunodeficiency caused by biallelic variants in the untranslated *RMRP* gene. Laboratory immune parameters in CHH vary and their potential to predict disease outcome is uncertain. Our aim was to describe longitudinal changes in lymphocyte counts during childhood and explore potential correlations between clinical manifestations and immunologic laboratory values in early childhood and the clinical outcome of CHH.

Methods: The study included 32 children (median follow-up time 6.1 years) with genetically verified CHH. Immunologic laboratory indices in early childhood, birth length, the presence of Hirschsprung disease and transfusion-dependent anemia were correlated to the primary endpoints of recurrent, opportunistic and severe infections.

Results: Median values of lymphocyte subclass counts were subnormal and did not show age-related decline apart from NK cells. Lymphocyte subclass counts in early childhood or immunoglobulin levels did not correlate with the number of infections. In contrast, lymphocyte proliferation responses correlated with the incidence of severe or opportunistic infections; CD4+ cell counts correlated with severity of immunodeficiency. Birth length below -4.0 SDS correlated with lower lymphocyte counts, but not with incidence of infections. Many CHH patients with low lymphocyte subclass counts managed well without clinical interventions.

Conclusions: Lymphocyte subclass counts alone do not predict clinical outcomes in CHH. We conclude that clinical management decisions in CHH, such as prophylactic antibiotics, immunoglobulin replacement therapy or hematopoietic stem cell transplantation, should not be based solely on laboratory immune parameters.

Disclosure: No.

Keywords: SCID, Cartilage-Hair Hypoplasia, RMRP, immunodeficiency

PD162

VARIANT of UNKNOWN SIGNIFICANCE IN CARMIL2 RESULTS IN HYPOMORPHIC FUNCTION WITH DECREASED INTERLEUKIN-2 (IL-2) PRODUCTION

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Asha Elmi, Amel Hassan, Rafah Mackeh, Khaled Machaca, Satanay Hubrack
Sidra Medicine, Research, Doha, Qatar

Background and Aims: CARMIL2 (Capping protein Regulator and Myosin 1 Linker 2) is a cytoplasmic protein that is involved in cytoskeletal organization which mediates cell migration, and it is indispensable for CD28 co-stimulation of T cells. It has been reported that mutations in CARMIL2 result in primary combined immunodeficiency represented by cytoskeletal dynamics distortion, impaired CD28- T cells co-signaling, and Epstein Barr Virus-induced smooth muscle tumors. Here, we report a 9-years old female patient with homozygous missense VUS in the helical dimerization domain of the CARMIL2 protein in exon 21. Patient was diagnosed with infantile hemorrhagic edema at age 22 months. Starting at age 3.5 years, she presented with recurrent infections, mainly pneumonia complicated with pleural effusion and requiring PICU admission. She also had gastroenteritis, viral upper respiratory tract infections, skin abscesses, rashes, keratosis pilaris, and a family history of early infant deaths.

Methods: CFSE was done to assess T cells proliferation. ELISA was conducted to quantify IL-2 cytokine.

Results: Analysis of T cell subsets showed normal Treg distribution and an increase in naïve T cells compared to healthy donors. TCR-induced T-cell proliferation assays using anti-CD3 or anti-CD3/anti-CD28 soluble antibodies showed a partial decrease in the proliferation and CD25 expression that are both rescued by IL-2 addition. Quantification of IL-2 showed a reduction in IL-2 secretion compared to healthy controls and a heterozygous family member.

Conclusions: Collectively these data confirm the hypomorphic effect of this CARMIL2 variant located at the helical dimerization domain of this protein, expanding the genotypic and phenotypic spectra of CARMIL2 mutations.

Disclosure: No.

Keyword: CARMIL2, Epstein Barr Virus-induced smooth muscle tumors (EBV-SMTs), helical dimerization domain

PD163

EXPLORING THE DNA METHYLATION PATTERN IN IMMUNE CELLS of A FAMILY WITH VARIABLE MANIFESTATION of ICF2 SYNDROME

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Natalia Dubrowinskaja[1,2], Manfred Anim[1], Georgios Sogkas[1,2], Sören Franzenburg[3], Torsten Witte[1,2], Faranaz Atschekzei[1,2]
[1]Hannover Medical School, Rheumatology And Immunology, Hannover, Germany, [2]Hanover Medical School, Resist-Cluster of Excellence, Hannover, Germany, [3]Kiel University (CAU), Institute of Clinical Molecular Biology, Kiel, Germany

Background and Aims: Immunodeficiency, centromeric instability and facial anomalies syndrome 2 (ICF2) is a rare autosomal recessive primary immunodeficiency disorder. Immune deficiency in these patients ranged from late-onset combined immunodeficiency (CID) with severe respiratory tract infections and recurrent shingles to asymptomatic selective antibody deficiency. Here, we present three siblings with ICF2, including two dizygotic twin sisters. Evident clinical heterogeneity manifested despite the same deleterious mutation in *ZBTB24* and common genetic background, suggesting the relevance of aberrant epigenetic modification in disease pathogenesis.

Methods: DNA methylation was estimated in CD19+ B and CD4+ T cells of the patients and healthy controls utilising the Infinium Methylation 850k EPIC array. R statistical program was used for the data analysis. The results were validated using the standard gold method of pyrosequencing.

Results: Individual CpG sites with significantly altered methylation, the so-called differentially methylated positions (DMPs) and differentially methylated regions (DMRs), were identified between affected and healthy individuals. The identified DMPs/DMRs were immune cell-specific and located in gene coding and non-gene coding regions. For some selected DMRs, the results in Pyrosequencing were confirmed.

Conclusions: Our results indicate the role of aberrant DNA methylation as one of the epigenetic mechanisms involved in the pathogenesis of PIDs. Further investigations are required to examine the potential of DNA methylation as a diagnostic, prognostic or predictive marker.

Disclosure: No.

Keywords: immunodeficiency, primary immunodeficiency, antibody deficiency, Epigenetic, DNA methylation

PD164

AUTOIMMUNITY IN MONOGENIC COMBINED IMMUNE DEFICIENCIES WITH ASSOCIATED OR SYNDROMIC FEATURES

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Niusha Sharifinejad[1], Gholamreza Azizi[1], Zahra Chavoshzadeh[2], Seyed Alireza Mahdaviani[3], Mahnaz Seifi Alan[4], Marzieh Tavakol[1], Homa Sadri[1], Mohammad Nabavi[5], Sareh Sadat Ebrahimi[6], Afshin Shirkani[7], Ahmad Vosughi Motlagh[8], Molood Safarirad[8], Fatemeh Aghamahdi[1], Farzad Nazari[9], Samaneh Delavari[9], Mahnaz Jamee[10], Farimah Fayaz[11], Parham Samimisedeh[12], Rahman Matani[1], Marzie Esmaeili[9], Nima Rezaei[9], Reza Yazdani[9], Hassan Abolhassani[9,13]
[1]Alborz University of Medical Sciences, Non-communicable Diseases Research Center, Karaj, Iran, [2]Pediatric Infections Research Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3]National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Pediatric Respiratory Diseases Research Center, Tehran, Iran, [4]Alborz University of Medical Sciences, Karaj, Iran, Cardiovascular Research Center, Karaj, Iran, [5]Iran University of Medical Science (IUMS), Allergy & Clinical Immunology, Tehran, Iran, [6]Kerman University of Medical Sciences, Department of Immunology And Allergy, Kerman, Iran, [7]Bushehr University of Medical Science, Allergy And Clinical Immunology Department, Bushehr, Iran, [8]North Khorasan University of Medical Sciences, Department of Pediatrics, Bojnurd, Iran, [9]Tehran University of Medical Sciences, Research Center For Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran, Iran, [10]Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Pediatric Nephrology Research Center, Tehran, Iran, [11]Iran University of Medical Scienses, Colorectal Research Center, Tehran, Iran, [12]Alborz University of Medical Sciences, Cardiovascular Research Center, Karaj, Iran, [13]Karolinska Institute, Division of Clinical Immunology, Department of Biosciences And Nutrition, Stockholm, Sweden

Background and Aims: Combined immune deficiencies (CIDs) with associated or syndromic features are a highly heterogeneous subgroup of inherited immune disorders. These patients represent specific clinical manifestations with an increased risk of autoimmune conditions.

Methods: We analyzed data of monogenic patients with syndromic CIDs obtained from the Iranian inborn errors of immunity registry. A comparison was provided between patients with and without autoimmunity and also among three mutation groups with the most registered cases including ataxia-telangiectasia (AT), hyper-IgE syndromes (HIES), and immunodeficiency with centromeric instability and facial anomalies (ICF).

Results: A total of 137 patients with monogenic syndromic CIDs were included; mainly with mutations in the *ATM* [80 (58.4%)] and *STAT3* [19 (13.9%)] genes, followed by *DNMT3B* [11 (8%)], and *WAS* [11 (8%)]. More than 18% of all patients with syndromic CIDs, including most ICF patients, were clinically diagnosed with antibody deficiencies before genetic evaluation. Autoimmune disorders were diagnosed in 24 patients at a median age of 3.5 (2.6-6.0) years, 70.6% of which were diagnosed prior to the diagnosis of immunodeficiency. Lymphoproliferation was significantly higher in patients with autoimmunity (p=0.004). Syndromic CID patients with autoimmunity had significantly lower IgG levels. Hematologic autoimmunity mainly immune thrombocytopenic purpura was the most frequent autoimmunity among AT, HIES and ICF, however AT patients present more diversified involved organs including rheumatologic, gastrointestinal and dermatologic autoimmunity.

Conclusions: About 18% of patients with monogenic syndromic CIDs developed autoimmunity, mainly in the form of hematological immune diseases. Autoimmunity could be an early-onset involvement with a potential diagnostic impact on suspicious cases of syndromic CIDs.

Disclosure: No.

Keywords: Inborn errors of immunity, primary immunodeficiency, combined immunodeficiency syndrome, Autoimmunity, Immune Dysregulation

PD165

A NOVEL NFKB1 SPLICE VARIANT PRESENTING WITH MULTIPLE LYMPHOCYTIC BONE LESIONS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Anne Ari, Tal Freund, Dikla Adir, Shira Benor, David Hagin
Tel-Aviv Sourasky Medical Center, Allergy And Clinical Immunology Unit, Tel-Aviv, Israel

Background and Aims: Heterozygous *NFKB1* mutations cause a wide clinical phenotype including common variable immunodeficiency (CVID), multi-organ immune dyregulation, lymphproliferation and susceptibility to infections. We aim to descibe the clinical phenotype af a novel *NFKB1* variant.

Methods: Genetic evaluation was performed using a custom NGS panel, followed by flow cytometry-based lymphocyte immunophenotyping.

Results: A 36y/o male was evaluated for incidental finding of multiple bone lesions. The patient first presented 8 years prior with abdominal pain, elevated liver functions and elevated inflammatory markers. Full GI evaluation was unrevealing, and accompanying immune workup showed low IgG levels (~600mg/dL) and low anti-pneumococcal antibody titers. While CVID was suspected, given the absence of infections and spontaneous clinical resolution, no treatment was initiated. At age 35, he acutely presented with severe lower back pain. MRI showed multiple hyperintense bone lesions involving the spine and pelvis, and PET-CT demonstrated hypermetabolic retroperitoneal lymphadenopathy and hypermetabolic activity in the pelvic bones bilaterally. Biopsy of a bone lesion showed reactive lymphocytic infiltrates without evidence of clonality (NGS seq). of note, family history was significant for a sister with mild hypogammaglobulinemia and inguinal lymphadenopathy. This was followed by genetic evaluation which revealed a novel *NFKB1* splice variant (c.2227+2T>G) located downstream to exon 19, and predicted to affect the ANK domain of the p105 precursor. Both the proband's sister and their asymptomatic father were carriers of the same variant, and all showed significantly low class-switched (IgM-/IgD-, IgG+ or IgA+) memory B-cells on immunophenotyping.

Conclusions: We describe non-malignant lymphocytic bone infiltration as a novel manifestation of *NFKB1* haplo-insufficiency. The patient is now awaiting sirolimus and bisphosphonate treatment.

Disclosure: No.

Keywords: Lymphocytic infiltration, Bone lesions, IEI, NFKB1, Immune Dysregulation

PD166

NEUROINFLAMMATORY LESIONS IN CVID

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Anju Sivadasan[1], Intisar Abdelhakam[2], Shanti Mahabir[1]
[1]University Hospitals Leicester, Immunology, Leicester, United Kingdom, [2]University Hospital of Leicester, Immunology, Leicester, United Kingdom

Background and Aims: More than a third of patients with CVID develop non-infectious complications due to immune dysregulation including autoimmune cytopenia, granulomatous disease, and inflammatory bowel disease (IBD). CNS involvement is a rare but serious complication and appears to be a manifestation of systemic immune dysregulation.

Methods: Case series. We present 2 such patients who were diagnosed with neuroinflammatory lesions in the brain which proved to be CNS vasculitis.

Results: 2 patients with CNS manifestation and previous diagnosis of CVID were identified. Both had background of autoimmune cytopenia, one had granulomatous-lymphocytic interstitial lung disease (GLILD) and the other had IBD. Infection was excluded as a cause in both patients and brain biopsy showed vasculitis with predominant lymphoid infiltrate. Both patients had CD4, NK and B cell lymphopenia with class switched memory B cells < 2%. One patient had subsequent genetic diagnosis of CTLA4 deficiency. Both patients responded well to high-dose steroids, but one of them had a relapse after steroids were tapered and stopped.

Conclusions: CNS disease in CVID is rare but may be severe. A high index of suspicion and extensive diagnostic workup may be required to reach a diagnosis. Underlying monogenic disorder should be looked for in such patients. CNS disease usually responds well to high dose steroids but may require maintenance therapy to prevent relapse. **References:** Structural Noninfectious Manifestations of the Central Nervous System in Common Variable Immunodeficiency Disorders - van de Ven, Annick et al. Journal of Allergy and Clinical Immunology. In Practice; Vol. 8, Iss. 3, (Mar 2020): 1047-1062.e6.

Disclosure: No.

Keywords: Neuroinflammatory lesions, Non-infectious complication, CVID, Immune Dysregulation

PD167

DOWN SYNDROME; A COMBINED IMMUNODEFICIENCY WITH IMMUNE DYSREGULATION!

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Gonca Hancioglu[1], Aysegul Yilmaz[2], Alisan Yildiran[1]
[1]ondokuz mayis university, Pediatric Immunology, Samsun, Turkey, [2]ondokuz mayis university, Genetics, samsun, Turkey

Background and Aims: Down Syndrome(DS) is a multi-systemic disease associated with congenital malformations. In these patients, infections are the most common cause of hospital admissions and mortality. Although structural defects in congenital anomalies relatively explain the susceptibility to infections, the chromosomal disorder, which constitutes the genetic basis of innate and acquired immunity, should not be ignored. Not only increased susceptibility to infection, but also immune dysregulation findings such as hematological malignancies, autoimmunity and autoinflammatory diseases are observed. In this study, the clinical and immunological data of our DS patients were reviewed.

Methods: Clinical and laboratory findings of 40 DS patients who applied to pediatric immunology clinic between 2020-2021 were evaluated retrospectively.

Results: 75% of the patients admitted with the complaint of frequent respiratory tract infections whereas 50% had a history of intensive care hospitalization. Moreover, findings of chronic inflammations such as autoimmune thyroiditis, alopecia, autoimmune hepatitis, enteropathy, hidradenitis supirativa were present in 83% of the patients. IgM and IgE levels of 61% of the patients were low for their age. The CD4/CD8 ratio was reversed in 40% of patients. B cells and Memory B cells were found to be low in 61% of patients.

Conclusions: A limited number of studies have shown that both innate and adaptive immunity are affected in DS. Although they are similar in some aspects to monogenic primary immunodeficiencies, they differ from these diseases in many aspects. DS patients should be considered as 'non-monogenic combined immunodeficiency' similar to the 22q11.2 deletion syndrome.Necessary examination and follow-up should be performed by the immunology clinics.

Disclosure: No.

Keyword: Down Syndrome, Immune Dysregulation, Combine Immune deficiency

PD168

PUNCTATE INNER CHOROIDOPATHY IN A PATIENT WITH COMMON VARIABLE IMMUNODEFECIENCY ASSOCIATED WITH POINT MUTATION IN THE TUMOUR NECROSIS FACTOR RECEPTOR SUPERFAMILY 13B (TNFRSF13B) GENE

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Hiba Salih[1], Charu Chopra[2], Kelvin Chengkahwai[3], Justin Mckee[4]
[1]Royal Infirmary of Edinburgh-NHS Lothian, Registrar-immunology, Edinburgh, United Kingdom, [2]Royal Infirmary of Edinburgh-NHS Lothian, Consultant-immunology, Edinburgh, United Kingdom, [3]Princess Alexandra Eye Pavilian - NHS Lothian, Registrar-ophthalmology, Edinburgh, United Kingdom, [4]Princess Alexandra Eye Pavilian - NHS Lothian, Consultant-ophthalmology, Edinburgh, United Kingdom

Background and Aims: To report a case of punctuate inner choroidopathy(PIC) in a patient with common variable immunodeficiency(CVID).

Methods: Clinical case, investigations results review; literature review.

Results: A lady with CVID, autoimmune thrombocytopenia, treated with immunoglobulin and Eltrombopag experienced deteriorating vision. Fundal examination and optical coherence tomography revealed multifocal retinal choroidal lesions consistent with unilateral PIC, an idiopathic inflammatory condition, with secondary choroidal neovascularisation. Testing for toxoplasma gondii and mycobacterial infections were negative. Intraretinal anti-VEGF therapy stabilised fundal appearances. Molecular testing revealed a heterozygous pathogenic variant in TNFRSF13B, a gene associated with ~10% of CVID cases(1). Single allele mutations in TNRSF13B have been reported in patients with CVID and associated autoimmunity, and in a patient with CVID and submacular choroiditis(2).

Conclusions: Autoimmunity (most commonly cytopenias) may be seen in up to 17% of CVID cases (3). We report a case of PIC in a patient with CVID and a heterozygous TNFRSF13B pathogenic mutation. PIC, to the best of our knowledge, has not been previously reported in CVID. Molecular pathogenesis and role of targeted therapy for PIC in CVID requires further research. References: 1. John et al.2008: Transmembrane activator calcium-modulator cyclophilin ligand interactor mutations in common variable immunodeficiency. Curr Allergy Clin Immunol 2008Dec;8(6):520 2. Peng et al.2020: Submacular choroiditis in common variable immunodeficiency associated with a pathogenic mutation in tumor necrosis factors gene.Am J Opthalmol Case Rep.2020 Dec;20:100909. 3. Quinti et al.2007: Longterm Followup and outcome of large cohort of patient with Common Variable Immunodefeciency. J Clin Immunol. 2007;27:308-316.[PubMed]

Disclosure: No.

Keyword: Autoimmunity; Immunodeficiency

PD169

IMMUNE DYSREGULATION IN KABUKI SYNDROME: A CASE REPORT

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Lucia Leonardi[1], Roberto Paparella[1], Francesca Conti[2], Antonio Marzollo[3], Fiorina Giona[4], Gian Marco Andreoli[1], Francesco Costantino[1], Alberto Spalice[1], Luigi Tarani[1]
[1]Policlinico Umberto I- Sapienza University, Maternal Infantile Department, roma, Italy, [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Pediatric Unit, Bologna, Italy, [3]Univerita degli Studi di Padova, Paediatrics, Padova, Italy, [4]Policlinico Umberto I- Sapienza University, Department of Translational And Precision Medicine, Sapienza University, Rome, Italy, roma, Italy

Background and Aims: A 23-year-old woman, clinically diagnosed with Kabuki Syndrome (KS) and Evans Syndrome (ES) was referred to our Pediatric Department for corticosteroid-induced diabetes onset. The patient underwent several courses of corticosteroids due to ES relapses and presented with recurrent respiratory infections.

Methods: When admitted to our hospital, the patient presented with peculiar KS clinical feature and clinical side-effects of systemic glucocorticoids therapy. Splenomegaly and signs of chronic lung inflammation and interstitial lung disease were also described at HRTC. An immunological study was performed highlighting severe hypogammaglobulinemia (IgG= 200 mg/dl, IgA= 2 mg/dl and IgM= 149 mg/dl). Nonsense variant in the *KMT2D* (NM_003482.3) gene: c.8974G>T, p.Glu2992Ter was detected. Supportive treatment with amoxicillin/clavulanate prophylaxis and facilitated subcutaneous immunoglobulin replacement was immediately started. Six months later, no infections were reported. Conversely, ITP had partially been responsive to high-dose prednisone treatment. Alternative therapies, including Rituximab have been considered.

Results: KS is a rare multisystemic disease due to mutations in the *KMT2D* or *KDM6A* genes, which act as epigenetic modulators of different processes, including immune response. Failure of both B-cell development and autoreactive immune cells suppression leads to immunodeficiency and autoimmunity that, however, may be undiagnosed for long time. Our patient's case is paradigmatic, since she presented, years after disease onset, with iatrogenic morbidity and severe lung disease.

Conclusions: This case emphasizes the importance of suspecting immune-dysregulation in KS patients. It also highlights the need to perform immunologic evaluations at the time of both KS diagnosis and during disease follow up in order to allow proper treatment while avoiding preventable morbidity in these patients.

Disclosure: No.

Keywords: Kabuki syndrome, EVANS SYNDROME, hypogammaglobulinemia, Immune Dysregulation

PD170

THE NEXT GREAT MASQUERADER: FOUR PATIENTS WITH ACTIVATING PIK3CD MUTATIONS AND DIVERSE PHENOTYPES

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Elma Fuentes[1], Michelle Arenas Hernandez[1], Estefania Vazquez Echeverri[1], Maria Zarate Hernandez[2], Mario Cruz Muñoz[3], Selma Scheffler-Mendoza[4], Edgar Medina Torres[1], Lina Castaño Jaramillo[4], Juan Carlos Bustamante Ogando[1], German De La Garza Fernandez[1], Laura Berron Ruiz[1], Maria Edith González Serrano[1], Gabriela Lopez Herrera[1], Marco Yamazaki-Nakashimada[4], Sara Espinosa Padilla[1], Saúl Lugo Reyes[1]
[1]National Institute of Pediatrics, Primary Immunodeficiency Research Unit, Mexico City, Mexico, [2]University Hospital "Dr. José Eleuterio González", Regional Center of Allergy And Clinical Immunology, Monterrey, Mexico, [3]Autonomous University of the State of Morelos, Molecular Immunology Laboratory, School of Medicine, Cuernavaca, Mexico, [4]National Institute of Pediatrics, Immunology, Mexico City, Mexico

Background and Aims: BACKGROUND:
PIK3CD-GOF is an inborn error of immunity (IEI) with variable phenotypic characteristics even with the same variant. Lymphoproliferation, autoimmunity, and dysgammaglobulinemia may lead to suspicion of the diagnosis.

Methods: Here we present four unrelated Mexican patients from nonconsanguineous families with a diagnosis of PIK3CD-GOF with exome sequencing.

Results: Case reports:
-A 2-year-old female with a history of very early-onset inflammatory bowel disease (VEO-IBD) at 8 months, late omphalorrhexis, hyper-IgA, hyperleukocytosis, and low B and NK cells.

-A 12-year-old male with a family history of lymphoma. Sepsis due to Listeria, periodontal abscess, systemic lupus erythematosus, Sjögren's syndrome, bronchiectasis, hepatosplenomegaly, lymphadenopathy, autoimmune hemolytic anemia, chronic EBV/CMV infection; leukocytosis and hyper-IgM.

-A 2-year-old male with chronic rhinosinusitis, chronic suppurative otitis media, diarrhea; enlarged lymph nodes, splenomegaly, thrombocytopenia, low IgG and IgA and normal IgM with poor antibody response to pneumococcal vaccine. Hyper-IgM syndrome was suspected so he underwent successful stem cell transplantation.

-An 11-year-old male child whose both parents were HIV+. Presented at 4-months with episodic fever and recurrent respiratory infections, bronchiectasis, mild mental retardation elevated IgM, low IgG, lymphopenia, and decreased lymphocyte proliferation. HIV were suspected in this patient.

We identified heterozygous pathogenic variants related to PIK3CD: 3 of them in exon 24 (p.Glu1021Lys); and a novel variant in exon 7 (p.Ile262Val).

Conclusions: PIK3CD-GOF is a combined immunodeficiency disorder (CID) with variable phenotype characteristics even with the same variant. Lymphoproliferation, autoimmunity, and dysgammaglobulinemia may raise suspicion. By behaving like a great simulator, genetic diagnosis is necessary to identify the specific pathogenic variant.

Disclosure: No.

Keywords: immunodeficiency, gain of function mutation, PIK3CD, mutations, immunologic deficiency syndromes

PD171

THE EXPANDING PHENOTYPE of MKL1 DEFICIENCY: FROM INFECTIOUS SUSCEPTIBILITY TO IMMUNE DYSREGULATION

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Marta Benavides-Nieto[1,2,3], Alexandre Kauskot[4], Frédéric Adam[4], Antoine De Giacomoni[1,2], Alice Corsia[1,5], Benjamin Fournier[1,5,6], Jean-Claude Bordet[7], Yanick Crow[1,8], Marie-Louise Frémond[1,5,8], Capucine Picard[1,5,6,9], Jean-Pierre De Villartay[1,2], Despina Moshous[1,2,5]
[1]Université Paris Cité, Imagine Institute, Paris, France, [2]Genome Dynamics in the Immune System Laboratory, Inserm, Umr1163, Imagine Institute, Paris, France, [3]Supported by the ESID Research Grant (ERG), 2021/2022, Paris, France, [4]Paris-Saclay University, Inserm Umr S 1176, LE KREMLIN BICETRE, France, [5]Necker Hospital, Pediatric Hematology-immunology And Rheumatology Unit, Paris, France, [6]Laboratory of Lymphocyte Activation and Susceptibility to EBV Infection, Inserm, Umr 1163, Institut Imagine, Paris, France, [7]Laboratoire d'Hémostase, Centre De Biologie Est, Hospices Civils De Lyon, Bron, France, [8]INSERM UMR1163, Imagine Institute, Laboratory of Neurogenetics And Neuroinflammation, Paris, France, [9]APHP, Study Center For Primary Immunodeficiencies, Paris, France

Background and Aims: Megakaryoblastic leukemia 1 (MKL1) or myocardin-related transcription factor A (MRTF-A) is a coactivator of serum response factor (SRF), which regulates transcription of actin and actin cytoskeleton–related genes. MKL1 is predominantly expressed in neutrophils and monocytes (Bagger-2019) and is found in the cytoplasm in complex with globular actin. Upon actin polymerization MKL1 is released and translocated to the nucleus activating SRF-dependent transcription. Homozygous frameshift *MKL1* mutations have been reported in patients with susceptibility to bacterial infections and neutrophil dysfunction (Record-2015; Sprenkeler-2020)

Methods: Real-time-PCR (qPCR), Western blotting, platelets and mesenchymal stem cell (MSC) functional analysis.

Results: We investigated a female patient presenting since birth with repeated ulcerative lesions, fever, neutrophilia, and high inflammation markers, but without microbiologic documentation. She presented mild CD4+ lymphopenia, increased IL-6, TNFα and IL-1 serum levels and responded to biotherapy (Anakinra, Canakinumab) as bridging therapy to HSCT. NGS panel revealed a novel homozygous mutation c.1384C>T p.R462X in *MKL1*. Analysis of relative gene expression by qPCR showed present, but significantly diminished MKL1 in patient's whole blood cells and MSC as well as reduced β-actin and SRF. Patient's platelets showed decreased cytoskeleton-associated protein expression and functional defects. MSC migration was normal. p50 and NF-Kb2 expression was increased in patient's MSC as well as IL-1β-induced p65 activation.

Conclusions: Our observations expand the phenotype of *MKL1* mutations and their impact in dysregulation of cytoskeleton proteins, platelet function and NF-kB activation suggesting that biallelic MKL1 mutations should be considered as a novel cause of inborn errors of immunity associated with immune dysregulation and hyperinflammation.

Disclosure: No.

Keywords: myocardin-related transcription factor A (MRTF-A), Megakaryoblastic leukemia 1 (MKL1), p65 activity, Immune Dysregulation, impaired cytoskeleton dynamics

PD172

SYSTEMS BIOLOGY AND MACHINE LEARNING APPROACHES IDENTIFY COMMON VARIABLE IMMUNODEFICIENCY PATIENTS WITH IMMUNE DYSREGULATION MANIFESTATIONS

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Antonios Gkantaras[1], Andigoni Malousi[2], Evangelia Farmaki[1]
[1]Aristotle University of Thessaloniki, Paediatric Immunology And Rheumatology Referral Center, 1st Department of Paediatrics, Thessaloniki, Greece, [2]Aristotle University of Thessaloniki, Laboratory of Biological Chemistry, School of Medicine, Thessaloniki, Greece

Background and Aims: The lack of sensitive biomarkers to identify common variable immunodeficiency (CVID) patients with immune dysregulation/non-infectious manifestations remains a major challenge, given the excess mortality among this subgroup compared to the only-infections phenotype. Hence, we employed a bioinformatics pipeline to identify a gene expression signature associated with immune dysregulation in CVID, followed by implementing supervised machine learning (ML) models to evaluate the classification accuracy of the identified transcriptomic signature.

Methods: From Gene Expression Omnibus, we retrieved the dataset **GSE51405** containing 48,803 peripheral blood mRNA expression patterns from 59 CVID subjects (only-infections:30; immune dysregulation:29). Using R programming language, differential expression analysis was performed to identify differentially expressed genes (DEGs) between CVID patients with *vs* without immune dysregulation, followed by Reactome pathway analysis to investigate their biological significance. Using DEGs as features, we further employed a set of supervised ML algorithms [kNN (k=3,4,5), SVM (linear-, RBF-, cubic polynomial-kernel), Decision Tree, Random Forest] to predict immune dysregulation in CVID.

Results: We identified 92 DEGs (adj.*p*-value<0.05; 73 upregulated in CVID with immune dysregulation *vs* only-infections). Top enriched Reactome pathways included: interferon signalling, complement cascade, NOD-like receptor signalling, and ER-phagosome pathway. Excluding kNN(k=3), all examined classifiers demonstrated 100% sensitivity in predicting immune dysregulation in CVID patients, whereas kNN(k=4) and cubic kernel-SVM achieved the best global accuracy of 93.3%.

Conclusions: CVID subjects with immune dysregulation were distinguished by pronounced upregulation of multiple innate immunity pathways. The high sensitivity of the employed classifiers indicates that the identified DEGs may represent potent biomarkers with diagnostic, prognostic and therapeutic target value for CVID.

Disclosure: No.

Keywords: Machine Learning, Transcriptomics, Common variable immunodeficiency, Immune Dysregulation, Innate Immunity, Bioinformatics

PD173

RECOMBINANT ADA ENZYME REPLACEMENT THERAPY (ERT) IN PATIENTS AFTER LONG TERM TREATMENT

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Fulvio Porta[1], Stefano Rossi[1], Alessandra Beghin[2], Marta Comini[2], Federica Bolda[2], Elena Soncini[1], Giulia Baresi[1], Arnalda Lanfranchi[2]
[1]Spedali Civili di Brescia, Bone Marrow Transplant Unit 'monica E Luca Folonari', Brescia, Italy, [2]ASST Spedali Civili di Brescia, Stem Cell Laboratory, Section of Hematology And Blood Coagulation, Clinical Chemistry Laboratory, Diagnostic Department, Brescia, Italy

Background and Aims: Adenosine Deaminase (ADA) deficiency represents approximately 10-15% of all Severe Combined Immunodeficiency (SCID), the therapeutic options being enzyme replacement therapy (ERT), hematopoietic stem cell transplantation (HSCT) and gene therapy (GT).

Methods: Here we report on 34 patients diagnosed with ADA-SCID with biochemical and molecular test: ADA activity in red blood cells (RBC) (nv 0.8-2.5 U/gHb) Dosage of ADA toxic metabolites: AXP (nv 0.8-1.6 µmol/ml RBC), dAXP (nv <0.005 µmol/ml RBC); %dAXP (nv <0.5%) ADA gene sequencing

Results: We diagnosed a total amount of 34 patients with ADA-SCID. ADA activity was available at diagnosis, before beginning of ERT, for 18/34 patients; median values was 0.655 U/gHb 0.13-1.18. ADA toxic metabolites dosage was available at diagnosis for 25/34 patients (AXP median value 1.4215 µmol/ml RBC 0,187-2.656), (dAXP 0.9455 µmol/ml RBC 0.005- 1.886), (%dAXP 35.31% 0.6-70.02). All patients were diagnosed with bi-allelic variants in ADA gene. 15 patients are currently followed by other centers while 16 underwent allogenic hemopoietic cell transplant (8 MFD, 6 MUD, 2 haplo). The patients receiving long term ERT displayed normalized metabolic tests after introduction of ERT up to 10-15 years, then a decline in lymphocyte numbers, in enzyme activity and increased in toxic metabolites was observed. The new recombinant ERT reverted the immunological decline in all our long term treated patients.

Conclusions: Dosage of ADA toxic metabolites in mandatory for the diagnosis and follow-up of ADA-SCID patients. New recombinant ERT can be used as a first-line therapy before HSCT or GT, but also safely as a long term therapy.

Disclosure: No.

Keywords: Hematopoietic stem cell transplantation, adenosine deaminase deficiency, enzyme replacement therapy

PD174

PRIMARY IMMUNODEFICIENCIES IN CHILDHOOD AUTOIMMUNE HEMOLYTIC ANEMIA AND EVANS SYNDROME: WHICH PREVALENCE?

POSTER DISPLAY 04: IMMUNE DYSREGULATION & AUTOIMMUNE DISORDERS

Monia Ben Khaled, Zaid Zaroui, Nessrine Zekri, Takwa Lamouchi, Samya Rekaya, Ilhem Benfraj, Ridha Kouki, Mohamed Bejaoui, Fethi Mellouli, Monia Ouederni
University Tunis el Manar Faculty of Medicine of Tunis, Pediatrics: Immunology, Hematology And Stem Cell Transplantation, Rue jebel lakhdhar bab Saadoun Tunis, Tunisia

Background and Aims: Primary immunodeficiencies (PIDs) are associated with an increased susceptibility to autoimmune diseases such as autoimmune hemolytic anemia (AIHA) and Evans syndrome (ES). We aimed to describe the prevalence of PIDs in childhood AIHA and ES.

Methods: It was a descriptive and retrospective study conducted in immune-hematology pediatric service of Tunisia over 20 years (1998 and 2017), including patients with isolated AIHA or ES.

Results: Fifty tow patients were enrolled (20 with AIHA and 32 with ES), We identified 32 children with PID (19 boys and 13 girls) whose age ranged from 2 months to 17 years with a median age of 3.3 years. Family history of hematologic diseases including immune dysregulation, malignancies or autoimmune diseases was found in 23 cases. The most frequent revealing clinical sign was pallor. Most frequent identified PID were ALPS: (n=9), ALPS like disorders (n=4), combined immunodeficiency (n=3), Wiscott-Aldrich syndrome (n=2), Hyper IgM syndrome (n=2), common variable immune deficiency (n=2) and LRBA deficiency (n=2). Other PIDs were less frequent. Treatment consisted of steroids in all cases, the infusion of immune globulin intravenous in 15 cases and immunosuppressive drugs in 14 cases. Finally, nine of our patients died and 16 of them experienced relapse during the follow up. In multivariate analysis, abnormal IgG level was predictive of PID (RR=21.16, 95% CI [2.5–177], p=0.005).

Conclusions: First presentation of PIDs may include autoimmune manifestations such as autoimmune cytopenias. Managing the underlying PID can helps controlling the autoimmune process.

Disclosure: No.

Keywords: Deficiency Syndromes, Immunologic, EVANS SYNDROME, pediatrics

PD175

CHARACTERISATION of A MUTANT SAMHD1 ZEBRAFISH MODEL IMPLICATES DYSREGULATION of CHOLESTEROL BIOSYNTHESIS IN AICARDI-GOUTIÈRES SYNDROME

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Sarah Withers[1], Charles Rowlands[2], Tracy Briggs[2], Paul Kasher[1]
[1]University of Manchester, Faculty of Biology, Medicine And Health, Division of Neuroscience And Experimental Psychology, Manchester, United Kingdom, [2]University of Manchester, Manchester Centre For Genomic Medicine, Manchester Academic Health Science Centre, Manchester, United Kingdom

Background and Aims: Aicardi-Goutières syndrome (AGS1-9) is a rare inflammatory mediated encephalopathy, which occurs due to mutations in genes involved in nucleic acid sensing, regulation and metabolism. As well as significant physical disability, this condition is characterised by excessive type I interferon (IFN) activity, coupled with upregulation of IFN-stimulated genes (ISGs), which can be explained by the vital role these proteins play in self-non-self-discrimination. To date, few mouse models fully replicate the vast clinical phenotypes observed in AGS patients. Therefore, we aimed to investigate the use of zebrafish as an alternative species for generating a clinically relevant model of AGS.

Methods: Using CRISPR-cas9 technology we produced a stable mutant zebrafish line recapitulating AGS5, which arises from mutations in SAMHD1.

Results: The resulting homozygous mutant zebrafish larvae possess a number of neurological phenotypes: exemplified by upregulation of several ISGs in the head region, a significant increase in brain cell death, microcephaly, and also significant locomotion deficit. A link between type I IFN signalling and cholesterol biosynthesis has been highlighted by others, but not previously implicated in the type I interferonopathies. Through qPCR analysis we identified a significant dysregulation of cholesterol biosynthesis in the zebrafish model, which we then confirmed through RNA sequencing of AGS patient whole blood.

Conclusions: From this novel finding, we hypothesise that cholesterol dysregulation may play a part in AGS disease progression, and could contribute to some hallmarks of the condition, such as intracranial calcifications. Further experimentation will lend critical insight into the molecular pathophysiology of AGS and the potential links with cholesterol metabolism.

Disclosure: No.

Keywords: Aicardi-Goutières syndrome, Zebrafish disease modelling, type I interferon, Cholesterol

PD176

LONGITUDINAL IFN SCORES AND CLINICAL STATE IN FOUR ADA2 PATIENTS

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Marjon Wouters[1], Lisa Ehlers[1], Selket Delafontaine[1], Anneleen Hombrouck[1], Giorgia Bucciol[1], Carine Wouters[2], Lien De Somer[3], Leen Moens[1], Isabelle Meyts[1]
[1]KU Leuven, Laboratory Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [2]University Hospitals Leuven, Department of Pediatrics, Leuven, Belgium, [3]KU Leuven, Microbiology, Immunology And Transplantation Laboratory of Adaptive Immunology & Immunobiology, Leuven, Belgium

Background and Aims: Deficiency in adenosine deaminase type 2 (DADA2) is a rare autoinflammatory disease characterized by a broad clinical spectrum including livido reticularis, polyarteritis nodosa, early-onset recurrent strokes, mild immunodeficiency and recurrent fevers (1). A diagnosis of DADA2 is based on clinical evaluation, genetics and measuring ADA2 enzyme activity. A link between DADA2 and interferon signature has been reported in literature. Skral-Baumgartner et al. (2) reported a type I interferon signature in 2 DADA2 patients. We sought to investigate the potential diagnostic utility of IFN scoring in DADA2 patients.

Methods: Quantitative real-time PCR (qPCR) was performed measuring 6 interferon stimulated genes (ISGs). Interferon score was calculated based on the median fold change from qPCR.

Results: A longitudinal follow up of type I interferon score (IS) was performed in four confirmed DADA2 patients in combination with clinical assessment of disease status. The IS score was decreased in 2 of the 4 patients after starting and/or adjusting the dose of treatment. Follow-up of disease status revealed disease stability in these 2 patients. of these 2 patients one patient reached a normal IS (below cut-off of 2,7). The other 2 patients showed a constitutively elevated IS under treatment. Assessment of disease status showed active disease in these 2 patients.

Conclusions: Longitudinal follow up of IS reflects disease status of DADA2 patients and could be used as an additional diagnostic tool for ADA2 deficiency. References (1) Meyts. I and Aksentijevich. I et al. 2018 (2) Skrabl-Baumgartner. A et al. 2017

Disclosure: No.

Keywords: ADA2 DEFICIENCY, DADA2, Type 1 interferon signature

PD177

HYPER-INFLAMMATION AND JUVENILE MYELOMONOCYTIC LEUKEMIA LIKE MANIFESTATIONS ARE ATTRIBUTABLE TO GM-CSF AND IL-3 HYPERSENSITIVITY IN A PATIENT WITH NEMO DEFICIENCY BY DEEP INTRONIC BASE SUBSTITUTION

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Masahiro Ueki[1], Shinsuke Hirabayashi[1], Shunichiro Takezaki[1], Hiroki Ohata[1], Shimaa Abdrabou[1], Saori Sawai[1], Yukayo Tershita[1], Minako Sugiyama[1], Yuko Cho[1], Masaufumi Yamada[2], Atsushi Manabe[1]
[1]Hokkaido University Hospital, Department of Pediatrics, Sapporo, Japan, [2]Hokkaido University Hospital, Rakuno Gakuen University, Ebetsu, Japan

Background and Aims: Juvenile myelomonocytic leukemia (JMML) is a pediatric malignant disease attributable to the hypersensitivity to GM-CSF and IL-3, leading to aberrant RAS signaling activation. There have been several causes for JMML or JMML-like manifestations including germline or somatic pathogenic gene variants associated with RAS signaling, Wiskott-Aldrich syndrome (WAS), or infection such as cytomegalovirus. Herein, we present a patient with NEMO deficiency caused by deep intronic base substitution in IKBKG, complicated with anhidrotic ectodermal dysplasia, bacterial septicemia, severe inflammation, pneumocystis pneumonia, hepatosplenomegaly, monocytosis, and appearance of immature granulocytes, monocytes with dysplastic forms and erythroid precursors in peripheral blood. We examined the pathophysiology of hyper-inflammation and JMML-like manifestations focusing on RAS signaling.

Methods: We performed genetic analysis of anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) or JMML. To analyze the pathophysiology, we evaluated the activation of RAS signaling after stimulations of LPS, GM-CSF, IL-3, or phorbol 12-myristate 13-acetate (PMA) with Western blot analysis or quantitative-PCR.

Results: Gene sequence analysis of coding exons and exon-intron boundaries associated with EDA-ID or JMML demonstrated no significant genetic variant. Sequence analysis of full length IKBKG cDNA demonstrated characteristic insertion indicating deep intronic base substitution previously reported. Hemizygous IVS4+866 C>T substitution in IKBKG was identified. Peripheral mononuclear cells and bone marrow derived mesenchymal stem cells from the patient demonstrated aberrant activation of RAS signaling with stimulations of GM-CSF, PMA or IL-3.

Conclusions: This report indicates that RAS signaling hyper-activation in NEMO deficiency may be responsible for hyper-inflammation and JMML-like manifestations of the disease.

Disclosure: No.

Keywords: juvenile myelomonocytic leukemia, GM-CSF, IL-3, NEMO deficiency, hyper-inflammation

PD178

ADA2 DEFICIENCY IN IDENTICAL TWINS: THE SAME FATE DESPITE DIFFERENT TIME COURSE?

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Federica Barzaghi[1], Maria Pia Cicalese[1,2], Matteo Zoccolillo[3], Immacolata Brigida[3], Matteo Barcella[3,4], Ivan Merelli[4], Claudia Sartirana[3], Monica Zanussi[5], Valeria Calbi[1], Maria Ester Bernardo[1,6,7], Francesca Tucci[1], Maddalena Migliavacca[1], Fabio Giglio[8], Matteo Doglio[1], Daniele Canarutto[1], Francesca Ferrua[1], Giulia Consiglieri[1], Giulia Prunotto[1,9], Francesco Saettini[9], Sonia Bonanomi[9], P Rovere-Querini[10], Giulia Di Colo[10], Raisa Jofra Hernández[11], Georgia Fousteri[11], Federica Penco[12], Marco Gattorno[12], Michael Hershfield[13], Sarah Marktel[8], Raffaella Milani[14], Jacopo Peccatori[8], Fabio Ciceri[2], Alessandra Mortellaro[15], Alessandro Aiuti[1,6,15]
[1]IRCCS San Raffaele Scientific Institute, Pediatric Immunohematology And Bone Marrow Transplantation Unit, Milano, Italy, [2]Vita-Salute San Raffaele University, ., Milano, Italy, [3]IRCCS San Raffaele Scientific Institute, San Raffaele Telethon Institute For Gene Therapy, Milano, Italy, [4]National Research Council, Institute For Biomedical Technologies, Milano, Italy, [5]IRCCS Policlinico San Donato, San Raffaele Hospital, Clinical Genomics-molecular Genetics Service, Milano, Italy, [6]Vita-Salute San Raffaele University, ., Milan, Italy, [7]San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), Irccs San Raffaele Scientific Institute, Milan, Italy, [8]IRCCS San Raffaele Scientific Institute, Hematology And Bone Marrow Transplantation Unit, Milano, Italy, [9]Milano-Bicocca University, Monza e Brianza per il Bambino e la sua Mamma Foundation, Bone Marrow Transplantation Unit, Pediatric Department, Monza, Italy, [10]IRCCS San Raffaele Scientific Institute, Immunology, Rheumatology, Allergy And Rare Disease Unit, Milano, Italy, [11]IRCCS San Raffaele Scientific Institute, Diabetes Research Institute, Milano, Italy, [12]IRCCS Giannina Gaslini, Clinica Pediatrica – Reumatologia E Centro Malattie Autoinfiammatorie, Genova, Italy, [13]Duke University Medical Center, Department of Medicine And Biochemistry, Durham, United States of America, [14]IRCCS San Raffaele Hospital, Immunohematology And Transfusion Medicine Unit,, Milano, Italy, [15]IRCCS San Raffaele Scientific Institute, San Raffaele Telethon Institute For Gene Therapy (sr-tiget), Milano, Italy

Background and Aims: Deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive disease associated with a variable clinical presentation, including vasculitis, immunodeficiency and hematologic manifestations, potentially progressing over time. We describe the long-term evolution of the immuno-hematological features and therapeutic challenge of two DADA2 identical adult twin sisters.

Methods: The absence of plasmatic adenosine deaminase 2 (ADA2) activity in both twins suggested the diagnosis of DADA2, then confirmed by genetic analysis. Exon sequencing revealed a missense (p.Leu188Pro) mutation on the paternal ADA2 allele, while whole genome sequencing identified a deletion in intron 6 (IVS6_IVS7del*) on the maternal allele.

Results: The patients experienced strokes during childhood, subsequently followed by other shared DADA2-associated features, including neutropenia, hypogammaglobulinemia, reduced switched memory B cells, inverted CD4:CD8 ratio, increased naïve T cells, reduced follicular regulatory T cells, almost complete absence of NK cells, T-large granular cell leukemia, and osteoporosis. Disease evolution differed: clinical manifestations appeared earlier and more severe in Patient-1 than in Patient-2. Due to G-CSF refractory neutropenia, Patient-1 underwent urgent hematopoietic stem cell transplantation (HSCT). Patient-2 experienced a similar, although delayed, evolution of the disease and is currently on anti-TNF therapy.

Conclusions: Heterozygous patients with null ADA2 activity deserve deep investigation for possible structural variants on a single allele. Timely diagnosis of DADA2 is crucial to allow appropriate follow-up and identification of disease progression. Therapeutic management raises concerns as these twins share a similar phenotype, with a delayed but almost predictable evolution in one of them, who could benefit from an early definitive treatment, as allogeneic HSCT.

Disclosure: No.

Keywords: Adenosine deaminase 2 deficiency, neutropenia, T large granular lymphocytes, DADA2, HSCT, ADA2

PD179

SIMULTANEOUS KIDNEY TRANSPLANTATION AND HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) WITH TCR ALPHA/BETA DEPLETION IN A PATIENT WITH DNASE2 DEFICIENCY

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Nelli Kan[1], Anna Kozlova[2], Haichao Wang[3], Vasiliy Burlakov[2], Yulia Rodina[2], Anna Roppelt[2], Anna Khoreva[2], Daria Yukhacheva[2], Galina Novichkova[2], Mikhail Kaabak[4], Dmitry Balashov[5], Ivona Aksentijevich[3], Anna Shcherbina[2]
[1]1- Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [2]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [3]National Human Genome Research Institute, Inflammatory Disease Section, Bethesda, United States of America, [4]Medical university Reaviz, Nephrology, Moscow, Russian Federation, [5]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Hematopoietic Stem Cell Transplantation, Moscow, Russian Federation

Background and Aims: DNaseII deficiency is a rare primary interferonopathy, presenting with a severe phenotype and lack of generally accepted treatment protocols.

Methods: case report

Results: We report a patient from a consanguineous marriage, with disease onset during infancy, presenting with recurrent fevers, rash, subcutaneous nodules, arthritis, thrombocytopenia, anemia. Via whole-exome sequencing, she was found to be homozygous for the two likely pathogenic variants: one in DNASE2: c.511+5G>A and one in USP43: c.2509 G>A. DNase2 activity was decreased in fibroblasts and EBV-B cells of the patient, as demonstrated by in vitro DNA degradation assay. Cytokine profiling identified a strong type I interferon signature in her blood samples. Treatment with JAK inhibitor ruxolitinib controlled the symptoms for six years, however at the age of nine years, the patient developed hyporegenerative anemia and kidney damage, presumably due to the interferonopathy and BK viruriaviremia, with subsequent renal failure. The patient received a kidney transplant from her mother. Immunosuppression before/after kidney transplantation included induction with alemtuzumab and eculizumab, maintenance with tacrolimus and mycophenolate mofetil. Haploidentical HSCT also from the mother was performed 15 days after the kidney transplantation (conditioning included treosulfan, fludarabin, ATG, rituximab). Currently, the patient is 17 months post-HSCT: both transplants have normal function, hematological chimerism is 99% donor, and the patient has no symptoms of systemic inflammation

Conclusions: HSCT may be a curative option for patients with DNaseII deficiency. Sequential solid organ transplantation and HSCT from the same donor can be the treatment option for patients with inborn immune disorders who have hematological and visceral problems

Disclosure: No.

Keywords: Solid organ transplantation, DNASE2, nephropathy, JAK inhibitor, HSCT, interferonopathy type 1

PD180

HUMAN DEFICIENCY of ADENOSINE DEAMINASE 2 - MYRIAD FACES IN A FAMILY!

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Rakesh Kumar Pilania[1], Deepti Suri[1], Murugan Sudhakar[2], Rajni Kumrah[1], Amit Rawat[3], Surjit Singh[3]
[1]Post Graduate Institute of Medical Education and Research, Pediatric Allergy Immunology Unit, Department of Pediatrics, Advanced Pediatrics Centre, Chandigarh, India, [2]Post graduate Institute of Medical Education and Research, Pediatrics, Chandigarh, India, [3]Post Graduate Institute of Medical Education and Research, Chandigarh, Allergy-immunology Unit, Dept of Paediatrics, Chandigarh, India

Background and Aims: Deficiency of adenosine deaminase 2 (DADA2) is a multifaceted autosomal recessive autoinflammatory disorder due to defect in ADA2 gene. Phenotypic descriptions of DADA2 have been expanded considerably. We report a family with an expanded phenotype of DADA2 and a novel genetic variant.

Methods: A 10-year-boy (Pt.1), presented with fever, pallor, generalized lymphadenopathy, and massive firm hepatosplenomegaly. First younger brother (Pt.2; 5 years) revealed asymptomatic firm splenomegaly. Another younger brother (Pt.3; 18 months) was diagnosed with pure red cell aplasia (PRCA) and transfusion-dependent.

Results: Patient.1 revealed pancytopenia and HLH. Lymph-node biopsy was suggestive of Hodgkin lymphoma (Nodular sclerosis-syncytial variant). Bone marrow biopsy showed CD20+ and CD45+ positive large cells with prominent nucleoli. Immunological investigations showed pan-hypogammaglobulinemia and markedly reduced CD19+ B cells. The Btk, CTLA-4, and DNT cells were normal. EBV viral load was 1.7 million copies/ml. Next-generation sequencing revealed compound heterozygous mutations in exon 5 of ADA2 gene [nonsense mutation: c.806dup,(p.Tyr269Ter)]; and a frameshift mutation with premature truncation: c.777_780dup, (p.Asp261ProfsTer2)]. Bone marrow examination in Pt.3 was consistent with PRCA. Serum ADA2 levels were deficient. Pt.2 and Pt.3 confirmed same compound heterozygous mutation as the index child. Father was heterozygous carrier of frameshift mutation in exon 5 of ADA2 gene [c.777_780dup, (p.Asp261ProfsTer2)]. Hence, mother is expected to be a carrier of c.806dup (p.Tyr269Ter). Variants found in index family were novel and not reported before.

Conclusions: We report novel variants in the ADA2 gene in three brothers showing an extended phenotype of DADA2 - Pt.1 hypogammaglobulinemia, EBV, Hodgkin lymphoma, and HLH; Pt.2 asymptomatic splenomegaly; Pt.3 PRCA phenotype.

Disclosure: No.

Keywords: ADA2 gene, Deficiency of adenosine deaminase 2, Novel variant, hematological manifestations, autoinflammatory disorder

PD181

EARLY-ONSET AUTOINFLAMMATORY DISEASE RESEMBLING CRYOPYRINOPATHY DUE TO SOMATIC NLRC4 MOSAICISM

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Anna Mensa-Vilaro[1,2], Walaa Shoman[3], Yasmine El Chazli[3], Heba Shaher[3], Susana Plaza[1], Virginia Fabregat[1], Rocío Lara[1], Eva González-Roca[1], Jordi Yagüe[1,2], Nourhan Ragab[3], Juan Ignacio Aróstegui[1,2]
[1]Hospital Clinic, Department of Immunology, Barcelona, Spain, [2]Institut d'Investigacions Biomèdiques August Pi i Sunyer, Immunogenetics, Barcelona, Spain, [3]Alexandria University, Department of Pediatrics, Alexandria, Egypt

Background and Aims: Inflammasomopathies are caused by overactivation of different inflammasomes, which are defined by their respective sensing proteins (NLRP3, NLRC4, pyrin). Gain-of-function mutations in these sensing proteins lead to caspase-1-mediated overproduction of IL-1b and IL-18, and increased pyroptosis. The aim of this study was to identify the cause of the disease in an infant with suspected cryopyrinopathy.

Methods: DNA was extracted from whole blood and molecular analysis was performed by next generation sequencing (NGS) methods.

Results: The patient is a 4-year-old Egyptian girl born from a non-consanguineous healthy couple, who also has two older healthy brothers. At the age of 6-months, she started with recurrent episodes (7-10 days) of fever, irritability and increase acute-phase reactants. Urticarial rash and bilateral knee arthritis were present in some episodes. Between 6-12 months of age she was hospitalized up to 6 times for aseptic meningitis. Physical examination revealed frontal bossing and marked growth retardation (below 3rd centile). Treatment with the anti-IL-1 drug anakinra showed rapid and marked improvement of clinical manifestations. NGS studies detected the pathogenic p.His443Gln NLRC4 variant with an allele frequency of 12.0%, which supported for the presence of somatic mosaicism. Patients with both germline and postzygotic NLRC4 variants have been associated with i) cryopyrinopathy-like manifestations including late-onset disease, ii) painful erythematous nodules and iii) early-onset enterocolitis with recurrent macrophage activation syndrome.

Conclusions: Herein, we describe a young patient afflicted by an early-onset cryopyrinopathy-like disease that is consequence of a postzygotic NLRC4 variant. These results expand the phenotypic spectrum of NLRC4-associated autoinflammatory disease.

Disclosure: No.

Keywords: NLRC4, Interleukin-18, somatic mosaicism, cryopyrinopathy, Autoinflammatory diseases, inflammasome

PD182

NOVEL INSIGHTS INTO IMMUNE DYSREGULATION- AND HYPER-INFLAMMATION-RELATED NEUROLOGICAL DISORDERS AS SIGNS SUSPICIOUS FOR INBORN ERRORS of IMMUNITY

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Mattia Moratti[1], Lorenzo Muccioli[2], Lidia Di Vito[3], Raffaella Minardi[3], Francesca Bisulli[4], Caterina Campoli[5], Giovanni Vitale[6], Maria Morelli[6], Franco Trevisani[7], Pierluigi Viale[5], Paolo Tinuper[4], Andrea Pession[8], Francesca Conti[8]
[1]Alma Mater Studiorum, Università di Bologna, Specialty School of Paediatrics, Bologna, Italy, [2]University of Bologna, Department of Biomedical And Neuromotor Sciences, Bologna, Italy, [3]Reference Center for Rare and Complex Epilepsies-EpiCARE, Irccs, Istituto Delle Scienze Neurologiche Di Bologna, Bologna, Italy, [4]Department of Biomedical and Neuromotor Sciences, University of Bologna, Irccs, Istituto Delle Scienze Neurologiche Di Bologna (reference Center For Rare And Complex Epilepsies-epicare), Bologna, Italy, [5]University of Bologna, Infectious Diseases Unit, Irccs Azienda Ospedaliero-universitaria Di Bologna, Department of Medical And Surgical Sciences, Bologna, Italy, [6]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Policlinico di Sant'Orsola, Internal Medicine Unit For The Treatment of Severe Organ Failure, Bologna, Italy, [7]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Division of Medical Semeiotics, Bologna, Italy, [8]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Pediatric Unit, Bologna, Italy

Background and Aims: Immune-dysregulation with hyper-inflammation represents one of the potential expressions of inborn errors of immunity (IEIs), congenital disorders once thought to be dominated by infectious susceptibility, actually constituting only a facet of a large spectrum of IEI-related phenomena. High-throughput genomic technologies critically contributed to the identification of molecular pathways involved in IEI-related neuroinflammatory disorders, such as febrile infection-related epilepsy syndrome (FIRES), a condition characterized by cryptogenic new-onset super-refractory status epilepticus (NORSE) following a febrile illness, recently linked to molecular-defined IL-1beta-mediated autoinflammatory disorders (Lindahl H, Bryceson YT. Neuroinflammation Associated With Inborn Errors of Immunity. Front Immunol. 2022)

Methods: We report two cases of IEI-related FIRES.

Results: The first patient is a 42-year-old woman with infancy-onset mild psoriasis and chromosomally-integrated HHV6, otherwise healthy until the age of 40 years, when she developed FIRES requiring a prolonged hospitalization to manage status epilepticus. This was complicated by cryptosporidiosis, multi-focal pneumonia, liver and intra-abdominal abscesses on sclerosing cholangitis with hepato-splenomegaly and recurrent bloodstream infections by carbapenem-resistant Enterobacteriaceae (CRE). Her immunophenotype showed marked B-lymphopenia with IgG/IgM hypogammaglobulinemia. A Next Generation Sequencing 56-gene-panel for primary immune regulatory disorders detected no potentially causative variants. The second patient is a 21-year-old man presenting with FIRES, requiring a prolonged ICU hospitalization to manage a status epilepticus complicated by CRE-related bloodstream infections. His immunophenotype showed marked B-lymphopenia with normal gammaglobulins. Whole exome sequencing revealed a variant of unknown significance in XIAP, inherited by the mother.

Conclusions: We provide elements concerning the emerging field of IEI-related neuroinflammation, addressing FIRES as an onset sign for IEI.

Disclosure: No.

Keywords: neuroinflammatory disorders, primary immune regulatory disorders, Febrile infection-related epilepsy syndrome, hyper-inflammation, Immune Dysregulation, Inborn errors of immunity

PD183

PATHOPHYSIOLOGICAL ANALYSIS AND THERAPEUTIC EXPLORATION USING PSTPIP1-ASSOCIATED MYELOID-RELATED PROTEINEMIA INFLAMMATION (PAMI) SYNDROME DISEASE-SPECIFIC INDUCED PLURIPOTENT STEM CELL MODEL

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Fumiko Honda-Ozaki, Eri Kumaki-Matsumoto, Tomohiro Morio
Tokyo Medical and Dental University, Developmental Biology, Tokyo, Japan

Background and Aims: PAMI syndrome is a rare autoinflammatory disease characterized by high serum levels of calprotectin and zinc. Mutations in PSTPIP1 are known to cause the disease, but the detailed pathogenesis of this disorder has not been clarified. PAMI syndrome is distinguished from PAPA syndrome, which is caused by different mutations of the same gene. These disease clusters are classified as a group of diseases linking PSTPIP1 and disease with abnormal IL-1β production and abnormal neutrophil responses (PSTPIP1-associated autoinflammatory diseases (PAIDs)). Various autoinflammatory pathologies are thought to exist in neutrophilic pyogenic skin diseases in these disorders. Recently, anti-IL-1β antibody therapy was introduced as a treatment for this disease. Since responses to these therapies vary widely, with some cases responding well and others not, there is a need to develop more effective therapies for each conditions.

Methods: In this study, we focused on PAMI syndrome and performed phenotypic analysis using monocytes as well as neutrophils induced from disease-specific iPSCs to establish a disease model for the development of more effective therapies.

Results: PAMI-iPSC neutrophils showed high ROS production, were prone to cell death, and had high extracellular calprotectin levels compared to healthy-iPSC neutrophils. Our study also showed that PAMI-iPSC monocytes had higher intracellular calprotectin production and enhanced inflammatory signals such as IL-18 and IL-1β.

Conclusions: Since these phenotypes were consistent with those of patient-derived peripheral neutrophils, we successfully reproduced the patient's condition in vitro using PAMI-iPSC. Furthermore, we explored the causes of induced inflammation and chronicity in PAMI syndrome by comprehensive RNA-Seq gene expression profiling.

Disclosure: No.

Keywords: Autoinflammatory Disease, PSTPIP1-associated myeloid-related proteinemia inflammatory (PAMI) syndrom, PSTPIP1-associated inflammatory diseases: PAID, Calprotectin, Hyperzincemia/Hypercalprotectinemia (Hz/Hc) syndrome

PD184

AN UNUSUAL CASE of HEPATOMEGALY, PANCYTOPENIA AND AUTOINFLAMMATORY SYNDROME IN A COLOMBIAN GIRL: ABOUT A CASE of PSTPIP1-ASSOCIATED MYELOID-RELATED PROTEINEMIA INFLAMMATORY (PAMI) SYNDROME

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Fabio Vargas Cely[1], Andrés Zea Vera[2]
[1]Universidad del Valle, Immunology And Microbiology, Cali, Colombia, [2]National institute of health, Immunology, Bethesda, United States of America

Background and Aims: To describe an unusual case of a patient with an autoinflammatory syndrome

Methods: Case report

Results: 17-year-old female with a 2-month history of periodic fevers, fatigue, odynophagia and cervical lymph node swelling. Previous medical records showed long standing pancytopenia diagnosed as myelodysplastic syndrome since the age of 10, pyogenic aseptic arthritis of the knee and aseptic anorectal fistula. She exhibited pallor, cervical lymph node enlargement measuring 3x2 cm, dry mucous membranes, non-exudative pharyngeal erythema and hepatosplenomegaly. Laboratories displayed severe neutropenia and mild anemia, procalcitonin was negative, pharyngeal, urine and blood cultures including fungal cultures were negative and chronic infections were ruled out. A cervical lymph node biops exhibited reactive hyperplasia with parafollicular expansion and unrevealing microbiologic studies. Bone marrow evaluation only showed megakaryocytic hyperplasia. Auto-antibodies panel were negative, complement fraction C4 was slightly low, with T-cell and NK cell lymphopenia given her borderline absolute lymphopenia and serum immunoglobulin levels showed IgG/IgA hypergammaglobulinemia Finally, having ruled out hematologic malignant transformation and autoimmunity a whole exome sequence (WES) was done to study for bone marrow failure syndromes, autoinflammatory syndromes or other inborn errors of immunity. WES showed a pathogenic heterozygous germline mutation c.748G>A (p.E250K) in PSTPIP1 gene confirmed by sanger sequencing identified as the cause of PAMI syndrome. Zinc and calprotectin serum levels were performed, zinc was five-fold the upper normal limit of zinc with borderline high normal calprotectin levels.

Conclusions: PAMI must be included in the differential diagnosis as a rare disorder in patients exhibiting hepatomegaly with unexplained cytopenia, immunodeficiency or uncontrolled systemic inflammation.

Disclosure: No.

Keywords: autoinflammation, pancytopenia, Inborn errors of immunity, Immune Dysregulation

PD185

REGRESSION of SEVERE CARDIAC AA-AMYLOIDOSIS UNDER 5-YEAR TREATMENT WITH ANAKINRA IN A PATIENT WITH DOUBLE-HOMOCYGOTE FMF-MUTATIONS(C.2080A>G; C.605G>A).

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Rainald Zeuner[1], Oliver Mueller[2], Bimba Hoyer[3], Florian Tran[4]
[1]Universitätsklinikum Schleswig Holstein, Campus Kiel, Sektion Rheumatologie, Klinik Für Innere Medizin I, Kiel, Germany, [2]Universitätsklinikum Schleswig Holstein, Campus Kiel, Klinik Für Innere Medizin Iii, Kiel, Germany, [3]University Hospital Schleswig-Holstein, Campus Kiel, Excellence Center For Inflammation Medicine, Clinic For Rheumatology And Clinical Immunology, Kiel, Germany, [4]University Hospital Schleswig-Holstein, Campus Kiel, Excellence Center For Inflammation Medicine, Clinic For Internal Medicine I, Kiel, Germany

Background and Aims: Here we report about a patient with severe Familiar Mediterranean Fever carrying double homozygote mutations in the FMF-Gene (c.2080A>G; c.605G>A). The patient is of consanguineous Armenian ancestry and has been treated with colchicine. The patient came to our institution already with end stage renal disease due to generalized amyloidosis.

Methods: On initial presentation the patient – although on adequate dialysis treatment - was in heart failure NYHA 3-4 with a reduced walking distance. Echocardiography showed a slightly reduced EF with septal hypertrophy and inhomogeneous septal density (granular sparkling). Especially the basal longitudinal strain was highly reduced. AA-amyloidosis was confirmed by myocardial biopsy.

Results: The patient was consequently treated with Anakinra (4 doses per week). Under treatment with Anakinra, the fever attacks stopped and Serum-Amyloid A levels fell from 40.5mg/dl to <0,64mg/dl (NV). The patient´s clinical condition improved steadily over the treatment period of now 5 years. In current cardiac assessment clinical signs of heart failure decreased to NYHA 1-2. NT-proBNP fell from 57066nl/l to 6031nl/l. Echocardiography shows an improvement of LV-function and basal longitudinal strain. The patient is currently listed for renal transplantation.

Conclusions: Since cardiac involvement of AA-amyloidosis is rare, this is to our knowledge the first report of a reduction of cardiac AA-amyloidosis in severe FMF under treatment and underscores the importance of a consequent long-term therapy even in advanced disease.

Disclosure: No.

Keywords: familiar mediteranean fever, cardiac AA-amyloidosis

PD186

A FAMILY WITH A DE NOVO LOF-VARIANT IN TNFAIP3 SHOWING DISTINCT PHENOTYPES

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Nina-Christine Knopf[1], Mara Niemuth[1], Leonora Pietzsch[1], Julia Körholz[1], Clemens Kastl[1], Joachim Roesler[1], Min Ae Lee-Kirsch[2], Catharina Schuetz[1]
[1]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Pediatric Immunology, Dresden, Germany, [2]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Molecular Pediatrics, Dresden, Germany

Background and Aims: Heterozygous loss-of-function variants in the TNFAIP3 gene encoding for A20 protein is leading to haploinsufficiency of A20 (HA20), an autoinflammatory disease. In HA20 the NF-κB regulatory protein A20 is decreased, which results in amplified action of NF-κB, a central mediator of innate immunity and inflammatory pathways. The pathogenic significance of an unreported variant of the TNFAIP3 gene in three related cases of HA20 showing distinct phenotypes was investigated.

Methods: Clinical and immunological data of three family members with a de novo variant in TNFAIP3 (c.176_177delAG, p.Gln59fs) is reported. The functional analyses included induction of A20 expression after stimulating with proinflammatory mediators, e.g. tumor necrosis factor α (TNF-α) as well as detection of cytokine-induced p65 phosphorylation.

Results: The clinical features within this family vary from autoimmune phenomena to gastrointestinal symptoms such as hepatitis and pancreatic insufficiency, as well as to autoinflammatory symptoms such as recurrent fever, ulcers, gingivitis and lymphadenopathy. The p.Gln59fs variant leads to a frameshift and premature STOP codon at the beginning of exon 2 and thereby most probably to nonsense mediated decay.

Conclusions: TNFAIP3-LOF variants cause an autoinflammatory syndrome and/or autoimmune symptoms with heterozygous phenotypes, even among the same genetic variant within one family. Further investigations are needed in order to clarify pathophysiological mechanisms and to identify potential therapeutic approaches.

Disclosure: No.

Keywords: in vitro assay, TNFAIP3-LOF variants, A20 haploinsufficiency

PD187

HEMATOLOGIC MANIFESTATIONS IN A GROUP of PATIENTS WITH MONOGENIC AUTOINFLAMMATORY DISEASES (AID): SINGLE CENTER EXPERIENCE

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Zoya Nesterenko[1], Anna Kozlova[1], Vasiliy Burlakov[1], Alexandra Laberko[1], Yulia Rodina[1], Ekaterina Deordieva[1], Anna Mukhina[1], Natalia Kuzmenko[1], Darya Bogdanova[1], Nelly Kan[1], Anna Khoreva[1], Daria Yukhacheva[1], Viktoriya Bludova[1], Anna Moiseeva[1], Ekaterina Viktorova[1], Dmitry Balashov[2], Anna Shcherbina[1]
[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [2]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Hematopoietic Stem Cell Transplantation, Moscow, Russian Federation

Background and Aims: AIDs are a growing group of disorders caused by dysregulation of innate immunity, leading to systemic inflammation and a range of clinical phenotypes.

Methods: We analyzed a group of 123 patients with monogenic AIDs treated at our center in 2012-2022.

Results: 31/123 (25%) patients had persistent hematological symptoms: pancytopenia - in 9/31 patients, including 5/14 with autoimmune hemolytic anemia (AIHA); isolated aplastic anemia - in 2/31; neutropenia – in 2/31; thrombocytopenia – in 1/31; aplastic anemia+neutropenia – in 4/31, AIHA+neutropenia – in 1/31, neutropenia + thrombocytopenia – in 3/31, aplastic anemia + thrombocytopenia – in 4/31, myelodysplastic syndrome - 1/31, hemophagocytic lymphohistiocytosis – in 4/31. The forms of AIDs included: PSTPIP1-associated syndrome (PAID)-8, adenosine deaminase 2 deficiency (DADA2)-8, type I Interferonopathies -8, mevalonate kinase deficiency (MKD)-4, A20 haploinsufficiency (HA20)-1, POMP-related autoinflammation and immune dysregulation (PRAID)–1, NLRC4-associated autoinflammatory disorder-1. Median age of onset of any disease symptoms was 2 months (range 0–16 years). Median age of onset of hematologic manifestations was 2.5 years (range 0–33 years). Hematological manifestations as the first symptom of AID were seen in 23/31 patients. Median age at diagnosis was 8 years (range 0.5-33), with the mean diagnostic delay of 4 years (range 0.5-32).

Conclusions: Patients with AIDs frequently manifest with hematological symptoms. Yet, our study indicates significant diagnostic delay. High awareness of hematologists of this group of disease is required for timely diagnosis and targeted therapy initiation.

Disclosure: No.

PD188

ADA2 DEFICIENCY: AN EVER-EXPANDING PHENOTYPE

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Martina Rossano[1], Federica Lucioni[2], Lucia Baselli[1], Sofia Torreggiani[1], Francesco Baldo[2], Rosa Dellepiane[1], Francesca Minoia[1]
[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlnico, Pediatric Department, Milano, Italy, [2]Università degli Studi di Milano, Pediatric Department, Milan, Italy

Background and Aims: ADA2 deficiency is a monogenic autoinflammatory disease characterized by heterogeneous presentation. The large phenotypic variability, makes the diagnosis challenging.

Methods: We report an unusual case of ADA2 deficiency presenting with myositis, owing to a new compound heterozygosity in ADA2.

Results: A 7-year old boy came to our attention for intermittent bilateral leg pain. Lab exams revealed elevated inflammatory markers and normal LDH and CPK. Moderate lymphopenia and low levels of IgM were observed. Signs of myositis at lower limbs were detected with the MRI and EMG (active denervation). MRI presented bilateral signs of myositis of the lower limbs. He subsequently developed nocturnal fever, lymphadenopathy, splenomegaly and infiltrative burning nodular skin lesions. Infectious, haematological (PET, bone marrow aspiration and lymph node biopsy) and autoimmune workup were performed with no evidence of infection or malignancies. Muscle biopsy did not reveal clear sign of vasculitis. Genetic sequencing of ADA2 revealed compound heterozygosity for a novel frameshift deletion in the catalytic domain, c.1100_1113del:p.I367Tfs*41, inherited from the father, and a maternally inherited missense variant, c.1148G>A:p.G383D. ADA2 functional enzyme analysis confirmed pathological low activity. Etanercept was started with prompt normalization of symptoms, inflammatory markers and regression of lymphoproliferation.

Conclusions: We report a new compound mutation with a novel ADA2 deletion leading to premature protein truncation in heterozygosity with the recently described c.1148G>A mutation. DADA2 phenotype spectrum is ever-expanding and description of peculiar cases and new mutations could improve genotype/phenotype correlation leading to significant progresses in diagnosis, management and prognosis of these patients.

Disclosure: No.

Keywords: DADA2, myositis, Immune Dysregulation, Vasculitis

PD189

CLINICAL CHARACTERIZATION AND TYPE I INTERFERON ACTIVATION of A COHORT of PATIENTS WITH UNDEFINED INFLAMMATORY SYNDROMES FROM THE EUROFEVER REGISTRY

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Gioacchino Andrea Rotulo[1,2], Stefano Volpi[3], Simona Matarese[2], Elettra Santori[4], Margherita Ricci[2], Paolo Picco[3], Gillian I Rice[5], Roberta Caorsi[3], Alessandra Tesser[6], Alice Grossi[7], Isabella Ceccherini[7], Alberto Martini[2], Alberto Magnasco[8], Yanick Crow[9], Alberto Tommasini[6], Fabio Candotti[4], Marco Gattorno[3,10]
[1]Ospedale Pediatrico Bambino Gesù, Academic Department of Pediatrics (dpuo), Research Unit of Clinical Immunology And Vaccinology, Roma, Italy, [2]Università di Genova, Dinogmi, Genova, Italy, [3]IRCCS Giannina Gaslini Institute, Center For Autoinflammatory Diseases And Immunodeficiencies, Genova, Italy, [4]Division of Immunology and Allergy, Chuv, Lausanne, Switzerland, [5]University of Manchester, Genetic Medicine, UK, Manchester Academic Health Science Centre, Manchester, United Kingdom, [6]IRCCS Burlo Garofolo, Department of Pediatrics, Trieste, Italy, [7]Istituto Giannina Gaslini,, Uoc Genetica Medica E Uosd Genetica E Genomica Delle Malattie Rare, Genova, Italy, [8]Istituto Giannina Gaslini, Nephrology, Dialysis, Transplantation Unit, Genova, Italy, [9]Imagine Institute, Aicardi-goutières Syndrome And Type 1 Interferonopathies, Paris, France, [10]IRCCS Giannina Gaslini, Clinica Pediatrica – Reumatologia E Centro Malattie Autoinfiammatorie, Genova, Italy

Background and Aims: The role of type I interferon (IFN) in autoimmune and autoinflammatory diseases has been widely demonstrated.

Methods: Between 2015 and 2021, we evaluated 217 consecutive patients with defined or undefined pediatric inflammatory conditions for type I IFN activation using quantitative Real-Time PCR. The IFN Score was calculated as the median of the relative quantification of six IFN inducible genes compared to the healthy control.

Results: Eleven patients had a diagnosis of type I interferonopathy (COPA,SAVI,Aicardi Goutières syndrome,DNASE1L3 and DNASE2 deficiency, RALD) with 8 presenting a positive IFN score. Three patients had a diagnosis of immunodeficiency (STAT1 GOF, ARPC1B) and elevated IFN levels. A monogenic autoinflammatory disease was found in 21 patients, 10 had positive IFN signatures. In 65 cases an autoimmune condition was known with a rate of IFN positivity of 61,5 %. 117 patients presented with presumed undefined autoinflammatory diseases without a genetic diagnosis. For these patients, onset symptoms included fever (31%), lymphoproliferation signs (28%), musculoskeletal (60%), cardiac (15%), gastrointestinal (14%), ocular (6%), neurologic (56%), mucocutaneous symptoms (71%). 39% of these patients had positivity for IFN signature. An increase in median IFN values was found for all the patients of our cohort presenting with signs of lymphoproliferation at the first clinical evaluation: 1.7 (IQR-0.4-11.6) vs 0.6 (IQR-0.3-3.6)($p<0.01$).

Conclusions: Due to a lack of response to standard treatment, six patients have started a therapy targeting IFN pathway (JAK inhibitor) with overall good response and limited toxicity. Our data confirm the activation of type I IFN pathway in pediatric patients with defined/undefined inflammatory/autoimmune conditions.

Disclosure: No.

Keywords: interferon, Jak-inhibitors, type 1 interferonopathies, Autoinflammatory Disease

PD190

EVALUATION of THE RISK FOR VASCULAR DAMAGE IN CHILDREN AND YOUND ADULTS WITH FAMILIAL MEDITERRANEAN FEVER

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Panagiota Karananou[1], Olga Vampertzi[1], Kyriaki Papadopoulou-Legbelou[1], Areti Triantafyllou[2], Nikolaos Koletsos[2], Sofia Alataki[2], Stella Douma[2], Efimia Papadopoulou-Alataki[1]
[1]Papageorgiou General Hospital, 4th Department of Pediatrics, Thessaloniki, Greece, [2]Papageorgiou General Hospital, 3rd Department of Internal Medicine, Thessaloniki, Greece

Background and Aims: Familial Mediterranean Fever (FMF) is the most common, inherited autoinflammatory disease. This study aims to assess the possible presence of subclinical vascular inflammation in children with FMF and the possibility of an increased risk of endothelium dysfunction, subclinical atherosclerosis, and cardiovascular disease from a young age.

Methods: The clinical and laboratory data (inflammation markers, lipid profile) from all participants were recorded. Detailed medical history was obtained, physical examination including Blood Pressure (BP) Measurement was conducted andAtherogenic Index of Plasma (AIP) was estimated. Additionally vascular function indices including Pulse wave velocity (PWV), Central Augmentation Index (Aix), Subendocardial viability ration (SEVR) and Carotid-intima thickness (cIMT) were evaluated. FMF patients were examined during attack-free periods.

Results: The arterial stiffness parameters (PWV, Aix, SEVR, c-IMT)did not display any significant differences between patients andhealthy individuals. However, a positive correlation between Aix and C-reactive protein (CRP) and a negative correlation between SEVR and erythrocyte sedimentation rate (ESR) were detected in the pediatric subgroup. Moreover, significantly higher ESR,CRP and fibrinogen levels were found in the total population of FMF patients. Higher amyloid levels and AIPvalues in FMF children, compared to controls, were also measured which indicates the presence ofsubclinical inflammation even during asymptomatic periods of the disease.

Conclusions: Patients with FMF need to be close monitored for the inflammatory markers and vascular function indices and adhere to the colchicine therapy which may have a cardioprotective role against vascular damage.

Disclosure: No.

Keywords: cardiovascular inflammation, inflammatory markers, familial mediterranean fever

PD191

AN UNUSUAL PRESENTATION of FAMILIAL MEDITERRANEAN FEVER WITH FEATURES of BEHÇET'S DISEASE: A CASE REPORT AND LITERATURE REVIEW

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Adhora Mir[1], Catherine Ivory[2], Juthaporn Cowan[2]
[1]The Ottawa Hospital, Internal Medicine, Ottawa, Canada, [2]The Ottawa Hospital, Medicine, Ottawa, Canada

Background and Aims: Familial Mediterranean fever (FMF) and Behçet's disease describe distinct disorders that are prevalent in the Mediterranean and Middle Eastern populations and are characterized by unprovoked inflammatory episodes caused by overexpression of proinflammatory cytokines. Although reported previously, the overlapping presentation of FMF and Behçet's disease remains uncommon. Here, we describe a case of a patient with FMF presenting with features of Behçet's disease, and review the existing case reports on the coexistence of these two diseases.

Methods: A search of existing case reports was conducted with the words “Familial Mediterranean fever and Behçet's disease; FMF; Familial Mediterranean fever syndrome; Behçet's disease” on the PubMed database.

Results: Several common FMF related MEFV gene mutations have been associated with Behçet's disease. Additionally, Behçet's disease has been reported to have occurred more frequently in patients with FMF compared to the general population. Nine case reports were found on literature review on the coexistence of the two diseases. Common symptoms among reviewed cases included recurrent oral aphthous and urogenital ulcers, episodic fevers, and arthralgias. Our case differs from previous cases in the timeline of his symptoms and minimal responsiveness to anti-inflammatory therapies.

Conclusions: Our case contributes to the growing literature demonstrating the presentation of predominantly Behçet's disease-like features in the setting of genetic diagnosis of FMF. These findings emphasize that clinicians should be aware that patients with FMF may present with Behçet's disease-like clinical manifestations.

Disclosure: No.

Keywords: behcets disease, familial mediterranean fever, auto inflammatory disease, case report, fmf

PD192

FAMILIAL MEDITERRANEAN FEVER IN THE CENTRAL EUROPE – EXPERIENCE FROM SLOVAKIA AS AN INSPIRATION FOR DISEASES AWARENESS IN CEE REGION

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Milos Jesenak[1,2,3], Eva Jurkova[1], Katarina Hrubiskova[4], Lenka Kapustova[1], Anna Bobcakova[2], Otilia Petrovicova[1], Veronika Urdova[2], Adam Markocsy[1], Peter Banovcin[1]
[1]Jessenius Faculty of Medicine, Comenius University in Bratislava, Centre For Periodic Fever Syndromes, Department of Pediatrics, Martin, Slovak Republic, [2]Jessenius Faculty of Medicine, Comenius University in Bratislava, Centre For Periodic Fever Syndromes, Department of Pulmonology And Phthisiology, Martin, Slovak Republic, [3]University Hospital Martin, Department of Allergology And Clinical Immunology, Martin, Slovak Republic, [4]University Hospital in Bratislava, 5th Department of Internal Medicine, Bratislava, Slovak Republic

Background and Aims: Although is familiar Mediterranean fever (FMF) the most common monogenic autoinflammatory diseases in the world, its prevalence in the central Europe was expected to be very low (1:465.500). The true prevalence data from CEE region and clinical experience are usually scarce.

Methods: We analyzed the whole Slovakian cohort of FMF patients followed-by the National Centre for Periodic Fever Syndromes in University Hospital in Martin, Slovakia. The patients were collected from the whole are of Slovakia through the collaboration with the rheumatologists and clinical immunologists.

Results: Altogether, we identified 115 patients (estimated prevalence of 1:47 385; 25.2% children; 46.1% males; aged 36.42±18.91 years) with the clear clinical FMF phenotype and genetic confirmation. 5.2%were homozygous for pathogenic mutation in MEFV gene, 14.8% compound heterozygotes, 67.8% heterozygotes and 12.2%with the genetic finding of unknown significance. The mean age of first symptoms was 14.86±14.9 years, age of diagnosis confirmation 32.65±19.22 ys. With the diagnostic delay of 17.41±15.63 ys. The most prevalent clinical symptoms were abdominal pain (88.7%), recurrent fever (86.9%), accelerated fatigue (72.2%), arthralgia (70.4%), chest pain (45.2%), cervical lymphadenopathy (36.5%) and tonsillitis (33.0%). 86.1% were treated with colchicine, 17.4% with anakinra on demand and 15.7% with canakinumab. Elevation of serum amyloid A outside the flares was detected in 41.7% patients before the therapy initiation and elevated IgD in 5 patients.

Conclusions: Our experience strongly encourages the need for FMF awareness even in the countries with the expected low prevalence. Early diagnosis could lead to appropriate therapy with improved prognosis and quality of life.

Disclosure: Milos Jesenak has received honoraria, consultancy and speaker fees from ALK, CSL Behring, Ewopharma, GSK, Novartis, Sanofi-Genzyme, AstraZeneca, SOBI, Stallergenes Greer and Takeda, and served as a principal investigator for trials sponsored by BioCryst,

Keywords: disease awareness, biological therapy, autoinflammation, familial mediterranean fever, periodic fever syndromes

PD193

SUCCESSFUL USE of SECUKINUMAB IN A PATIENT WITH SYNOVITIS, ACNE, PUSTOLOSIS, HYPEROSTOSIS, OSTEITIS (SAPHO) SYNDROME

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Roberta Romano[1], Giuliana Giardino[2], Francesca Cillo[3], Elisabetta Toriello[3], Federico Habetswallner[1], Antonio De Rosa[1], Emma Coppola[1], Emilia Cirillo[1], Claudio Pignata[1]
[1]University of Naples Federico II, Translational Medical Sciences, Section of Pediatrics, Naples, Italy, [2]University of Naples "Federico II", Translational Medical Science, Napoli, Italy, [3]University of Naples "Federico II", Translational Medical Science, Naples, Italy

Background and Aims: SAPHO syndrome is an autoinflammatory disorder characterized by osteo-articular manifestations and pustolar dermatosis. Increased cytokine production and involvement of T helper-17 pathway have been suggested as possible pathogenetic mechanisms, paving the way to the current therapeutics.

Methods: we describe the case of a 14-year-old boy presenting with fever, arthralgia, tender, diffuse maculo-papular pustular lesions of face and trunk, unresponsive to an oral antibiotics. On physical examination, a right sterno-clavicular joint swelling was noted. Biochemical and cultural tests were undertaken and an intravenous antibiotic regimen associated with corticosteroid therapy was established; imaging was requested to define the nature of the hyperostosis.

Results: screening for infectious diseases resulted negative; immunological work-up only showed increase in interleukin 6. CT-scan revealed erosion of cortico-medullary component with periosteal thickening. No significant improvement of dermatosis was obtained after 14 days of antibiotic treatment whereas, upon steroid weaning, worsening of skin lesions was observed, deemed severe through Global Acne Grading System Score (GAGS). A diagnosis of SAPHO syndrome was made based on acne fulminans and chondro-sternal involvement, as of Kahn criteria. Weekly therapy with 4 mg/kg anti-interleukin 17 monoclonal antibody, secukinumab, was started. After 4 weeks, no adverse event was observed, resulting in a significant improvement of skin lesions and GAGS reduction .

Conclusions: SAPHO syndrome is a rare autoinflammatory disorder in which a role of dysregulated interleukin production, in particular of IL-17, has been described. Targeted treatment with a monoclonal antibody against this cytokine determined the remission on cutaneous manifestation in the absence of adverse reactions in our patient.

Disclosure: No.

Keywords: acne fulminans, sapho, secukinumab, Targeted therapy

PD194

TRISOMY 8 INFORMS INFLAMMATORY MECHANISMS IN BEHÇET'S DISEASE

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Camila Astudillo, Yasmin Espinosa, Pamela Morales, Evelyn Nuñez, Cecilia Poli
Hospital Roberto del Rio, Immunology And Reumathology, Santiago, Chile

Background and Aims: Behçet's disease (BD) is within the spectrum of autoinflammatory disorders as severe BD can be caused by monogenic mutations in TNFAIP3 leading to A20 haploinsufficiency. Trisomy 8 (T8) is associated with hematologic malignancies, and BD has been reported in patients with T8 and myelodysplastic syndrome (MDS). We present two cases of BD in patients with T8.

Methods: Literature on BD and T8 was reviewed

Results: The first case is a 16-year-old female previously diagnosed with T8 who presented at age 1 with recurrent fever, recurrent oral and genital ulcers. At 11 years she was hospitalized due to a genital and multiple ileum ulcers that evolved with ileal perforation. In that opportunity she was diagnosed with BD and started on colchicine with a good response. The second patient is a 15-year-old female, with neurodevelopmental delay and dysmorphic features who presented at 1 month with recurrent fevers. At 9 yrs. she developed recurrent ulcers and was diagnosed with BD. She was started on colchicine, azathioprine and later mycophenolate. Due to poor response,infliximab was recently indicated. In this context a karyogram was requested confirming T8. Both children have had normal CBC since diagnosis.

Conclusions: Chromosome 8 harbors a critical region with 31 genes possibly associated with these manifestations, these include IKBKB, SHARPIN, OTUD6B which could all be contributing to NF-κB activation, a key player in BD pathogenesis. Other genes including GSDMD and USP17L1 could also play a role in BD susceptibility. Further studies in patients with T8 could lead to further understanding of BD pathogenesis

Disclosure: No.

Keywords: behcet, trisomy 8, autoinflammatory

PD195

PERIODIC FEVER, APTHOUS STOMATITIS, PHARYNGITIS AND ADENITIS (PFAPA) SYNDROME – OUR EXPERIENCE FROM TERTIARY CARE CENTRE IN NORTH INDIA

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Vibhu Joshi[1], Aaqib Banday[2], Deepti Suri[3], Vignesh Pandiarajan[1], Ankur Jindal[3], Amit Rawat[3], Anju Gupta[2]
[1]Postgraduate Institute of Medical Education and Research, Department of Pediatrics, Advanced Pediatrics Centre, Chandigarh, India, [2]Postgraduate Institute of Medical Education & Research, Pediatrics, Chandigarh, India, [3]Postgraduate Institute of Medical Education and Research, Pediatrics, Chandigarh, India

Background and Aims: PFAPA is the commonest autoinflammatory syndrome in pediatric population. Associated risk factors with PFAPA are being increasingly evaluated; however, etiology is still unknown. Diagnosis of PFAPA is purely clinical and is diagnosed based on Eurofever/PRINTO criteria. There is a significant paucity of relevant data from Indian subcontinent. Herein, we present our experience regarding the diagnosis and management of PFAPA.

Methods: We included 15 children with PFAPA syndrome who fulfilled the recent Eurofever/PRINTO criteria.

Results: Data regarding clinico laboratory features, treatment and outcomes were analyzed. Among clinical features periodicity of disease episodes was noted in all patients, 3-6 day duration of episodes in 14, cervical adenitis in 11 patients, pharyngitis in 12 and tonsillitis in 6 patients. Before the diagnosis of PFAPA, all patients received multiple courses of antimicrobials and even ATT. Most patients were managed conservatively with oral paracetamol and non steroidal anti inflammatory drugs. Intermittent steroid therapy was used in 10 patients. Trial with oral colchicine was given in 3 patients. Median duration of follow-up was 4.06 years with a total follow-up duration of 64.66 patient-years. Improvement in fever spikes was noted with increasing age in 3/4th of our patients. of the remaining, 3 continued to be febrile and patients had not followed up for the past 2 years.

Conclusions: A considerable diagnostic delay of upto 7.3 years was noted in our study. Use of antimicrobials prior to diagnosis was common. Few patients also received many months of ATT. Increased awareness is imperative to ensure timely diagnosis of PFAPA and prevent significant morbidity.

Disclosure: No.

Keywords: Paediatric Rheumatology International Trials Organisation (PRINTO), Anti Tubercular Therapy (ATT), Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome

PD196

INFECTIONS IN RHEUMATOID ARTHRITIS AND BIOLOGICAL USE: A SYSTEMATIC REVIEW AND META-ANALYSIS

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Barbara Bergmans[1,2], Biniyam Gebeyehu[1,3], Jean-Luc Murk[2,4], Eugène Van Puijenbroek[5], Esther De Vries[1,2]
[1]Tilburg University, Tranzo, Tilburg, Netherlands, [2]Elisabeth-TweeSteden Hospital, Laboratory of Medical Microbiology And Immunology, Tilburg, Netherlands, [3]Tilburg School of Social and Behavioral Sciences, Department of Methodology And Statistics, Tilburg, Netherlands, [4]Elisabeth-TweeSteden Hospital, Microvida, Tilburg, Netherlands, [5]Netherlands Pharmacovigilance Centre Lareb, Scientific Department, 's-Hertogenbosch, Netherlands

Background and Aims: Due to their effectivity, biologics and Janus-Kinase (JAK) inhibitors are a cornerstone in rheumatoid arthritis (RA) treatment. However, suppressing the immune system causes increased infection risk in some patients. We performed a systematic review and meta-analysis to identify previously established risk factors that predict infection risk in RA patients using biologics and JAK-inhibitors.

Methods: We searched Pubmed and Cochrane for studies reporting infectious adverse events (IAEs) in RA patients using biologics or JAK-inhibitors. Descriptive statistics were used to summarize serious infections in case reports. A random-effects meta-regression was used to identify potential predictors for contracting an infection in trials, open label studies and registries.

Results: The final selection yielded 377 case reports (509 cases), and 254 other studies (524 study arms). 66% of cases were bacterial infections (of which 48% mycobacterial), 20% fungal, 8% parasitic and 6% viral. Meta-analysis of the other studies revealed a pooled proportion of any infection of 30.9%, and 3.2% for serious infection. To account for significant heterogeneity (I^2>91%), subgroups were identified based on study design, in- and exclusion criteria and follow-up duration. No variable was identified as a potential predictor across all groups.

Conclusions: Due to inconsistent IAE reporting and high between-study heterogeneity, it was challenging to identify potential predictors. Significant heterogeneity was mainly found in nonserious infections as opposed to serious infections, even though the corresponding incidence ratio was approximately 10:1. Prospective research using a standardized reporting system and a particular focus on nonserious infections and patient-experienced burden are urgently needed to shed light on this matter.

Disclosure: No.

Keywords: Infection, adverse event, JAK-inhibitor, rheumatoid arthritis, biologics

PD197

COPA DEFECT: ABOUT 2 MOROCCAN PATIENTS

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Hind Ouair[1], Rahma Manyundo[2], Ibtihal Benhsaien[1], Assiya Elkettani[1], Asmaa Drissi Bourhanbour[1], Jalila El Bakouri[1], Ahmed Aziz Bousfiha[1], Fatima Ailal[1]
[1]Faculty of Medecine and Pharmacy, University Hassan II, Casablanca, Laboratory of Clinical Immunology, Inflammation And Allergy (licia), CASABLANCA, Morocco, [2]HAROUCHI Children's Hospital, Clinical Immunology Unit-pediatric Infectious Diseases Department-, CASABLANCA, Morocco

Background and Aims: COPA syndrome is an inherited autoimmune disease caused by mutations in the COPA gene. The COPA gene encodes the α subunit of the COP1 protein. The pattern of COPA syndrome is acquired with an autosomal dominant inheritance, and patients with interstitial lung disease usually present with pulmonary hemorrhage and then develop arthritis.

Methods: We report the observation of two twin sisters with COPA deficiency. Aged 8 years old and from a first-degree consanguineous marriage with a similar clinical picture. The onset of symptomatology dates back to the age of 2 years, by repeated respiratory infections, thoracic and abdominal tuberculosis with hepato-splenomegaly treated with antibacillaries. The diagnosis of sarcoidosis was then posed with prolonged fever, hepato-splenomegaly, pulmonary involvement, non-necrotizing tuberculoid granulomatous involvement in liver biopsy with an increase in the Angiotensin Conversion Enzyme.The standard immune assessment performed (HIV serology, Ig: Ig A, Ig G, Ig M and Ig E, SPL and DHR test) was normal.

Results: Both binoculars were treated with corticosteroids for sarcoidosis and immunoglobulin infusion. The course was marked by the onset of cytopenia, repeated infections and the death of one of the twins at 9 years and 11 months of age. A genetic study was carried out in a single patient at the age of 10 years and diagnosed with COPA deficiency (Genetic result in the process of publication)

Conclusions: COPA deficiency is a rare autoinflammatory disease. The genetic study is essential to make the diagnosis, the normal classic immune assessment does not make it possible to make the diagnosis.

Disclosure: No.

Keyword: COPA- IEI- Autoinflammation-COP1 protein-prolonged fever-genetic study

PD198

VEXAS SYNDROME A NEWCOMER IN AUTOINFLAMMATORY DISEASE

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Ana Lucia Jimenez Portillo[1], Cinthya Fusi[2], Sergio Mora[2], Maikel Bravo Gonzales[1], Ernesto Tovar[3], Juan Ignacio Aróstegui[2], Mariano Andres[2], Francisco Marco De La Calle[1]
[1]General University Hospital of Alicante Dr. Balmis, Immunology, Alicante, Spain, [2]Hospital Clínic, Immunology Department, Barcelona, Spain, [3]General University Hospital of Alicante Dr. Balmis, Rheumatology, Alicante, Spain

Background and Aims: VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is an adult-onset inflammatory syndrome caused by a mutation affecting methionine codon 41 of the UBA1 gene which encodes ubiquitin activating enzyme (E1). We describe a case of VEXAS syndrome in a patient with a autoinflammatory features.

Methods: Review of clinical history after family authorization.

Results: A 73-year-old man presented episodes of fever, erythematous subcutaneous nodules (panniculitis-like) in lower limbs, ankle arthritis and syncopal episodes. Laboratory tests showed persistent inflammatory anemia and severe systemic inflammation (increased CRP-ESR), interpreted as active infection. Antibiotic treatments were not effective suggesting autoinflammatory etiology. Several lines of immunomodulation were tried including corticosteroids, azathioprine, colchicine without improvement. Diagnostic workup included skin biopsy that revealed neutrophilic infiltration and leukocytoclastic vasculitis. Bone marrow aspiration informed abundant cytoplasmatic vacuoles. As clinical features and refractoriness to treatment suggested VEXAS syndrome, we performed a UBA1 Sanger sequencing which showed a pathogenic variant p.Met41Val in the form of genetic mosaicism. In the subsequent evolution he developed a progressive neurological worsening with non-convulsive status epilepticus that required intensive care admission. Following the diagnostic of VEXAS syndrome a final therapeutic trial with ruxolitinib was attempted with poor response and fatal outcome. A postmortem examination revealed vasculitis affecting esophagus, lungs, kidneys, and mild diffuse involvement in several encephalic structures and spinal cord.

Conclusions: VEXAS syndrome is a recently described entity that should be considered as a differential diagnosis, in male with severe late onset autoinflammatory disease and refractoriness to treatment, even though it continues to be fatal.

Disclosure: No.

Keyword: UBA1 gene; vexas syndrome; autoinflammatory disease

PD199

HYPER-IGD AND PERIODIC FEVER SYNDROME DUE TO TWO VARIANTS IN MEVALONATE KINASE GENE IN A 26-YEAR-OLD PATIENT.

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Lydia García-Serrano[1,2], Mario Framil Seoane[1,2], Blanca Urban[1,2], Francisco Morandeira Rego[1,2], Arnau Antolí Gil[2,3], Gemma Rocamora Blanch[2,3], Anna Esteve Garcia[2,4], Roger Colobran[5], Xavier Solanich Moreno[2,3]
[1]Hospital Universitari de Bellvitge, Immunology, L'Hospitalet de Llobregat, Spain, [2]Hospital Universitari de Bellvitge, Adult Primary Immunodeficiency Unit, L'Hospitalet de Llobregat, Spain, [3]Hospital Universitari de Bellvitge, Internal Medicine, L'Hospitalet de Llobregat, Spain, [4]Hospital Universitari de Bellvitge, Genetic Counsellor, L'Hospital de Llobregat, Spain, [5]Hospital Universitari Vall d'Hebron, Immunogenetic Department, Barcelona, Spain

Background and Aims: Hyper-IgD and periodic fever syndrome (HIDS) is a rare autosomal recessive inflammatory disorder caused by pathogenic variants in the mevalonate kinase (MVK) gene, resulting in depressed enzyme activity. Clinical features of HIDS include recurrent fever and inflammation. This is a 26-year-old female patient who presents a febrile syndrome since the first year of life lasted from 3 to 4 days with a bimonthly periodicity. She suffered repeatedly from acute otitis and bacterial pneumonias during her first year or life. At the age of 7, IgG4 deficiency was detected and treated with polyclonal immunoglobulins. At the age of 23 the febrile episodes worsened and she also presented diarrhea.

Methods: Laboratory tests including blood cell count, lymphocyte subpopulations, immunoglobulin levels and complement assays were performed. Next-generation sequencing (NGS) study of autoinflammatory diseases and familial segregation studies were also performed.

Results: Laboratory findings showed no relevant alterations except for elevated IgD levels. Acute phase reactants between febrile episodes were normal. NGS panel for autoinflammatory diseases detected two heterozygous variants in MVK gene: c.1129G>A/p.Val377Ile (Common – pathogenic) and c.1006G>A/p.Gly336Ser (Rare - probably pathogenic). The family segregation study confirmed that each parent is a carrier of one of the mutations, confirming the patient presents those variants in trans.

Conclusions: This result could explain the patient's clinical presentation, as these both pathogenic and probably pathogenic biallelic variants in the MVK gene are associated with mild forms of HIDS. This case illustrates a long delay in diagnosis due to insufficient knowledge of the underlying disease.

Disclosure: No.

Keywords: Next-generation sequencing, Fever, Variants, Immunoglobulin, autoinflammatory

PD200

NEMO-NDAS; TWO FURTHER CASES of A NOVEL AUTOINFLAMMATORY DISORDER WITH ASSOCIATED HYPOGAMMAGLOBULINEMIA

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Fatima Albreiki[1], Adriana De Jesus Rasheed[2], Emma Macdermott[3], Orla Killeen[3], Raphaela Goldback-Mansky[2], Timothy Ronan Leahy[4,5]
[1]CHI @ Crumlin, Immunology, Dublin, Ireland, [2]NIAID, Rheumatology, Bethesda, United States of America, [3]CHI @ Crumlin, Rheumatology, Dublin, Ireland, [4]Children's Health Ireland at Crumlin, Department of Paediatric Immunology And Infectious Diseases, Dublin, Ireland, [5]University of Dublin, Trinity College, Pediatrics, Dublin, Ireland

Background and Aims: We report two cases of a novel infantile-onset immunodysregulation disorder due to IKBKG (NEMO) variants that are predicted to disrupt a highly conserved donor splice site and skip exon 5 named as NEMO deleted exon 5-autoinflammatory syndrome phenotype (NEMO-NDAS).

Methods: A retrospective review of the patients' medical records, radiological and laboratory results was undertaken, along with evaluation of the immunological phenotype by functional testing. The molecular basis of disease was established by Sanger sequencing of the IKBKG gene.

Results: Both patients presented with early onset arthritis, recurrent fevers, panniculitis, uveitis and intracranial calcification. P1 has features of neurodevelopmental delay, P2 has features of hepatopathy with portal hypertension. Both patients have hypogammaglobulinemia and require immunoglobulin replacement therapy. Management of both cases remains challenging, P1 requiring a combination of tocilizumab, ruxolitinib and prednisolone to control symptoms. P2 remains stable on weekly adalimumab and low dose prednisolone.

Conclusions: Diagnosis of NEMO-NDAS can be challenging, and can be missed on whole exome sequencing due to the presence of IKBKG pseudogenes. Consideration should be given to this diagnosis, particularly with an interferonopathy/Blau syndrome phenotype and hypogammaglobulinemia.

Disclosure: No.

Keywords: NEMO-NDAS, Interferonopathy, hypogammaglobulinemia, arthritis, panniculitis, uveitis

PD201

THE CLINICAL PRESENTATION of HYPERIMMUNOGLOBULIN D SYNDROME

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Dragana Lazarevic, Jelena Vojinovic
Clinic of Pediatrics, University Clinical Center Nis; Faculty of Medicine, University of Nis, Nis, Serbia, Department of Pediatric Rheumatology And Immunology, Nis, Serbia

Background and Aims: Autoinflammatory syndromes are rare diseases with diverse clinical presentation and recurrent systemic inflammation.

Methods: To present a child with clinical features associated hyperimmunoglobulin D syndrome.

Results: Clinical symptoms have started just after birth. In the first days of life out patient was examined at gastroenterology department due to elevated parameters of inflammation, anemia, direct hyperbilirubinaemia, abdominal bloating and hepatosplenomegalia. Detailed hematological, virusological and gastroenterological diagnostic testing was performed. Liver biopsy has showed portal and lobular hepatitis with cholestasis without fibrosis. At five months she started with recurrent episodes of fever every month for few days with no associated infection, but always with digestive symptomatology and elevated inflammatory parameters. Despite antibiotics, episodes of fever continued to repeat twice monthly with occurrence of hypersalivation, small ulcers in the mouth, skin rash, cervical lymphadenopathy, hepatosplenomegaly, abdominal pain and abdominal bloating with elevated inflammatory markers. Clinical spectrum of presenting symptoms with hypertelorisms and frontal bossing were enough to suspect on hyper IgD syndrome. Genetic testing revealed presence of two heterozygous mutations in the mevalonate kinase deficiency gene confirming hyperimmunoglobulin D syndrome. Nonsteroidal anti-inflammatory drugs and corticosteroids have led to partial remission during a fever episodes. As fever episodes continued on every two weeks we are about to start with donated fully-humanized protein, highly efficacious in fever episodes resolution by blocking interleukin-1 beta cytokine.

Conclusions: Genetic testing is important to confirm the final diagnosis and start accurate treatment in order to prevent potential serious complications of untreated patients.

Disclosure: No.

Keyword: Autoinflammatory diseases, Genetic testing, Treatment options

PD202

NEONATAL ONSET MULTISYSTEM INFLAMMATORY DISEASE (NOMID)- A SERIES of TWO PATIENTS FROM A TERTIARY CARE CENTER IN NORTH INDIA.

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Harikrishnan Gangadharan[1], Sandeep Kansurkar[2], Amita Aggarwal[2]
[1]GOVERNMENT MEDICAL COLLEGE KOTTAYAM, General Medicine, Kottayam, India, [2]SANJAY GANDHI POSTGRADUATE INSTITUTE of MEDICAL SCIENCES, Clinical Immunology And Rheumatology, Lucknow, India

Background and Aims: Neonatal onset multisystem inflammatory disease (NOMID) is the most severe form of NLRP3 associated autoinflammatory disease characterized by recurrent fever, urticarial rash, arthropathy and neurological symptoms. We report 2 cases of NOMID which were diagnosed elsewhere as juvenile idiopathic arthritis and referred to our centre.

Methods: This is a hospital records based study of two patients with NOMID who attended the department of Clinical Immunology at a tertiary care centre in North India during the one- year period from April 2018 to April 2019.

Results:

	CASE 1
Age (years)	5
Gender	M
Clinical features	urticarial lesions since birth, episodic fever and bilateral knee joint painful from 18 months of age
Examination findings	stunting, frontal bossing, generalized urticarial lesions, lymphadenopathy hepatosplenomegaly and bilateral swollen and tender knee joints
Investigation	neutrophilic leukocytosis, raised ESR and CRP
X ray Knee	grossly enlarged epiphysis and patella
Gene sequencing	could not be done
Treatment	colchicine
Outcome	Lost to follow up

Conclusions: Though rare, NOMID should be thought of in any child with neonatal onset urticaria, deforming arthropathy and typical radiological changes. Gene sequencing is not mandatory to make a diagnosis.

Disclosure: No.

Keywords: JIA, NOMID, autoinflammatory

PD203

LATE DIAGNOSIS IN ADULTHOOD of A PATIENT WITH HYPER IMMUNOGLOBULIN D SÍNDROME (HIDS): IMPACT QUALITY of LIFE.

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Marisa Di Natale, Hector Balastegui, Joaquin Navarro, Carmen Rodriguez Sainz, Eduardo Fernandez Cruz, Elena Garcia Martinez
Hospital General Universitario Gregorio Marañon, Clinical Immunology, Madrid, Spain

Background and Aims: Genetic study is fundamental for diagnosis of Autoinflammatory syndromes which allows an early age diagnosis and treatment, avoiding associated complications.

Methods: Case report

Results: 28-year-old man from Venezuela with no family history of interest. Since on month of life begins episodes of recurrent fever accompanied by abdominal pain, nausea, adenopathies at the cervical level and monoarthritis. The duration of these episodes were 1 week and occurred monthly, which severely limited his school development. At 13 years old, he had admission to the ICU due to pneumonitis with mechanical ventilation without evidence of pathogens, with a favorable response to the intravenous corticosteroid. Since then has been in chronic treatment with prednisone 10mg/daily and colchicine. 14 years old, first episode of pericarditis with pericardial effusion. Up to now the patient has suffered 7 episodes of pericarditis. In 2019, he moved to Spain where he received the administration of anti-COVIDmRNA vaccine in Summer 2021 after with he presented an episode of fever and generalized arthrolamyalgia. March 2022 after the 3rd dose CovidmRNA vaccine he presents fever and chest pain diagnosis of pericarditis and referral to the Immunology Unit where we observed elevation of c-reactive-protein and IgD. Genomic DNA was isolated and Next Generation Sequencing was performed using a screening panel of 200 genes in relation with the Immunedeficiencies showed two heterozygous patogenic variants in MVK gen supporting the diagnosis of HIDS.

Conclusions: Currently, there are still countries where the genetic study of patients with suspected Autoinflammatory syndromes can`t be performed, which implies delay in diagnosis and treatment deteriorating the patient's quality of life.

Disclosure: No.

Keywords: quality of life, Autoinflammatory syndromes, HIDS, adulthood

PD204

DIVERSE CLINICAL PRESENTATION of HEREDITARY ALPHA TRYPTASEMIA IN SIBLINGS

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Vivian Hernandez-Trujillo, Daniel Urschel, Yaindra Gallego, Camile Ortega, William Blouin
Allergy and Immunology Care Center of South Florida, Allergy And Immunology, Miami Lakes, United States of America

Background and Aims: Patients with hereditary alpha tryptasemia have varied presentations. We present siblings with HATS with different disease manifestations. We aim to increase awareness in order to aid in earlier diagnosis of patients with mast cell disease.

Methods: Evaluation of total and fractionated tryptase is needed.

Results: A 10 year old male with history of food allergy, eczema, Food Protein-Induced Enterocolitis Syndrome, and failure to thrive. He had reactions of varying severity to multiple foods, including urticaria or prolonged vomiting, diarrhea, and abdominal pain. Specific IgE and skin prick testing were positive to several foods. He developed an oral aversion and extremely restricted diet. Symptoms of abdominal pain, hematochezia, rashes, arthralgias, headaches, fatigue, dyspnea, and palpitations increased. Laboratory markers demonstrated elevated inflammatory markers, anemia, iron deficiency, vitamin B12 deficiency, and vitamin C deficiency (scurvy). Gastroenterology workup did not identify pathology. He has had recurrent pseudotumor cerebri and recent diagnosis of seizures. Fractionated Tryptase revealed normal mature (beta) tryptase with elevated total tryptase with negative genetics for c-KIT mutation. His 13 year old sister has a history of oral allergy to apples and bananas, asthma and occasional abdominal pain. Total Tryptase was elevated with diagnosis of HATS.

Conclusions: Hereditary alpha tryptasemia syndrome is defined by elevated blood tryptase levels and involves multiple organ systems, including skin, gastrointestinal, connective tissue, cardiac, and neuropsychiatric. Increased levels of tryptase are caused by extra copies of the alpha tryptase gene (TPSAB1). Treatment is usually directed at symptom control. A need exists for early identification of patients with mast cell disorders.

Disclosure: I am a consultant and advisory board attendee for Takeda, CSL, Enzyvant, kaleo and Renegeron/Sanofi. None of the conflicts relate to this abstract.

Keywords: mast cell, tryptase, alpha tryptasemia, HATS

PD205

COMPARISON of IMMUNOLOGICAL BIOMARKERS AND LUNG HISTOLOGY IN PATIENTS WITH ELEVATED IL18 - PULMONARY ALVEOLAR PROTEINOSIS AND RECURRENT MACROPHAGE ACTIVATION SYNDROME (IL-18PAP-MAS)

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Alhanouf Alsaleem[1], Adriana De Jesus Rasheed[2], Raphaela Goldback-Mansky[2]
[1]KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTER, Pediatric Rheumatology, RIYADH, Saudi Arabia, [2]NIAID, Rheumatology, Bethesda, United States of America

Background and Aims: PAP and recurrent MAS have been reported in rare patients (pts) with systemic juvenile idiopathic arthritis (SJIA) like disease. The pathomechanisms of lung disease remain elusive. We aimed to characterize genetic and immunological biomarkers of IL-18PAP-MAS pts.

Methods: Eight pts with IL-18PAP-MAS were enrolled. Serum, whole blood RNA, bronchoalveolar lavage (BAL) samples and lung biopsies from IL-18PAP-MAS pts were compared to samples from pts with autoinflammatory diseases and healthy controls. Cytokines were measured by Luminex assay in serum and BAL, *CXCL9* and *CXCL10* transcript levels were measure by Nanostring. Lung biopsies scored for inflammatory and damage features.

Results: IL-18PAP-MAS pts had elevation of serum IL-18 levels similar to patients with NLRC4-MAS. *CXCL9* and *CXCL9*/*CXCL10* ratio were higher in IL-18PAP-MAS compared to controls. BAL fluid from IL-18PAP-MAS pts had high expression of IL-18 and free IL-18 solely detected in IL18 PAP-MAS in contrast to controls. Histologic features showed innate immune cells including high expression of neutrophils and alveolar macrophages with B cell infiltrates compared to controls. Cholesterol clefts and mucous plugging were cardinal features in IL18 PAP-MAS. Distinctive radiological features suggestive of active inflammation included consolidation, intralobular septal thickening, and pulmonary nodules, with higher inflammatory vs damage score in contrast to controls.

Conclusions: IL-18PAP-MAS is a recently characterized, not yet genetically defined syndrome. Histological pulmonary features of IL18 PAP-MAS differ from lung manifestations of control. BAL fluid shows high expression of total and free IL-18 in IL-18 PAP MAS pts versus controls; suggesting a role of free IL-18 in the distinct pathogenesis of PAP in IL-18PAP-MAS.

Disclosure: No.

Keywords: MAS, SJIA, lung disease, IL-18

PD206

POTENTIAL EFFECT of NOVEL VARIANT IN WDR1 GENE EXPAND THE PHENOTYPIC FEATURES of PERIODIC FEVER, IMMUNODEFIENCY, AND THROMBOCYTOPENIA (PFIT) SYNDROME.

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Alhanouf Alsaleem, Anas Alazami, Monther Alalwan, Abdullah Alsonbul, Sulaiman Almayouf
KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTER, Pediatric Rheumatology, RIYADH, Saudi Arabia

Background and Aims: Autoinflammatory periodic fever, Immunodeficiency, and thrombocytopenia (PFIT) is an autosomal recessive disease caused by a loss of function mutation in WDR1 gene. This resulted in pyrin activation and release of IL-18. We describe here the genotypic and phenotypic characteristics of a patient combining immune dysregulation and autoinflammatory features.

Methods: We retrospectively reviewed clinical data of a 10-year-old boy presenting with recurrent fever, skin rash, respiratory and gastrointestinal manifestations. Genomic analysis through whole exome sequencing (WES) was conducted.

Results: The patient initially presented in the neonatal period with dysmorphic features (frontal bossing, dolichocephaly, and depressed nasal bridge) and recurrent respiratory distress. Subsequently, he had recurrent fever and skin abscess. He required multiple ICU admissions with respiratory failure and one occasion with bowel obstruction. Laboratory evaluation revealed pancytopenia, elevated inflammatory markers, and hypogammaglobinemia. IL-1 inhibitor (Anakinra) was initiated with partial improvement. We elected to initiate long-acting IL-1 inhibitor (Canakinumab), this resulted in dramatic improvement in clinical parameters, attacks frequency and discontinuation of steroid use. Genetic material was submitted for WES, which identified a homozygous missense variant (p.H437D) in the WD Repeat Domain 1 (WDR1) gene. PBMC immunophenotyping revealed severely depressed T cell (< 10%) and NK cell (< 1%) populations, while $CD19^{+}$ memory cells were strongly downregulated.

Conclusions: We describe a likely pathogenic candidate variant in WDR1 known to activate and release IL-18. Although many aspects of our patient's phenotype correspond to PFITS syndrome, other described phenotypes are novel. The patient's dramatic response to Canakinumab illustrates that a non-IL-18 therapy can be effective in this regard.

Disclosure: No.

Keywords: WDR1, autoinflammatory, RECURRENT FEVER

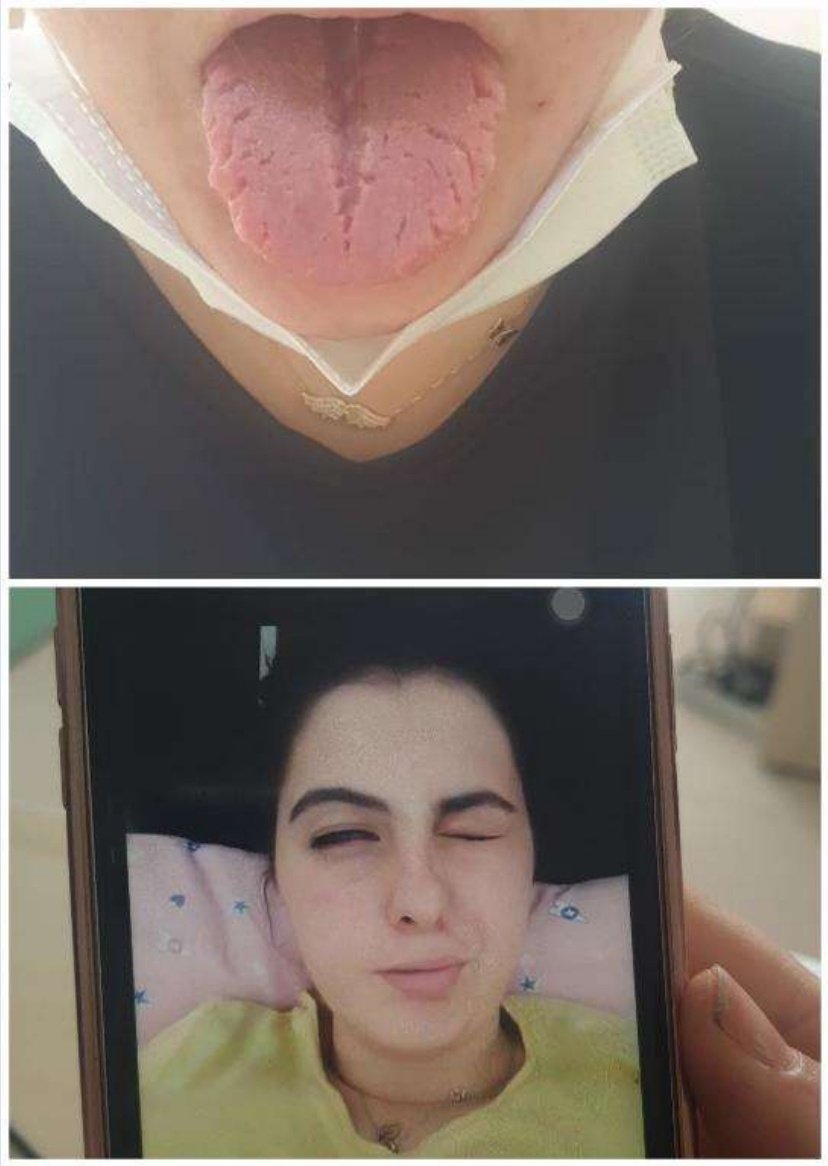
PD207

A CURIOUS DIAGNOSIS, MELKERSSON-ROSENTHAL SYNDROME PRESENTING AS DRUG ALLERGY

POSTER DISPLAY 05: AUTOINFLAMMATORY DISORDERS

Fatma Merve Tepetam, Özge Atik, Ali Burkan Akyıldız
süreyyapaşa göğüs hastalıkları ve göğüs cerrahisi hastanesi, Alerji Ve Immunoloji, istanbul, Turkey

Background and Aims: Melkersson-Rosenthal Syndrome (MRS) is a rare disease .Many factors such as infections, genetic predisposition, immunodeficiency are blamed in the etiopathogenesis. MRS is characterized by recurrent, long-lasting swelling of the face (edema), particularly of one or both lips (granulomatous cheilitis), facial muscle palsy and deep grooves on the tongue ***'lingua plicata'*** (fissured tongue). In this article, we present a case of MRS with a very unusual clinical presentation.



Methods: . A 23-year-old female patient stated that she had unilateral (left) facial paralysis 8 times in the last 8 years. She also stated that 2 of these facial paralysis occurred after doxycycline treatment , and 1 of them after isotretinoin treatment and 1 time after local anesthesia was given . Ultimately she was referred to an allergy and immunology clinic in terms of drug allergy. In the photographs, it was seen unilateral facial paralysis and angioedema of the lip and deep fissure grooves were observed on the tongue. (*Figure.1*) MRS was considered. Food and inhalant panel skin test were negative. β2-microglobulin, thyroid stimulating hormone and complement (C3, C4, C1q) Iga,ıgm,Igg levels were normal

limits.The patient did not accept lip biopsy. Tests are planned for the determination of safe alternative antibiotics and local anesthesia. .

Results: Labial biopsy and histopathological findings of Langhans cell noncaseating granulomatous inflammation can be seen in MRS. Its absence should not exclude the clinical diagnosis.

Conclusions: .Treatment of this syndrome remains empirical corticosteroids.It has recently reported successful results with antitumor necrosis factor alpha (anti-TNFα) agents such as adalimumab and infliximab.

Disclosure: No.

Keyword: inflammatory diseases,facial paralysis and drug allergy,Melkersson-Rosenthal Syndrome

PD208

PREVALENCE of CFTR VARIANTS IN PID PATIENTS WITH BRONCHIECTASIS - AN IMPORTANT MODIFYING CO-FACTOR

POSTER DISPLAY 06: GENETICS IN IEI

Dylan Lawless[1], Hana Lango Allen[2], James Thaventhiran[3], Sarah Goddard[4], Olly Burren[5], Evie Robson[6], N Ihr Bioresource–Rare Diseases Consortium[2], Daniel Peckham[6], Keneth Smith[5], Sinisa Savic[7]
[1]Global Health Institute, School of Life Sciences, Lausanne, Switzerland, [2]Cambridge University Hospital, Nihr Bioresource, Cambridge, United Kingdom, [3]University of Cambridge, Mrc Toxicology Unit, QR, United Kingdom, [4]University Hospitals of North Midlands NHS Trust, Immunology And Allergy, Stoke-on-Trent, United Kingdom, [5]University of Cambridge, Cambridge Institute For Therapeutic Immunology And Infectious Disease, Cambrigde, United Kingdom, [6]University of Leeds, Leeds Cystic Fibrosis Trust Strategic Research Centre, Leeds, United Kingdom, [7]St James's University Hospital, Clinical Immunology And Allergy, Leeds, United Kingdom

Background and Aims: Cystic fibrosis (CF) is one of the most common autosomal recessive disorders. Lung pathology of CF is similar to the state seen in some cases primary immunodeficiency (PID), the heterogeneity of which can make precise diagnosis difficult. The potential for heterozygous hypomorphic variants in CFTR impacting the severity of structural lung disease for PID patients has been suggested by never systemically tested.

Methods: We performed within-cohort and population level statistical genomic analysis for all patients with PID from a large European cohort using genome sequence data. As part of the NIHR BioResource – Rare Disease study, 1046 PID patients and relatives had their genomes sequenced. PID cohorts were assessed for the regions of GRCh37 CFTR; 7:117118017-117310718, as well as related genes SCNN1A; 12:6454009-6488523, SCNN1B; 16:23311591-23394620, and SCNN1G; 16:23192040-23230200, which encode subunits of an epithelial sodium channel complex (ENaC). Damging variants in ENaC can cause CF-like phenotype.

Results: p.Phe508del carriage was specifically enriched in PID patients who had structural lung disease and carriage of several pathogenic variants was enriched compared to the general population. This was not the case for ENaC coding variants. 5 patients were found to have compund heterozygous variants in CFTR, but further analysis showed that these variant pairs were not assoiated with typical cystic fibrosis phenotype.

Conclusions: The use of genome sequencing can identify cases of CFTR dysfunction in PID driving an increased susceptibility to structural lung damage. Large national genomics services provide an opportunity for precision medicine by interpreting subtle features of genomic diversity when treating traditional Mendelian disorders.

Disclosure: No.

Keywords: primary immunodeficiency, Cystic fibrosis, Bronchiectasis, CFTR

PD209

CAN WE PREDICT WHEN TO EVALUATE CVID GENETICALLY?

POSTER DISPLAY 06: GENETICS IN IEI

Marina Garcia-Prat[1], Alba Parra-Martínez[2], Aina Aguiló-Cucurull[3], Alejandro Pérez[3], Romina Dieli-Crimi[3], Eva Polverino[4], Xavier Solanich Moreno[5], Maria Antolin[6], Pere Soler-Palacin[7], Roger Colobran[8]
[1]Vall d'Hebron Barcelona Hospital Campus, Infection In Immunocompromised Pediatric Patients, Barcelona, Spain, [2]Vall d'Hebron Research Institute (VHIR), Infection In The Immunocompromised Child., Barcelona, Spain, [3]Vall d'Hebron Barcelona Hospital Campus, Immunology Division, Barcelona, Spain, [4]Vall d'Hebron Barcelona Hospital Campus, Pneumology Department, Barcelona, Spain, [5]Hospital Universitari de Bellvitge, Internal Medicine, L'Hospitalet de Llobregat, Spain, [6]Vall d'Hebron Barcelona Hospital Campus, Clinical And Molecular Genetics, Barcelona, Spain, [7]Vall d´Hebron Hospital, Pediatric Infectious Diseases And Immunodeficiencies Unit, Hospital Universitari Vall D'hebron (huvh), Vall D'hebron Research Institute (vhir), Universitat Autònoma De Barcelona, Catalonia, Spain. Jeffrey Modell Excellence Centre, Barcelona, Spain, [8]Hospital Universitari Vall d'Hebron (HUVH, Barcelona, Catalonia, Spain, Immunology Department.department of Clinical And Molecular Genetics, Barcelona, Spain

Background and Aims: Common variable immunodeficiency (CVID) is highly variable in terms of clinical presentation, age and severity. Although the polygenic and epigenetic contribution is evident, monogenic causes can explain 15-30% of cases. The aim of this study is to clinically, immunologically, genetically and molecularly characterize CVID patients to offer personalized treatment and preconception counselling.

Methods: Patients who meet the ICON2015 criteria were studied with a custom genetic panel including 323 IEI genes. Previously unreported mutations were functionally validated. All the variables collected were statistically studied to create a predictive model for CVID monogenic forms.

Results: From a cohort of 148 CVID patients (gender ratio (M:F) is 1.16:1, mean age of 43 (18 SD)), 136 were genetically studied. Thirty-six pathogenic mutations were identified (26%): 61% were considered causative (BTK, CTLA4, DKC1, IKBKG, IKZF1, LRBA, NFKB1, PIK3R1, RNU4ATAC and TNFRSF13B [homozygous and compound heterozygote] genes) and 39% risk factors (heterozygous TNFRSF13B variants). Segregation studies allowed us to identify 11 affected individuals and 14 carriers. Functional studies were performed for some specific variants to confirm its pathogenicity. Seven (5%) patients in the cohort could benefit from a targeted treatment after genetic diagnosis. Younger age, early age of symptom onset, an "infection plus" phenotype and high transitional B lymphocytes were significantly associated with a positive genetic result (AUC = 0.87).

Conclusions: A causative monogenic defect was identified in 16% of the CVID cohort. NGS seems mandatory in young CVID patients, those with early onset of symptoms, a clinical phenotype with infections plus non-infectious features and elevated transitional B cells.

Disclosure: This project was made possible thanks to funding from GRIFOLS, through an investigator led study agreement, in February 2018.

Keywords: Common variable immunodeficiency, Next generation sequencing, Monogenic diseases, Predictive model of monogenetic forms, CVID, Genetics

PD210

TNFAIP3 DELETIONS BECOME CLINICALLY APPARENT WITH IN TRANS EXPRESSION of THE HYPOMORPHIC DENISOVAN-DERIVED ADAPTIVELY INTROGRESSED I207L ALLELE

POSTER DISPLAY 06: GENETICS IN IEI

Paul Gray[1], Nathan Zammit[2], Owen Siggs[3], Jin Yap[3], Amanda Russell[3], Daniel Cultrone[3], Joanna Warren[3], Stacey Walters[3], Robert Brink[3], David Zahra[3], Deborah Burnett[3], Velimir Gayevskiy[3], Andre Minoche Minoche[3], John Ziegler[1], Maria Craig[4], Melanie Wong[5], Ted O'Laughlin[5], Paul Benitez-Aguirre[4], Juliana Teo[6], Mark Cowley[7], Marcel Dinger[8], Stuart Tangye[2], Catherine Burke[9], Tri Phan[2], Christopher Goodnow[2], Shane Grey[2]
[1]Sydney Children's Hospital, Immunology And Infectious Diseases, Randwick, Australia, [2]Garvan Medical Research Institute, Immunology, Darlinghurst, Australia, [3]Garvan Institute of Medical Reseach, Immunology, Darlinghurst, Australia, [4]Children's Hospital at Westmead, Endocrinology, Westmead, Australia, [5]Children's Hospital at Westmead, Immunology And Allergy, Westmead, Australia, [6]Children's Hospital at Westmead, Neurology, Westmead, Australia, [7]Children's Cancer Institute of Australia, Computational Biology, Randwick, Australia, [8]Garvan Medical Research Institute, Genomics, Darlinghurst, Australia, [9]University of Technology Sydney, School of Life Sciences, Ultimo, Australia

Background and Aims: Heterozygous deletions in TNFAIP3 cause childhood-onset inflammatory disease, which was thought to be completely penetrant before adulthood. The p.I207L polymorphism is globally rare, but has been adaptively introgressed from ancestral Denisovan Hominins to high prevalence in Oceanian populations.

Methods: Patients with TNFAIP3 deletions were identified from a cohort with paediatric autoimmune disease. IkB-dependent phosphorylation and activation of A20 was assessed in patient cells and cell lines containing p.I207L and other polymorphic TNFAIP3 variants. CRISPR/Cas9 gene-edited mice possessed either a TNFAIP3 deletion, the I207L variant, or both, and were exposed to pro-inflammatory conditions.

Results: Two unrelated patients with heterozygous deletions of TNFAIP3 manifested complex inflammatory disease. Both inherited the deletion from a healthy parent and expressed the hypomorphic p.I207L allele in trans, inherited from another healthy parent of Oceanian origin. Patient cells demonstrated increased degradation of IkB associated with the compound heterozygote state compared to the deletion alone or p.I207L carrier. Compound heterozygous mice were also more prone to gut and eye inflammation than heterozygous deletion or I207L carriers, in particular when removed from SPF conditions. Polymorphic variants in TNFAIP3 altered A20 phosphorylation and inflammatory response, altering clearance of viruses.

Conclusions: Haploinsufficiency of TNFAIP3 may not always manifest as inflammatory disease, which may require cofactors such as an in trans hypomorphic allele resulting in compound heterozygous inheritance, or a conducive microbial environment. Denisovan I207L appears to have facilitated adaptation to the evolutionary environment of Oceania, but may potentiate the risk of inflammatory disease. This unique genetic variant therefore has Mendelian, population, and species level relevance.

Disclosure: No.

Keywords: Phosphotuning, Immune Dysregulation, TNFAIP3, Denisovan

PD211

THE SPECTRUM of INBORN ERRORS of IMMUNITY IN PATIENTS WITH EBV FROM TURKEY

POSTER DISPLAY 06: GENETICS IN IEI

Cansu Özdemiral, Saliha Esenboga, Hacer Neslihan Bildik, Nadira Nabiyeva Cevik, Ilhan Tezcan, Deniz Cagdas
Hacettepe University, Pediatric Immunology, Ankara, Turkey

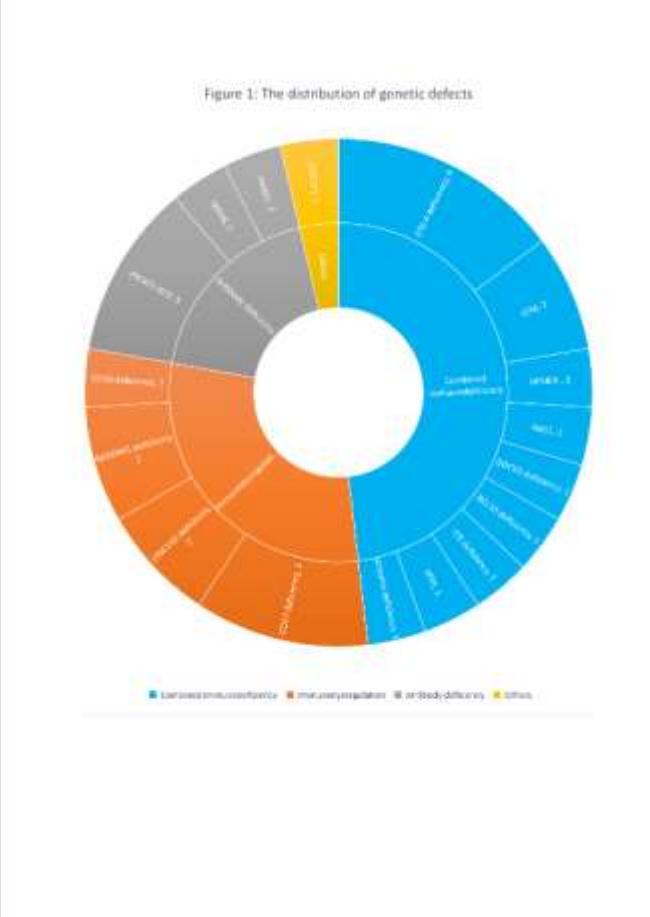
Background and Aims: EBV causes considerable morbidity and mortality because of the lymphoproliferative disorders, hemophagocytic lymphohistiocytosis (HLH), malignancy, and chronic active EBV infection in patients with immunodeficiencies This report presents the clinical course and outcome of a cohort of 50 patients with EBV-related disease with the aim of detecting the presence of any remarkable clinical findings to guide the genetic diagnosis of an underlying inborn errors of immunity (IEI).

Methods: This research was conducted in a tertiary reference center for IEI in Turkey and we retrospectively evaluated 50 patients who suffered from various clinical manifestations of EBV and were evaluated with NGS-PID panel analysis or WES.

Results: Patients had a median age of 14.6 (IQR: 8.9-20.7) years. The male/female ratio was 46/54. 68% of the patients were less than 18 years old.The most common EBV-related clinical manifestations were malignancy (48%) and lymphoproliferation (42%), HLH (16%), infectious mononucleosis (12%). 12% of the patients were asymptomatic. The characteristics of the patients are shown in Table 1. Six patients had persistant EBV viremia despite treatment. Genetic diagnosis was present in 27 (54 %) patients, most commonly STK4 (4), CD27 (3), PIK3CD (3). The distribution of genetic defects detected are shown in Figure 1.

Table 1: Demographical and clinical findings of the patients

	Total	With genetic diagnosis	Without genetic diagnosis	p
Number of patients, n	50	27	23	>0.05
Sex, male/female n(%)	23/27 (46%)/(54%)	14/13 (60%)/(40%)	9/14 (39.1%)/(60.8)	>0.05
Age,years, median(IQR), (min-max)	14.6 (8.9-20.7) (1-57)	14.6 (7-18) (1-57)	15.6 (9.8-33.2) (4-40)	>0.05
Consanguinity n(%)	26 (52%)	15 (57.6%)	11 (42.3%)	>0.05
Age at detection of EBV positivity, years, median(IQR),(min-max)	9 (6-17.5) (1-52)	9 (3.7-15.5) (1-52)	11 (7-26) (1-38)	>0.05
Clinical presentation of EBV, n(%)				
Infectious mononucleosis	6 (12%)	3 (11.1%)	3 (13%)	>0.05
Lymphoproliferation	21(42%)	11 (40.7%)	10 (43.4%)	>0.05
HLH	8 (16%)	6 (22.2%)	2 (8.6%)	>0.05
Malignancy	24(48%)	11 (40.7%)	13 (56.5%)	>0.05
Treatments n(%)				
IgRT	30 (60%)	13 (48.1%)	17 (73.9%)	>0.05
Acyclovir	16 (32%)	9 (33.3%)	7 (30.4%)	>0.05
Rituximab	10 (20%)	4 (14.8%)	6 (26%)	>0.05
Chemotherapy	26 (52%)	12 (44.4%)	14 (60.8%)	>0.05
HSCT	6 (12%)	5 (18.5%)	1 (4.3%)	>0.05
Outcome -Exitus n(%)	13 (26%)	8 (29.6%)	5 (21.7%)	>0.05



Conclusions: Clinicians should investigate monogenic IEI in patients with various clinical presentations including malignancy,lymphoproliferation or HLH with EBV. Early genetic diagnosis seems to have utmost importance since there are options of targeted therapy and HSCT related with the specific genetic defect.

Disclosure: No.

Keywords: IEI, genetic, EBV

PD212

GENETIC CHARACTERISTICS of A LARGE PEDIATRIC COHORT of PATIENTS WITH INBORN ERRORS of IMMUNITY (IEI): SINGLE-CENTER EXPERIENCE FROM 2012 TO 2021

POSTER DISPLAY 06: GENETICS IN IEI

Natalia Kuzmenko[1], Anna Mukhina[1], Maxim Alexenko[2], Yulia Rodina[1], Elena Deripapa[1], Daria Yukhacheva[1], Anna Kozlova[1], Oxana Shvets[1], Ekaterina Deordieva[1], Vasiliy Burlakov[1], Anna Khoreva[1], Nelly Kan[1], Zoya Nesterenko[1], Irina Mersiyanova[2], Anna Shcherbina[1]
[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [2]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Laboratory of Molecular Biology, Moscow, Russian Federation

Background and Aims: More than 450 genes' defects are responsible for IEI. Their distribution in particular cohorts depends on national characteristics and other factors.

Methods: We report results of genetic analysis in 1871 Russian children with IEI. Test methods included Sanger sequencing, NGS custom panel, WES, WGS. Large deletions/chromosomal anomalies were identified by MLPA, CMA and FISH.

Results: Genetic defects confirmatory of an IEI were found in 1180/1871 (63%) of patients, including defects in 116 single genes (88% of patients), and aberrations in 6 chromosomes (12%). Three patients had pathogenic variants in more than one IEI gene. of the 864 original variants 330 (38%) were newly described, and 5% of all variants were large deletions. Rare genetic defects (10 or less patients per gene) were described in 20% of the patients. In 1025 patients with germline mutations, 28% of the patients had AD inherited defects, 35% – X-linked, and 37% - AR. Four females with non-random X-inactivation had symptoms of X-linked diseases (BTK, WAS, CYBB, IKBKG gene defects). Though Russia has a relatively low rate of consanguineous marriages, about 50% of AR gene defects were in homozygous state, yet, 34% of them were patients with "Slavic" mutation of the NBN gene, or with hot-spot mutations in other genes. 5% of the families (60) underwent prenatal genetic testing.

Conclusions: Diversity of IEI genetic forms and high frequency of the newly described variants reflects genetic heterogeneity of Russian IEI group. The majority of defects were represented by SNV, yet presence of large deletions requires additional genetic testing methods.

Disclosure: No.

Keywords: Inborn errors of immunity, children patients, genetic defects, genes, genetic characteristics

PD213

THE EXPANDING SPECTRUM of WAS-RELATED DISORDERS: AN INTERMEDIATE CLINICAL PHENOTYPE BETWEEN WISKOTT ALDRICH SYNDROME AND X-LINKED NEUTROPENIA CAUSED BY THE NOVEL WAS R431W MUTATION

POSTER DISPLAY 06: GENETICS IN IEI

Alejandro Palma[1], Lia Gonçalves Pinho[2], Rhaissa Calixto Vieira[2], Minghui He[3], Roberta D'Aulerio[3], Lisa Westerberg[3]
[1]IWK Health Centre/Dalhousie University, Pediatrics; Division of Immunology, Halifax, Canada, [2]Karolinska Institutet, Department of Microbiology Tumor And Cell Biology, Stockholm, Sweden, [3]Karolinska Institutet, Microbiology, Tumor And Cell Biology, Solna, Sweden

Background and Aims: The Wiskott-Aldrich Syndrome protein (WASp) encoded by WAS is a fundamental regulator of actin polymerization in hematopoietic cells. Mutations in WAS cause Wiskott-Aldrich syndrome (loss-of-function) whereas its gain-of-function causes X-linked Neutropenia (XLN), caused by mutations in the GTPase binding domain. We report a patient with a novel mutation in the verprolin cofilin acidic (VCA) domain of WAS linked to severe neutropenia, eczema and lymphocyte alterations causing an intermediate phenotype between WAS and XLN.

Methods: Next generation sequencing; flow cytometry analysis and cell culture.

Results: We describe a 1-year old patient that presented a chronic severe neutropenia, moderate eczema, repeated bacterial and viral infections and elevated levels of IgE and IgA. Bone marrow examination showed normal tri-lineage hematopoiesis and anti-neutrophil antibodies were negative. The variant c.1291C>T (p.Arg431Trp) located in the WAS VCA domain and predicted to be deleterious. Functional analysis of patient's CD4 lymphocytes showed increased rate of phosphorylation of WASp initially but overall reduced final phosphorylation compared to control cells. Survival of CD8 T lymphocytes and naïve B lymphocytes was impaired; however, a persistently elevated IgA was documented. Globally, lymphocyte proliferation against antigens (but not mitogens) was decreased. The patient showed an excellent response to G-CSF treatment that lasted 48 hours.

Conclusions: We present a patient with neutropenia linked to WAS that affects a domain not yet described for XLN and that presents with clinical features resulting in an intermediate phenotype between WAS and XLN. This underlines the importance of functional testing to define the vast spectrum of WAS related disorders.

Disclosure: No.

Keywords: neutropenia, X-linked neutropenia, Wiskott-Aldrich Syndrome, WAS

PD214

LACK of STAT3 MODIFIES MACROPHAGE ACTIVATION IN S. AUREUS INFECTION TOWARDS AN ENHANCED INFLAMMATORY PHENOTYPE WITHOUT AFFECTING BACTERIAL CLEARANCE

POSTER DISPLAY 06: GENETICS IN IEI

Susan Farmand[1,2], Vicky Sender[1], Jens Karlsson[1], Padryk Merkl[1], Staffan Normark[1], Birgitta Henriques Normark[1,3]
[1]Karolinska Institutet, Department of Microbiology, Tumor And Cell Biology, Stockholm, Sweden, [2]University Medical Center Hamburg-Eppendorf, Division of Pediatric Stem Cell Transplantation And Immunology, Hamburg, Germany, [3]Karolinska Hospital, Clinical Microbiology, Stockholm, Sweden

Background and Aims: Patients with STAT3-deficient autosomal-dominant Hyper-IgE syndrome (HIES) show increased susceptibility to S. aureus infections which frequently lead to defective tissue healing. Macrophage activation and the associated inflammatory response is relevant for both the initial pathogen defense but also for subsequent tissue healing. Within this work we aimed to elucidate how deficient STAT3 signaling in murine myeloid cells affects pathogen clearance and inflammatory response during S. aureus infection.

Methods: Bone marrow derived macrophages (BMDM) from STAT3LysMCre+ (KO) and Cre- (WT) mice were stimulated with S. aureus in vitro. Activation pattern was compared to vehicle, IL-4 and LPS by several methods (Cytokines, NO, Surface markers, RNA expression). In vivo staphylococcal killing and inflammatory scores were assessed within a murine pulmonary infection model.

Results: STAT3-deficient BMDM showed enhanced and prolonged cytokine response and upregulation of co-stimulatory molecules. Although bacterial clearance was unaffected by the lack of myeloid STAT3 an enhanced inflammatory phenotype was observed in our infection model.

Conclusions: Myeloid STAT3 deficiency leads to a hyper-inflammatory response in BMDM upon stimulation with S. aureus without any additional beneficial effect on pathogen clearance. Our observation might be one potential explanation for the defective lung tissue healing which is frequently observed in HIES patients with pulmonary staphylococcal infection.

Disclosure: No.

Keywords: S. aureus, Macrophages, BMDM, STAT3, HIES

PD215

WHOLE EXOME SEQUENCING of 31 NON-FAMILIAL HLH PATIENTS: MONOGENIC DEFECTS IN HAVCR2, TNFRSF9 AND MADD GENES

POSTER DISPLAY 06: GENETICS IN IEI

Laura Batlle-Masó[1], Clara Franco Jarava[2], Laura Viñas-Giménez[2], Marina Garcia-Prat[1], Alba Parra-Martínez[1], C Díaz De Heredia[3], Ivon Cusco[4], Anna Maria Cueto-Gonzalez[4], Jacques Rivière[1], Pere Soler-Palacin[1], Laia Alsina[5], M Martinez-Gallo[2], Roger Colobran[2], Ferran Casals[6]
[1]Vall d'Hebron University Hospital, Pediatric Infectious Diseases And Immunodeficiencies Unit, Barcelona, Spain, [2]Vall d'Hebron Barcelona Hospital Campus, Immunology Division, Barcelona, Spain, [3]Hospital Universitari Vall d'Hebron (HUVH), Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Catalonia,, Spain, Pediatric Oncology And Hematology Department, Barcelona, Spain, [4]Hospital Universitari Vall d'Hebron, Department of Clinical And Molecular Genetics, barcelona, Spain, [5]Hospital Sant Joan de Déu, Allergy And Clinical Immunology Department, Esplugues del Llobregat, Spain, [6]Pompeu Fabra University, Genomics Core Facility, Barcelona, Spain

Background and Aims: Hemophagocytic lymphohistiocytosis (HLH) is a severe and life-threatening syndrome characterized by a strong hyperactivation of the immune system. Familial HLH (FHL) is caused by biallelic variants in the genes PRF1, UNC13D, STX11 and STXBP2. Non-familial HLH (nFHL) may be caused by other genetic entities or may be sporadic or secondary to other conditions.

Methods: To elucidate other genetic mechanisms driving nFHL we studied a cohort of 31 nFHL patients (25 European, 5 North-African and 2 Asian). All cases had an immunological diagnosis of HLH but remained unsolved at a genetic level after excluding pathogenic variants in FHL genes.

Results: Using WES data, we first evaluated the possibility of the disease being originated by a monogenic defect. We found the genetic diagnosis for three of the patients i) one patient who carried a compound heterozygous variant at HAVCR2, ii) one with a homozygous nonsense variant at TNFRSF9, and iii) one with a homozygous deletion at MADD. Next, we looked for pathogenic variants over-represented in our cohort in comparison to healthy populations. We also identified monoallelic variants that could be acting as risk factors, and explored the digenic model in genes of the cytotoxic pathway.

Conclusions: Altogether, we showed that WES is a valuable diagnostic tool in nFHL patients, provided new insights into the physiopathology of the disease, and highlighted the importance of a genetic diagnosis on the clinical management and genetic counseling of the patients and their families.

Disclosure: No.

Keywords: Genetics, hemophagocytic, Whole Exome Sequencing

PD216

CLINICAL HETEROGENEITY IN A FAMILY WITH A GAIN-OF-FUNCTION VARIANT IN IKBKB: DOES SP110 FUNCTION AS A MODIFIER GENE?

POSTER DISPLAY 06: GENETICS IN IEI

Hanna Ijspeert[1], Pieter Fraaij[2], Iris Hollink[3], Godelieve De Bree[4], Taco Kuijpers[5], Martin Van Hagen[6], Willem Dik[1], Virgil Dalm[6]
[1]Erasmus MC, University Medical Center Rotterdam, Immunology, Rotterdam, Netherlands, [2]Eramsus Mc, University Medical Center Rotterdam, Pediatrics, Rotterdam, Netherlands, [3]Erasmus Medical Center, Clinical Genetics, Rotterdam, Netherlands, [4]Amsterdam University Medical Center, Internal Medicine, Amsterdam, Netherlands, [5]Amsterdam University Medical Center, Pediatric Hematology, Immunology And Infectious Diseases, Amsterdam, Netherlands, [6]Erasmus University Medical Center Rotterdam, Internal Medicine, Rotterdam, Netherlands

Background and Aims: IKBKB encodes for the IKK2 protein which can activate NF-kB signaling. We identified six family members with a heterozygous variant of unknown significance (VUS) (c.194T>C) in the IKBKB gene. They all had a combined immunodeficiency, but the clinical phenotype was highly variable. The proband (48y) developed lethal CMV disease and her daughter (26y) suffered from colitis and warts. The brother (55y) of the proband and his son (15y) had recurrent upper respiratory tract infections. Two other family members (18y, 21y) had no clinical features. The proband and her daughter, who were clinically most severely affected, harbored an additional heterozygous VUS in the SP110 gene (c.1447G>A). SP110 protein has been described to modulate NF-kB signaling. Therefore we hypothesized that SP110 may function as a modifier gene of NF-kB activity.

Methods: Western blot analysis, phophoflow, and stimulation assays on fibroblasts and EBV immortalized lymphoblastoid cell lines (LCLs) were conducted to explore NF-kB activity. Luciferase assays were performed to measure IKBKB and SP110 function.

Results: Fibroblasts and LCLs from the family members with the IKBKB variant had constitutive phosphorylation of P65, increased degradation of IkBa, and increased secretion of IL-6 and IL-8 after stimulation. Luciferase assays showed that the SP110 variant enhanced the effect of IKBKB variant on the expression of the TNF promotor, suggesting that SP110 indeed might function as a modifier gene.

Conclusions: The c.194T>C variant in IKBKB results in increased NF-kB activity, suggesting a gain-of-function of the IKK2 protein. The SP110 variant likely functions as a modifier gene, increasing the clinical heterogeneity.

Disclosure: No.

Keywords: NF-kB pathway, IKBKB, SP110, CMV, combined immunodeficiency, modifier gene

PD217

COMBINED IMMUNODEFICIENCY AND IMPAIRED PI3K SIGNALING IN A PATIENT WITH BIALLELIC LCP2 VARIANTS

POSTER DISPLAY 06: GENETICS IN IEI

Emily S.J. Edwards[1,2], Samar Ojaimi[1,3,4,5,6], James Ngui[3], Go Hun Seo[7], Sunjeev Chunilal[8], Robyn O'Hehir[1,2,9], Menno Van Zelm[1,2,9]
[1]JMF Centre Melbourne, The Jeffrey Modell Diagnostic And Research Centre For Primary Immunodeficiencies, Melbourne, Australia, [2]Monash University, Immunology And Pathology, Melbourne, Australia, [3]Monash Health, Monash Pathology, Melbourne, Australia, [4]Monash Health, Monash Infectious Diseases, Melbourne, Australia, [5]Monash Health, Monash Lung Sleep Allergy Immunology, Melbourne, Australia, [6]Monash Health, Department of Medicine, Melbourne, Australia, [7]3 billion Inc., 3billion Inc., Seol, Korea, Republic of, [8]Monash Health, Department of Pathology And Radiology, Melbourne, Australia, [9]Alfred Hospital, Department of Allergy, Immunology And Respiratory Medicine, Melbourne, Australia

Background and Aims: Inborn errors of immunity affecting the T-cell receptor signaling pathway cause combined immunodeficiency (CID) with varying degrees of severity. A homozygous LCP2 variant was recently reported in a young boy with severe (S)CID due to T- and B-cell defects, accompanied by impaired neutrophil and platelet function. Our aim is to identify and functionally validate the genetic cause of disease in a young man who presented since early childhood with antibody deficiency, autoimmunity and inflammatory bowel disease.

Methods: Genetic analysis by whole-exome sequencing of genomic DNA was performed. Patient whole blood was examined to determine impacts on neutrophils, platelets, T- and B-cells, and SH2 domain-containing leukocyte protein 76kD (SLP76) expression levels. Tonic and ligand-induced PI3K signaling was examined by flowcytometric detection of phosphorylated S6 in B- and T-cells.

Results: Biallelic missense variants were identified in LCP2, affecting the proline rich repeat domain of SLP76 (p.P190R and p.R204W). Both variants are highly conserved in vertebrates. The patient's B- and T-cell numbers were within the normal range, as were neutrophil and platelet function. However, numbers of unswitched and class-switched memory B-cells, and serum IgA were dramatically decreased. Intracellular SLP76 protein levels were reduced in patient $CD4^+$ T-, $CD8^+$ T-, B-, and NK cells. Tonic and ligand-induced levels of phosphorylated S6 were decreased in patient $CD4^+$ T-, $CD8^+$ T- and B-cells.

Conclusions: Biallelic mutations in LCP2 impair T-cell and B-cell receptor signaling and can cause CID with early onset immune dysregulation, even in the absence of neutrophil and platelet defects.

Disclosure: No.

Keywords: functional genomics, combined immunodeficiency, LCP2, SLP76, antigen receptor signalling, early onset immune dysregulation

PD218

FUNCTIONAL ANALYSIS of VARIANTS of UNKNOWN SIGNIFICANCE IN THE STAT-1 GENE

POSTER DISPLAY 06: GENETICS IN IEI

Adriana Albuquerque[1], Alexander Mckenna[1], Jesmeen Maimaris[1], Sameer Bahal[1], Jonathan Lambourne[2], Nihr Bioresource Nihr Bioresource[3], Emma Morris[1], Siobhan Burns[1]
[1]University College London, Institute of Immunity And Transplantation, London, United Kingdom, [2]Royal London NHS Foundation Trust, Immunology, London, United Kingdom, [3]NIHR Bioresource, Nihr Bioresource, Cambridge, United Kingdom

Background and Aims: Gain-of-function (GOF) variants in STAT1 gene lead to monogenic susceptibility to Chronic Mucocutaneous Candidiasis (CMC), characterized by impaired immunity against Candida species. Functional assays are required to functionally validate variants of unknown significance (VUS) and their contribution to disease development. Here, we identified and performed functional validation for five novel variants of unknown significance in the STAT-1 gene.

Methods: IFN-α-induced phosphorylation of STAT-1, total STAT-1 expression, CXCL-10 upregulation and TH17 cells were evaluated by flow cytometry in T-cells or monocytes from six patients carrying five different variants of unknown significance in the STAT-1 gene. Data was normalized to a healthy control assessed in parallel and compared to patients carrying previously described mutations causing CMC and a CVID disease control group.

Results: We analysed 5 VUS, 4 known STAT1 GOF and 2 STAT1 loss-of-function (LOF) mutations. Compared to healthy controls and CVID patients, levels of STAT1 phosphorylation were significantly increased in T-lymphocytes from patients with VUS that we re-designated novel STAT1-GOF mutations. LOF mutations resulted in reduced STAT1 phosphorylation. All patients with STAT1-GOF had low TH17+ cells and fungal infections while patients with STAT-1 LOF mutations had no fungal infections and a similar frequency of TH17+ cells as healthy controls. Levels of induction of CXCL10 expression was variable between all variants, whether they were STAT1-VUS, STAT1-LOF or STAT1-GOF.

Conclusions: A combined analysis of IFNα-induced STAT1 phosphorylation and quantification of TH17 cells represent a useful approach to functionally define STAT1 VUS as GOF.

Disclosure: No.

Keywords: Chronic Mucocutaneous Candidiasis, STAT-1 phosphorylation, Functional Assays, IL-17, Variants of Unknown Significance, STAT-1

PD219

CLINICAL AND FUNCTIONAL EVALUATION of E57K HYPOMORPHIC MUTATION IN IKBKG GENE

POSTER DISPLAY 06: GENETICS IN IEI

Alba Parra-Martínez[1], Marina Garcia-Prat[1], Clara Franco Jarava[2], Daniel Álvarez-Sierra[2], Jacques Rivière[3], Andrea Martín-Nalda[3], Aina Aguiló-Cucurull[2], Romina Dieli-Crimi[2], Eva Polverino[4], Pere Soler-Palacin[3], Roger Colobran[5] [1]Vall d'Hebron Barcelona Hospital Campus, Infection In Immunocompromised Pediatric Patients, Barcelona, Catalonia, Spain, [2]Vall d'Hebron Barcelona Hospital Campus, Immunology Division, Barcelona, Catalonia, Spain, [3]Vall d´Hebron Hospital, Pediatric Infectious Diseases And Immunodeficiencies Unit, Hospital Universitari Vall D'hebron (huvh), Vall D'hebron Research Institute (vhir), Universitat Autònoma De Barcelona, Catalonia, Spain. Jeffrey Modell Excellence Centre, Barcelona, Spain, [4]Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, Pneumology Department, Barcelona, Spain, [5]Hospital Universitari Vall d'Hebron (HUVH, Barcelona, Catalonia, Spain, Immunology Department.department of Clinical And Molecular Genetics, Barcelona, Spain

Background and Aims: Hypomorphic mutations in IKBKG (NEMO) impair NF-κB activation and are typically associated with anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID), but also with immunodeficiency without EDA. The p.Glu57Lys (E57K) mutation has been described in only two patients with normal IκBα degradation and low IL-6 production. We describe the clinical manifestations and pathogenicity of this mutation in 4 patients.

Methods: The NF-κB pathway was evaluated with the expression of p105 (non-phosphorylated and phosphorylated), p50 and IκBα by western blotting after stimulation for 0, 15, 30 and 60 minutes with PMA and ionomycin. Production of IFNγ, IL-1β, IL-10, IL-6 and TNFα was analysed in supernatants of cultured PBMCs after 72 hours of in vitro stimulation.

Results: None of the 4 patients studied presented EDA. P1 started the clinical course with severe neutropenia and parotitis due to Staphylococcus aureus, P2 was diagnosed with Crohn's disease, P3 presented CVID with chronic diarrhoea and P4 is totally asymptomatic and is P1's grandfather. All of them showed a normal expression of p105, P-p105, p50, and a normal degradation of IκBα. P1 showed a generalized impairment in the production of the cytokines. P2 and P4 showed a slight decrease in IL-10 and IL-6 production and P3 showed normal values.

Conclusions: Alterations in the IKBKG gene should not be discarded even in absence of EDA. The E57K variant does not affect the NF-κB pathway in general, but it does affect the production of cytokines. We consider this variant as hypomorphic with incomplete penetrance and variable expressivity.

Disclosure: No.

Keywords: NF-κB essential modulator (NEMO), NF-κB pathway, IKBKG, immunodeficiency, hypomorphic NEMO mutations

PD220

MUTATIONS IN SLP76 ASSOCIATED WITH SEVERE IMMUNODEFICIENCY INCLUDING EBV-RELATED LYMPHOMA

POSTER DISPLAY 06: GENETICS IN IEI

Raz Somech[1], Atar Lev[2], Yu Nee Lee[1], Shiran Levy[1], Amos Simon[1], Mahdi Asleh Asleh[1], Arnon Broides[3,4]
[1]Sheba Medical Center, Pediatrics, Immunology, Ramat Gan, Israel, [2]Sheba medical center, Pediatric Department A And The Immunology Service, Ramat Gan, Israel, [3]Soroka medical center, Ambulatory Center, Beer sheva, Israel, [4]Soroka medical center, Pediatric Ambulatory Center, Beer sheva, Israel

Background and Aims: Background: High susceptibility to develop severe forms of Epstein Barr Virus (EBV) infection in early age is a significant hallmark of an underlying primary immunodeficiency (PID). SLP76 protein, a TCR signaling molecule, was recently linked by us to human disease of the immune system. Encountering EBV by patients with of SLP76 deficiency was hypothesized also to lead to a severe EBV infection phenotype, similar to other copartners in the TCR signaling.

Methods: Immunologic and genetic evaluations were performed on a 3-year old child with severe EBV infection who succumbed to EBV related lymphoma.

Results: The patient born to first cousin had recurrent infections, failure to thrive and severe EBV related infection and proliferation. A diagnosis of diffuse large B-cell lymphoma was made. Immunological work up was suggestive of T cell immunodeficiency. Whole exome sequencing revealed homozygous c.991del.C; p.Q331fs*6 mutation in the SLP76 gene. In order to examine the effect of the specific mutation on T cell signaling, SLP76-deficient cells were transduced with wild-type (WT) or the specific mutant SLP76, or with mock vector. Downstream events including ERK phosphorylation, CD69 expression and Ca2+ mobilization were significantly reduced in cells harboring the reported mutation, linking the specific mutation to the expected immunological outcome.

Conclusions: Conclusion: SLP76 deficiency should be added to the growing list of monogenetic diseases that predisposed affected individuals to acquire severe and uncontrolled EBV infections and to develop significant complications. This case further links mutations in the SLP76 gene to significant human immunodeficiency and extends its clinical phenotype.

Disclosure: No.

Keywords: SLP76, Severe combined immunodeficiency, EBV, TCR signalling, LCP2, combined immunodeficiency

PD221

PROVIDING A GENETIC DIAGNOSIS FOR GENOMICS ENGLAND 100,000 GENOMES PROJECT PARTICIPANTS WITH AN INBORN ERROR of IMMUNITY

POSTER DISPLAY 06: GENETICS IN IEI

Helen Griffin[1], Karin Engelhardt[1], Carme Camps[2], Jenny Taylor[2], Sophie Hambleton[1,3]
[1]Newcastle University, Translational & Clinical Research Institute, Immunity & Inflammation Theme, Newcastle Upon Tyne, United Kingdom, [2]University of Oxford, Wellcome Centre For Human Genetics, Oxford, United Kingdom, [3]Great North Children's Hospital, Newcastle upon Tyne Hospital NHS Foundation Trust, Children's Haematopoietic Stem Cell Transplant Unit, Newcastle upon Tyne, United Kingdom

Background and Aims: Genomics England (Gel) 100,000 Genomes Project sequenced whole genomes of 70 thousand individuals from UK families with rare diseases. We have reviewed clinical information and genetic variants from a heterogeneous set of 913 families with an inborn error of immunity (IEI) to identify pathogenic mutations.

Methods: Within the Gel research environment, we developed an analysis pipeline to integrate per family phenotype data and genetic variants to perform a detailed interrogation of rare variants predicted to alter protein sequence in a virtual panel of 509 genes where mutations are known to cause an IEI. We used a case/control method to identify novel genetic causes of immune disorders where damaging variants cluster in specific genes in patients at a higher frequency compared to individuals without an IEI.

Results: Genomic Medicine Centre Exit Questionnaires reported 42 families with a confirmed or likely genetic diagnosis and 68 families with a variant of unknown significance (VUS), requiring functional testing to establish pathogenicity. Our detailed gene centric and, to a lesser extent, case/control analyses revealed an additional 11 families with a likely genetic diagnosis and 66 families with a VUS in a gene compatible with the patient's phenotype, but where the variant had not previously been reported. of genes outside the virtual IEI panel, identified as bearing an excess variant burden through the case/control analysis, 2 have since been confirmed and reported as novel disease genes.

Conclusions: Detailed study of genomes from patients with IEI will ultimately help to improve clinical interpretation pipelines, providing faster and precise diagnoses.

Disclosure: No.

Keywords: Genomics, IEI, Bioinformatics

PD222

SEVERE VZV CNS INFECTION - A ROLE FOR AUTOPHAGY?

POSTER DISPLAY 06: GENETICS IN IEI

Johanna Heinz[1], Anne Hollensen[2], Michelle Thomsen[2], Madalina Carter-Timofte[2], Joanna Von Hofsten[3], Anna Grahn[4], Trine Mogensen[2]
[1]Aarhus University (AU), Department of Biomedicine, Aarhus, Denmark, [2]Aarhus University, Department of Biomedicine, Aarhus C, Denmark, [3]University of Gothenburg, Department of Clinical Neuroscience, Gothenburg, Sweden, [4]University of Gothenburg, Department of Infectious Diseases, Gothenburg, Sweden

Background and Aims: Varicella Zoster Virus (VZV) is a common pathogen; its invasion into the central nervous system (CNS) however constitutes a rare, yet severe complication of VZV infection. We hypothesize, that the susceptibility to viral CNS infections is, at least partly, explained by host genetics. Autophagy is a highly conserved, cellular degradation pathway which has previously been described to play a role in viral infections (1). We aim to identify novel single gene mutations predisposing to severe disease with VZV in the autophagy pathway, followed by functional characterization of the affected gene products in patient cells and neuronal cell lines. References (1) Heinz, J., P.G.E. Kennedy, and T. H. Mogensen. "The Role of Autophagy in Varicella Zoster Virus Infection." Viruses 13.6 (2021): 1053.

Methods: DNA of patients with VZV CNS infection was subjected to Whole Exome Sequencing (WES). Variants were filtered in VarSeq according to frequency, technical quality, biological relevance and deleteriousness as estimated by different bioinformatical tools.

Results: To date we have identified 17 potentially disease causing variants in genes involved in the autophagy pathway in patients suffering from severe VZV CNS infection.

Conclusions: We observed an accumulation of genetic defects in genes involved in the autophagy pathway in a cohort of patients suffering from VZV CNS infection. These gene candidates are currently being validated. This serves as an indicator for the importance of functional autophagy induction as a defence mechanism against VZV CNS infection.

Disclosure: No.

Keywords: primary immunodeficiency, Innate Immunity, Antiviral Defense, Whole Exome Analysis, Varicella Zoster Virus, Autophagy

PD223

OPPORTUNISTIC INFECTION AND IMMUNE-DYSREGULATION ASSOCIATED WITH A NOVEL FRAMESHIFT MUTATION IN SMAD3

POSTER DISPLAY 06: GENETICS IN IEI

Julius Köppen[1], Mike Recher[1,2]
[1]University Hospital Basel, Immunodeficiency Group, Basel, Switzerland, [2]University Hospital Basel, Outpatient Clinics Immunology, Basel, Switzerland

Background and Aims: Loeys-Dietz syndrome 3 (LDS3) is a congenital, multisystemic connective tissue disorder. Thoracic aortic aneurysms and dissections reflect life-threatening features. In association skeletal abnormalities and large joint cartilage degeneration characterise the clinical phenotype. LDS3 is caused by mutations in SMAD3, encoding a transcription factor of the TGF-β pathway, pivotal for immune regulation. Immune-dysregulation in patients with LDS3 is largely underreported.

Methods: Clinical characterisation of a patient presenting with features of LDS3. Immunephenotyping was performed in the context of an opportunistic atypical mycobacterial infection. Whole exome sequencing and locus specific Sanger sequencing detected a novel mutation in SMAD3. SMAD3 related gene expression in TGF-β stimulated immune cells was analyzed by real-time PCR.

Results: We detected a novel frameshift mutation in SMAD3 (c.1074delG; p.Q358QfsX8) in a patient consistent with LDS3. Failure of dental exfoliation - a frequent characteristic of autosomal dominant Hyper IgE syndrome - and opportunistic infection prompted us to perform extensive immunephenotyping: The patient had mild hypogammaglobulinemia including low serum IgE, low terminally differentiated memory T cells and CD21low B cells were almost undetectable. SMAD3 related gene expression in TGF-β stimulated peripheral blood derived mononuclear cells is currently being performed.

Conclusions: We present a rare case of LDS3 due to a novel frameshift mutation in SMAD3 extending the spectrum of mutations of LDS3 with opportunistic infections. To our knowledge we describe the first extensive immunephenotypic evaluation in a patient with LDS3. LSD3 has to be considered in the differential diagnosis in patients with opportunistic infections.

Disclosure: No.

Keywords: Loeys-Dietz syndrome, TGF-β, Genetics

PD224

GENOME SEQUENCING REVEALS CCDC88A VARIANTS UNDERLYING MALFORMATIONS of CORTICAL DEVELOPMENT, PROFOUND DEVELOPMENTAL DELAY, EPILEPSY, AND IMMUNE DYSFUNCTION

POSTER DISPLAY 06: GENETICS IN IEI

Johanna Lehtonen[1], Anna Hakonen[2], Antti Hassinen[3], Anna-Maija Sulonen[3], Henrikki Almusa[3], Maarit Palomäki[4], Sirpa Kivirikko[2], Sanna Wickman[5], Kristiina Avela[2], Kaarina Heiskanen[6], Vilja Pietiäinen[3], Janna Saarela[1], Kristiina Aittomäki[7]
[1]Centre for Molecular Medicine Norway, Faculty of Medicine, University of Oslo, Oslo, Norway, [2]HUSLAB, Helsinki University Hospital, and University of Helsinki, Department of Clinical Genetics, Helsinki, Finland, [3]Institute for Molecular Medicine Finland (FIMM), Hilife, University of Helsinki, Helsinki, Finland, [4]Helsinki University Hospital, Department of Radiology, Helsinki, Finland, [5]Hyvinkää Hospital, Department of Pediatric Neurology, Hyvinkää, Finland, [6]New Children's Hospital, Hus, Helsinki University Hospital, And University of Helsinki, Helsinki, Finland, [7]University of Helsinki, Department of Medical And Clinical Genetics, Helsinki, Finland

Background and Aims: Truncating homozygous CCDC88A variants cause progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO)-like syndrome. CCDC88A encodes girdin which is essential for various cell functions, such as actin remodeling, cell proliferation, migration, and autophagy. We aimed to determine the genetic etiology of brain malformations, microcephaly, epilepsy, and cognitive impairment in two siblings, and further, characterize the disease mechanisms associated with the gene defect.

Methods: Genome sequencing, copy number variant analysis, segregation study, RT-PCR, western blotting, proliferation assay, wound-healing assay, high-content image-based cell phenotyping (immunofluorescence staining), and flow-based immune cell phenotyping.

Results: Both siblings were compound heterozygous for CCDC88A variants: a missense variant (NM_018084:c.929A>C,p.Asp310Ala) and a deletion (exons 14–16). Full-length girdin containing the missense variant was not degraded more than control wild-type protein, whereas only a small amount of truncated protein was expressed from the deletion allele. Proliferation and wound-healing assays revealed that patient fibroblasts preferred proliferation over migration when compared to the age-matched healthy fibroblasts. Image-based cell phenotyping showed that the patient fibroblasts were smaller in size, and cell organelles involved in autophagy-lysosomal pathways were accumulated in the perinuclear region of a cell compared to controls. Immune cell phenotyping revealed a reduced number of monocytoid and plasmacytoid dendritic cells in both patients.

Conclusions: We describe here the first CCDC88A missense variant and intragenic deletion underlying cortical malformations and characterize defects in the immunity of these patients. We show that girdin dysfunction in patient fibroblasts causes alterations in morphology and in the migration-proliferation dichotomy.

Disclosure: No.

Keywords: CCDC88A, Migration, girdin, brain malformation, dendritic cell, proliferation

PD225

NEWS FROM THE CVID-SPECTRUM: NOVEL MUTATION AND EXPANDING PHENOTYPE IN IRF2BP2 DEFICIENCY

POSTER DISPLAY 06: GENETICS IN IEI

Julia Körholz[1], Anastasia Gabrielyan[1], Henrike Sczakiel[2], Livia Schulze[3], Manuela Rejzek[3], Martin Laass[4], Nicolai Leuchten[5], Oliver Tiebel[6], Dianiela Aust[7], Nadja Röber[3], Karsten Conrad[3], Eva Jacobsen[8], Nadja Ehmke[9], Joachim Roesler[1], Axel Roers[10], Timm Amendt[11], Catharina Schuetz[1]
[1]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Pediatric Immunology, Dresden, Germany, [2]Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institute of Medical Genetics And Human Genetics, Berlin, Germany, [3]Institute of Immunology, Medical Faculty Carl Gustav Carus, Dresden, Germany, [4]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Pediatrics, Dresden, Germany, [5]Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Division of Rheumatology, Department of Medicine Iii, Dresden, Germany, [6]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Laboratory Medicine And Clinical Chemistry, Dresden, Germany, [7]University Hospital Carl Gustav Carus, Technische Universität Dresden, Institute of Pathology, Dresden, Germany, [8]University Medical Center Ulm, Germany, Department of Pediatrics And Adolescent Medicine, Ulm, Germany, [9]Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Institute of Medical Genetics And Human Genetics, Berlin, Germany, [10]University Hospital Heidelberg, Institute For Immunology, Heidelberg, Germany, [11]University Hospital Ulm, Institute of Immunology, Ulm, Germany

Background and Aims: Inborn errors of immunity (IEI) may initially present with autoinflammatory or autoimmune symptoms. IRF2BP2 is one of about 20 genes associated with a CVID- like phenotype and has been reported in two families so far. It is a nuclear protein which interacts with interferon regulatory factor 2 (IRF2) to form a transcriptional repressor and has recently been described as positive and negative regulator of gene expression. We add another IRF2BP2 deficient patient with a novel pathogenic variant and phenotype.

Methods: We performed trio exome and sanger sequencing, immunophenotyping, intracellular calcium mobilization upon B-cell receptor (BCR) crosslinking as well as T-cell-proliferation.

Results: The 33-year-old male patient presented with recurrent respiratory infections since childhood, colitis, and aggressively progressive rheumatoid arthritis beginning at age 25. We identified the de novo nonsense IRF2BP2 variant c.1618C>T;p.(Q540*), resulting in expression of a truncated IRF2BP2 protein lacking some highly conserved amino acids and leading to the inability to properly form the RING domain. IgG deficiency was detected as consequence of severe B-cell differentiation defect. Plasmablast formation upon stimulation with CpG was severely impaired and intracellular Ca2+-mobilization upon BCR-stimulation was reduced. No serum autoantibodies were detected. T-cell phenotyping and functional analyses were normal, whereas intracellular cytokine production was impaired.

Conclusions: The identified loss-of-function variant in IRF2BP2 severely impairs B-cell development and T-cell homeostasis, and was associated with colitis and rheumatoid arthritis. Our results expand the phenotype of IRF2BP2 deficiency and contribute to understand the underlying pathomechanism.

Disclosure: No.

Keywords: IRF2BP2, CVID, Genetics, rheumatoid arthritis, B cell maturation disorder

PD226

CHARACTERIZATION of A LARGE COHORT of PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY (CVID) USING HUMAN PHENOTYPE ONTOLOGY (HPO)

POSTER DISPLAY 06: GENETICS IN IEI

Luiza Campos[1], Gaia Mancuso G[2], Jesmeen Maimaris[3], Olga Shamardina[4], Daniel Greene[5], Ernest Turro[5], Giulia Di Colo[2], L Dagna[2], P Rovere-Querini[2], Adrian Trasher[2,6], Siobhan Burns[1]
[1]UCL, Institute of Immunity And Transplantation, London, United Kingdom, [2]Vita-Salute San Raffaele University, Unit of Immunology, Rheumatology, Allergy, And Rare Diseases, Milan, Italy, [3]University College London, Institute of Immunity And Transplantation, London, United Kingdom, [4]University of Cambridge, Department of Medicine, Cambridge, United Kingdom, [5]Mount Sinai, Icahn School of Medicine, New york, United States of America, [6]University College London, Institute of Child Health, London, United Kingdom

Background and Aims: Heterogeneity in the clinical phenotype of primary immunodeficiencies (PID) presents major diagnostic and therapeutic challenges. To cluster patients by clinical phenotype to enable gene discovery following whole genome sequencing, we aimed to collect detailed HPO-coded phenotype for a large cohort of CVID patients. We also aimed to test whether different groups of HPO terms associate with subsets of CVID as defined by EUROclass classification, as an approach for clustering patients for genetic analysis.

Methods: Medical records of patients with CVID followed up at the Royal Free Hospital London were reviewed and HPO terms were annotated in a web-based tool specifically developed for the data collection. Data was analysed using ontologyX R packages. Patients were assigned into groups as per EUROclass and sets of HPO terms were used to determine the presence of specific phenotypic abnormalities.

Results: HPO-coded phenotypic profile was annotated for 156 CVID patients. B cell phenotyping was available for 110. 438 different HPO terms were listed for our CVID cohort. 27 terms missing from the HPO database were identified - mainly related to granulomas in different organs, recurrent/chronic infection, and infections by specific pathogens. Specific combinations of terms were associated with patients with different EUROclass groups.

Conclusions: Defining a more comprehensive set of HPO terms to depict PID patients is important to allow the use of advanced methods of statistic association to find similarities between phenotypic profiles to support gene discovery and diagnosis. Further work is required to determine whether different monogenic causes of CVID associate with specific HPO phenotypes.

Disclosure: No.

Keywords: CVID, Genetic diagnosis, HPO, Common variable immunodeficiency, human phenotype ontology, Whole genome sequencing

PD227

CHARACTERIZATION of EXPANDED GAMMA DELTA T CELLS FROM ATYPICAL X-SCID PATIENT REVEALS PRESERVED FUNCTION AND IL2RG-MEDIATED SIGNALING

POSTER DISPLAY 06: GENETICS IN IEI

Elina Tuovinen[1], Sakari Pöysti[2], Firas Hamdan[1], Léa Minier[1], Kaarina Heiskanen[3], Kim Le[1], Vincenzo Cerullo[1], Juha Kere[4], Mikko R J Seppänen[5], Arno Hänninen[2], Juha Grönholm[1]
[1]University of Helsinki, Translational Immunology Research Program, Helsinki, Finland, [2]Turku University Hospital, Turku, Finland; 5, Department of Clinical Microbiology And Immunology,, Turku, Finland, [3]New Children's Hospital, Hus, Helsinki University Hospital, And University of Helsinki, Helsinki, Finland, [4]Karolinska Institutet, Stockholm, Sweden; 1 Stem Cells and Metabolism Research Program, University of Helsinki, Helsinki, Finland; 1 Folkhälsan Research Center, Helsinki, Finland; en, Department of Biosciences And Nutrition, Huddinge, Sweden, [5]University of Helsinki and HUS Helsinki University Hospital, Rare Disease Center, Children's Hospital, And Adult Primary Immunodeficiency Outpatient Clinic, Inflammation Center, Helsinki, Finland

Background and Aims: Abnormally high γδ T cell numbers are common among atypical SCID patients, yet detailed immunophenotyping and functional characterization of these expanded γδ T cells remains limited. We have previously reported atypical SCID phenotype caused by hypomorphic IL2RG c.172C>T;p.(Pro58Ser) mutation causing failure in IL2RG plasma membrane targeting and impaired IL-2 responses. Our aim was to investigate the phenotype and function of index patient's γδ T cells.

Methods: IL2RG cell surface expression, STAT tyrosine phosphorylation, blast formation in response to interleukin stimulation and immunophenotyping was studied by flow cytometry. TCRvγ repertoire was studied by next generation sequencing and in vitro target cell killing by LDH release assay.

Results: In contrast to his αβ T cells, the patient's γδ T cells showed normal IL2RG cell surface expression and normal or enhanced IL2RG-mediated signaling. Vδ2+ population was proportionally increased with a preponderance of memory phenotypes and high overall tendency towards perforin expression. The patient's γδ T cells showed enhanced cytotoxicity towards A549 cancer cells. TCRvγ repertoire was versatile but sequencing of IL2RG revealed a novel c.534C>A; p.(Phe178Leu) somatic missense variant restricted to γδ T cells. Over time this variant became predominant in γδ T cells.

Conclusions: Our results suggest that expansion of γδ T cells associated with atypical SCID warrants more investigation and cannot exclusively be deemed as a homeostatic response to low numbers of conventional T cells. More detailed understanding on γδ T cell function in immune-mediated diseases may help in the development of future therapies.

Disclosure: No.

Keywords: interleukin receptor common subunit gamma, IL2RG, X-linked combined immunodeficiency, severe combined immunodeficiency, atypical, gamma-delta T-Cell Receptor

PD228

RECOMBINASE ACTIVATING GENE DEFECTS, PHENOTYPIC DIVERSITY: TWO CENTERS' EXPERIENCE FROM TURKEY

POSTER DISPLAY 06: GENETICS IN IEI

Yagmur Hazal Sadirvan Oguzkaya[1], Sukru Cekic[1], Melek Yorğun Altunbaş[2], Zuhal Karali[1], Elif Karakoc-Aydıner[2], Ahmet Ozen[2], Safa Baris[2], Sara Sebnem Kilic[3]
[1]Uludag University Faculty of Medicine, Pediatric Allergy And Immunology, Bursa, Turkey, [2]Marmara University Pendik Research and Training Hospital, Pediatric Allergy And Immunology, Istanbul, Turkey, [3]Uludag University, Faculty of Medicine, Pediatric Immunology, Bursa, Turkey

Background and Aims: Mutations in recombinase activating genes 1 and 2 (RAG1/2) are associated with different clinical manifestations from asymptomatic to severe combined immunodeficiency (SCID). This study aims to present our series of patients who had immunodeficiency with RAG mutations.

Methods: This retrospective cross-sectional study was conducted in two centers. The patients who were followed for immunodeficiency with RAG mutations were included. Demographic data were obtained from the clinical records. The clinical status of the patients, treatment modalities, mutation types, laboratory findings, and survival rates were analyzed.

Results: A total of 26 patients were included in the study with a mean age of 11.05 ± 13.9. There were 11 male and 16 female patients. The mean age at the time of diagnosis was 6.15± 11.12 years. The time between the onset of symptoms and diagnosis was 5.07 ± 10.63 years. RAG 1 mutation was observed in 18 (69.2%) patients and RAG 2 mutation was observed in 8 (30.8%). Six patients (23%) had a concomitant autoimmune disease and 25 patients (96.1%) received IVIG treatment. Sixteen patients (61.5%) whom 2 with Omenn syndrome, 4 with atypical severe combined immunodeficiency and 7 with severe combined immunodeficiency received bone marrow transplantation. During the follow-up period, 7 (26.9%) patients died.

Conclusions: The clinical course of RAG mutation shows great variation. The present study is one of the largest series about the RAG mutations in the literature. Multicenter studies are needed to improve the knowledge for the diagnosis and treatment of RAG-related immunodeficiencies.

Disclosure: No.

Keywords: RAG1/2, Autoimmunity, SCID, Omenn, immunodeficiency, Turkey

PD229

INTRA AND INTER-FAMILIAL CLINICAL VARIABILITY IN PATIENTS WITH 22Q11.2 DELETION SYNDROME: GENOTYPE TO PHENOTYPE CORRELATION

POSTER DISPLAY 06: GENETICS IN IEI

Francesca Cillo[1], Giuliana Giardino[1,2], Roberta Romano[1], Elisabetta Toriello[1], Antonio De Rosa[1], Emma Coppola[1], Emilia Cirillo[1], Claudio Pignata[1]
[1]University of Naples Federico II, Translational Medical Sciences, Section of Pediatrics, Naples, Italy, [2]University of Naples "Federico II", Translational Medical Science, Napoli, Italy

Background and Aims: 22q11.2 Deletion Syndrome (22q11.2DS) is the most common microdeletion syndrome characterized by high phenotypic variability. The origin of this variability has not been elucidated yet and most of the molecular pathways involved in the pathogenesis of the different clinical features are still unknown.

Methods: The present study was conducted on a cohort of 54 patients. In all of them 22q11.2 deletion was documented using FISH. We performed a global clinical evaluation of the patients, characterizing the phenotypes both in de novo and familial cases of 22q11.2DS, and in 18 patients we performed CGH-array to define the precise size of the deletion, additional CNVs elsewhere in the genome, additional mutations responsible for dual diagnosis.

Results: 180 different clinical features were described in the cohort. Clinical phenotypes ranged from barely symptomatic to severe multiple organ impairment, both in patients with de novo deletions and in those belonging to the same family. 67% of patients evaluated carried the typical ~3 Mb deletion between LCR22-A and D, whereas 33% of patients had a smaller deletion. A higher prevalence of congenital heart disease was observed in patients carrying the typical deletion (92%) than in those with smaller deletions (25%). In 44% of patients additional CNVs located outside 22q11.2 region were identified through CGH-array and one patient received a dual diagnosis of 22q11.2 DS and Klinefelter Syndrome.

Conclusions: Further investigations on small deletions and epigenetic regulatory mechanisms need to be conducted, to better define the mechanisms underlying the clinical variability observed in patients.

Disclosure: No.

Keyword: 22q11.2 DS, variability, deletion, CNVs, pathogenesis

PD230

DUPLICATION of CD70 AND 4-1BBL CAUSES IMMUNODEFICIENCY AND IMMUNODYSREGULATION

POSTER DISPLAY 06: GENETICS IN IEI

Boaz Palterer[1], Manuela Capone[1], Marco Del Carria[1], Alberto Magi[2], Gianluca Mattei[2], Alessia Mingrino[2], Lucia Tiberi[3], Rosangela Artuso[4], Marilena Pantaleo[4], Silvia Guarducci[4], Alessandra Vultaggio[5], Andrea Matucci[5], Francesco Liotta[1], Francesco Annunziato[1]
[1]University of Florence, Department of Experimental And Clinical Medicine, Firenze, Italy, [2]University of Florence, Department of Information Engineering, Firenze, Italy, [3]University of Florence, Department of Biomedical Experimental And Clinical Sciences "mario Serio", Firenze, Italy, [4]Meyer Children's Hospital, Unit of Medical Genetics, Firenze, Italy, [5]Careggi University Hospital, Unit of Immunoallergology, Firenze, Italy

Background and Aims: Microduplications of 19p13.3 are associated with Facial dysmorphia, Urogenital malformation, growth, and neurodevelopmental Retardation and Immunodeficiency (FURID19). Reported duplications span over 3Mb and the cause of their immunologic phenotype has not been identified. The CD70 and TNFSF9 (4-1BBL) genes are found in the 19p13.3 locus. Mice constitutively over-expressing CD70 or 4-1BBL develop immunodeficiency, immune system exhaustion, and IFN-γ induced B cell depletion. We report a novel 19p13.3dup presenting with immunodeficiency and identify the putative molecular mechanism of the immunologic defect.

Methods: Genetic data was acquired through WES, CNVs were confirmed with CGH-array and long-read sequencing. Flowcytometry was used to identify leukocytes subpopulations and the expression of CD70 and 4-1BBL at baseline and after stimulation.

Results: We report an adult male presenting as CVID with IBD-like enteropathy, without non-immunologic features, harboring a de novo 830Kb structural variant in the 19p13.3 locus, causing a duplication of the CD70 and TNFSF9 genes. The patient showed reduced B cells with an absent memory compartment; an inverted CD4/CD8 ratio due to CD4+ lymphopenia. CD8+ lymphocytes showed senescence and increased IFN-γ production. Surface expression of CD70 and 4-1BBL was comparable to controls in resting cells, but it was significantly increased after stimulation.

Conclusions: We narrowed down the region responsible for the immunologic defect of 19p13.3 duplications and expanded the phenotype to CVID-like disease. Remarkably, the phenotype closely recapitulates the mice models of CD70 and 4-1BBL overexpression. Therefore, we propose the over-expression of CD70 and 4-1BBL as a novel immunodysregulation mechanism in humans.

Disclosure: No.

Keywords: Copy number variants, Whole Exome Sequencing, 19p13.3, CVID, CD70, 4-1BBL

PD231

UNEXPECTED PHENOTYPE of A KNOWN PATHOGENIC IL2RG VARIANT IN A 38-YEAR-OLD MALE PATIENT

POSTER DISPLAY 06: GENETICS IN IEI

Catherine Freeman[1], Scott Ennis[2], Crescent Isham[2], Ann Moyer[2], Attila Kumanovics[2], Yul Yang[3], Harry Teaford[1], Amir Sadighi Akha[2]
[1]Mayo Clinic, Allergy, Asthma And Clinical Immunology, Scottsdale, United States of America, [2]Mayo Clinic, Laboratory Medicine And Pathology, Rochester, United States of America, [3]Mayo Clinic, Dermatology, Scottsdale, United States of America

Background and Aims: Pathogenic variants in IL2RG typically result in T-B+NK- X-linked severe combined immunodeficiency (X-SCID). Partial loss of function may result in a less severe phenotype, potentially delaying diagnosis. We present a 38-year-old gentleman with epidermodysplasia verruciformis, a history of recurrent sinopulmonary infection, bronchiectasis, chronic rhinosinusitis with nasal polyposis, nonmelanoma skin cancer and dependence on immunoglobulin replacement since childhood, who was referred for further evaluation.

Methods: Gene panel sequencing, flow-cytometric analysis, TREC and TCR Vb spectratyping were used for assessment.

Results: Gene sequencing identified a hemizygous pathogenic variant in IL2RG (VAF:100%). No abnormality was reported in TMC6 or TMC8. Immunophenotyping showed normal T and B cell numbers, but decreased memory B cells and plasmablasts; inordinately decreased NK cells; and marginally decreased pDCs. TREC was undetectable, CD4RTEs were inordinately decreased and TCR Vb repertoire was abnormal. T cell proliferation to mitogens and anti-CD3 were normal. CD107 expression and IFN-γ production in CD8+ T cells, and IFN-α production in pDCs were normal. The patient's T and B cells expressed IL-2γc. STAT5 phosphorylation in response to IL-2, IL-7, IL-15, and GM-CSF, were comparable to the control.

Conclusions: The pathogenic variant identified in our patient has been reported once previously, in a patient with a typical SCID phenotype who died in early childhood. Our patient highlights the distinct manifestations and outcomes of an identical pathogenic variant in different individuals. Further studies are under way to determine the mechanisms underlying the unexpected expression of IL-2γc in this case and its consequent downstream effects.

Disclosure: No.

Keywords: IEI, X-SCID, phenotype, IL2RG, STAT5 phosphorylation

PD232

GENETIC CHARACTERISTIC of PATIENTS FROM BULGARIAN PID REGISTRY

POSTER DISPLAY 06: GENETICS IN IEI

Snezhina Mihailova[1], Spaska Lesichkova[1], Veneta Milenova[2], Petya Yankova[1], Nedelcho Ivanov[2], Mariya Spasova[3], Hasan Burnusuzov[3], Elissaveta Naumova[1]
[1]University Hospital "Alexandrovska", Medical University, Clinic of Clinical Immunology With Stem Cell Bank, Expert Center For Rare Diseases-pid, Sofia, Bulgaria, [2]University Hospital "Alexandrovska", Clinic of Clinical Immunology With Stem Cell Bank, Expert Center For Rare Diseases-pid, Sofia, Bulgaria, [3]Medical University, Department of Pediatrics And Medical Genetics, Plovdiv, Bulgaria

Background and Aims: In 2017, the National PID Register became operational as a database containing clinical and genetic information for Bulgarian individuals with inborn errors of immunity. Overall, 191 patients were included, representing a rate of 2.7 per 100,000. The aim is to present the results of the genetic testing performed and their significance for good clinical practice.

Methods: Ninety-six patients (50.26%) were genetically evaluated. Sanger-based and targeted panel sequencing (GRID program, INVITAE, TruSight-One Sequencing Panels, Illumina) have been done.

Results: Disease-causative variants were found in 66.7% of all samples tested, with the majority having autosomal recessive defects (50%). Autosomal dominant pathogenic variants were established in 33.9% and X-linked in 16.1%. Three of the pathogenic variants have not been reported. Most genetically tested were from the group of CIDs with syndromic features (87.8%), followed by SCID (80%), antibody (34%) and complement deficiency (18%). A total of 265 variants were of uncertain significance. Thirty-nine of them have not been described yet. Fifty-six of the uncertain variants were in genes with autosomal dominant or X-linked mode of inheritance. The Slavic NBN c.657_661del was estimated with high carrier status of 4,166.6 per 100,000. Following genetic testing, confirmation of the phenotypic diagnosis was achieved in 82.8% of cases, and in 17.2% there was diagnostic re-evaluation.

Conclusions: Genetic analysis is an integral part of PID diagnosis and contributes to better clinical management in a number of cases. Patients with negative results are likely to be suitable for whole exome/genome studies, and those with uncertain variants require close follow-up and timely re-evaluation.

Disclosure: No.

Keywords: National PID Register, Bulgaria, Genetic characteristic

PD233

IMPLEMENTATION of EARLY NEXT-GENERATION SEQUENCING FOR INBORN ERRORS of IMMUNITY: DIAGNOSTIC YIELD AND CLINICAL IMPLICATIONS IN DUTCH GENOME DIAGNOSTIC CENTERS

POSTER DISPLAY 06: GENETICS IN IEI

Kim Elsink[1], Manon Huibers[2], Iris Hollink[3], Annet Simons[4], Evelien Zonneveld[5], Lars Van Der Veken[2], Helen Leavis[6], Stefanie Henriet[7], Marcel Van Deuren[8], Frank Van De Veerdonk[8], Judith Potjewijd[9], Dagmar Berghuis[10], Virgil Dalm[11], Clementine Vermont[12], Annick Van De Ven[13], Annechien Lambeck[14], Kristin Abbott[5], Martin Van Hagen[11], Godelieve De Bree[15], Taco Kuijpers[16], Geert Frederix[17], Marielle Van Gijn[5], Joris Van Montfrans[18]
[1]University Medical Center Utrecht, Pediatric Immunology And Infectious Diseases, Utrecht, Netherlands, [2]University Medical Center Utrecht, Genetics, Utrecht, Netherlands, [3]Erasmus Medical Center, Clinical Genetics, Rotterdam, Netherlands, [4]Radboud University Medical Center, Human Genetics, Nijmegen, Netherlands, [5]University Medical Center Groningen, Genetics, Groningen, Netherlands, [6]University Medical Center Utrecht, Utrecht University, Department of Rheumatology & Clinical Immunology, Utrecht, Netherlands, [7]Radboud University Nijmegen Medical Centre, Pediatric Infectious Diseases And Immunology, Nijmegen, Netherlands, [8]Radboud University Medical Center, Internal Medicine, Nijmegen, Netherlands, [9]Maastricht University Medical Center, Nephrology And Clinical Immunology, Maastricht, Netherlands, [10]Leiden University Medical Center, Pediatrics, Leiden, Netherlands, [11]Erasmus University Medical Center Rotterdam, Internal Medicine, Rotterdam, Netherlands, [12]Erasmus Medical Center, Immunology And Rheumatology, Rotterdam, Netherlands, [13]University Medical Center Groningen, Internal Medicine And Allergology, Groningen, Netherlands, [14]University Medical Center Groningen, Laboratory Medicine, Groningen, Netherlands, [15]Amsterdam University Medical Center, Internal Medicine, Amsterdam, Netherlands, [16]Amsterdam University Medical Center, Pediatric Hematology, Immunology And Infectious Diseases, Amsterdam, Netherlands, [17]University Medical Centre Utrecht, Julius Center For Health Sciences And Primary Care, Utrecht, Netherlands, [18]Wilhelmina's Children Hospital, Department of Pediatric Immunology And Infectious Diseases, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

Background and Aims: Inborn errors of immunity (IEI) are a heterogeneous group of disorders, with over 450 IEI related genes identified. This makes the early application of next-generation sequencing (NGS) as a diagnostic method a promising development. We aimed to provide an overview of the diagnostic yield and time to diagnosis in a cohort of patients suspected of IEI and evaluated by an NGS based IEI panel.

Methods: We performed a prospective observational cohort study. We collected data of 165 patients with a clinical suspicion of IEI without prior NGS based panel evaluation that were referred for early NGS. The diagnostic yield, time to diagnosis and clinical implications was assessed.

Results: For children, the median time from first consultation to diagnosis was 119 days versus 124 days for adult patients. The median turn-around time (TAT) was 56 days in pediatric patients and 60 days in adult patients. A definitive molecular diagnosis was made in 25/65 (24.6%) of pediatric patients and 9/100 (9%) of adults. Most diagnosed disorders were identified in the categories of immune dysregulation (n=10/25; 40%), antibody deficiencies (n=5/25; 20%), and phagocyte diseases (n=5/25; 20%). Inconclusive outcomes were found in 76/165 (46.1%) patients.

Conclusions: In this cohort, the highest yields of NGS based evaluation for IEI early in the diagnostic trajectory were found in pediatric patients, and in the disease categories immune dysregulation and phagocyte diseases. In cases where a definitive diagnosis was made, this led to important disease management implications in a large majority of patients.

Disclosure: No.

Keywords: gene panel, Inborn errors of immunity, Next-generation sequencing, clinical implication, diagnostic yield

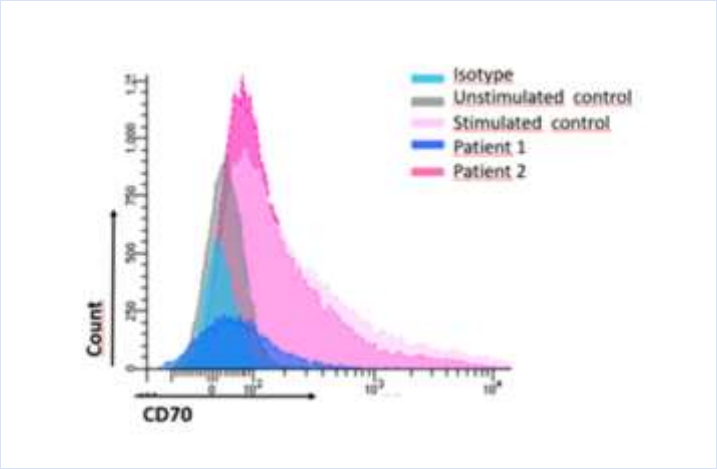
PD234

EBV RELATED LYMPHAMATOID GRANULOMATOSIS of CENTRAL NERVOUS SYSTEM IN A PATIENT WITH CD70 DEFICIENCY

POSTER DISPLAY 06: GENETICS IN IEI

Sidem Tekeoğlu[1], Saliha Esenboga[2], Elif Soyak Aytekin[3], Hacer Neslihan Bildik[1], Begum Cicek[1], Ismail Yaz[1], Sevil Oskay Halacli[1], Deniz Cagdas Ayvaz[2], Ilhan Tezcan[2]
[1]Hacettepe University, Institute of Child Health, Immunology, Ankara, Turkey, [2]Hacettepe University School of Medicine, Pediatric Immunology, Ankara, Turkey, [3]School of Medicine, Pediatric Immunology, Ankara, Turkey

Background and Aims: CD70 deficiency is a rare AR IEI predisposing to EBV. CD70, expressed on B cell, interacts with its ligand CD27 on T cells surface and this interaction is important for T cell survival. Here, we present two adult brothers with CD70 deficiency with variable expressivity. A 19 year old male patient was admitted to hospital with fever, vomiting, tonic-clonic seizures, loss of consciousness. There was first-degree cousin marriage between parents. His cranial MRI revealed cerebral,cerebellar atrophy; signal changes in tha basal ganglai and cortex. The CSF cytology was positive for large granular lymphoid cells. Liver biopsy revealed EBV hepatitis. EBV DNA was 16507 copies/mL. The immunological work-up of the patient is shown in Table 1. The patient was treated with rituximab and IVIG . Acyclovir prophylaxis was started.
Methods: The WES analysis revealed a pathogenic variant in CD70 gene (c.437G>T p.S146I),confirmed with Sanger sequencing. HLA analysis revealed that his brother was fully-matched. However Sanger sequencing of brother before HSCT showed the same CD70 mutation.
Results: The brother had no clinical findings, negative for EBV and his immunological investigation was normal. The flow cytometric CD70 expressions are shown in Figure 1. Since his brother has the same mutation, unrelated donor screening for the patient is still pending. Figure1.



Conclusions: Here, we saw that the environmental effects and epigenetics have high importance. It is important to check the family donor for the presence of the mutation before HSCT since sometimes the expressivity is variable, clinical findings may not be seen despite the mutation.

Disclosure: No.

Keywords: EBV, Immune Dysregulation, flow cytometry, CD70, IEI, WES

PD235

NEW APPROACHES IN THE GENETIC DIAGNOSIS of PRIMARY IMMUNODEFICIENCIES: DEVELOPMENT of A NEW STRATEGY FOR THE EVALUATION of CNVS THROUGH NGS

POSTER DISPLAY 06: GENETICS IN IEI

Elisabet Matas Pérez[1], Andrea González Torbay[1], Ángela Del Pozo Mate[2,3,4], Maria Ángeles Mori Álvarez[2,4], Ricardo Cuesta Martín De La Cámara[1], Carmen Rodríguez Jiménez[4], Rebeca Rodríguez Pena[1,2], María Bravo García-Morato[1,2]
[1]La Paz University Hospital, Department of Immunology, Madrid, Spain, [2]CIBERER, Isciii, Madrid, Spain, [3]La Paz University Hospital, Ern-ithaca, Madrid, Spain, [4]IdiPaZ, La Paz University Hospital, Institute of Medical And Molecular Genetics (ingemm), Madrid, Spain

Background and Aims: Recent advances in the genetic field have allowed the expansion of phenotypes and the description of new diseases. However, the analysis of copy number variantions (CNVs) already represents a diagnosis limitation since the usual sequencing methodologies are not sensitive enough for their detection. The aims of this work were the development of a filtering strategy for the evaluation of CNVs through NGS using VarSeq and the comparison of its sensitivity to the routine analysis.

Methods: Twenty-five samples with known deletions were processed by NGS and analysed using VarSeq. The deletions had been previously detected by MLPA, array CGH and/or breakpoint PCR. All of them were also evaluated using our routine strategy based on XHMM and LACONv softwares.

Results: For the analysis of CNVs with Varseq, four filter groups were defined according to the number of deleted exons and the zygosity of the deletion. Each filter group included the following parameters: CNV-State, #Samples, #Target, Avg-Ratio and Avg-Z-Score. This analysis allowed the detection of 23/25 deletions and showed a higher sensitivity than the routine strategy (95.5% vs 63.6%). Two of the undetected deletions were located in non-captured regions. There was a good correlation between VarSeq and the gold standard methodologies, MLPA and array-CGH.

Conclusions: VarSeq showed better sensitivity in the detection of CNVs when compared to our routine strategy. Its main limitation was that non-captured regions could not be evaluated. NGS could be a powerful screening tool for the detection of CNVs in a near future.

Disclosure: No.

Keywords: CNV, Deletions, NGS, MLPA, array CGH, Genetic diagnosis

PD236

A DE NOVO THR325ARG MUTATION IN CDCA7 CAUSES IMMUNODEFICIENCY, CENTROMERIC REGION INSTABILITY, FACIAL ANOMALIES SYNDROME, AND DEFECTIVE B AND T CELL DIFFERENTIATION

POSTER DISPLAY 06: GENETICS IN IEI

Lia Pinho[1], Rhaissa Vieira[1], Minghui He[2], Julien Record[2], Per Marits[3], Ann-Charlotte Wikström[3], Olov Ekwall[4], Vinicius Cotta-De-Almeida[5], Lisa Westerberg[2]
[1]Karolinska Institutet, Microbiology, Tumor And Cell Biology, Solna, Sweden, [2]Karolinka Institutet, Microbiology, Tumor And Cell Biology, Solna, Sweden, [3]Karolinska University Hospital, Clinical Immunology And Transfusion Medicine, Stockholm, Sweden, [4]Univ Gothenburg, Dept Pediatrics, Gothenburg, Sweden, [5]Oswaldo Cruz Foundation, Oswaldo Cruz Institute, Rio de Janeiro, Brazil

Background and Aims: Immunodeficiency-centromeric instability-facial anomalies (ICF) syndrome is an autosomal recessive disorder. Mutations in cell division cycle-associated protein 7 (CDCA7) cause ICF3 subtype. CDCA7 is a protein related to dynamics and rearrangement of the actin cytoskeleton in immune cells. Here we report a patient with a de novo Thr325Arg mutation in CDCA7 with severe immunodeficiency disease. The patient presented pseudomonas septicemia, low T cell proliferation upon PHA and ConA stimulation, and reduced levels of IgA and IgG after stimulation using EBV and PWM. The patient had detectable levels of peripheral naïve B and T cells, but no detectable levels of memory B cells and a low number of effector T cells.

Methods: Flow Cytometry analysis, cell culture, gene editing.

Results: We generated activated CD4 T cells and lymphoblastoid B cell lines of the patient, sister, mother, father, and unrelated control samples. Compared to the other samples, the CDCA7^{T325R} patient cells showed poor proliferation. Peripheral B cells presented high levels of transitional and naïve B cells compared to control samples. Anti-CD3/CD28 activation of patient CD4 T cells showed reduced proliferation and increased apoptosis. We generated CDCA7 knockout cell lines using CRISPR/Cas9 gene editing. CDCA7 knockout Raji B cells grew abnormally and formed giant cells over time in culture. Cell cycle analysis revealed a significant increase in the population with more than double DNA content (>4n), indicative of genomic instability.

Conclusions: This study identifies how the CDCA7^{T325R} mutation in rare primary immunodeficiency patients affects cell cycle leading to reduced B and T cell differentiation into effector cells.

Disclosure: No.

Keywords: T cells, Cell Differentiation, CDCA7, ICF3, B cells

PD237

CLINICAL AND MOLECULAR PROFILE of PATIENTS WITH INBORN ERRORS of IMMUNITY (IEI) FROM NEPAL

POSTER DISPLAY 06: GENETICS IN IEI

Dharmagat Bhattarai[1], Aaqib Banday[2], Pratap Patra[3], Saket Jha[4], Asmita Neupane[1]
[1]Advanced Centre for Immunology & Rheumatology, Pediatric Immunology, Kathmandu, Nepal, [2]Postgraduate Institute of Medical Education & Research, Pediatrics, Chandigarh, India, [3]All India Institute of Medical Sciences, Patna, India., Department of Paediatrics, Patna, India, [4]Om Hospital and Research Centre, Rheumatology, Kathmandu, Nepal

Background and Aims: Inborn errors of immunity (IEIs) are increasingly being diagnosed in various regions of the world. With increasing awareness and diagnostics, IEIs are diagnosed with increasing frequency and accuracy in Nepal. IEIs are also being evaluated in children presenting with autoimmune manifestations. We describe the profile of patients diagnosed with IEIs in Nepal during 2020-2021.

Methods: Records of all patients with IEIs who were diagnosed and treated at our tertiary care center in Nepal from August 2020 to October 2021 were analyzed. Lead author (DB) has examined and diagnosed all cases. IEIs were diagnosed based on the European Society for Immunodeficiencies (ESID) diagnostic criteria and genetic analysis.

Results: Twenty-eight patients with IEI (16 boys; 12 girls) and 201 children with autoimmune disorders were diagnosed during the study period. Genetic analysis was done on 15 patients. The diagnostic profile of the patients includes patients with the chronic granulomatous disease, X-linked agammaglobulinemia, severe combined immunodeficiency, Job syndrome, selective IgA deficiency, specific antibody deficiency, Wiskott-Aldrich Syndrome, CTLA4 deficiency, IPEX syndrome, IFN-IL12 axis defect, hereditary angioedema, MonoMac syndrome, ARPC1B deficiency, leukocyte adhesion defect, PAPA syndrome, autoimmune lymphoproliferative syndrome, ADA2 deficiency, early-complement deficiency lupus, familial cold auto-inflammatory syndrome, and Blau syndrome. Some patients succumbed before the scope of diagnosis. HSCT is planned for 3 patients.

Conclusions: We present our experience of IEIs in resource-limited settings. Low socio-economic status coupled with a lack of awareness among laity and pediatrician accounted for a missed or late diagnoses, and poor outcomes. Antimicrobial prophylaxis reduced the incidence of breakthrough infections.

Disclosure: No.

Keywords: Inborn errors of immunity, immunodeficiency, Resource-limited settings, Immunogenetics, diagnostics

PD238

NOVEL DIAPH1 MUTATION ASSOCIATED WITH COMBINED IMMUNODEFICIENCY AND MICROCEPHALY

POSTER DISPLAY 06: GENETICS IN IEI

Royala Babayeva[1], Mehmet Cihangir Catak[1], Asena Pinar Sefer[1], Ezgi Yalcın Gungoren[1], Melek Yorğun Altunbaş[1], Alper Bulutoglu[1], Adem Yasar[2], Metin Eser[3], Sevgi Bilgic Eltan[1], Elif Karakoc-Aydıner[1], Ahmet Ozen[1], Safa Baris[1]
[1]Marmara University, Pediatric Allergy And Immunology, Istanbul, Turkey, [2]Istanbul Haseki Training and Research Hospital, Pedaitric Allergy And Immunology, Fatih, Turkey, [3]University of Health Sciences, Pedaitric Genetics, Uskudar, Turkey

Background and Aims: Homozygous loss of function mutations in DIAPH1 lead to seizures, cortical blindness, and microcephaly syndrome (SCBMS). Herein we report two unrelated families with 3 individuals having the same novel mutation, presenting with postnatal microcephaly, vision impairment, early-onset seizures, respiratory complications, and combined immunodeficiency.

Methods: The clinical and immunological features of the patients were evaluated. Next-generation sequencing was performed for definitive diagnosis. Flow cytometry was used to determine T-, B- and NK-cell subpopulations, and T-cell proliferation.

Results: Both unrelated families had the same novel homozygous mutation in DIAPH1 (c.1051C>T; p. Arg351*). Clinical features of patients were failure to thrive (n:3, 100%), microcephaly (n:3, 100%), intellectual disability (n:3, 100%), epilepsy (n:2, 67%), cortical blindness (n:1, 33%). Recurrent sinopulmonary infections were observed in all patients. One patient showed splenomegaly, immune thrombocytopenia, and mycobacterium tuberculosis infection. The other one had autoimmune hemolytic anemia. Low serum immunoglobulins and impaired antibody responses were detected in two patients. Flow cytometric analysis revealed low levels of T cells with severely decreased naive compartment and recent thymic emigrants, accompanied by defective lymphocyte activation and proliferation. Decreased memory B-cell formation was observed in one patient.

Conclusions: Syndromic combined immunodeficiency caused by DIAPH1 deficiency should be envisaged in patients with microcephaly and failure to thrive. Supported by TUBITAK (318S202).

Disclosure: No.

Keywords: combined immunodeficiency, microcephaly, DIAPH1

PD239

NOVEL HOMOZYGOUS MUTATION IN TRANSCOBALAMIN II GENE (TCN2) CAUSES PRIMARY IMMUNODEFICIENCY AND PANCYTOPENIA

POSTER DISPLAY 06: GENETICS IN IEI

Daifulah Alzahrani, Tariq Alasaad
King Saud Bin Abdulaziz Uni. for Health Sciences, KAMC- WR, Pediatric, Jeddah, Saudi Arabia

Background and Aims: Transcobalamin transports vitamin B12 from blood into the cells. Transcobalamin II deficiency is a rare autosomal recessive disorder, that is characterized by failure to thrive, diarrhea, anaemia, pancytopenia or agammaglobulinemia.

Methods: We describe 22-months-old boy who presented to use at the age of 6-months with fever, diarrhea and pancytopenia, that was required weekly platelet and PRBC transfusions. Both parents are first degree consanguineous. His complete blood counts showed WBC count of 7.6×10^9/L, neutrophils count of 0.7×10^9/L, lymphocyte count of 6.5×10^9/L, Hb level of 5.3 g/dL (normal: 12.5-15), platelet count of 20×10^9/L (normal; 150-450), mean corpuscular volume (MCV) of 106 fL (normal: 75-95), mean corpuscular Hb (MCH) of 33.5 pg/cell.

Results: Bone Marrow aspiration and biosy rules out malagnacies. Whole exome sequencing showed Novel homozygous mutation in transcobalamin-II gene (TCN2) and both parents are heterozygous. He was started on cyanocobalamin 100 mcg intramuscular injection weekly that resolved his pancytopenia within few weeks. He has normal immunoglulin levels; IgG 3.29, IgA 0.90 and IgM 0.38 (g/L). Lymphocye markers (cells/µL) showed CD3+= 7,686, CD4+= 4,131, CD8+= 3,576, CD19+= 1279, CD3-CD16+CD56+= 1809, CD19+CD27+= 3% (reference %:6.3-52.8), CD27+/IgM+/IgD+CD19+B-cells =0.0% (reference %:1.7-29.3), CD27+/IgM-/IgD-/CD19+B-cells= 1% (reference %:2.3-26.5). He received all vaccination and tow extra doses of tetanus, MMR and varicella vaccines, but he countinoued to have poor antibody response; Measles IgG 7.71 (normal >13.5), VZV-IgG 104.90 (normal >135), AntiHbs 6.75 (normal >10), TetanusIgG 0.34 IU.

Conclusions: We describe the first novel homozygous transcobalamin-II gene mutation with defective B-cells and poor response to vaccines after resolution of cytopenia with cyanocobalamin therapy.

Disclosure: No.

Keywords: pancytopenia, primary immunodeficiency, Transcobalamin II gene (TCN2), Diarrhea, Megaloblastic anemia

PD240

CLINICAL AND IMMUNOLOGICAL FEATURES of BCL10 DEFICIENCIES

POSTER DISPLAY 06: GENETICS IN IEI

Blanca Garcia-Solis[1], Ana Van Den Rym[1], Jareb J. Pérez-Caraballo[2], Silvia Sánchez-Ramón[3], Reem Mohammed[4], Mukesh M. Desai[5], Ruben Martinez-Barricarte[2], Jean-Laurent Casanova[6], Rebeca Perez De Diego[1]
[1]IdiPAZ Institute for Health Research, La Paz Hospital, Laboratory of Immunogenetics of Human Diseases, Madrid, Spain, [2]Division of Genetic Medicine, Department of Medicine, Vanderbilt Genetics Institute,vanderbilt University Medical Center, Nashville, United States of America, [3]San Carlos Clinical Hospital, Clinical Immunology Department, Madrid, Spain, [4]King Faisal Hospital and Research Center, Pediatric Allergy And Immunology, Riyadh, Saudi Arabia, [5]Bai Jerbai Wadia Hospital for Children, Division of Immunology, Parel, Mumbai, India, [6]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, New York, United States of America

Background and Aims: Combined immunodeficiencies (CID) form a group of phenotypically heterogeneous genetic disorders characterised by low T and B-cell counts and functionality, resulting in impaired cellular and humoral immunity, with infectious and autoimmune manifestations (Roifman et al., 2012). Next-generation sequencing techniques allow new genetic aetiologies to be found and characterised. The aim is to find the common clinical and immunological features of these patients, allowing early diagnosis and personalised treatment.

Methods: Through massive sequencing, a BCL10 genetic defect is found and validated by Sanger sequencing in three patients. Protein expression levels are studied by western blot and innate immunity by ELISA assays. Immunological characterisation is performed by flow cytometry and mass cytometry together with unsupervised clustering and machine learning computational methods.

Results: Autosomal recessive BCL10 deficiency is found in three non-related patients. All are consanguineous and have homozygous mutations. One of them generates a splice codon mutation and two other patients stop codons (g.85741978C>T; IVS1+1G>A, g.85270702G > A; R88X, g. 85270779A>T; K63X). Clinically, all patients share severe respiratory infections since first months of life. At immunological level it is showed that fibroblast immunity is BCL10-dependent in TLR4, TLR2/6 and Dectin-1 signalling. Finally, these patients show a reduction of memory B and T cells, NK cells, γδT, Tregs and TFH.

Conclusions: These studies show the importance of early genetic diagnosis for the management of patients with BCL10 deficiency and how haematopoietic progenitor transplantation (HSCT) is the recommended treatment.

Disclosure: No.

Keywords: BCL10, combined immunodeficiency, primary immunodeficiency, autosomal recessive, CBM complex, Next-generation sequencing

PD241

MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASES; A SMALL COHORT WITH DIFFERENT DIAGNOSES

POSTER DISPLAY 06: GENETICS IN IEI

Hatice Betul Gemici Karaaslan[1], Sezin Kisabacak[1], Yasemin Kendir Demirkol[2], Jacinta Bustamante[3], Nevin Hatipoğlu[4], Ayca Kiykim[1], Haluk Cezmi Cokugras[1]
[1]Istanbul University-Cerrahpasa, Pediatric Allergy And Immunology, Istanbul, Turkey, [2]University of Health Sciences, Umraniye Education and Research Hospital, Division of Pediatric Genetics, Istanbul, Turkey, [3]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Paris, France, [4]University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital,, Department of Pediatric Infection, Istanbul, Turkey

Background and Aims: Mendelian susceptibility to mycobacterial disease(MSMD) is a rare congenital disorder characterized by a selective predisposition to infection by weakly virulent mycobacteria and other types of intracellular pathogens. The 19 genes associated with MSMD represent 34 distinct disorders with different clinical presentations and prognoses.

Methods: We have described here a series of 11 Turkish MSMD cases in which four different types of molecular defects were identified.

Results: STAT1 monoallelic loss-of-function mutation was detected in 4 patients(P1,P2,P3,P4) from the same family, only one had BCG-osis and three others were asymptomatic. These patients have a partial dominant STAT1 deficiency.
Homozygous IFN-γR1 deficiency was detected in one patient(P5) who was from consanguineous parents. He had BCG-osis associated to splenomegaly, abdominal lymphadenopathies and multifocal osteomyelitis. He developed pneumonia with ARDS. The patient died of acute fulminant hepatitis after HSCT.
The NEMO deficiency was discovered in two brothers(P6,P7). They developed infection by Mycobacterium bovis.
Finally, IL-12Rß1 deficiency was detected in 4 patients(P8,P9,P10,P11). Only P9 was asymptomatic and the otherS had abnormal local reactions to BCG vaccine. P8 and P10 had also mucocutaneous candidiasis. Symptomatic patients with ILRB1 deficiency received IFN-γ.

Conclusions: MSMD can present as atypical mycobacterial infections and lymphadenitis post-BCG vaccine, which are often not investigated by clinicians. The presence of clinical presentations in varying forms and severity complicates diagnosis. Consideration of family history, evaluation of immunologic markers, and genetic testing in patients with BCG disease or environmental mycobacterial infections may contribute to early diagnosis of affected individuals, improved prognosis, and prevention of similar birth defects in a family.

Disclosure: No.

Keywords: Mendelian Susceptibility to Mycobacterial Diseases, immunodeficiency,, pediatrics

PD242

IMMUNE DEFECTS EXPAND THE SPECTRUM of KBG SYNDROME

POSTER DISPLAY 06: GENETICS IN IEI

Axel André[1], Arthur Simonnet[1], Anne-Marie Milesi-Lecat[2], Guillaume Le Guenno[3], Eric Oksenhendler[1], Benjamin Fournier[4], Nizar Mahlaoui[5], David Boutboul[1]
[1]Hopital Saint Louis, Université de Paris Cité, Clinical Immunology, Paris, France, [2]Centre hospitalier de Vichy, Internal Medicine, Vichy, France, [3]CHU de Clermont-Ferrand, Internal Medicine, Clermont-Ferrand, France, [4]Necker Hospital for Sick Children, Pediatric Immunology, Hematology And Rheumatology Unit, Paris, France, [5]HOPITAL NECKER, Ceredih & Uihr, PARIS, France

Background and Aims: KBG syndrome is an autosomal dominant disorder caused by loss-of-function mutations in ANKRD11 and 200 cases have been reported to date. Clinical presentation include typical cranio-facial and skeletal features with neurodevelopmental delay. Recurrent respiratory infections (RTI) have been reported but immune defects have not been studied. We here describe the immune phenotype of 4 patients with KBG syndrome.

Methods: We screened the databases from two tertiary care centres specialized in primary immune deficiencies and found 4 patients with confirmed KBG syndrome and immunological abnormalities.

Results: We identified 4 KBG patients with signs of immune deficiency (three children, one adult) : three had recurrent upper and/or lower RTI, two had low immunoglobulin levels and altered polysaccharide responses and one had profound and chronic global lymphopenia. The adult patient later developed nodular regenerative hyperplasia (NRH) and enlarged secondary lymphoid organs caused by follicular hyperplasia, which mimicked CVID combining hypogammaglobulinemia and a decreased memory B-cell compartment. We found no evidence of cellular defects in these patients.

Conclusions: To our knowledge it is the first description of the immune defects observed in KBG. Clinicians should be aware of potentially severe infectious and non-infectious complications related to the immune phenotype of the disease. This should lead to prompt treatment of infections and regular screening of non-infectious complications such as NRH. ANKRD11 is closely related to KMT2D which has been found mutated in type 1 Kabuki syndrome, a craniofacial disorder associated with variable immune defects. Together these observations underline the role of histone acetylation/methylation in immune system homeostasis.

Disclosure: No.

Keywords: KBG syndrome, ANKRD11 mutation, Humoral defects, Nodular regenerative hyperplasia

PD243

THE IMPACT of A NOVEL NFKB2 GENE VARIANT ON CVID CLINICAL SPECTRUM: A NON-CANONICAL NF-KB PATHWAY HAPLOINSUFFICIENCY?

POSTER DISPLAY 06: GENETICS IN IEI

Beatrice Martini[1], Ebe Schiavo[1], Maria Luisa Coniglio[2], Filippo Consonni[3], Claudio Favre[2], Eleonora Gambineri[2]
[1]University of Florence, Department of Neurosciences, Psychology, Drug Research And Child Health (neurofarba), Florence, Italy, [2]Meyer Children's Hospital, Centre of Excellence, Division of Pediatric Oncology/hematology, Florence, Italy, [3]University of Florence, Department of Health Sciences, Florence, Italy

Background and Aims: The NF-κB signalling pathway plays a key role in lymphocytes activation. Autosomal dominant NFKB2 mutations are associated with common variable immunodeficiency (CVID), and act either by haploinsufficiency or dominant-negative mechanisms. Due to the incomplete clinical penetrance and the variable clinical expressivity described for several of these mutations, dissecting their impact on the immunological landscape is challenging.

Methods: We report a 15-years old boy displaying recurrent upper and lower respiratory infections with multiple benign abdominal lymphadenopathies. Immunologic workup showed borderline/low levels of IgG3 and IgG4, decreased T follicular helper and B transitional cells and apoptosis resistance. Whole exome sequencing analysis was performed, and functional validation was set-up by western blotting on patient- and controls-derived PBMCs, upon anti-CD3/CD28+IL-2 activation.

Results: Genetic analysis identified a heterozygous de novo c.2249C>T (p.A750V) variant in NFKB2, localized in the protein C-terminal domain. Western blot analysis showed a specific NF-kB2 signal in response to T cell activation in healthy controls (N=4), while the patient displayed a comparable expression, in both unstimulated and stimulated PBMCs, of NF-kB2 unprocessed isoform (p100).

Conclusions: We observed NF-kB2 A750V protein aberrant activation, and we hypothesize that p100 accumulation in the cytoplasm may be causative of NF-kB2 non-canonical pathway haploinsufficiency, as reported for CVID. Strikingly, we did not observe the B cell alterations typically associated with CVID; thus, further investigations on both the non-canonical and canonical NF-kB pathway will be required to assess the variant's biological impact.

Disclosure: No.

Keywords: NF-kB signalling, NF-kB2, immunophenotyping, western blot, Immune Dysregulation, Whole Exome Sequencing

PD244

RETROSPECTIVE STUDY: ABOUT 14 CONFIRMED CASES DIGEORGE

POSTER DISPLAY 06: GENETICS IN IEI

Asmaa Gaadi[1], Ahmed Aziz Bousfiha[1], Laila Boughenouch[2], Said Trhanint[2], Mouna Lehlimi[3]
[1]Faculty of Medecine and Pharmacy, University Hassan II, Casablanca, Laboratory of Clinical Immunology, Inflammation And Allergy (licia), CASABLANCA, Morocco, [2]Faculty of Medecine and Pharmacy, Fez, Genetics, FEZ, Morocco, [3]Faculty of Medecine and Pharmacy, University Hassan II, Casablanca, Neonatal Medicine And Intensive Care Unit. Hôpital Mère-enfant A. Harouchi, Chu Ibn Rochd, Hassan Ii University, Faculty of Medicine And Pharmacy, CASABLANCA, Morocco

Background and Aims: 22q11.2 deletion syndrome (22q11DS) is one of the autosomal dominant human genetic syndromes, usually caused by microdeletion at chromosome 22 and rarely at chromosome 10. It is characterized by a wide phenotypic spectrum. Our retrospective study which took place in the department of Pediatrics 1 (P1) of the Children's Hospital Abderrahim Harouchi, CHU Ibn Rochd of Casablanca, aims to report 14 cases confirmed Digeorge by the FISH technique, in order to establish a probable clinico-genetic correlation.

Methods: For this, we used data from an American study by Burnside et al, in order to compare it to our series. We were able to establish a relationship between the phenotype and the deletion that the patient could probably carry.

Results: All children have a 22q11 microdeletion which has been confirmed by FISH technique. At the end of the clinical and paraclinical analysis of our patients, and based on the literature, we were able to establish a relationship between the phenotype and the deletion that the patient could probably carry.

Conclusions: We concluded that not all symptoms are always present in a given type of deletion. The overlap of the different clinical signs does not allow for accurate prediction of the genotype-phenotype correlation. The use of molecular cytogenetic techniques remains necessary and fundamental.

Disclosure: No.

Keywords: Digeorge Syndrome, 22q11 deletion, Proximal deletion, Central deletion, Distal deletion

PD245

A NOVEL PATHOGENIC MUTATION IN MAGT1 IN X-LINKED MAGNESIUM DEFICIENCY WITH EPSTEIN-BARR VIRUS (EBV) INFECTION AND NEOPLASIA (XMEN) DISEASE

POSTER DISPLAY 06: GENETICS IN IEI

Giulio Tessarin[1], Mohammad Sina[2], Manuela Baronio[1], Luisa Gazzurelli[1], Stefano Rossi[3], Marco Chiarini[4], Daniele Moratto[4], Raffaele Badolato[1], Silvia Clara Giliani[2], Vassilios Lougaris[1]
[1]Pediatrics Clinic and "A. Nocivelli" Institute for Molecular Medicine, Department of Clinical And Experimental Sciences, University of Brescia, Asst- Spedali Civili of Brescia, Brescia, Italy, [2]Institute for Molecular Medicine A. Nocivelli, Department of Molecular And Translational Medicine, University of Brescia, brescia, Italy, [3]Spedali Civili di Brescia, Bone Marrow Transplant Unit 'monica E Luca Folonari', Brescia, Italy, [4]Flow Cytometry Laboratory, Diagnostic Department, Asst Spedali Civili, Brescia, Italy, brescia, Italy

Background and Aims: XMEN disease is a rare inborn error of immunity caused by loss-of-function mutation in MAGT1. Patients usually present persistent EBV viral load with subsequently EBV-driven lymphoid neoplasia, and a variable B and T cells involvement. Up to date, only missense or null mutations have been reported in affected patients.

Methods: we report on clinical, immunological, and genetic findings in a pediatric patient affected by X-MEN syndrome.

Results: The index patient is a 12-year-old male born from non-consanguineous Italian parents. Since early in childhood, he presented recurrent respiratory tract infections requiring multiple antibiotic treatments. Immunological work-up showed reduced IgG and IgA serum levels with normal IgM. Targeted NGS analysis performed with a panel of IEI genes revealed a novel hemizygous variant in the MAGT1 gene (NM_032121:c.627+2T>C). RT-PCR analysis showed skipping of exon 4, demonstrating a causal effect of the variant. Peripheral lymphocyte evaluation showed increased total B cells with a reduction of the switched memory, IgM memory and terminal differentiated subsets, as well as modestly expanded double negative T cells, in line with previously published data. Lymphocyte proliferation tests upon stimulation with aCD3, aCD3+IL-2 and PHA were normal. EBV serostatus revealed a previous infection and EBV-viral load was undetectable; cervical and abdominal ultrasound excluded lymphoproliferative diseases. Our patient did not present any autoimmune manifestation, in contrast with previously reported patients.

Conclusions: we report on the first Italian patient affected by X-MEN syndrome due to a novel pathogenic MAGT1 mutation.

Disclosure: No.

Keywords: MAGT1, X-MEN, EBV, LYMPHOPROLIFERATION, Inborn errors of immunity

PD246

CONTIGUOUS XP11.4 DELETIONS IN PATIENTS WITH ORNITHINE TRANSCARBAMYLASE DEFICIENCY AND CHRONIC GRANULOMATOUS DISEASE: CLINICAL AND MOLECULAR CHARACTERISTICS of TWO CASES

POSTER DISPLAY 06: GENETICS IN IEI

Nel Dabrowska Leonik[1], Dominika Gladysz[1], Dariusz Rokicki[2], Agata Pleskaczynska[3], Karolina Tomaszewska-Szuszkiewicz[4], Joanna Teisseyre[5], Marlena Mlynek[6], Malgorzata Pac[1]
[1]Children's Memorial Health Institute, Department of Immunology, Warsaw, Poland, [2]Children's Memorial Health Institute, Department of Pediatrics, Nutrition And Metabolic Diseases, Warsaw, Poland, [3]Children's Memorial Health Institute, Neonatology And Neonatal Intensive Care Unit,, Warsaw, Poland, [4]Children's Memorial Health Institute, Oncology Department, Warsaw, Poland, [5]Children's Memorial Health Institute, Department of Pediatric Surgery And Organ Transplantation, Warsaw, Poland, [6]Children's Memorial Health Institute, Department of Medical Genetics, Warsaw, Poland

Background and Aims: We aim to present diagnostic and therapeutic dilemma in two patients with ornithine transcarbamylase deficiency (OTCD) and chronic granulomatous disease (CGD) resulting from contiguous gene deletions on X chromosome.

Methods: Analysis of patient's clinical data, neutrophil oxidative burst test and array comparative genomic hybridization (aCGH).

Results: Patient 1, with family history of older brother death, was treated for hyperammonemia with hemodialysis, diet and pharmacology. During first 2 months he presented lymphadenitis and skin abscess. Neutrophil oxidative burst test showed no activated neutrophils. aCGH analysis revealed 7,47 Mb deletion at Xp21.1-p11.4 encompassing OTC, CYBB, DMD, TMEM47, MAGEB16, PRRG1, XK, DYNLT3, SRPX, RPGR, TSPAN7, MID1P1 genes. Due to neurological complications, the patient was disqualified from further treatment: liver transplantation (LTx) and hematopoietic stem cell transplantation (HSCT), died at the age of 12 weeks. In Patient 2 OTCD was diagnosed after birth due to positive family history. At the age of 7 months he underwent a liver transplant from his mother, complicated by post-transplant lymphoproliferative disorder (12 m.o.). Three months later he presented pneumonia and focal lesions in the lungs and spleen. aCGH analysis showed 838,1 kb deletion at Xp11.4 spanning OTC, CYBB and DYNLT3, SRPX, RPGR, TSPAN7 genes. At the age of 2,5 years in transplanted liver four abscesses were found.

Conclusions: The genetic analysis in OTCD individuals needs detailed evaluation including large deletion investigation. In a patient with OTCD and CGD after maternal LTx: haploidentical HSCT from CGD carrier, matched unrelated donor HSCT or gene therapy may be considered.

Disclosure: No.

Keywords: Ornithine transcarbamylase deficiency, Xp11.4 deletions, Hematopoietic stem cell transplantation, Chronic Granulomatous Disease

PD247

THE IMPORTANCE of GENETIC ANALYSES IN THE DIAGNOSIS of INBORN ERRORS of IMMUNITY (IEI)

POSTER DISPLAY 06: GENETICS IN IEI

Dogan Kaymaz[1], Sule Haskologlu[1], Dilara Besli Celik[1], Sevgi Kostel Bal[1,2], Candan Islamoglu[1], Avniye Baskin[1], Nazli Deveci Demirbas[1], Sevgi Keleş[3], Talal A. Chatila[3], Helen Su[4], Michael Lenardo[4], Ayşenur Öztürk[5], Lale Tufan[6], Baran Erman[7], Kaan Boztug[2], Gülay Ceylaner[8], Serdar Ceylaner[8], Figen Dogu[1], Aydan Ikinciogullari[1]
[1]Ankara University School of Medicine, Department of Pediatrics, Division of Immunology And Allergy, Ankara, Turkey, [2]Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, Department of Genetics, vienna, Austria, [3]Harvard Medical School, Division of Immunology, Department of Pediatrics, Boston, United States of America, [4]Intramural Research Program, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Laboratory of Clinical Immunology And Microbiology,, Bethesda, United States of America, [5]Ankara University School of Medicine, Department of Pediatrics, Division of Genetic Diseases, Ankara, Turkey, [6]Ankara University School of Medicine, Department of Forensic Medicine Forensic Genetics Laboratory, Ankara, Turkey, [7]Hacettepe University, Can Sucak Research Laboratory For Translational Immunology, Center For Genomics And Rare Diseases, Ankara, Turkey, [8]Intergen Genetics and Rare Diseases Diagnosis Research & Application Center, Department of Genetics, ANKARA, Turkey

Background and Aims: Inborn Errors of Immunity (IEI) are inherited diseases characterized by highly different clinical, immunological, and genetic features. The variety of IEI necessitates genetic testing for accurate diagnosis and treatment planning. We aimed to evaluate the genotypic characteristics in a cohort of IEI patients who were diagnosed and treated in our center.

Methods: The data obtained by the hospital / department files of 1407 patients who were diagnosed and followed up between January 2010 to January 2020 evaluated retrospectively. Chromosomal Microarray Analysis (CMA), Targeted Gene Panels (TGP), and Whole Exome Sequencing (WES) were the main methods performed in the study.

Results: The disease-causing genetic defect was identified in 325 (77.9%) of the 417 patients who underwent genetic analyses. The success of diagnosis was prominent and found as 88.5% (116/131) in combined immuno deficiencies (CID), 94.7% (89/94) in CID with syndromic features, 72% (41/57) in phagocytic defects. The meanage at genetic diagnosis was 6.2 years, with a 2.8 years gap between clinical and genetic diagnosis. TGP and WES were the most common methods performed in 66.8% (101/151) and 68.4% (76/111) among all patients respectively.

Conclusions: Clinical and immunological evaluation continue in guiding the precise genotypic characterization of patients with IEI. In order to provide quick and exact diagnosis, genetic analysess hould be performed as early as possible and in close collaboration between geneticists and the clinical team responsible from each individual patient.

Disclosure: No.

Keyword: Inborn Errors of Immunity, genetic analysis, exact diagnosis

PD248

A NOVEL HOMOZYGOUS STOP MUTATION IN IL23R CAUSES MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE

POSTER DISPLAY 06: GENETICS IN IEI

Frederik Staels[1,2], Flaminia Lorenzetti[2], Kerstin De Keukeleere[2], Mathijs Willemsen[2], Margaux Gerbaux[2], Julika Neumann[2], Thomas Tousseyn[3], Emanuela Pasciuto[2], Paul De Munter[4], Xavier Bossuyt[5], Rik Gijsbers[6], Adrian Liston[7], Stephanie Humblet-Baron[2], Rik Schrijvers[1]
[1]KU Leuven, Allergy And Clinical Immunology Research Group, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [2]KU Leuven, Laboratory For Adaptive Immunology, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [3]UZ Leuven, Pathology, Leuven, Belgium, [4]UZ Leuven, Internal Medicine, Leuven, Belgium, [5]KU Leuven, Clinical And Diagnostic Immunology, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [6]KULeuven, Molecular Virology And Gene Therapy, Leuven, Belgium, [7]Babraham Research Campus, Immunology Programme, Babraham Institute, Cambridge, United Kingdom

Background and Aims: Mendelian susceptibility to mycobacterial disease (MSMD) is caused by inborn errors of IFN-γ immunity. The most frequent genetic defects are found in IL12 or a subunit of its receptor. IL23R deficiency in MSMD has only been reported once, in two pediatric patients from the same kindred with isolated disseminated Bacille Calmette-Guérin disease. We evaluated the impact of a homozygous stop mutation in IL23R (R381X), identified by whole exome sequencing, in an adult patient with disseminated non-tuberculous mycobacterial disease.

Methods: We performed functional validation of the R381X mutation by evaluating IL23R expression and IL-23 signaling (STAT3 phosphorylation, IFN-γ production) in primary cells (PBMCs, EBV-B cells) and cell lines (HeLa) with or without back-complementation of wild type IL23R.

Results: We report on a 48-year old male with disseminated non-tuberculous mycobacterial disease. We identified and characterized a homozygous loss-of-function stop mutation underlying IL23R deficiency, resulting in near absent expression of membrane bound IL23R. IL23R deficiency was characterized by impaired IL-23-mediated IFN-γ secretion in $CD4^+$, $CD8^+$ T and mucosal-associated invariant T (MAIT) cells and low frequencies of circulating Th17 ($CD3^+CD45RA^-CCR4^+CXCR3^-RORγT^+$), Th1* ($CD45RA^-CCR4^-CXCR3^+RORγT^+$), and MAIT ($CD3^+CD8^+Vα7.2^+CD161^+$) cells. Although the patient did not have a history of recurrent fungal infections, impaired Th17 differentiation and blunted IL-23-mediated IL-17 secretion in PBMCs was observed.

Conclusions: We demonstrate that impaired IL-23 immunity caused by a homozygous R381X mutation in IL23R underlies MSMD, corroborating earlier findings with a homozygous p.C115Y IL23R mutation. Our report further supports a model of redundant contribution of IL-23 to IL-17-mediated anti-fungal immunity.

Disclosure: FS (11B5520N) and JN (11C3521N) are fellows of the Fonds Wetenschappelijk Onderzoek - Vlaanderen National Fund for Scientific Research (FWO). RS is FWO senior clinical investigator fellows (1805518N, respectively) and received funding from KU Leuven C1 (C

Keywords: MAIT cells, MSMD, IL23 receptor, Th17, Interferon gamma, STAT3

PD249

A NOVEL FRAMESHIFT CXCR4 MUTATION CAUSES A MILDER FORM of WHIM SYNDROME

POSTER DISPLAY 06: GENETICS IN IEI

Laura Dotta[1], Rajesh Kumar[2], Samantha Milanesi[3], Martyna Szpakowska[4], Di Silvestre Dario[4], Mauro Giacomelli[2], Manuela Benedito[5], Joana Azevedo[5], Emilia Cortesao[5], Alessandro Vacchini[6], Alessandra Castagna[6], Marinella Pinelli[2], Daniele Moratto[2], Massimo Locati[3], Andy Chevigné[4], Elena Borroni[3], Raffaele Badolato[1]
[1]ASST Spedali Civili di Brescia, Department of Pediatrics, Brescia, Italy, [2]ASST Spedali Civili of Brescia, Institute For Molecular Medicine Angelo Nocivelli, Brescia, Italy, [3]University of Milan, Department of Medical Biotechnologies And Translational Medicine, Milan, Italy, [4]Department of Infection and Immunity, Immuno-Pharmacology and Interactomics, Institute of Health (lih), Esch-sur-Alzette, Luxembourg, [5]CHUC, S.hematologia, Coimbra, Portugal, [6]IRCCS, Humanitas Clinical And Research Center, Rozzano, Italy

Background and Aims: WHIM syndrome is characterized by phenotypic variability, particularly in the frequency of infections, the development of Human Papilloma Virus-related malignancies, and the occurrence of neurological or autoimmune manifestations. Description of novel cases may contribute to define a genotype-phenotype correlation.

Methods: We characterized a novel CXCR4 frameshift mutation.

Results: We identified the Leu317fsX3 mutation in the CXCR4 gene by Sanger sequencing in a Portuguese pedigree. The 22-year-old man onset at 2 years of age with neutropenia but remained free of major infection except a cellulitis of his hallux at the age of 11 years, while his 15-year-old brother was found to be neutropenic when he experienced a pneumonia at the age of 1 year. Their mother presented neutropenia, had periodontal disease and sinusitis in her adolescence. They all had a single wart that resolved without recurrence. All the three patients maintained a normal total lymphocyte count and normal serum immunoglobulins. The novel variant truncates most of the intracellular portion of the protein. We observed that the L317fsX3 mutation impairs the ligand-induced CXCR4 internalization and the β-arrestin recruitment, while, in contrast with the most common R334X mutation, does not affect calcium flux, chemotaxis in response to CXCL12, and ERK1/2 phosphorylation.

Conclusions: The novel CXCR4 Leu317fsX3 mutation may associate to a milder phenotype characterized by neutropenia that normalizes during acute infection, but normal total lymphocyte count and immunoglobulin levels, and minor infections. Different signaling properties may lead to a further genotype-phenotype correlation and may influence prognosis.

Disclosure: No.

Keywords: neutropenia, warts, lymphopenia, CXCR4, WHIM

PD250

NEW HYPOMORPHIC CYBB VARIANT IN A 12 YEARS OLD BOY WITH IBD: FUNCTIONAL ANALYSIS, SEGREGATION STUDY AND CLINICAL INTERPRETATION

POSTER DISPLAY 06: GENETICS IN IEI

Ricardo Cuesta Martín De La Cámara[1], Elisabet Matas Pérez[1], Jesús Sarriá[2], Teresa Del Rosal Rabes[3], María Bravo García-Morato[1,4], Rebeca Rodríguez Pena[1,4]
[1]University Hospital La Paz, Department of Immunology, Madrid, Spain, [2]University Hospital La Paz, Department of Gastroenterology, Madrid, Spain, [3]University Hospital La Paz, Department of Pediatrics, Madrid, Spain, [4]Health Institute Carlos III, Ciberer U767, Madrid, Spain

Background and Aims: Chronic granulomatous disease (CGD) is an inborn error of immunity caused by defects in the NADPH oxidase, characterized by increased susceptibility to infections and inflammatory manifestations, including inflammatory bowel-like disease (IBD). We report a 12 years old boy with severe IBD without infection susceptibility, in which we have detected a novel CYBB variant. The aim of the study is to characterize this new variant to better explain its potential association with the patient's pathology.

Methods: Genetic analysis was performed by targeted next-generation sequencing (NGS) and variant confirmation was accomplished by Sanger sequencing. $O2^{\cdot-}$ production was quantified by the Ferricytochrome c reduction assay. H_2O_2 production was assessed using the flow cytometry DHR assay. Quantification of $gp91^{phox}$ expression was made by flow cytometry.

Results: NGS identified the missense variant in CYBB c.1537C>T(p.Arg513Trp). Reduced $O_2^{\cdot-}$ and H_2O_2 production with normal gp91phox protein expression was found. The family segregation study confirmed the presence of the variant in several members of the maternal family including his healthy 45 years old uncle, with quite similar enzymatic results, and his mother, who had double peak DHR assay consistent with her carrier status.

Conclusions: Sometimes it is not so simple to stablish the causality relationship between a genetic variant and clinical manifestations. This case proves the importance of trying to correlate functional assays and segregation studies. Residual enzymatic activity suggested an hypomorphic CYBB variant, but the absolute absence of clinical manifestation in his uncle doesn't allow us to clearly attribute the IBD to the CYBB variant found.

Disclosure: No.

Keywords: CYBB, Chronic Granulomatous Disease, Inflammatory bowel disease, NADPH OXİDASE

PD251

CLUSTERING of CASES of HEREDITARY ANGIOEDEMA IN A DISTRICT IN INDIA: A UNIQUE EXPERIENCE WITH A FOUNDER MUTATION

POSTER DISPLAY 06: GENETICS IN IEI

Prabal Barman, Ankur Jindal, Archan Sil, . Sanchi, Rahul Tyagi, Amit Rawat, Ridhima Aggarwal, Suprit Basu, Reva Tyagi, Thangaraj Abarna, Sanjib Mondal, Sathish Loganathan, Deepti Suri, Pandiarajan Vignesh, Surjit Singh
Post Graduate Institute of Medical Education and Research, Chandigarh, Allergy-immunology Unit, Dept of Paediatrics, Chandigarh, India

Background and Aims: Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by non-pruritic episodic swellings. The genetic profile of HAE varies across ethnicities. However, a founder mutation has not been previously reported. We, herein, report the clinical and genetic profile of one such cluster of HAE patients from a district in India.

Methods: A field survey was conducted on March 13, 2022 in Reasi district of Jammu and Kashmir. Cases were traced from 4 families with clinical suspicion of HAE. Detailed clinical profile of each patient was noted and samples were collected for analysis.

Results: In 18/24 patients of HAE (4 families), clinical data and laboratory investigations were carried out. Median age at onset of symptoms and diagnosis were 15.5 (range: 5-25) and 33.5 years (range: 6-70) respectively. Median delay in diagnosis was 20.5 years (range: 3-50) (male:female=2:7). While history suggestive of laryngeal edema was elicited from 15/18 (83.3%) patients, abdominal symptoms were present in 14/18 (77.8%) patients. Swelling episodes were characterized by average frequency and duration of 2 episodes/ month and 3 days respectively. C4 level was reduced in all patients (Mean:0.058 g/L). C1-esterase-inhibitor level was normal in 7/18 (38.8%) patients indicative of type-II HAE. A pathogenic variant in exon 8 of SERPING1 gene (c.1396 C>T, p.Arg466Cys) was identified in 3 families while no variant was found in 4th family. No link could be established between these 4 families.

Conclusions: We report a founder mutation in SERPING1 gene from a small district in India leading to clustering of several cases in a small geographical area. The epidemiological link remains unclear.

Disclosure: No.

Keywords: District, India, Hereditary Angioedema, Cluster, Genetics, SERPING1

PD252

PHENOTYPE-GENOTYPE CORRELATION of TWO CHILDREN WITH FOXN1 DEFICIENT SEVERE COMBINED IMMUNODEFICIENCY: A CASE SERIES FROM NORTH INDIA

POSTER DISPLAY 06: GENETICS IN IEI

Prabal Barman, Sanjib Mondal, . Sanchi, Ankur Jindal, Pandiarajan Vignesh, Amit Rawat, Surjit Singh
Post Graduate Institute of Medical Education and Research, Chandigarh, Allergy-immunology Unit, Dept of Paediatrics, Chandigarh, India

Background and Aims: FOXN1 deficient severe combined immunodeficiency (SCID) [Nude SCID] is characterised by athymia and resultant immunodeficiency, alopecia universalis and nail dystrophy. A spectrum of clinical manifestations may be associated with different mutations and zygosity. Herein, we report 2 nude SCID children: one of whom (compound heterozygous) had a rapidly-progressing fatal pneumonia whilst the other (heterozygous) had a stable course with prophylactic antimicrobials and replacement intravenous immunoglobulin (IVIg).

Methods: Data of 2 patients with FOXN1 defect from Primary Immunodeficiency clinic (PGIMER, Chandigarh), were retrieved and analysed.

Results: Case 1: A 13-month-old girl presented with recurrent sinopulmonary infections since early infancy. At presentation, she had severe pneumonia and Bacillus Calmette-Guerin vaccine (BCG) adenitis. She also had an ulcerated BCG vaccination site, alopecia universalis, with dystrophic nails (koilonychia and canaliform dystrophy) of hands and feet. Genetic analysis revealed pathogenic compound heterozygous variants in FOXN1 gene in exon 6[c.1026del] and exon 5[c.880G>A]. Inspite of broad spectrum anti-microbials and supportive measures, she succumbed to respiratory failure and sepsis. Case 2: A 22-month-old-girl presented with persistent pneumonia and features of alopecia universalis and dystrophic nails (koilonychia) of feet. Genetic analysis revealed a heterozygous variant in FOXN1 gene in exon 4[c.689C>G]. She responded to a short-course of antimicrobials, and is currently doing well.

Conclusions: This case series highlights that phenotypic-genotypic correlation may be seen in children with nude SCID. Homozygous or compound heterozygous mutations usually have a fulminant course without thymic transplantation whilst heterozygous variants may have a relatively benign course, and may respond to prophylactic antimicrobials and replacement IVIg.

Disclosure: No.

Keywords: compound heterozygous, heterozygous, FOXN1, Severe combined immunodeficiency, phenotype-genotype

PD253

SEVERE COMBINED IMMUNODEFICIENCIES: EXPANDING THE MUTATION SPECTRUM IN TURKEY AND IDENTIFICATION of 4 NOVEL VARIANTS

POSTER DISPLAY 06: GENETICS IN IEI

Neslihan Karaca[1], Ayça Aykut[2], Asude Durmaz[2], Guzide Aksu[1], Necil Kutukculer[1]
[1]Ege University, Faculty of Medicine, Department of Pediatrics, Izmir, Turkey, [2]Ege University Medical Faculty, Department of Genetics, Izmir, Turkey

Background and Aims: Human Inborn Errors of Immunity (IEIs) are clinically and genetically heterogeneous groups of diseases, with relatively mild clinical course or severe types that can be life-threatening. Severe combined immunodeficiency (SCID) is the most severe form of IEIs, which is caused by monogenic defects that impair the proliferation and function of T, B, and NK cells. According to the most recent report by the International Union of Immunological Societies (IUIS), mutations in IL2RG, JAK3, FOXN1, CORO1A, PTPRC, CD3D, CD3E, CD247, ADA, AK2, NHEJ1, LIG4, PRKDC, DCLRE1C, RAG1, and RAG2 genes may cause SCID.

Methods: The targeted next-generation sequencing (TNGS) workflow based on Ion AmpliSeq™ Primary Immune Deficiency Research Panel was designed for sequencing 264 IEI-related genes on Ion S5™ Sequencer.

Results: Eight disease-causing variants (4 novel) were identified in 9 patients in 4 different SCID genes, namely IL2RG (n=4), RAG2 (n=3), NHEJ1 (n=1), and DCLRE1C (n=1) genes between 2019-2021.

Conclusions: Next generation sequencing allowed a rapid and accurate diagnosis in SCID patients.

Disclosure: No.

Keyword: scid, IL2RG, RAG2, NHEJ1, DCLRE1C

PD254

CHRONIC GRANULOMATOUS-LIKE PRESENTATION of A PATIENT WITH AUTOSOMAL RECESSIVE PKCΔ DEFICIENCY

POSTER DISPLAY 06: GENETICS IN IEI

Anna-Lena Neehus[1,2], Karen Tuano[3], Tom Le Voyer[1,2], Sarada Nandiwada[3], Kruthi Murthy[3], Anne Puel[1,2,4,5], Jean-Laurent Casanova[1,2,4,5,6], Javier Chinen[3], Jacinta Bustamante[1,2,5,7]
[1]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1163, Paris, France, [2]Imagine Institute, Paris Cité University, Paris, France, [3]Baylor College of Medicine and Texas Children's Hospital, The David Clinic, Allergy And Immunology Division, Department of Pediatrics, The Woodlands, United States of America, [4]Howard Hughes Medical Institute, -, New York, United States of America, [5]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, New York, United States of America, [6]Necker Hospital, Pediatric Hematology-immunology And Rheumatology Unit, Paris, France, [7]Paris Hospital, Study Center For Primary Immunodeficiencies, Paris, France

Background and Aims: Chronic granulomatous disease (CGD) is an inborn error of immunity caused by deficiencies in any of the six NADPH oxidase subunits (CYBA, CYBB, CYBC1, NCF1, NCF2, NCF4). It is characterized by increased susceptibility to infectious diseases caused by an abnormal phagocytic oxidative burst. PKCδ has been shown to be important for the activation of the NADPH oxidase complex and thus the host defense against pathogens. However, patients with autosomal recessive PKCδ deficiency have mostly been recognized for their autoimmune phenotype, often presenting with child-hood onset autoimmunity.

Methods: We studied a five-year-old girl who presented clinical infectious manifestations resembling those observed in CGD. She had no history of autoimmunity, including no detectable auto-antibodies, and a normal B cell phenotyping. We performed targeted genetic panel sequencing and studied her underlying genetic defect in vitro.

Results: Targeted panel analysis revealed no potentially pathogenic variants in known CGD-causing genes, but two heterozygous candidate variants in PRKCD, encoding for PKCδ. Both variants were shown to result in non-sense mediated mRNA decay and abolish protein expression in the patient's phagocytes. Consistent with an initial suspected diagnosis of CGD, the patient presented with an impaired oxidative burst in her neutrophils and monocytes. The patient's monocyte-derived macrophages displayed and impaired oxidative burst and a reduced phosphorylation of the cytosolic NADPH oxidase subunit $p40^{phox}$.

Conclusions: PKCδ deficiency should be considered in the differential diagnosis of young patients that present with an impaired oxidative burst and CGD-like clinical manifestations, even in the absence of clinical manifestations of autoimmunity.

Disclosure: No.

Keywords: PKCδ deficiency, NADPH OXİDASE, Chronic Granulomatous Disease, inborn error of immunity

PD255

SHWACHMAN–DIAMOND-LIKE SYNDROME: DIAGNOSTIC CHALLENGE

POSTER DISPLAY 06: GENETICS IN IEI

Raquel Muñoz García[1], Carmen Morales Garcia[1], Begoña Carazo Gallego[2], Laura Martín Pedraz[3], Jose Manuel Lucena Soto[1]
[1]Hospital Universitario Virgen del Rocio, Inmunología, Sevilla, Spain, [2]Hospital Universitario Regional de Málaga, Infecciosos Pediátricos, Málaga, Spain, [3]Hospital Universitario Regional de Málaga, Inmunodeficiencias, Málaga, Spain

Background and Aims: An 8-year-old patient without family consanguinity, with recurrent infections (cellulitis, skin abscesses, pneumonia and otitis media) and severe intermittent neutropenia since the age of 3 months, with counts below 500 neutrophils/µL in different blood tests. Antibodies against neutrophil-specific antigens were not found. Bone marrow smear showed myeloid maturation arrest. Molecular analysis by next generation sequencing (NGS) for 17 genes related to congenital neutropenia was negative, including ELANE, GFI1, HAX1, G6PC3, VPS45, G6PT1 (SLC37A4), TAZ, C16ORF57 (USB1), WAS, JAGN1, ROBLD3 (LAMTOR2), GATA2 and CSF3R. At 8 years of age, when clinical suspicion persisted, a whole-exome sequencing (WES) was performed, finding the c.337G>C (p.G113R) variant, de novo, in heterozygosis of the SRP54 gene, already described as pathogenic and associated with Shwachman–Diamond-like phenotype with autosomal dominant inheritance[1]. Given the persistent clinical manifestations and the genetic confirmation of the disease, the patient has been proposed as a candidate for hematopoietic stem cell transplantation.

Methods: NGS was performed using AmpliSeq strategy (Ion Torrent PGM platform). WES was performed from genomic DNA extracted from peripheral blood sample, using NexSeq 500 sequencing system platform (Illumina) and raw data were analyzed by SOPHiA DDM Platform.

Results: Diagnosis of SRP54 deficiency due to the presence of the pathogenic genetic c.337G>C (p.G113R) variant in heterozygosis.

Conclusions: Description of pathogenic variants of new genes associated with Inborn errors of immunity (IEI), as well as the review of cases with suggestive clinical features, may be crucial for their definitive diagnosis and therapeutic decisions. 1. Carapito et al, J Clin Invest. 2017;127(11):4090–4103.

Disclosure: No.

Keywords: SHWACHMAN–DIAMOND-LIKE, SRP54, whole-exome sequencing (WES), neutropenia

PD256

VARIANTS IN TNFSF13B ARE ASSOCIATED WITH COMMON VARIABLE IMMUNODEFICIENCY IN A WESTERN MEXICAN POPULATION.

POSTER DISPLAY 06: GENETICS IN IEI

Denisse Becerra Loaiza[1,2], Bricia Gutiérrez-Zepeda[1], Miguel Chávez-Meléndez[3], Margarita Ortega Cisneros[3], Maria Enriqueta Nuñez Nuñez[4], Carlos Torres-Lozano[3], Adrián Daneri-Navarro[2], Alicia Del Toro-Arreola[2], Antonio Topete[2], Yeminia Valle-Delgadillo[1], Antonio Quintero Ramos[1,2]
[1]Universidad de Guadalajara, Departamento De Biología Molecular Y Genómica, Guadalajara, Mexico, [2]Universidad de Guadalajara, Fisiología, Guadalajara, Jalisco, Mexico, [3]Hospital de Especialidades, Instituto Mexicano del Seguro Social, Departamento De Inmunología Clínica Y Alergia, Guadalajara, Jalisco, Mexico, [4]Hospital Civil de Guadalajara "Dr. Juan I. Menchaca", Jalisco, México., Servicio De Inmunología Clínica Y Alergias, Guadalajara, Mexico

Background and Aims: Common Variable Immunodeficiency (CVID) is characterized by being heterogeneously clinic, immunologic and genetic, however, B cells are distinctive in the disease. The 90% of the cases are sporadic, SNVs in TNF superfamily highlights, TNFSF13B encodes BAFF, a cytokine with functions in survival and ontogeny of B cells. For that, we aimed to associate the variants rs9514828(C/T), rs201543678(G/A), rs1224141(T/G) and rs10508198(G/C) of TNFSF13B with CVID in a Western Mexican population.

Methods: We genotyped by allelic discrimination (TaqMan) four SNVs in TNFSF13B gene in 25 CVID patients and 99 individuals as a reference group (RG) from Western Mexico. The Hardy-Weinberg Equilibrium (HWE), genetic association, linkage disequilibrium and haplotypes were determined in SNPstats. P-values <0.05(CI95%) were statistically significant.

Results: All variants were in according to HWE. The TG (OR=0.18, CI95%=0.06-0.56, p=0.003) and TG+GG (OR=0.16, CI95%=0.05-0.48, p=0.001) genotypes (rs1224141) suggests being a protector factor. On the other hand, the variants rs201543678-rs10508198 are in strong LD (D'=0.99, p=0.005) while contrary to expectation rs9514828-rs1224141 (D'=0.40, p=0.000) and rs9514828-rs10508198 (D'=0.17, p=0.011) are in weak LD; CGTG was the most frequent haplotype (51 %=CVID and 69%=RG), moreover, CGGG haplotype could be a protector factor for CVID (OR=0.07, CI95%=0.01-0.80, p=0.03).

Conclusions: Variants and haplotypes in TNFSF13B gene are associated to CVID in a Western Mexican population. This is the first report about genetic susceptibility in sporadic CVID in Mexico.

Disclosure: No.

Keywords: CVID, Western Mexico, TNFSF13B, SNVs, Haplotypes

PD257

WHOLE EXOME SEQUENCING (WES) IN REFRACTORY CYTOPENIA of CHILDHOOD (RCC) UNVEILS INBORN ERRORS of IMMUNITY: A LESSON FROM TWO CASES of ERCC6L2 AND RTEL1 DEFICIENCY

POSTER DISPLAY 06: GENETICS IN IEI

Filippo Consonni[1], Francesco Pegoraro[1], Beatrice Martini[2], Ebe Schiavo[2], Maria Luisa Coniglio[3], Giorgio Costagliola[4], Claudio Favre[3], Marinella Veltroni[3], Eleonora Gambineri[2]
[1]University of Florence, Department of Health Sciences, Firenze, Italy, [2]University of Florence, Department of Neurosciences, Psychology, Drug Research And Child Health (neurofarba), Florence, Italy, [3]Meyer Children's Hospital, Centre of Excellence, Division of Pediatric Oncology/hematology, Florence, Italy, [4]University hospital of Pisa, Division of Pediatric Oncology/hematology, Pisa, Italy

Background and Aims: RCC is the most common myelodysplastic syndrome in pediatric age, though its genetic background is still largely unknown. We report two cases of RCC eventually diagnosed with an inborn error of immunity (IEI) with bone marrow failure.

Methods: Patient A (PtA) is a 12 years-old female displaying persistent moderate thrombocytopenia, noticed after an episode of severe epistaxis. She had unremarkable past clinical and family history, normal infectious and immunological workups and regular platelet function and coagulation assays. Patient B (PtB) came to our attention at 18 years-old for a progressively worsening pancytopenia associated with dysphagia due to an upper esophageal stricture. Immunological workup showed low B and NK cells and high titer (1:640) anti-nuclear antibodies. Both patients underwent bone marrow aspiration and biopsies, which were consistent with RCC due to marrow hypocellularity and dysmyelopoiesis. No cytogenetic abnormalities were detected.

Results: WES was performed in order to exclude inherited bone marrow failure syndromes and revealed compound heterozygous mutations in ERCC6L2 (PtA: p.I486fs; p.T922fs) and RTEL1 (PtB: p.P671L; p.V222G), that defined Hebo deficiency (PtA) and Dyskeratosis Congenita (PtB). PtA is regularly followed-up at our clinic and in good clinical conditions, while PtB underwent hematopoietic stem cell transplantation (HSCT) but eventually deceased due to a severe transplant-associated thrombotic microangiopathy.

Conclusions: These cases demonstrate that IEI may hide behind unusual clinical presentations such as RCC. Symmetrically, RCC should be regularly investigated with WES at disease onset: an early genetic diagnosis may help defining the best HSCT strategy and potentially unveil other cases in the same family.

Disclosure: No.

Keywords: Refractory Cytopenia of Childhood, Whole Exome Sequencing, rtel1 deficiency, ercc6l2 deficiency, Dyskeratosis congenita, Hebo deficiency

PD258

WHOLE-GENOME SEQUENCING REVEALED A NOVEL BTK VARIANT IN PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA

POSTER DISPLAY 06: GENETICS IN IEI

Doo Ri Kim[1], In Hwa Jeong[2], Kyung-Ran Kim[3], Hwanhee Park[4], Sohee Son[1], Areum Shin[1], Jong-Won Kim[2], Kay Tanita[5], Hirokazu Kanegane[6], Ja-Hyun Jang[2], Eun Suk Kang[2], Yae-Jean Kim[1]
[1]Samsung Medical Center, Pediatrics, Seoul, Korea, Republic of, [2]Samsung Medical Center, Laboratory Medicine And Genetics, Seoul, Korea, Republic of, [3]Gyeongsang National University Changwon hospital, Pediatrics, Changwon, Korea, Republic of, [4]Soonchunhyang University Bucheon Hospital, Pediatrics, Bucheon, Korea, Republic of, [5]Tokyo Medical and Dental University, Developmental Biology, Tokyo, Japan, [6]Tokyo Medical and Dental University, Child Health And Development, Tokyo, Japan

Background and Aims: X-linked agammaglobulinemia (XLA) is caused by Bruton Tyrosine kinase (BTK) gene mutation. We report a novel pathogenic variant of BTK gene in two male maternal cousins.

Methods: Intracellular flow cytometry for BTK protein was performed using three different antibodies. Diagnostic exome sequencing (DES), whole-genome sequencing (WGS), and RNA sequencing were performed.

Results: The proband is a 12-year-old boy, who presented with hypogammaglobulinemia and low B cell count (32-71 cells/microliter, 1-2% of total lymphocyte (TLC)), and started regular intravenous immunoglobulin (IVIG) therapy at the age of 2. There was no family history of immunodeficiency at that time. Five years later, the second patient, a maternal cousin of the proband was referred to our hospital at the age of 5. He had a history of recurrent pneumonia and was also diagnosed with hypogammaglobulinemia and low B cell count (6 cells/mL, 0.2% of TLC) at the age of 4 and started monthly IVIG therapy at outside hospital. BTK flow cytometry using three different antibodies showed results with discrepancies (normal BTK expression and deficient BTK expression). DES was non-diagnostic. WGS and RNA sequencing were performed under strong suspicion for XLA. Finally, a novel structural variant resulting from inversion of two breakpoints in intron 14 of BTK and intergenic region between ARL13A and TRMT2B was found. The proband's mother harbored the same inversion variant, therefore confirming X-linked inheritance.

Conclusions: A novel mutation disrupting BTK gene was identified in two male Korean cousins. WGS and RNA sequencing are useful for detecting genomic large rearrangement.

Disclosure: Lee Kun-Hee Pediatric Cancer and Rare Disease Grant

Keywords: BTK, RNA sequencing, Agammaglobulinemia, XLA, Whole-genome sequencing

PD259

RS34557412 IN TNFRSF13B GENE AS A PROTECTOR FACTOR IN COMMON VARIABLE IMMUNODEFICIENCY IN A WESTERN MEXICAN POPULATION.

POSTER DISPLAY 06: GENETICS IN IEI

Antonio Quintero Ramos[1,2], Bricia Gutiérrez-Zepeda[2], Miguel Chávez-Meléndez[3], Margarita Ortega Cisneros[3], Maria Enriqueta Nuñez Nuñez[4], Carlos Torres-Lozano[3], Adrián Daneri-Navarro[1], Alicia Del Toro-Arreola[1], Antonio Topete[1], Yeminia Valle-Delgadillo[2], Denisse Becerra Loaiza[2]
[1]Universidad de Guadalajara, Fisiología, Guadalajara, Mexico, [2]Universidad de Guadalajara, Departamento De Biología Molecular Y Genómica, Guadalajara, Mexico, [3]Hospital de Especialidades, Instituto Mexicano del Seguro Social, Departamento De Inmunología Clínica Y Alergia, Guadalajara, Jalisco, Mexico, [4]Hospital Civil de Guadalajara "Dr. Juan I. Menchaca", Jalisco, México., Servicio De Inmunología Clínica Y Alergias, Guadalajara, Mexico

Background and Aims: B cells are the hallmark in Common Variable Immunodeficiency (CVID), TACI is a key receptor for B cell: activated, marginal zone, memory and plasmatic. The function of these depends on SNVs in its gene TNFRSF13B in 17p11.2, and recently had been related with CVID. For that, we aimed to associate the variants rs8079130(T/C), rs121908379(GG/CC), rs4792800(A/G) and rs34557412(A/G) of TNFRSF13B with CVID in a Western Mexican population.

Methods: We genotyped by allelic discrimination (TaqMan) four SNVs in TNFRSF13B gene in 25 patients with CVID and 99 individuals as a reference group (RG) from Western Mexico. The Hardy-Weinberg Equilibrium (HWE), genetic association, linkage disequilibrium were determined in SNPstats. P-values <0.05(CI95%) were statistically significant.

Results: All variants were in according to HWE, except for rs121908379 where only GGGG was identified. Global allelic and genotypic frequencies in every SNV were the following for: rs8079130 (C=89%, CC=78%, TC=21%, TT=1%) rs4792800 (A=89%, AA=77%, AG=22%, GG=1%) and rs34557412 (A=97%, AA=96%, AG=2%, GG=2%). In the dominant model AG+GG (OR=0.08, CI95%=0.01-0.83, p=0.02) (rs4792800) suggests being a protector factor for CVID. On the other hand, the study variants segregates independently (p>0.05).

Conclusions: Rs4792800 in TNFRSF13B gene is associated to CVID as protector factor in a Western Mexican population. This is the first report about genetic susceptibility in sporadic CVID in Mexico.

Disclosure: No.

Keywords: SNVs, Sporadic, CVID, TNFRSF13B, Western Mexico

PD260

HLA-G RS66554220 (14-BP INS/DEL) IS NOT ASSOCIATED WITH COMMON VARIABLE IMMUNODEFICIENCY IN A WESTERN MEXICAN POPULATION.

POSTER DISPLAY 06: GENETICS IN IEI

Adrian Villanueva Briseño[1], Denisse Becerra Loaiza[1,2], Bricia Gutiérrez-Zepeda[1,2], Miguel Chávez-Meléndez[3], Margarita Ortega Cisneros[3], Maria Enriqueta Nuñez Nuñez[4], Carlos Torres-Lozano[3], Adrián Daneri-Navarro[1], Alicia Del Toro-Arreola[1], Yeminia Valle-Delgadillo[2], Antonio Quintero Ramos[1,2]
[1]Universidad de Guadalajara, Fisiología, Guadalajara, Mexico, [2]Universidad de Guadalajara, Departamento De Biología Molecular Y Genómica, Guadalajara, Mexico, [3]Hospital de Especialidades, Instituto Mexicano del Seguro Social, Departamento De Inmunología Clínica Y Alergia, Guadalajara, Jalisco, Mexico, [4]Hospital Civil de Guadalajara "Dr. Juan I. Menchaca", Jalisco, México., Servicio De Inmunología Clínica Y Alergias, Guadalajara, Mexico

Background and Aims: Common variable immunodeficiency (CVID) is the most prevalent Inborn Error of Immunity, characterized by an inadequate response against pathogens resulting in recurrent infections, in this sense, the Human Leukocyte Antigen G (encoded by HLA-G gene and located at 6p21.3) which acts as an immunosuppressant for humoral and cellular response could lead to an immunodeficient state that predispose to infections and it's associated to poor prognosis. SNVs in their 3'UTR have been associated with susceptibility to infections. So far, we aimed to elucidate the association of HLA-G rs66554220 in this gene region with CVID.

Methods: 21 CVID patients and 196 individuals as reference group (RG) from Western Mexico were recruited. The rs66554220 variant was amplified by SSP-PCR and the fragments were visualized in PAGE. Hardy-Weinberg equilibrium and study association were performed in SNPstats and SPSS.

Results: Both study groups were in agreement with Hardy-Weinberg equilibrium. Allelic and genotypic frequencies are the following for CVID and RG, respectively, Del=50%, Ins=50%, Del/Del=19%, Del/Ins=62%, Ins/Ins=19% and Del=51%, Ins=49%, Del/Del=24%, Del/Ins=53% and Ins/Ins=23%.

Conclusions: This is an approach for the possible role of rs66554220 variant, which is not associated with CVID or any clinic features of it in our population. In Mexico, this is the first study of genetic association of CVID and HLA-G. We suggest functional studies to elucidate the role of HLA-G in CVID.

Disclosure: No.

Keywords: 14-bp Ins/Del, Western Mexico, immunosuppression, CVID, HLA-G

PD261

COMBINED IMMUNE-DEFICIENCY IN A YOUNG BOY WITH ADNP VARIANT: EXPANDING THE PHENOTIPIC SPECTRUM of HELSMOORTEL-VAN DER AA SYNDROME

POSTER DISPLAY 06: GENETICS IN IEI

Roberta Romano, Giuliana Giardino, Francesca Cillo, Elisabetta Toriello, Antonio De Rosa, Federico Habetswallner, Emma Coppola, Emilia Cirillo, Claudio Pignata
University of Naples Federico II, Translational Medical Sciences, Section of Pediatrics, Naples, Italy

Background and Aims: Helsmoortel-Van Der Aa Syndrome (HVDAS) is a rare neurodevelopmental disorder caused by heterozygous mutation of ADNP gene, characterized by dysmorphisms, intellectual disability, visual impairment, short stature, obesity among a handful of other features. We describe a patient with relevant immune system alterations in whom we identified a heterozygous variant in ADNP gene.

Methods: a 15-year-old male was assessed due to peculiar facial features including beak-shaped nose, hypotelorism, small, sunken and hypermetropic eyes, mild intellectual disability, obesity, recurrent respiratory tract infections and bilateral diffuse bronchiectasis on HRCT scan. An immunological and genetic work up was performed to rule out an inborn error of immunity with syndromic features.

Results: CD4+ naive cells and CD19+ lymphopenia was detected; mitogen proliferative response, TRECS, anti-pneumococcal response assays were decreased while total immunoglobulin levels were normal. The Array CGH resulted negative and Fragile-X and Cohen syndrome were excluded by Sanger sequencing. A preliminary diagnosis of combined immune deficiency (CID) was made and a whole exome sequencing was performed, resulting negative. Later in his follow-up, a genetic diagnosis was re-evaluated through a next generation sequencing analysis targeting 5200 mendelian diseases associated genes: a de novo heterozygous c.817C>T variant was eventually identified in ADNP gene causing HVDAS. Due to its mode of inheritance and overlapping clinical phenotype, a pathogenic role was deemed likely.

Conclusions: we described the first patient with CID associated with HVDAS, expanding the spectrum of this rare condition. Our experience also underpins the importance of the re-evaluation of undiagnosed yet highly suspicious cases with an updated genetic analysis.

Disclosure: No.

Keywords: Whole Exome Sequencing, combined immune deficiency, syndromic IEI, Helsmoortel-Van Der Aa Syndrome

PD262

NOVEL COMPOUND HETEROZYGOUS VARIANTS IN THE HELLS GENE CAUSE IMMUNODEFICIENCY–CENTROMERIC INSTABILITY–FACIAL ANOMALIES SYNDROME

POSTER DISPLAY 06: GENETICS IN IEI

Carmen Morales Garcia[1], Raquel Muñoz García[1], Begoña Carazo Gallego[2], Vanesa Rosa Camacho[3], Jose Manuel Lucena Soto[1]
[1]Hospital Universitario Virgen del Rocio, Inmunología, Sevilla, Spain, [2]Hospital Universitario Regional de Málaga, Infecciosos Pediátricos, Málaga, Spain, [3]Hospital Universitario Regional de Málaga, Unidad De Cuidado Crítico Pediátrico, Málaga, Spain

Background and Aims: 8-month-old female patient with a personal history of intrauterine growth restriction and hypoglycemia at birth. At approximately one month of age, she was admitted to the pediatric intensive care unit for a period of 6 months for respiratory symptoms due to initial infection by SARS-CoV-2 and later bacterial superinfection with poor evolution. The immunological study resulted in severe hypogammaglobulinemia and lymphopenia (mainly at the expense of B cells).

Methods: Exome sequencing with targeted analysis of 461 genes associated with Inborn Errors of the Immune System was performed using the Twist HCExome_v2 Kit with the NextSeq 500 sequencing system platform (Illumina). The SOPHiA DDM platform was used for bioinformatics analysis.

Results: In this study, two mutations in compound heterozygosis in the HELLS gene not previously described were identified: a deletion of 7 nucleotides (c.2089-5_2090del), and a nucleotide change (c.2185G>A). The first mutation is considered pathogenic as it results in a truncated, non-functional protein. The variant that results in an amino acid change, D729N, is also considered pathogenic according to bioinformatics algorithms.

Conclusions: Based on the clinical and immunological data, we reached the conclusion of a diagnosis of Immunodeficiency-Centromeric Instability-Facial Anomalies syndrome type 4 (ICF4)[1]. This is an autosomal recessive disorder that falls into the category of Combined Immunodeficiencies due to errors in DNA repair. 1. Thijssen, P., Ito, Y., Grillo, G. et al. Mutations in CDCA7 and HELLS cause immunodeficiency– centromeric instability–facial anomalies syndrome. Nat Commun 6, 7870 (2015).

Disclosure: No.

Keywords: Combined Immunodeficiencies, SARS-CoV-2, HELLS

PD263

T-CELL DEFICIENCY AND NOVEL RNU4ATAC VARIANT FOUND IN SISTERS WITH ROIFMAN SYNDROME

POSTER DISPLAY 06: GENETICS IN IEI

Julie Therese Skaugen[1], Kristian Assing[1], Klas Raaschou-Jensen[2], Olav Larsen[3], Christina Fagerberg[4]
[1]Odense University Hospital, Dept. of Clinical Immunlogy, Odense, Denmark, [2]Odense University Hospital, Dept. of Hematology, Odense, Denmark, [3]Odense University Hospital, Department of Infectious Diseases, Odense, Denmark, [4]Odense University Hospital, Department of Genetics, Odense C, Denmark

Background and Aims: Roifman syndrome (RS) is a rare autosomal recessive condition characterized by skeletal- and ophthalmological abnormalities, developmental delay, dysmorphic features and immunodeficiency. The immunodeficiency in these patients has been linked to hypogammaglobulinemia and low levels of circulating B-cells, rendering patients dependent on immunoglobulin substitution therapy. Despite several reports of skin conditions such as eczema and recurrent viral infections, suggesting compromised cellular immunity, normal levels of circulating T-cells have generally been reported. We present two sisters with B- and T-cell deficiency and genetically verified RS (one sister being diagnosed post mortem).

Methods: Comprehensive immunological screening was done in order to characterize the sisters` immunological phenotype. Medical history focusing on diseases of infectious, autoimmune, skeletal, and dermatological origin were retrieved from medical records. Whole Genome Sequencing (WGS) was used to genetically verify the diagnosis of RS.

Results: Both sisters presented with a history of infectious, autoimmune, skeletal, and dermatological symptoms congruent with the RS diagnosis. WGS found both sisters compound heterozygous for two variants, n.18G>A and n.46G>A, in RNU4ATAC. The variant n.18G>A has to our knowledge not previously been reported. Both sisters showed markedly decreased levels of circulating T-cells (both CD4+ and CD8+ subsets) measured by flow cytometry.

Conclusions: The n.18G>A novel variant has been found in two sisters with the RS phenotype. The low levels of circulating T-cell found in both sisters is expanding the immunological phenotype seen in patients with RS.

Disclosure: No.

Keywords: Roifman, RNU4ATAC, T-cell deficiency

PD264

NOVEL CD19 MUTATION CAUSES REMARKABLY LOW B CELL NUMBERS AND P-ANCA POSITIVE IMMUNE-COMPLEX GLOMERULONEPHRITIS

POSTER DISPLAY 06: GENETICS IN IEI

Meryem Demir[1], Gizem Korkut[2], Reyhan Gumusburun[3], Ceyda Tunakan Dalgiç[3], Ayça Aykut[4], Asude Durmaz[4], Omur Ardeniz[3]
[1]Ege University Medical Faculty, Department of Internal Medicine, Division of Allergy And Immunology, Izmir, Turkey, [2]Ege University Medical Faculty, Department of Internal Medicine, Division of Nephrology, Izmir, Turkey, [3]Ege University Medical Faculty, Department of Internal Medicine, Division of Allergy And Clinical Immunology, Izmir, Turkey, [4]Ege University Medical Faculty, Department of Genetics, Izmir, Turkey

Background and Aims: Few mutations have been described affecting different proteins of the CD19 complex which cause hypogammaglobulinemia and different clinical manifestations. We aimed to describe the specific clinical phenotype of the PID patient with a novel mutation in the CD19 gene.

Methods: An 18-year-old male patient was diagnosed with CVID at the age of 8. When he was referred to our clinic, his renal function tests were elevated. He had a recurrent infection history since he was 1 year old. Third-degree consanguinity was found between his parents. A renal biopsy was performed due to hypocomplementemia and nephrotic syndrome. The Next-Generation (NGS) and Sanger Sequencing (SS) were analyzed.

Results: Urine analysis revealed nephrotic (8.5 gr/day) proteinuria. Renal biopsy revealed immune-complex mediated glomerulonephritis with proliferative segmental sclerosis. The targeted next-generation sequencing panel showed a novel homozygous frameshift c.650_651delTG (p.Val217AlafsTer6) variant of the exon 4 of the CD19 gene. This variant was not found in the gnomAD exomes and genomes. Using the in-silico tools Mutation Taster, PROVEAN, and PolyPhen, the pathogenic effect of this novel mutation were tested; it was predicted to be “disease-causing,” with high pathogenicity scores and as likely pathogenic according to American College of Medical Genetics guideline. The parents were heterozygous for the same mutation.

Table 1. Immunological characteristics of patient

	Values at diagnosis	Normal range	Current status	Normal range
Gender	Male			
Age (year)	8		18	
Ig serum levels (g/L)				
IgG	1.29	5.91-27.60	13.9	7.67 - 15.90
IgG1	1.41	3.65-16.18	9.1	4.90 - 11.40
IgG2	0.24	0.57-6.44	4.02	1.50 - 6.40
IgG3	0.03	0.2-3	0.25	0.12 - 0.62
IgG4	0.01	0-1.2	0.43	0.03 - 2
IgA	0.45	0.49-4.37	<0.26	0.610 - 3.560
IgM	0.67	0.44-6.44	0.67	0.370 - 2.860
IgE (IU/ml)	< 25	0-90	1.36	0 - 87
Complement 3 (mg/dL)	126	80-170	108	90 - 180
Complement 4 (mg/dL)	35.6	14-44	<6	10 - 40
Immunophenotyping by flow cytometry				
Lymphocytes (cells/µL)	1230	1500-7600	880	1000 - 4800
CD3+ T cells	959	1000-4900	774	700 - 2100
CD3+ CD4+ T cells	602	500-2700	554	300 - 1400
CD3+ CD8+ T cells	221	300-2100	220	200 - 900
CD19+ B cells	24	200-2200	0	100 - 500
CD20+ B cells	N/A	200-2000	14	100 – 500
CD21+ B cells	N/A	200-2000	14	100 - 500
CD22+ B cells	N/A	200-2000	14	100 – 500
CD3- CD16/56+ cells	209	200-900	88	90 - 600
B-cell subsets	N/A		N/A	
PHA T cell proliferation	N/A		Normal	
Isohemagglutinins	Absent (Blood group was AB Rh+)		Absent (Blood group was AB Rh+)	
Vaccination responses	N/A		N/A (It was not measured before immunoglobulin therapy)	
Autoantibodies	N/A		p-ANCA: 1/40 positive (formalin-resistant), Anti-MPO: 3 positive (ELISA: 127 ru/ml)	

Conclusions: Unlike the cases defined in the literature, this case was considered unique on the grounds of remarkably low B cell numbers and p-ANCA positive immune-complex glomerulonephritis.

Disclosure: No.

Keyword: CD19 mutation, primary immunodeficiency, inborn errors of immunity, immunecomplex glomerulonephritis

PD265

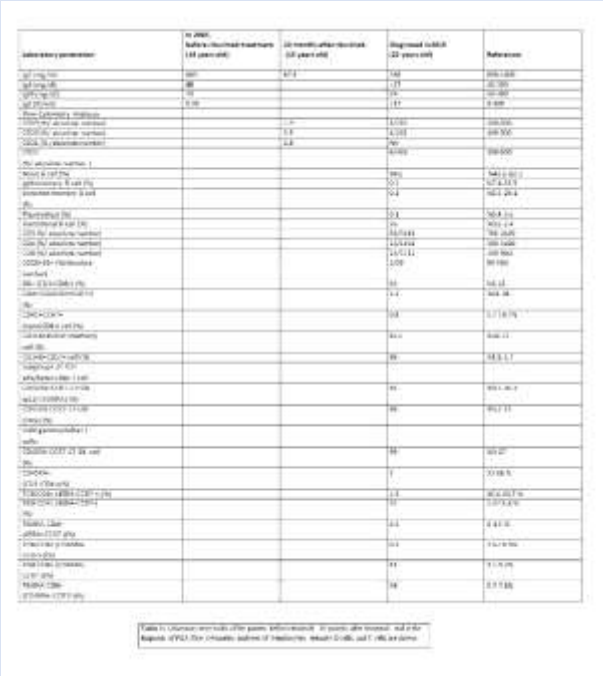
A CASE of CVID CLINICAL OVERLAPS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA PRESENTING WITH MUTATIONS IN BOTH EPHB4 AND INPP5D GENES

POSTER DISPLAY 06: GENETICS IN IEI

Ceyda Tunakan Dalgiç[1], Reyhan Gumusburun[1], Meryem Demir[1], Nur Akad Soyer[2], Hüseyin Onay[3], Ayça Aykut[3], Fatma Ömür Ardeniz[1]
[1]Ege University Medical Faculty, Department of Internal Medicine, Division of Allergy And Clinical Immunology, Izmir, Turkey, [2]Ege University Medical Faculty, Department of Internal Medicine, Division of Hematology, Izmir, Turkey, [3]Ege University Medical Faculty, Department of Genetics, Izmir, Turkey

Background and Aims: INPP5D (SHIP1) gene variant was reported to be pathogenic for PIDs in the limited literature. SHIP1 functions as a negative regulator of cell proliferation and survival. Until now, hereditary hemorrhagic telangiectasia (HHT) has not been reported with CVID yet. We aimed to define the characteristics of our unique case presenting both EPHB4 and INPP5D gene mutations.

Methods: The 29-year-old male patient had Evans Syndrome (ES) at 7 years old. Because of steroid resistance, he had a splenectomy. 8 months after, rituximab was administered due to recurrent autoimmune hemolytic anemia (AHA). Before rituximab, his immunoglobulin G (IgG) and IgM were normal; however, IgA was lower than normal (Table 1). 10 months after rituximab, he was hospitalized due to purulent meningitis. Hypogammaglobulinemia and B cell lymphopenia was detected; IVIG was started. He developed recurrent epistaxis at the age of 15. At 17 years, massive cervical and axillary lympadenomegalies with high FDG uptake in PET-CT (atypical lymphoid hyperplasia in serial biopsies); fascial, conjunctival, and oral mucosal telangiectasias, portal hypertension together with hepatic cavernous hemangioma and esophageal varices were developed gradually. He was considered as HHT overlapped with PID (Table 2).



Laboratory results	units	Diagnose (2015)	Current (2022)	references
SGOT	U/L	38	36	< 35
SGPT	U/L	39	23	< 45
ALP	U/L	146	119	40 - 129
GGT	U/L	60	103	< 55
Total Protein	g/dL	6.2	6.2	6.4 - 8.3
Albumin	g/dL	4.3	3.9	3.5 - 5.2
Globulin	g/dL	1.9	2.3	2.5 - 3.5
Total Bilirubin	mg/dL	2.12	3.1	0.1 - 1
Direct Bilirubin	mg/dL	0.8	1.9	< 0.25
Iron	µg/dL	20	31	59 - 158
Total iron binding capacity	µg/dL	447	183	228 - 428
Ferritin	ng/mL	7.1	154	30 - 400
Vitamin B12	pg/ml	614	435	197 - 866
Folic acid	ng/mL	7.68	11.5	4.6 - 18.7
WBC	10^3/µL	11.2	8.46	4.5 – 11
Neutrophil % /#	10^3/µL	18.5 /2.07	24/2.03	45 – 68/ 2.02 - 7.46
Lymphocyte %/#	10^3/µL	72.5/8.11	57/4.85	22 – 31/ 1.01 - 3.38
Monocyte %/#	10^3/µL	3.39/0.379	17/1.44	0 – 7/ 0.0 - 0.8
Eosinophil %/#	10^3/µL	3.8/0.425	4/0.30	0 - 4.1/ 0 - 0.45
Basophil %/#	10^3/µL	1.87/0.209	1.3/0.1	0 - 1.8/ 0.0 - 0.2
Erytrocyte	10^6/µL	5.05	3.14	3.8
Hemoglobin	g/dL	10.9	10.3	11.7 - 16
Hematocrit	%	33.2	31.6	35 - 47
Platelet	10^3/µL	442	49	150 - 400
MCV	fL	65.7	100	81 - 101

Table 2: Laboratory parameters of the patient at the time of diagnosis and current.

Results: He terozygous p.G516R mutation in the EPHB4 gene, as well as heterozygous p.T974M mutation in the INPP5D gene, was detected in the analysis.

Conclusions: We have described clinically significant mutations in the overlap of HHT and CVID for the first time in the literature. HHT cases with no variant detected in an HHT gene (ENG, ACVRL1, or SMAD4) should also be analyzed for the EPHB4 variant.

Disclosure: No.

Keywords: Primary Immune deficiency, hereditary hemorrhagic telangiectasia, EPHB4, INPP5D

PD266

ADA2 DEFICIENCY MIMICKING ACUTE DISSEMINATED ENCEPHALOMYELITIS

POSTER DISPLAY 06: GENETICS IN IEI

Lisa Ehlers[1], Giorgia Bucciol[1], Selket Delafontaine[1], Diane Beysen[2], Matthias De Wachter[2], Leen Moens[1], Benson Ogunjimi[2], Isabelle Meyts[1]
[1]KU Leuven, Laboratory Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [2]Antwerp University Hospital, Department of Paediatrics, Edegem, Belgium

Background and Aims: Deficiency of adenosine deaminase 2 (DADA2) is caused by biallelic mutations in the ADA2 gene. Neurological manifestations are present in 51% of patients. Here, we present a case of DADA2 mimicking acute disseminated encephalomyelitis (ADEM) caused by a novel splice variant in the ADA2 gene.

Methods: A case of ADEM is described. We validate the pathogenicity of a novel ADA2 splice variant: Sanger sequencing was performed on gDNA and cDNA samples. ADA2 enzyme activity was measured in patient serum and supernatant of HEK293 cells overexpressing the ADA2 variant.

Results: A boy born to Turkish consanguineous parents presented at seven months of age with encephalopathy and left-sided hemiparesis. CSF analysis revealed monocytosis and cMRI showed basal ganglia edema. The patient was treated for suspected ADEM with high-dose glucocorticoids leading to resolution of the clinical phenotype. At 3.5 years of age, left ocular paresis and gait disturbances appeared and another glucocorticoid pulse for suspected ADEM was given. He also developed recurrent fever episodes and a livedoid rash. Sanger sequencing revealed a homozygous novel splice variant in ADA2 (c.881+1 G>A; CADD score 22.90; MSC 6.827) causing a predicted deletion of amino acids 276-294. ADA2 enzyme activity was reduced in serum and upon overexpression in HEK293 cells, confirming DADA2.

Conclusions: This case of DADA2 mimicking ADEM in a patient with a novel ADA2 splice variant underlines the multifaceted manifestations of the disease and the need for a high index of clinical suspicion in children with complex neurological manifestations.

Disclosure: No.

Keywords: neurological manifestations, diagnostics, Genetics, autoinflammation

PD267

GENETIC EVALUATION of INBORN ERRORS of IMMUNITY IN INDIAN POPULATION

POSTER DISPLAY 06: GENETICS IN IEI

Gandham Bhavani[1], Harsha Lashkari[2], Suma Balan[3], Prathvi Shenoy[1], Sheela Nampoothiri[4], Katta Girisha[1]
[1]Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Medical Genetics, Manipal, India, [2]Kasturba Medical College, Paediatrics, Mangalore, India, [3]Amrita Institute of Medical Sciences, Rheumatology And Clinical Immunology, Cochin, India, [4]Amrita School of Medicine, Paediatrics, Cochin, India

Background and Aims: Inborn errors of immunity (IEIs) are heterogeneous group of genetic conditions characterized by recurrent and unusual susceptibility to infection. There is a lack of studies reporting new phenotypes, genetic variants, or novel genes from India, one of the most populous countries. With the high consanguinity rate, diverse ethnicity, and huge population, we hypothesize, the application of next generation sequencing techniques will help in identifying novel genetic defects in Indian population.

Methods: Families with one or more individuals with a phenotype suggestive of inborn errors of immunities are evaluated using targeted gene testing, exome sequencing, and genome sequencing.

Results: We evaluated a total of 38 unrelated patients. Among these 38 affected individuals, a disease-causing variant is identified in 16 patients (PEPD, ADA2, CD40LG, DOCK8, SPINK5, IL12RB1, PSTPIP1, WAS, ELANE, MVK, ATM, G6PC3, SLC29A3, DKC1, WDR1, and RAG1). Thus, the diagnostic yield of our study is 42%. The median age of onset of symptoms is six months ranging from birth to 12 years. The median age of diagnosis is nine years ranging from seven months to 21 years. According to the IUIS classification, four patients were observed with autoinflammatory diseases. Combined immunodeficiencies, combined immunodeficiencies with syndromic features, and congenital defects of phagocytes were seen in three patients each. Diseases of immune dysregulation, defects in intrinsic and innate immunity, and bone marrow failure groups were noted in one patient each.

Conclusions: These are the preliminary results of our study. We identified 11 novel variants in nine known IEI genes thus expanding the mutation spectrum of IEIs.

Disclosure: No.

Keywords: primary immunodeficiencies, Genetics, Inborn errors of immunity, Exome sequencing, diagnostic yield, India

PD268

CLINICAL AND IMMUNOLOGICAL ANALYSIS of A LARGE KINDRED AFFECTED BY AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS) DUE TO A NOVEL TNFRSF6 MUTATION DISPLAYING AGE DEPENDENT DISEASE ACTIVITY

POSTER DISPLAY 06: GENETICS IN IEI

Giulio Tessarin[1], Manuela Baronio[1], Luisa Gazzurelli[1], Stefano Rossi[2], Chiara Gorio[2], Elisa Bertoni[2], Marco Chiarini[3], Daniele Moratto[3], Cinzia Mazza[4], Raffaele Badolato[1], Fulvio Porta[2], Vassilios Lougaris[1]
[1]Pediatrics Clinic and "A. Nocivelli" Institute for Molecular Medicine, Department of Clinical And Experimental Sciences, University of Brescia, Asst- Spedali Civili of Brescia, Brescia, Italy, [2]Spedali Civili di Brescia, Bone Marrow Transplant Unit 'monica E Luca Folonari', Brescia, Italy, [3]Flow Cytometry Laboratory, Diagnostic Department, Asst Spedali Civili, Brescia, Italy, brescia, Italy, [4]Medical Genetics Laboratory, Asst-spedali Civili, Brescia, Italy, brescia, Italy

Background and Aims: ALPS is an inborn error of immunity caused by defective FAS-mediated apoptosis, usually a heterozygous germline mutation in TNFRSF6 is found. Analysis of families bearing the same TNFRSF6 mutation suggests a variable clinical and laboratory phenotype with some ALPS features that tend to decrease over time.

Methods: we report on clinical and immunological findings in a large kindred affected by ALPS.

Results: the index patient is a 6-year-old Italian male born to non-consanguineous parents. He was referred to our Clinic with a clinical history characterized by recurrent lymphoproliferative episodes with splenomegaly, autoimmune thrombocytopenia, and autoimmune neutropenia. Family history was positive for lymphoproliferative episodes and autoimmune cytopenia in pediatric age, which resolved during adulthood. Laboratory work-up showed increased vitamin B12 levels and expanded CD4-CD8-αβ+ double negative T (DNT) cells. NGS analysis of ALPS-associated genes revealed a novel germline heterozygous variant in the TNFRSF6 gene (c.731A>G;p.Q244R). Familial genetic analysis identified the same heterozygous TNFRSF6 mutation in the patient's father, brother, paternal grandfather, paternal great-aunt, and paternal second cousin. DNT cells were modestly expanded in the younger subjects of the kindred and tended to show a reduction towards the generations. Flowcytometry analysis of FAS/CD95 expression revealed reduced FAS/CD95 expression on all patients' lymphocytes compared to healthy controls.

Conclusions: we report on a large kindred affected by ALPS due to a novel pathogenic TNFRSF6 mutation. In this family, disease activity and specific biomarkers seem to present an inversely age-related trend. More data on intrafamilial variability in ALPS mutated patients are warranted to confirm our findings.

Disclosure: No.

Keywords: Autoimmunity, double negative T cells, LYMPHOPROLIFERATION, Inborn errors of immunity, ALPS, FAS

PD269

IKZF 1,2 AND 3 TRANSCRIPTION FACTOR FAMILY AND AUTO-IMMUNE CYTOPENIA IN THE OBS'CEREVANCE FRENCH COHORT : A NOVEL ENTITY ?

POSTER DISPLAY 06: GENETICS IN IEI

Audrey Petit[1], Helder Fernandes[2], Isabelle Thuret[1], Edeline Coinde[3], Marlene Pasquet[4], Morgane Cheminant[5], Fanny Rialland[6], Louis Terriou[6], Wahid Abouchahla[6], Marie Roelens[5], Capucine Picard[5,7], Frédéric Rieux-Laucat[8], Nathalie Aladjidi[2]
[1]CHU de la Timone, Pediatric Hematology, Marseille, France, [2]CHU de Bordeaux, Pediatric Immunology, bordeaux, France, [3]CH d'Ajaccio, Pediatric, Ajaccio, France, [4]Hospital Center University De Toulouse, Hemato-immunology, Toulouse, France, [5]Necker enfant malade, Immunology, PARIS, France, [6]CHU de Nantes, Pediatric, Nantes, France, [7]Necker Children's Hospital, Assistance Publique-Hôpitaux de Paris, Université De Paris, Institut Imagine Institut Des Maladies Genetiques, Paris, France, [8]1. Institut National de la Santé et de la Recherche Médicale, Mixed Research Unit 1163, Laboratory of Immunogenetics of Paediatric Autoimmunity- Necker Enfants Malades Hospital, PARIS, France

Background and Aims: The Ikaros (IKZF) family of transcription factors regulate lymphocyte development. Heterozygous variants of IKZF 1, 2 and 3 have been described leading to a large array of immune disorders including auto-immune cytopenias (AIC). Here we report on 6 unrelated pediatric patients identified amongst the OBS'CEREVANCE cohort, presenting with heterozygous variants of IKZF.

Methods: The OBS'CEREVANCE registry is a prospective national cohort of children with early-onset AIC collecting clinical information on a prolonged follow-up. Genetic variants are explored using targeted NGS.

Results: Three patients, aged 2 to 5 years old at initial diagnosis of AIC, had heterozygous IKZF1 variants. Two patients, aged 2 and 11 at initial diagnosis of AIC, had heterozygous IKZF2 variants. One patient, aged 13 at initial diagnosis of AIC, had IKZF3 variant. All patients presented with associated immunopathological manifestations ranging from subclinical hypogammaglobinemia to multiple auto immune manifestations. In all patients, chronic thrombocytopenia required several lines of treatment. With a median follow-up of 8 years (4-18), 4 patients were still under therapy.

Conclusions: Ongoing clinical and biological investigations aim to better describe this small subgroup of AIC pediatric patients, to understand whether it is a specific entity of childhood AIC.

Disclosure: No.

Keywords: DICV, IKAROS, auto-immune cytopenia

PD270

DIFFERENT PATTERNS of IMMUNE SYSTEM ACTIVATION IN HEREDITARY ANGIOEDEMA BASED ON DISEASE SEVERITY

POSTER DISPLAY 06: GENETICS IN IEI

Lucie Ballonova[1], Premysl Soucek[1], Roman Hakl[2], Peter Slanina[2], Marcela Vlkova[2], Marta Sobotkova[3], Pavlina Kralickova[4], Irena Krcmova[4], Jana Hanzlikova[5], Martina Vachova[5], Milos Jesenak[6], Hana Grombirikova[1], Kamila Reblova[7], Viktor Bily[1], Ondrej Zapletal[1], Tomas Freiberger[1]
[1]Centre of Cardiovascular Surgery and Transplantation, Molecular Genetics Laboratory, Brno, Czech Republic, [2]Medical Faculty, Masaryk University, Clinical Immunology And Allergology, Brno, Czech Republic, [3]University Hospital Motol, Clinical Immunology And Allergology, Prague, Czech Republic, [4]University Hospital Hradec Kralove, Clinical Immunology And Allergology, Hradec Kralove, Czech Republic, [5]University Hospital Plzen, Clinical Immunology And Allergology, Plzen, Czech Republic, [6]University Hospital in Martin, Department of Allergology And Clinical Immunology, Martin, Slovak Republic, [7]Ceitec, Masaryk University, Molecular Medicine, Brno, Czech Republic

Background and Aims: Hereditary angioedema (HAE) is a life-threatening immunodeficiency characterized by recurrent attacks of swelling. Defective SERPING1 gene leads to decreased level and/or function of C1 inhibitor, which results in local bradykinin overproduction and subsequent angioedema development. An immune response can modulate disease course as it involves molecules potentially participating in edema development.

Methods: We analyzed expression patterns of selected genes in monocyte-macrophage cell lineage using targeted RNA-seq to reveal differences between HAE patients with mild and severe disease courses compared to controls.

Results: Although the differences between patients with different disease courses were subtle, we identified several individual genes, which were up- or down-regulated in at least one analyzed cell type. Not surprisingly, SERPING1 mRNA was decreased in both macrophages and monocytes of HAE patients, more markedly in patients with severe HAE. Downregulation of gene expression was further confirmed for CXCL10 in monocytes or CXCL8 in macrophages. Conversely, FCGR1A in monocytes or NEAT1 in both macrophages and macrophages treated with interferon-gamma were up-regulated. And additionally, specific groups of co-expressed genes were formed in HAE patients differently from controls and in dependence on cell type and HAE severity.

Conclusions: While we were not able to find any sequence variants contributing significantly to different HAE phenotypes at the genomic level, transcriptomic analysis of monocytes and macrophages revealed significant shifts in the expression of some genes. Our findings indicated a different pattern of immune system activation in HAE patients compared to controls and also between HAE patients with different disease severity.

Disclosure: This project was supported by MZd grant NV18-05-00330 and specific research MSMT grant (MUNI/A/1244/2021).

Keywords: Hereditary Angioedema, RNA-seq, mRNA expression, disease severity

PD271

PRIMARY IMMUNE REGULATORY DISORDERS (PIRD): EXPANDING THE MUTATION SPECTRUM IN TURKEY AND IDENTIFICATION of SEVEN NOVEL VARIANTS

POSTER DISPLAY 06: GENETICS IN IEI

Necil Kutukculer[1], Neslihan Karaca[2], Asude Durmaz[3], Guzide Aksu[1], Ayça Aykut[3]
[1]Ege University, Faculty of Medicine, Depatment of Pediatric Allergy And Immunology, IZMIR, Turkey, [2]Ege University Faculty of Medicine, Department of Pediatrics, Izmir, Turkey, [3]Ege University Medical Faculty, Department of Genetics, Izmir, Turkey

Background and Aims: Background: Human Inborn Errors of Immunity (IEIs) are clinically and genetically heterogeneous group of diseases, with relatively mild clinical course or severe types that can be life-threatening. Primary immune regulatory disorders (PIRDs) are a subgroup of IEIs characterized by heterogeneous clinical phenotypes, predominated by severe atopy, autoimmunity, lymphoproliferation, hyperinflammation, autoinflammation, and malignancy. According to the most recent report by the International Union of Immunological Societies (IUIS), PIRDs caused by mutations in LYST, RAB27A, AP3B1, AP3D1, PRF1, UNC13D, STX11, STXBP2, FAAP24, SLC7A7, RASGRP1, CD70, CTPS1, RLTPR, ITK, MAGT1, PRKCD, TNFRSF9, SH2DIA, XIAP, CD27 (TNFRSF7), FAS (TNFRSF6), FASLG (TNFSF6), CASP10, CASP8, FADD, LRBA, STAT3, AIRE, ITCH, ZAP70, TPP2, JAK1, PEPD, FOXP3, IL2RA, CTLA4, BACH2, IL2RB, DEF6, FERMT1, IL10, IL10RA, IL10RB, NFAT5, TGFB1 and RIPK1 genes.

Methods: The targeted next-generation sequencing (TNGS) workflow based on Ion AmpliSeq™ Primary Immune Deficiency Research Panel was designed for sequencing 264 IEI related genes on Ion S5™ Sequencer.

Results: We present 19 disease-causing variants (7 novel) which were identified in 20 patients in 12 different PIRD genes (LYST, RAB27A, PI3KCD, SH2D1A, XIAP, LRBA, CTLA4, STAT3, AIRE, FOXP3, ZAP70, IL10RB).

Conclusions: Conclusion: Next generation sequencing allowed a rapid and an accurate diagnosis PIRD patient.

Disclosure: No.

Keyword: Primary immune regulatory disorders, genetics, novel variants

PD272

A NOVEL MUTATION IN NSMCE3 GENE IN AN IRANIAN INFANT WITH COMBINED IMMUNODEFICIENCY.

POSTER DISPLAY 06: GENETICS IN IEI

Mehrdad Yasaei[1], Mohammad Keramatipour[2], Hassan Abolhassani[3], Narjes Ahamdizadeh[4], Zahra Chavoshzadeh Natanzi[1]
[1]Mofid Children's Hospital, Department of Immunology And Allergy, Tehran, Iran, [2]Tehran University of Medical Sciences, Department of Medical Genetics, Tehran, Iran, [3]Karolinska Institute, Division of Clinical Immunology, Department of Biosciences And Nutrition, Stockholm, Sweden, [4]Mofid Children's Hospital, Department of Intensive Care Medicine, Tehran, Iran

Background and Aims: Chromosomal breakage syndromes are rare conditions among Primary immunodeficiency syndromes (PID) that result in chromosomal instability and DNA damage. We described a novel NSMCE3 gene mutation in a patient with failure to thrive and progressive lung injury.

Methods: A 2-year-old boy was admitted to our hospital with failure to thrive, respiratory distress, skin rash, and hydrocephaly. His parents were first cousins and had no history of previous medical complications in relatives. Despite aggressive treatment with wide-spectrum antimicrobial agents, he died from progressive pneumonia.

Results: Chest radiography showed bilateral patchy alveolar opacities and diffused haziness. CBC showed mild lymphopenia (2500 cells/mcL). He tested positive for Cytomegalovirus in plasma. CD flow cytometry demonstrated a decreased level in CD4+ (10%), CD8+ (26%), and CD4+/CD8+ ratio (0.38). Immunoglobulins levels were within normal limits except for IgE, which was significantly elevated (1830 mg/dl). Based on ESID diagnostic criteria for PID, combined immunodeficiency was suggested for our patient. Whole-exome sequencing revealed a homozygote mutation in the NSMCE3 gene (Variant c.790C>G p.L264V, Chromosomal position Chr15: 29,561,120) which was segregated in both parents with the Sanger sequencing technique.

Conclusions: Other mutant variants of the NSMCE3 gene were reported lately in four Dutch children with severe lung disease, combined immunodeficiency, and chromosomal breakage syndrome. This novel variant is compatible with the clinical features of previous cases and can be considered as a pathogenic mutation.

Disclosure: No.

Keywords: Chromosomal breakage, combined immunodeficiency, Pneumonia, Whole-exome sequencing, NSMCE3

PD273

SLAVIC FOUNDER MUTATION P.S44R IN IL7RA GENE IN CHILDREN WITH POSTMORTEM DIAGNOSIS SEVERE COMBINED IMMUNODEFICIENCY

POSTER DISPLAY 06: GENETICS IN IEI

Ekaterina Polyakova[1], Inga Sakovich[1], Christoph Geier[2], Alexander Leiss-Piller[2], Aleksandra Kupchinskaya[3], Larysa Kostuchenko[4], Alexander Migas[1], Oksana Rozhko[5], Anna Hilfanova[6], Taisiya Mikhalevskaya[1], Tatsiana Kugeiko[1], Mikhail Belevtsev[1], Irina Naumchik[7], Elena Golovatya[7], Oksana Prebushenia[7], Oksana Boyarchyk[8], Tatyana Hariyan[8], Dzmitry Varabyou[9], Olga Aleinikova[1], Peter Lisuk[10], Petro Dudash[11], Jolan Walter[12,13], Svetlana Sharapova[1]
[1]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Research Department, Borovlyany, Belarus, [2]Immunology Outpatient Clinic, Research Department, Vienna, Austria, [3]Belarussian Centre for Pediatric Oncology, Hematology and Immunology, Research Department, Минск, Belarus, [4]West-Ukrainian Specialized Children's Medical Center, Pediatric Department, Lviv, Ukraine, [5]Regional Children's Clinical Hospital, Department Pediatric Immunology, Brest, Belarus, [6]Shupyk National Medical Academy for Postgraduate Education, Department of Pediatric Infectious Diseases And Pediatric Immunology, Kyiv, Ukraine, [7]Republican Medical Center «Mother and Child», Research Department, Minsk, Belarus, [8]I.Horbachevsky Ternopil National Medical University, Department of Children's Diseases And Pediatric Surgery, Ternopil, Ukraine, [9]Belarusian State University, Department of Geography, Minsk, Belarus, [10]Regional Pathology bureau, Department of Pediatric Pathology, Brest, Belarus, [11]Regional Pathologoanatomic bureau, Pediatric Laboratory, Lviv, Ukraine, [12]Morsani College of Medicine, University of South Florida, Division of Allergy And Immunology, Department of Pediatrics, Tampa, United States of America, [13]Massachusetts General Hospital for Children, Division of Allergy And Immunology, Boston, United States of America

Background and Aims: Severe combined immunodeficiency with IL-7Rα-chain deficiency has immunologic phenotype T-B+NK+, frequency~10% of SCID cases.

Methods: We conducted a multicenter retrospective study, enrolling patients' DNA with clinically suspected-SCID without genetic confirmation from Belarus(n=22) and Ukraine(n=24); children were selected from the mortality lists who died before the age of 1 year due to complications from generalized infections in infants (21–DNA was obtained from newborn cards, 16–FFPE, 2–FFT,1–FT,6–PB). We investigated a NGS PID panel of 102-SCID/CID genes.

Results: We studied DNA from 20 females and 26 males. In 19/46 patients' DNA TREC/KRECs were determined, TRECs–mediana-4.2x10^3(0-2.0x10^4)/10^6leukocytes) and KREC–mediana-4.6x10^3(0-3.9x10^4)/10^6leukocytes). In three patients with T-B+SCID, TREC were undetectable and KREC-normal were (8.2x10^3(2.7x10^3-2.1x10^4)/10^6leukocytes). In 2/4 patients, the genetic variant of p.S44R in the IL7Ra gene was detected in the homozygous state, in 2 of patients-in the heterozygous state, one patient had heterozygous compound with other mutations in the IL7Ra gene. p.C57R, p. R206Q, which is described by Clivar database as Uncertain significance. Variant p.S44R is not annotated in ClinVar database. According to Mutation Taster, SIFT, and PolyPhen-2 programs predicting the functional consequences of non-synonymous substitutions, this variant is classified as probably pathogenic by Pathogenicity Scores (9/10). The patients with homozygous p.Ser44Arg were born in Western part of Ukraine (n=1) and Belarus (n=1) from unrelated families, heterozygous state in 2 patients from Belarus.

Conclusions: Based on our data, a repeated substitution in the IL7Ra gene may be classified as mutation and may have the "founder effect" in East Slavic countries.

Disclosure: No.

Keywords: SCID, IL-7Rα, founder mutation

PD274

NEXT GENERATION SEQUENCING HELPS TO DISTINGUISH A DOCK8 DEFICIENCY FROM AD-HYPER IGE SYNDROME FORM

POSTER DISPLAY 06: GENETICS IN IEI

Roukaya Yaakoubi[1], Najla Mekki[1], Imen Ben-Mustapha[1], Jamel Ammar[2], Agnès Hamzaoui[3], Koon Wing Chan[4], Yu Lung Lau[5], Mohamed-Ridha Barbouche[1], Meriem Ben Ali[1]
[1]Institut Pasteur de Tunis, University Tunis El-Manar, Tunis, Tunisia., Laboratory of Transmission, Control And Immunobiology of Infections, Tunis, Tunisia, [2]Abderrahmen Mami Hospital, Ariana; Faculty of Medicine of Tunis, University of Tunis El-Manar, Tunis, Tunisia., Pulmonology B Department,, Tunis, Tunisia, [3]Abderrahmen Mami Hospital, Ariana; Faculty of Medicine of Tunis, University of Tunis El-Manar, Tunis, Tunisia., 2- pulmonology B Department,, Tunis, Tunisia, [4]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Department of Pediatrics And Adolescent Medicine, Hong Kong, China, [5]School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Department of Pediatrics And Adolescent Medicine, Hong Kong, Hong Kong PRC

Background and Aims: DOCK8 deficiency is a combined immune deficiency that was initially classified as an autosomal recessive form of Hyper IgE syndrome (HIES). Clinical symptoms may overlap with those found in the autosomal dominant form caused by STAT3 mutations, and include eczema, recurrent pneumonias, high IgE levels, and mucocutaneous candidiasis. DOCK8 deficient individuals are characterized by allergies, and cutaneous viral infections with associated cancers.

Methods: Herein we describe the case of a 12-year-old child born from a consanguineous family, with a history of a sister died at 6-year-old from severe infections. He was diagnosed with eczema, recurrent infections, bronchiectasis, staphylococcal skin abscesses, otitis, oral candidiasis, elevated IgE, and eosinophilia. He had a score of 46 points according to NIH-HIES scoring norms, thus STAT3 deficiency was suspected. Sclerosing cholangitis (SC) was detected later. Unfortunately, he died one year later from respiratory infections.

Results: Flow cytometry revealed that STAT3 phosphorylation was entirely defective, and the percentage of TH17 cells was decreased. Targeted Sanger sequencing revealed no STAT3 mutations in coding exons. Whole exome sequencing, revealed a novel deletion of 3420pb in the DOCK8 gene, resulting in a premature codon stop (G1988fsX1990).

Conclusions: DOCK8 deficiency is plausible in suspected HIES patients who have allergies and severe viral infections. SC was found in only 5% of a large cohort of DOCK8-deficient patients. Next Generation Sequencing could help with quicker and more efficient diagnosis, especially in altered disease's phenotype expression, and help to distinguish between HIES patients with a DOCK8 mutations from those with a STAT3 mutations.

Disclosure: No.

Keywords: Syndrome hyper IgE, Differential diagnosis, STAT3, DOCK8, Sclerosing cholangitis, Whole Exome Sequencing

PD275

NETHERTON SYNDROME PATIENTS IN SLOVENIA

POSTER DISPLAY 06: GENETICS IN IEI

Gasper Markelj[1], Meta Smerkolj[1], Andreja Kauran[1], Olga Točkova[2], Maruša Debeljak[3], Tadej Avcin[1]
[1]University Children's Hospital, University Medical Center Ljubljana, Department of Allergology, Rheumatology And Clinical Immunology, Ljubljana, Slovenia, [2]University Medical Centre Ljubljana, Department of Dermatovenereology, Ljubljana, Slovenia, [3]University Children's Hospital, University Medical Center Ljubljana, Department of Genetics, Ljubljana, Slovenia

Background and Aims: Netherton syndrome is a rare autosomal recessive genodermatosis characterized by congenital ichthyosiform erythroderma, trichorrhexis invaginata and immune dysregulation caused by SPINK5 mutation leading to reduction of LEKTI inhibition of proteolytic enzymes in the skin. Most complications of the disease occur in the first months of life with dehydration, failure to thrive and recurrent infections. We present clinical and genetic data of Slovenian Netherton patients treated in the University Medical Center Ljubljana, Slovenia in the last 30 years.

Methods: We have analyzed clinical documentation of Netherton patients treated in the University Children's Hospital and the Dermatology and Venereology Clinic. We have compared their clinical picture, time to clinical and genetic diagnosis and their mutations.

Results: In this study, we report on 7 unrelated patients with Netherton Syndrome aged 4 months to 30 years. All of our patients had more severe clinical course in the first five years of life. We have three patients with a homozygous mutation in our cohort with different clinical course. The most severe disease course has our youngest patient with c.1431-12G>A .

Conclusions: A Slovenian cohort of patients with Netherton syndrome has similar course of disease and complications as previously described Netherton syndrome. In our experience patients with different SPINK5 homozygous mutations can have different clinical course. The patient with the most severe course has an intronic homozygous mutation that leads to the absence of the LEKTIexpression. Some, if not all Netherthon patients could probably benefit from active antimicrobial prophylaxis and immunoglobulin prophylactic treatment in the first months of life.

Disclosure: No.

PD276

MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE: RETROSPECTIVE CLINICAL AND GENETIC STUDY IN MEXICO

POSTER DISPLAY 06: GENETICS IN IEI

Ana Karen Peñafiel Vicuña[1], Marco Yamazaki-Nakashimada[2], Maria Enriqueta Nuñez Nuñez[3], Tamara Staines-Boone[4], María Ramírez[5], Joel Barroso[6], Sara Espinosa Padilla[7], Jacinta Bustamante[8], Lizbeth Blancas Galicia[9]
[1]Insituto Nacional de Pediatría, Laboratorio De Investigación De Inmunodeficiencias, Ciudad de México Insurgentes Cuicuilco, Ecuador, [2]National Institute of Pediatrics, Immunology, Mexico City, Mexico, [3]Hospital Civil de Guadalajara "Dr. Juan I. Menchaca", Jalisco, México., Servicio De Inmunología Clínica Y Alergias, Guadalajara, Mexico, [4]UMAE-25 IMSS, Immunology, Monterrey, Mexico, [5]Hospital del Niño DIF, Immunology, Pachuca, Mexico, [6]Hospital del Niño DIF, Immunology, Mexico, Mexico, [7]National Institute of Pediatrics, Primary Immunodeficiency Research Unit, Mexico City, Mexico, [8]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Paris, France, [9]National Institute of Pediatrics, Research Unit For Immunodeficiencies, Ciudad de México Insurgentes Cuicuilco, Mexico

Background and Aims: BACKGROUND. Mendelian susceptibility to mycobacterial disease (MSMD) is a rare genetic disorder with impaired immunity against intracellular pathogens, such as mycobacteria, attenuated Mycobacterium bovis -Bacillus Calmette-Guérin (BCG) vaccine strains, and environmental mycobacteria, in otherwise healthy individuals. In Mexico, the estimated incidence of tuberculosis in 2019 was 23 cases/100,000 people. BCG vaccination is mandatory in Mexico. PURPOSE. To review the clinical, immunological, and genetic characteristics of MSMD patients followed in ten hospitals across Mexico.

Methods: METHODS. This retrospective study describes the clinical, immunological, and genetic characteristics of patients in Mexico diagnosed with MSMD from 2006 to 2021.

Results: RESULTS. Twenty-two patients from 17 kindreds were diagnosed with MSMD. Fourteen were male (64%) and eight were female. After BCG vaccination, 12 patients (70%) developed BCG infections. Six (22%) developed infections caused by Salmonella , and 11 (50%) developed infections caused by fungi, particularly Histoplasma . Thirteen different pathogenic variants were identified in IL12RB1 (n =13), IFNGR1 (n =3), and IFNGR2 (n =1). Seven of the 22 patients died; the main cause was disseminated BCG infection.

Conclusions: CONCLUSION. Interleukin-12Rβ1 deficiency was the main cause of MSMD in the Mexican cohort. The main etiologic agent responsible for morbidity and mortality was BCG.

Disclosure: No.

Keyword: BCG vaccine, Mendelian susceptibility to mycobacterial disease, interleukin-12, interferon-gamma, IL

PD277

DEFINITION of GATA2 DEFICIENCY IN A FAMILY AFTER EVALUATION of A BOY WITH RECURRENT AND RESISTANT PULMONARY DISEASE

POSTER DISPLAY 06: GENETICS IN IEI

Dilan Inan[1], Saliha Esenboga[2,3], Hacer Neslihan Bildik[3], Ismail Yaz[3], Begum Cicek[3], Ilhan Tezcan[2], Can Kalaycı[4], Deniz Cagdas Ayvaz[2]
[1]Hacettepe University, Pediatric Immunology, Ankara, Turkey, [2]Hacettepe University School of Medicine, Pediatric Immunology, Ankara, Turkey, [3]Hacettepe University, Institute of Child Health, Immunology, Ankara, Turkey, [4]Hacettepe University, Allergy And Immunology, Ankara, Turkey

Background and Aims: GATA binding protein 2 is a transcription factor vital for hematopoiesis and the maintenance and survival of HSCs. Germline mutations in GATA2 lead to an autosomal dominant disease which is characterized by a wide range of symptoms, including Emberger syndrome, familial MDS/AML, mycobacterial and viral infections, immunodeficiency, and malignancy. Affected immune cells are mainly monocytes, B cells, NK, and DC. This case report demonstrates the importance of genetic tests for patients with PIDDs for early diagnosis. The availability of molecular genetic analyses helps clinicians to diagnose and cure the patients at an early convenience.

Methods: NGS was performed for the patient and defect is confirmed on the patient and his father with Sanger sequencing. An 11 year-old male presented with recurrent lung infection, asthma, cockroach allergy, pneumonia, recurrent aptha, otitis, and warts in feet. He has decreased lymphocyte number, CD4+ T cell, and switch memory B cell percentages, in addition to high number of CD8+ T cells and naïve B cell percentage.

Results: Missense heterozygote c.1081C>T (p.R361C) mutation reported in the literature as a likely pathogenic was found in the patient. After family evaluation, we found that patient`s father with mild symptoms of cellular immunodeficiency had the same GATA2 mutation with lymphopenia.

Conclusions: Since there was a familial background, genetic analysis is planned in a relatively early age in the patient, and we saw that the clinical manifestations of GATA 2 gene deficiency are in a wide range in a same family. This is possibly due to the environmental and epigenetic factors.

Disclosure: No.

Keywords: GATA binding protein 2, genetic diseases

PD278

ASSOCIATION of RS1799889 (-675 4G/5G) IN SERPINE1 (PAI-1) GENE WITH COMMON VARIABLE IMMUNODEFICIENCY PATIENTS.

POSTER DISPLAY 06: GENETICS IN IEI

Bricia Gutiérrez-Zepeda[1,2], Denisse Becerra Loaiza[1,2], Miguel Chávez-Meléndez[3], Margarita Ortega Cisneros[3], Maria Enriqueta Nuñez Nuñez[4], Carlos Torres-Lozano[3], Adrián Daneri-Navarro[2], Alicia Del Toro-Arreola[2], Antonio Topete[2], Yeminia Valle-Delgadillo[1], Antonio Quintero Ramos[1,2]
[1]Universidad de Guadalajara, Departamento De Biología Molecular Y Genómica, Guadalajara, Mexico, [2]Universidad de Guadalajara, Fisiología, Guadalajara, Mexico, [3]Hospital de Especialidades, Instituto Mexicano del Seguro Social, Departamento De Inmunología Clínica Y Alergia, Guadalajara, Jalisco, Mexico, [4]Hospital Civil de Guadalajara “Dr. Juan I. Menchaca”, Jalisco, México., Servicio De Inmunología Clínica Y Alergias, Guadalajara, Mexico

Background and Aims: Patients with Common Variable Immunodeficiency (CVID) have recurrent pulmonary infections due the declivity of antibodies, characteristic of this Inborn Error of Immunity. Molecules as PAI-1 (encoded by SERPINE1), have been associated with tissue injury, inflammation and sepsis, especially in lungs as in the case of pneumonia, an initial clinical feature in patients with CVID. The SNV rs1799889 in -675 (4G/5G) of the SERPINE1 gene is related with the increase of soluble levels of PAI-1 and with higher incidence of acquired pneumonia. Therefore, the relationship between the rs1799889 variant in patients with CVID and their clinical characteristics was determined.

Methods: A total of 24 Mexican patients with a diagnosis of CVID and 176 individuals as reference group (RG) were included in the study and genotyping of the rs1799889 variant (4G/5G) was performed by AS-PCR followed by PAGE. Hardy-Weinberg Equilibrium (HWE) and association study were performed in SNPstats and SPSS. P values <0.05 (CI 95%) were statistically significant.

Results: Both study groups were in HWE. The allelic and genotypic frequencies were: 5G=67%, 4G=33%; 5G/5G=42%, 5G/4G=50%, 4G/4G=8% for CVID, and 5G=65%, 4G=35%, 5G/5G=42%, 5G/4G=46%, 4G/4G=12% for RG. There is a marginal association between rs1799889 and the clinical presentation of recurrent pulmonary infections (p=0.04).

Conclusions: We suggest the rs1799889 variant as a possible biomarker in clinical prognosis of CVID patients, also analyze the association with protein and genic expression could contribute to improve the understanding of the heterogeneous clinical picture of CVID and PAI-1 as a outcome biomarker.

Disclosure: No.

Keywords: rs1799889, CVID, SERPINE1, Inflammation, Mexicans

PD279

POLYGENIC CONTRIBUTION IN THE MOLECULAR DIAGNOSIS of VERY EARLY ONSET INFLAMMATORY BOWEL DISEASE

POSTER DISPLAY 06: GENETICS IN IEI

Elena García-Martínez[1], Hector Balastegui[2], Mercedes Díaz-Luna[1], Marisa Di Natale[2], Eduardo Fernandez Cruz[2], Elena Seoane-Reula[3], Carmen Rodriguez Sainz[2]
[1]Hospital General Universitario Gregorio Marañón, Immunology, Madrid, Spain, [2]Hospital General Universitario Gregorio Marañon, Immunology, Madrid, Spain, [3]Hospital General Universitario Gregorio Marañón, Immunology, madrid, Spain

Background and Aims: Inflammatory bowel disease (IBD) comprises an heterogeneous and complex group of disorders which has a multifactor etiology with contributions from genetics, environment and microbiota. Genetic factors affecting barrier function and intestinal immune homeostasis are increasingly demonstrated to be involved. Here we present two pediatric patients with very early onset IBD (VEO-IBD) and challenging molecular diagnosis.

Methods: Genomic DNA from peripheral blood of the patients was isolated and Next Generation Sequencing (Gene Systems) was performed using a screening panel of 200 genes associated with immunodeficiency.

Results: Case 1: 9-years-old boy in follow-up for severe VEO-IBD carrying end ileostomy and in treatment with ustekinumab. Genetic analysis revealed three heterozygous mutations: frameshift variants in TTC7A gene (p.Gly8AlafsTer4) and in TNFRSF6B gene (p.Asn173GlnfsTer18); and a missense variant in NFKB2 gene (p.Pro883Thr). It was also identified polimorphisms in NLRP3, CYBA and NCF2 genes, associated with increased risk and severity in inflammatory related-conditions. Case 2: 5-years-old with VEO-IBD, refractory to several treatments and currently with infliximab. He also presents developmental and language delay. Genetic analysis revealed a nonsense heterozygous mutation in TRAF3 gene (p.Glu363Ter), leading to a truncated protein without the TRAF C-terminal domain, and a well-known monoallelic deleterious variant in PRF1 gene (p.Lys285del).

Conclusions: A spectrum of single genetic defects is thought to underlie the pathogenesis of patients with VEO-IBD. However in many of them it is often found a complex polygenic background, rendering difficult the task of molecular interpretation to achieve a precise diagnosis and treatment of the patient.

Disclosure: No.

Keywords: Molecular diagnosis, Inflammation, Inflammatory bowel disease, Genetics, Immune Dysregulation

PD280

LACK of PERIPHERAL T CELLS REVEALING A NOVEL CD3E MUTATION IN A FAMILY WITH MULTIPLE INFANT DEATHS

POSTER DISPLAY 06: GENETICS IN IEI

Riccardo Papa[1], Maura Faraci[2], Silvia Clara Giliani[3], Andrea Secco[4], Francesca Buffelli[5], Matteo D'Alessandro[6], Roberta Caorsi[1], Stefano Giardino[2], Andrea Moscatelli[7], Marco Gattorno[1], Stefano Volpi[1]
[1]IRCCS Giannina Gaslini Institute, Center For Autoinflammatory Diseases And Immunodeficiencies, Genova, Italy, [2]IRCCS Istituto Giannina Gaslini, Hematopoietic Stem Cell Unit, Genova, Italy, [3]University of Brescia, ASST Spedali Civili of Brescia, Department of Molecular And Translational Medicine, Brescia, Italy, [4]Azienda Ospedaliera Nazionale SS. Antonio e Biagio e Cesare Arrigo, Uoc Pediatria, Alessandria, Italy, [5]IRCCS Istituto Giannina Gaslini, Uoc Anatomia Patologica, Genova, Italy, [6]IRCCS Istituto Giannina Gaslini, Uoc Pronto Soccorso E Medicina D'urgenza, Genova, Italy, [7]IRCCS Istituto Giannina Gaslini, Anestesia E Rianimazione, Genova, Italy

Background and Aims: Biallelic CD3E gene mutation causes a SCID leading to early death unless HSCT is performed. We describe a large Maroccan family with history of multiple infant deaths and carrying a novel CD3E mutation.

Methods: Data were obtained during the regular clinical workup of the patients.

Results: The proband displayed at one month of age a respiratory insufficiency caused by CMV and Haemophilus Influenzae pneumonia, requiring mechanical ventilation. Laboratory analysis showed absence of peripheral T cells and low serum immunoglobulin levels. Treatment included foscarnet, fluconazole, steroid, IVIG and teofillin. Family history revealed multiple consanguinity and five infant deaths. NGS analysis demonstrated a novel homozygous CD3E c.G60A, p.W20*. HSCT from the HLA-identical father was performed without conditioning. The patient required ECMO immediately after the procedure for respiratory deterioration, and passed away despite evidence of engraftment. One year later, a two months old cousin presented with a oxygen-dependent respiratory infection. Laboratory tests showed normal amount of WBC and 2200/ul total lymphocytes, but absent CD3+/CD45+ T cells and elevated copies of CMV-DNA. Brain MRI showed diffuse white matter abnormalities compatible with silent CMV infection. Foscarnet and IVIG were administered. CD3E gene Sanger sequencing confirmed the same homozygous mutation of the deceased cousin. HSCT was performed from an HLA-matched sibling donor with treosulfan/fludarabine conditioning regimen and post-transplant cyclophosphamide without complications. The patient is alive and well at 4 years post-transplant.

Conclusions: SCID may present with mildly decreased total lymphocytes count and should be suspected in patients with family history of infant deaths, consanguinity, and early onset severe infections.

Disclosure: No.

Keywords: T cell, CD3e deficiency

PD281

CLINICAL AND IMMUNOGENETIC FEATURES of WISKOTT-ALDRICH SYNDROME IN FIVE UNRELATED TUNISIAN PATIENTS

POSTER DISPLAY 06: GENETICS IN IEI

Najla Mekki[1], Firas Bouzakoura[1], Elhem Ben Fradj[2], Ines Maaloul[3], Afef Rais[1], Samia Rekaya[2], Saber Hammami[4], Ines Trabelsi[5], Fethi Mellouli[2], Monia Ouedrni[2], Imen Chabchoub[3], Imen Ben-Mustapha[1], Mohamed-Ridha Barbouche[1]
[1]Institut Pasteur de Tunis, Laboratory of Transmission, Control And Immunobiology of Infections (lr11ipt02), Tunis, Tunisia, [2]Bone MarrowTransplant Center, Tunis, Department of Pediatrics: Immunology, Hematology And Stem Cell Transplantation, Tunis, Tunisia, [3]Hédi Chaker Hospital of SFAX, Pediatrics, SFAX, Tunisia, [4]FAttouma Bourguiba Hospital of Monastir, Pediatrics, Monastir, Tunisia, [5]Bechir Hamza Hospital of Tunis, Pediatrics B, Tunis, Tunisia

Background and Aims: Wiskott-Aldrich syndrome (WAS) is a rare X-linked inborn error of immunity caused by loss-of-function (LOF) mutations in WAS gene. The clinical presentation ranges from moderate X-linked thrombocytopenia (XLT) to classical WAS characterized by microthrombocytopenia, eczema and infections associated with a high incidence of autoimmunity and an increased risk of malignancies.

Methods: Herein, we report clinical and immunogenetic features of five Tunisian patients harboring Loss-of-function WAS mutations.

Results: They presented at an early age with thrombocytopenia associated to eczema (P2 and P4) and autoimmune hemolytic anemia (P2, P3, P4 and P5). P4 had also Kaposi-Juliusberg's syndrome and P2 developped severe candidiasis, hypotrophy and coeliac disease. High level of IgA and inverted CD4/CD8 ratio were found in P2 and P5. Lymphoproliferative response to anti-CD3 was reduced in both P2 and P3. Intracellular WAS protein expression assessed by flow cytometry was absent in P1, P2, P4 and P5 and strongly reduced (10 %) in P3. Genomic DNA amplification of WAS gene showed the presence of a missense (A56V) mutation in P1, a novel frameshift (Q80*) in P4 and three splice site variations (g.7392T>G, c.360+1delG and c.789+1G>C in P5, P2 and P3, respectively). P1 showing an XLT phenotype is now 7 year-old with a good clinical course. Hematopoietic stem cell transplantation has been successfully performed in P3. P'4 and P5 died.

Conclusions: Our results highlight the lack of correlation between clinical, immunological and genetic phenotypes. Further investigations are needed to assess the effective consequences of these splice site mutations on mRNA expression.

Disclosure: No.

Keyword: Wiskott-Aldrich Syndrome, Molecular analysis, WAS

PD282

NEW CASE of CDC42 DEFICIENCY WITH ADDITIONAL PATHOGENIC VARIANTS IN UNC13D AND DNAH8 GENES

POSTER DISPLAY 06: GENETICS IN IEI

Inga Sakovich[1], Aleksandra Kupchinskaya[2], Yulia Zharankova[3], Svetlana Aleshkevich[3], Tatsiana Shman[1], Ekaterina Polyakova[1], Alina Tarasova[1], Tatyana Ermilova[1], Mikhail Belevtsev[1], Svetlana Sharapova[1]
[1]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Research Department, Borovlyany, Belarus, [2]Belarussian Centre for Pediatric Oncology, Hematology and Immunology, Research Department, Минск, Belarus, [3]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Outpatient Department, Borovlyany, Belarus

Background and Aims: CDC42-deficiency (or Takenouchi-Kosaki syndrome) is autosomal-dominant disorder associated with congenital malformations, bone marrow failure (BMF), HLH and autoinflammation.

Methods: We reported a case of 12-y.o girl with cytopenia since birth, congenital malformations and B-cell immunodeficiency.

Results: Patient manifested with thrombocytopenia firstly diagnosed in 3m. Congenital malformations includes perineal anus ectopia, sensorineural deafness and facial dysmorphism. Hepatosplenomegaly (+1.5-+6.5sm) was firstly noted at 8m and is preserved until now. Leucopenia (1-3.5×10^9/L) and thrombocytopenia (7-140×10^9/L) have been observed throughout patient's life. Infectious episodes have occurred infrequently: pneumonia at 3 and 10yrs, second episode was complicated with bronchiolitis, hydrothorax, hydropericardium. Chromosomal aberrations and instability were not revealed. DNA double-strand break repair was slightly impaired. Immunological tests revealed decreased B-cells (2.8%,26 cells/μl), slightly reduced IgG (4.5-6.5g/L) with normal B-mem, elevated CD21low B-cells (24%); naïve/memory T-cells and RTE were in normal ranges. Panel sequencing (Invitae immunodeficiency panel, 452 genes) revealed pathogenic variants in CDC42 (p.Arg68Gln), DNAH8 (p.Arg2123*) and UNC13D (p.Cys136Trpfs*7). Although patient has two HLH-associated pathogenic variants, phagocytizing macrophages was detected in bone marrow aspirate only at 7yrs, without any additional biochemical HLH sings (HLH score-160points).

Conclusions: We describe new case of CDC42-deficiency with additional genetic events.

Disclosure: No.

Keywords: Takenouchi-Kosaki syndrome, CDC42, Bone marrow failure, B-cell immunodeficiency

PD283

COEXISTENCE of TNFRSF13B AND IL2RG MUTATIONS IN A PATIENT WITH CVID

POSTER DISPLAY 06: GENETICS IN IEI

Ana García-Soidán[1], Ignacio Iturrieta Zuazo[1], Elena Manterola Navarro[1], Patricia Fernández San José[2], Ana De Andrés Martín[1]
[1]Hospital Universitario Ramón y Cajal, Clinical Immunology, Madrid, Spain, [2]Hospital Universitario Ramón y Cajal, Genetics, Madrid, Spain

Background and Aims: Background and aims: Common variable immunodeficiency (CVID) is a heterogeneous disorder characterized by low immunoglobulin serum levels and impaired vaccine responses with a wide variety of infectious and noninfectious complications. While the majority of cases occur sporadically, approximately 10-20% have a familial background hinting towards a genetic origin of disease. A genetic diagnosis has been shown to affect patient management.

Methods: Method: A case report

Results: We report the case of a 49 years-old man whose follow-up started after reporting severe panhypogammaglobulinemia while being treated for Hodgkin's disease at 29 years old. Reporting a clinical history of chronic sinusitis, thrombocytopenia and nodular regenerative hyperplasia and low levels of IgG, IgM and IgA and memory B-cells. He was diagnosed of CVID according to the ESID criteria. He also present a second hematologic neoplasms (Diffuse large B cell lymphoma) at age 47. He haven't present any impairment of the T or NK-cells. Recent NGS genetic analysis revealed two mutations: Heterozigous TNFRSF13B mutation (c.542C>A), classified as a likely pathogenic variant in CVID patients. Hemizigous IL2RG mutation (c.918C>A), classified as likely pathogenic and found in patients with severe and moderate X-linked severe combined immunodeficiency.

Conclusions: We report a case of a CVID patients with a TNFRSF13B mutation coexisting with a IL2RG mutation, presented in X-linked combined immunodeficiency patients. Despite the genetic results, our patient only meet criteria to CVID. Our next step is a deeper study of the mutations trying to elucidate its role.

Disclosure: No.

Keyword: CVID, MUTATION, TNFRSF13B, IL2RG

PD284

MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASES IN MOROCCAN KINDREDS: CLINICAL, IMMUNOLOGICAL AND GENETIC FEATURES

POSTER DISPLAY 06: GENETICS IN IEI

Abderrahmane Errami[1,2], Jamila El Baghdadi[2], Fatima Ailal[1,3], Ibtihal Benhsaien[1,3], Jalila El Bakouri[1,4], Laurent Abel[5,6], Jacinta Bustamante[7,8,9,10], Jean-Laurent Casanova[5,6], Ahmed Aziz Bousfiha[1,3]
[1]Faculty of Medicine and pharmacy of Casablanca, Research Laboratory In Clinical Immunology And Inflammation (licia), Casablanca, Morocco, [2]Military Hospital Mohammed V, Genetics Unit, Rabat, Morocco, [3]Abderrahim El Harouchi Children Hospital, University Hospital Center Ibn Rochd, Casablanca, Morocco., Clinical Immunology Unit, Department of Infectious Diseases, Casablanca, Morocco, [4]IBN Rochd University Hospital,, Immunology Laboratory, Casablanca, Morocco, [5]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1163, Paris, France, [6]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, New York, United States of America, [7]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Paris, France, [8]Paris Hospital, Study Center For Primary Immunodeficiencies, Paris, France, [9]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, New York, United States of America, [10]Imagine Institute, Paris Cité University, Paris, France

Background and Aims: The first molecular evidence of a monogenic predisposition to mycobacteria came from the study of MSMD, which confers a selective susceptibility to infections with low virulent mycobacteria. We aimed to study this mendelian susceptibility to mycobacterial diseases in Moroccan kindreds through clinical, immunological and genetic analysis.

Methods: Patients presented with clinical features of MSMD, were recruited into this study. Diagnosis of BCG was done according to ESID diagnostic criteria. We used whole blood samples from 17 patients and 16 age-matched healthy controls. To measure IL-12 and IFN-γ production, samples were activated by BCG plus recombinant human IFN-γ or recombinant human IL-12. Immunological assessments and genetic analysis were also done for patients and their families.

Results: Our study involved 17 index cases from 13 unrelated Moroccan families. Their median age at onset was 6 months, while that at diagnosis was 4 years. Ten index cases (64%) were born to consanguineous parents. All patients were vaccinated with BCG vaccine with the development of complications in 12 patients. Most of patients have normal serum immunoglobulin levels and numbers of subpopulations. Genetic mutations were identified on the following genes: IL12RB1 in 8 patients, STAT1 in 4 patients, SPPL2A in two patients, IFNGR1, TYK2 and TBX21 in one patient each, with different modes of inheritance.

Conclusions: These results confirm that the integrity of IFNγ-mediated immunity is required for host defense against mycobacterial infection. The study of these monogenic defects contributes to understanding the molecular mechanism of mycobacterial infections and to the development of new diagnostic and therapeutic approaches.

Disclosure: No.

Keywords: Mendelian susceptibility,, Monogenic, IFNγ, Mycobacterial diseases, Infectious

PD285

24 YEARS of DIAGNOSIS DELAY SAVED BY GENES

POSTER DISPLAY 06: GENETICS IN IEI

Abire Allaoui[1,2], Khaoula Mokhantar[1], Hind Ouair[1], Mina Moudatir[1], Ahmed Aziz Bousfiha[1]
[1]Faculty of Medecine and Pharmacy, University Hassan II, Casablanca, Laboratory of Clinical Immunology, Inflammation And Allergy (licia), CASABLANCA, Morocco, [2]Mohammed VI University of health sciences, Internal Medicine, CASABLANCA, Morocco

Background and Aims: LRBA deficiency associates immune deficiency, lymphoproliferation, and various organ-specific autoimmunity. it is thought to regulate the CTLA4 protein, an inhibitory immunoreceptor. It was considered as a common variable immunodeficiency (CVID)-like disease, now it is recognized as a well-individualized entity with specific treatment.

Methods: Here we present the first moroccan case of LRBA deficiency, retained after 24 years of diagnosis delay.

Results: A 25-year-old patient, with first-degree consanguinity, has began around the age of one year, to have a chronic diarrhea. Later, she presented with repeated lung infections, associated with a failure to thrive. At the age of 10, Crohn's disease was suspected and unsuccessfully treated with immunosuppressors. Warts, lymph nodes and autoimmune symptoms such as arthritis and a posterior uveitis, have began to occur. She developed bronchiectasis, at the age of 13. She had lymphopenia with negative HIV serology, thrombocytopenia. Protein electrophoresis and immunoglobulin assay showed severe hypogammaglobulinemia: IgG: 0.9 g/l (N: 6.6-12.8), IgM < 0.04 g/l (N: 0.4-2.3), Ig A < 0.01 g/l (N: 0.6-2.5)). Lymphocyte subpopulations study showed the absence of B cell anda decreased CD4+. CVID was diagnosed,within the spectrum of late onset combined immunodeficiency (LOCID). Intravenous immunoglobulins improved mildly, with no real digestive remission. Finally, genetic analysis revealed a homozygous mutation in the LRBA gene. Our patient is a candidate for abatacept.

Conclusions: This is the first report of LRBA deficiency in Morocco, where using biologics may significantly improve prognosis, after 24 years of diagnosis delay. WES is a promisisng tool to uncover diseases hidden under the CVID umbrella.

Disclosure: No.

Keyword: Immune deficiency disease. Common variable immune deficiency (CVID). Autoimmunity. LRBA deficiency

PD286

GENETIC PROFILE of PATIENTS WITH HEREDITARY ANGIOEDEMA AT A TERTIARY CARE REFERRAL HOSPITAL IN NORTH INDIA

POSTER DISPLAY 06: GENETICS IN IEI

. Sanchi[1], Anit Kaur[1], Rahul Tyagi[1], Ankur Jindal[1], Reva Tyagi[1], Prabal Barman[1], Sanghamitra Machhua[1], Archan Sil[1], Anuradha Bishnoi[2], Sunil Dogra[2], Vinay Keshavmurthy[2], Saniya Sharma[1], Amit Rawat[1], Deepti Suri[1], Priyankar Pal[3], Surjit Singh[1]
[1]Postgraduate Institute of Medical Education and Research, Department of Pediatrics, Advanced Pediatrics Centre, Chandigarh, India, [2]Postgraduate Institute of Medical Education and Research, Department of Dermatology, Venereology And Leprology, Chandigarh, India, [3]Institute of Child Health, Kolkata, Institute of Child Health, Kolkata, West Bengal, India

Background and Aims: Hereditary angioedema (HAE) is an uncommon genetic disorder with autosomal dominant mode of inheritance. Most cases of HAE are caused by pathogenic variants in SERPING1 gene. There is paucity of literature on genetics of HAE from India. We aim to study genetic landscape of patients with HAE from North India.

Methods: Genetic studies of patients suspected to have HAE were carried out either using SERPING1 gene sequencing or targeted next generation sequencing or whole exome sequencing. MLPA for SERPING1 gene was carried out in a few patients.

Results: We included 145 patients from 53 families. Exonic variants in SERPING1 gene in 25 families were reported. Eight families had variants in exon 7. Five families had variants in exon 8. Four families had variants in exon 3 and exon 6 each. Two families had variants in exon 5. Variant in exon 4 and exon 2 was found in 1 family each. Most common type of variant was missense followed by frameshift, nonsense and small deletion. Seven exonic variants detected were novel. Four families had variants in intron 6. Variant in intron 1, intron 2 was found in one family each. Eight families had no pathogenic variant. Llarge deletion in exon 8 of 1 family was confirmed through MLPA. Variants in XPNEP2 and CPN1 gene were found in one family each.

Conclusions: Genetic profile of patients with HAE in India may be different from that reported from other countries. Most variants are seen in the later part of the gene (i.e. exon 7 and 8).

Disclosure: No.

Keywords: Introns, Hereditary Angioedema, Next generation sequencing, Variants, Exons

PD287

PATIENT WITH GRANULOMAS, RECURRENT INFECTIONS AND ENTEROPATHY. ASSOCIATION of DEFECTS IN TAP2 AND NOD2.

POSTER DISPLAY 06: GENETICS IN IEI

Ileana Moreira, Maria Tejada, Agostina Llarens, Analia Seminario, Andrea Gómez Raccio, Daniela Di Giovanni, Patricia Carabajal
Hospital de Niños Ricardo Gutiérrez, Immunology, Buenos Aires, Argentina

Background and Aims: Scientific advances and greater accessibility to genetic studies allow diagnoses of different pathologies that present the same phenotype. We present the case of a patient with granulomas, recurrent infections and enteropathy whose clinical picture could be explained by the variants found in two different genes.

Methods: Review of clinical history.

Results: Clinical Case: Male patient, 5 years old, recurrent infections (suppurative otitis, pneumonias) and granulomatous lesions on both elbows. He has skin biopsies reporting granulomatous dermohypodermitis with necrobiosis No germ was found. No relevant family history. Normal immunoglobulins, inadequate antibody response to protein antigens. Normal number of B cells with decreased memory B cells and elevated transitional B cells. Normal CD4+ T cells and NK cells but CD8 lymphopenia. Normal DHR test. The patient consult 4 years later due to persistence of granulomatous lesions and newly recurrent perianal fistulas. Intestinal biopsy reported lymphoid follicular hyperplasia. A panel of genes is requested that reports a likely pathogenic variant, in homozygous state, in NOD2 and two pathogenic variants in TAP2. MHC class 1 expression by cytometry is pending.

Conclusions: The variants in TAP2 would explain a large part of the patient's clinical picture, but the variants in NOD2 could be responsible for his gastrointestinal manifestations. It is important to be able to carry out functional studies that help us elucidate the causation of each variant in the different clinical manifestations of the patient in order to define an adequate treatment.

Disclosure: No.

Keywords: Enteropathy, NOD2, TAP2, granulomas, recurrent infections

PD288

FOXI3 HAPLOINSUFFICIENCY CONTRIBUTES TO LOW T CELL RECEPTOR EXCISION CIRCLES AND T CELL LYMPHOPENIA.

POSTER DISPLAY 06: GENETICS IN IEI

Magdalena Walkiewicz-Yvon[1], Rajarshi Ghosh[1], Marita Bosticardo[2], Sunita Singh[3], Morgan Similuk[1], Ottavia Delmonte[2], Francesca Pala[2], Christine Peng[4], Colleen Jodarski[1], Michael Keller[4], Ivan Chinn[5], Andrew Groves[3], Luigi Notarangelo[2], Javier Chinen[5], Vanessa Bundy[4]
[1]National Institutes of Health, National Institute of Allergy And Infectious Diseases, Dir, Bethesda, United States of America, [2]Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, Niaid, Nih, Bethesda, United States of America, [3]Baylor College of Medicine, Department of Neuroscience, Houston, United States of America, [4]Children's National Hospital, Department of Allergy And Immunology, Washington, United States of America, [5]Baylor College of Medicine, Pediatrics-allergy And Immunology, Houston, United States of America

Background and Aims: Newborn screening can identify neonatal T cell lymphopenia (TCL) through the detection of low copies of T cell receptor excision circles (TRECs) in dried blood spots collected at birth. Identifying the underlying genetic etiology is necessary to guide subsequent clinical management and family planning. We sought to elucidate the molecular basis of patients with TCL without an apparent genetic diagnosis.

Methods: We used genomic testing, functional and immunological assays to identify and elucidate the genetic and mechanistic basis of TCL.

Results: We identified two unrelated males with abnormal TREC level at birth and non severe T-cell lymphopenia, with heterozygous truncating variants [c.280C>T (p.Gln94Ter) and c.74_75dup (p.Ala26Profs*116), respectively] in forkhead box I3 transcription factor, *FOXI3*. We performed a dual luciferase assay using the FOXI3-responsive AE4 promoter in which both variants showed the same low level of transcriptional activation as the control mock vector, consistent with nonsense mediated mRNA decay of *FOXI3* transcript. Utilizing the artificial thymic organoid (ATO) system, we determined that $CD34^+$ cells isolated from the individual with p.Gln94Ter variant retained the ability to differentiate into $CD4^+CD8b^+$ double positive and $TCRab^+CD3^+$ cells, with absolute count/ATO similar to controls, suggesting that FOXI3 haploinsufficiency is not affecting the T cell differentiation ability of hematopoietic stem and progenitor cells, but rather, the lymphopenia is likely caused by defects in thymic tissue functionality and/or development caused by the lack of FOXI3.

Conclusions: Our findings support the notion that haploinsufficiency of FOXI3 results in TCL and that FOXI3 may be a key modulator of thymus development.

Disclosure: No.

Keyword: T cell lymphopenia; FOXI3; T-cell receptor excision circles

PD289

NOVEL HYPERMORPHIC VARIANTS IN IRF2BP2 IDENTIFIED IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY AND AUTOIMMUNITY

POSTER DISPLAY 06: GENETICS IN IEI

Manfred Anim[1], Georgios Sogkas[1], Nadezhda Camacho-Ordonez[2], Natalia Dubrowinskaja[1], Michele Proietti[3], Torsten Witte[1], Bodo Grimbacher[4], Faranaz Atschekzei[5]
[1]Hannover Medical School, Rheumatology And Immunology, Hannover, Germany, [2]University Medical Center Freiburg, Institute For Immunodeficiency, Freiburg im Breisgau, Germany, [3]University Medical Center Freiburg, Center For Chronic Immunodeficiency, Freiburg, Germany, [4]Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany, [5]Hannover Medical School, Rheumatology/immunology, Hannover, Germany

Background and Aims: The nuclear IRF2BP2 protein (IFN regulatory factor 2 binding protein 2 was initially identified as a transcriptional corepressor dependent on Interferon regulatory factor-2 (IRF-2). Variants in *IRF2BP2* have recently been reported in familial CVID, immune dysregulation, and inflammatory conditions. This study investigated three rare novel variants identified in patients with primary antibody deficiency and autoimmunity by whole exome-sequencing (WES).

Methods: Following transient overexpression of EGFP-fused mutants in HEK293 cells and transfection in Jurkat cell lines, we used fluorescence microscopy, real-time PCR and Western blotting to analyze their effects on IRF2BP2 expression, subcellular localization, nuclear translocation of IRF2, and the transcriptional activation of NFkB1(p50) following stimulation.

Results: We found altered IRF2BP2 mRNA and protein expression levels in the mutants compared to the wildtype after IRF2BP2 overexpression. In confocal fluorescence microscopy, variants located in the C-terminal RING finger domain showed an irregular aggregate formation and distribution instead of the expected nuclear localization compared to the variants in the N-terminal zinc finger domain and their wildtype counterpart. Immunoblotting revealed an impaired IRF2 and NFκB1 (p50) nuclear localization in the mutants compared to the IRF2BP2 wildtype counterpart. LPS stimulation reduced both the expression and localization of IRF2BP2 to the nucleus.

Conclusions: Our data provide additional evidence for the clinical significance of *IRF2BP2* mutations in the pathogenesis of immunodeficiency and immune dysregulation. It suggests an impairment of the nuclear translocation of IRF2 and NFκB1 (p50) due to the upregulation of IRF2BP2, which may affect specific gene expression, involved in *immune regulation.*

Disclosure: No.

Keywords: primary immunodeficiency, IRF2BP2 (IFN regulatory factor 2 binding protein 2), NFκB1 (p50), CVID, Immune Dysregulation

PD290

GENIA DB - THE GENETIC IMMUNOLOGY ADVISOR DATABASE

POSTER DISPLAY 06: GENETICS IN IEI

Andrés Caballero-Oteyza[1], Xiao Peng[2], Laura Crisponi[3], Bodo Grimbacher[4], Michele Proietti[1]
[1]Department of Rheumatology and Clinical Immunology, Hannover Medical University, Hannover, Germany, [2]University Hospital Freiburg, Center For Chronic Immunodeficiency, Freiburg, Germany, [3]Consiglio Nazionale delle Ricerche (CNR), Istituto Di Ricerca Genetica E Biomedica (irgb), Monserrato, Italy, [4]Satellite Center Freiburg, Resolving Infection Susceptibility (resist) - Cluster of Excellence 2155 To Hannover Medical School, Freiburg, Germany

Background and Aims: There is currently no single database - whether OMIM, ClinVar, INFEVERS, or other – that has been able to capture in depth the vast realm of Inborn Errors of Immunity (IEI)-specific data. Many IEIs are multi-system disorders that may present at the doorstep of any clinician. However, the number of specialists comfortable with these conditions remains limited. Therefore, we aimed to develop a comprehensive public database (GenIA) that could collect this vast and complex information and that could become a reference for clinicians, geneticists and researchers.

Methods: GenIA is written in SQL and is accessible through a PHP-based web-application (geniadb.net). The stored demographic, genetic, clinical, functional and laboratory data has been extracted from the manual curation of published research articles. No sensitive or identifiable information is collected.

Results: Unlike other databases, which lack dimensions or are populated with largely computational and non-curated information, GenIA can store the specific considerations, pitfalls and diagnostic paradigms for each gene, its associated genetic conditions with their pathomechanism(s), and all reported variants and subjects with all their clinical manifestations and lab data. Our results show that some IEIs are not recognized in other public databases, such as OMIM, and that critical clinical information associated with a gene or genetic condition can be absent in widely used resources, such as HPO.

Conclusions: GenIA can be a practical tool for scientists and physicians to help inform their diagnostic strategies, interpretation of results, and/or patient counseling. GenIA could improve the current diagnostic odyssey that patients go through before getting the most appropriate treatment.

Disclosure: No.

Keywords: IEI, Immunogenetics, diagnostics, Genetics, database

PD291

NOVEL MUTATION IN TWO SIBLINGS WITH XLA WITH A HETEROGENOUS LEAKY PHENOTYPE

POSTER DISPLAY 06: GENETICS IN IEI

Eleanor Lee, Javeed Akhter, Divya Ramachandra
Advocate Children's Hospital, Pediatrics, Oak Lawn, United States of America

Background and Aims: X-linked agammaglobulinemia is caused by Bruton Tyrosine Kinase gene mutation, resulting in low B cell and immunoglobulin levels. We present two children with a leaky phenotype of XLA who have a novel c.1361A>C mutation.

Methods: We searched PubMed for case reports published in the past 10 years using keyword “BTK mutation XLA".

Results: We found 97 articles on PubMed pertaining to BTK mutation and XLA, of which 23 reported novel mutations. To our best knowledge, missense mutation c.1361A>C [p.His454Pro] has not yet been reported. Our proband is a 3-year-old Mexican male presented with *Haemophilus influenzae* meningitis, bacteremia, and septic arthritis. Immune workup showed severely low IgG, IgA, and IgE levels. Unexpectedly, patient was making IgM. The lymphocyte subset revealed absent CD19+ B lymphocytes. Patient was diagnosed with XLA and responded well to IVIG. History revealed his male sibling and maternal uncle died of infection in childhood. His five-year-old sibling has the same mutation with nearly normal IgG and low levels of IgA and IgM.

Conclusions: These two patients demonstrate an unusual phenotype of XLA caused by a novel mutation. Until his severe illness at 3 years of age, the proband had normal growth and no neutropenia. It is also worth noting his normal IgM level, albeit a bit low. His deceased brother and uncle may have had XLA. Another older sibling with the same mutation but a milder phenotype speaks to the heterogeneity of this mutation. Lastly, the data on BTK mutation in XLA patients with LatinX ethnicity is limited, and further study is needed.

Disclosure: No.

Keywords: XLA, novel mutation, BTK, leaky presentation, atypical

PD292

GENETIC DIAGNOSIS of INBORN ERRORS of IMMUNITY: A SINGLE TERTIARY CENTER EXPERIENCE IN TURKEY

POSTER DISPLAY 06: GENETICS IN IEI

Figen Çelebi Çelik, Özgen Soyöz, Idil Akay Haci, Mehmet Kaya, Ayça Demir, Nesrin Gülez, Ferah Genel
DR. BEHCET UZ PEDIATRIC DISEASES AND SURGERY TRAINING AND RESEARCH HOSPITAL, Pediatric Allergy And Immunology, Izmir, Turkey

Background and Aims: Human inborn errors of immunity (IEI) are rare diseases with a wide range of clinical phenotypes ranging from mild to life-threatening. In this study, it was aimed to examine the genetic diagnoses of patients with IEI, to reveal the change in the interval between clinical and genetic diagnosis according to years, and to reveal the effect of genetic diagnosis on patient management and treatment.

Methods: We retrospectively reviewed the medical records of patients in our clinic between 2005-2021. Patients' demographic,clinical and genetic data, time to reach genetic diagnosis, and effects of genetic diagnosis on treatment process were examined.

Results: Five hundred one patients who reached the genetic diagnosis were included in the study. There was a genetic diagnosis of IEI compatible with the clinical phenotype in 289 patients (57.7%). Although the rates of reaching genetic diagnosis were higher in autoinflammatory diseases (94.7%), syndromic CID (88.3%), complement diseases (76.2%), CID and SCID (72.1%), they were lowest for primary antibody deficiencies (36.4%) ($p<0.001$). The interval between clinical diagnosis and genetic diagnosis was median 12 months. While the interval between clinical and genetic diagnosis according to the birth years of the patients was 52.8±70.8 months on average in those born before 2000, it was found to be shorter with 9.2±10.6 months for those born after 2015 ($p<0.001$).

Conclusions: As a result of the increase in the diagnostic success of IEI with the routine use of genetic analysis; it has been made possible for patients to access reliable and effective treatments and to provide more effective genetic counseling to families.

Disclosure: No.

Keywords: Inborn errors of immunity, genetic, primary immunodeficiency, DIAGNOSIS

PD293

SCREENING of ELANE GENE IN PATIENS WITH NEUTROPENIA AND THEIR PARENTS

POSTER DISPLAY 06: GENETICS IN IEI

Mariana Hernandez Peralta[1], Angelica Tamayo Hernández[1], Denisse Becerra Loaiza[2], Antonio Quintero Ramos[2], Juan Lona Reyes[3], Maria Enriqueta Nuñez Nuñez[4]
[1]Hospital Civil Nuevo de Guadalajara "Dr. Juan I. Menchaca", Departamento De Pediatria, Guadalajara, Jalisco, Mexico, [2]Universidad de Guadalajara, Departamento De Biología Molecular Y Genómica, Guadalajara, Mexico, [3]Hospital Civil Nuevo de Guadalajara "Dr. Juan I. Menchaca", Departamento De Infectologia Pediatrica, Guadalajara, Jalisco, Mexico, [4]Hospital Civil de Guadalajara “Dr. Juan I. Menchaca”, Jalisco, México., Servicio De Inmunología Clínica Y Alergias, Guadalajara, Mexico

Background and Aims: The most common cause of neutropenia are mutations in *ELANE* (Elastase, Neutrophil Expressed) gene (19p13.3), mostly in exon 5 and distal portion of exon 4. In this sense, missense mutations mediate mRNA declivity, resulting in different clinical phenotypes of neutropenia.

Methods: We reported the pathogenic mutation c.607G>C (p.Gly203Arg) and the identification of the novel mutation c.416C>G (p. Pro139Arg) resulting of the screening of *ELANE* gene in saliva of 3 cases with neutropenia and their parents in two families from Jalisco, México.

Results: We identified the pathogenic mutation c.607G>C (p.Gly203Arg) in two sisters diagnosed with congenital severe neutropenia having different father. Their mother is not apparently carrier of the mutation, also, her laboratorial studies are normal. Both sisters debuts at 12-14 days of birth with infections and sever neutropenia without improvement, making an early diagnosis. As well, for the first time report the mutation c.416C>G (p. Pro139Arg) classified as pathogenic by *in silico* predictions in a 6-year-old boy diagnosed with clinical phenotype of cyclic neutropenia, derived from parents not carriers and non-consanguineous. At 2y5m old was hospitalized secondary to respiratory tract infeccion, presenting clinical and laboratorial evidence of neutropenia, which behaves cyclically with periods of normalization, presenting recurrent infections in the upper respiratory tract, canker sores associated with fever and difficulty swallowing.

Conclusions: Identifying variants in patients with inborn errors of immunity is useful for early clinical management. Likewise, it is interesting to rule out possible mosaicism in apparently non-carrier parents with more than one case in the family.

Disclosure: No.

Keywords: ELANE, neutropenia, Screening, Familial

PD294

TITLE: EXCLUDED IGG SUBCLASS GENES IN SEVERE VIRAL INFECTIONS AND PRIMARY IMMUNODEFICIENCIES (PIDS)

POSTER DISPLAY 06: GENETICS IN IEI

Vivi-Anne Oxelius
Institute of Laboratory Medicine, Department of Pediatrics, Department of Clinical Immunology22185, Lund, Sweden

Background and Aims: Background and Aims: IgG subclass genes are assessed serologically by GM allotypes, genetic markers of the Fc part of immunoglobulin constant heavy G chains, *IGHG*(Fcg)(GM) genes, from chromosome 14q32.3, expressing antibodies, with different structures and functions, inherited the Mendelian way, with allelic exclusion and IgG3-IgG1 linkage disequilibrium. A variation of IgG subclass genes was reported in immunological diseases. 6 *IGHG*(Fcg)(GM) gene variants are assessed in health and disease with focus is on excluded *IGHG*(Fcg)(GM) genes.

Methods: Methods: A competitive ELISA is introduced, using purified GM allotype specific myeloma proteins and GM specific monoclonal antibodies, assessing two alternative GM allotypes of IgG3, IgG1 and IgG2, respectively, by quality and quantity: IgG3*b & IgG3*g, IgG1*f & IgG1*a, IgG2*n & IgG2*-n, precise entities. 4 IgG3-IgG1-IgG2 haplotypes are genetic markers of B-cells.10 individual diplotypes are registered in healthy Caucasians (587).

Results: Results: Excluded *IGHG*(Fcγ)(GM) genes are found both in health and disease. In healthy: 11% loss of IgG3*b & IgG1*f, 45% loss of IgG3*g &IgG1*a, 34% loss of IgG2*n and 22% loss of IgG2*-n. Significantly increased numbers of excluded *IGHG2*n* genes and loss of IgG2*n antibodies are found in severe viral RSV (55%), Kawasaki (55%) and in PIDs, CVID (75%) Wiscott-Aldrich syndrome (67%)., compared to healthy (34%).Virus act as FcgR and discriminate IgG subclass molecules. Severe virus infections have the same *IGHG*(Fcγ)(GM) gene pattern as PIDs, Early IVIG treatment is successful in Kawasaki syndrome.

Conclusions: Conclusions: *IGHG*(Fcγ)(GM) genes control human immunity and disease severity. Excluded IgG genes are treated with IVIG. *IGHG*(Fcγ)(GM) genes have impact on immunotherapy.

Disclosure: No.

Keywords: IGHG genes defined by allelic genes, Excluded IGHG2*n genes in severe viral disea and in PIDs, Individual IGHG diplotypes in health and disease, Excluded IgG subclass genes and loss of IgG subclass antikroppar, Excluded IGHG genes can be treated with IVIG, Individual IGHG diplotypes and innate lymphoid B cells in health and disease

PD295

CLARIFYING MIRAGES - A DILEMMA LEADING TO A DIAGNOSIS

POSTER DISPLAY 06: GENETICS IN IEI

Paul Torpiano[1], John Achermann[2], Emma Wakeling[3], Maaike Kusters[1], Catherine O'Sullivan[1]
[1]Great Ormond Street Hospital, Immunology, London, United Kingdom, [2]Great Ormond Street Hospital, Endocrinology, London, United Kingdom, [3]Great Ormond Street Hospital, Clinical Genetics, London, United Kingdom

Background and Aims: We present three cases of MIRAGE syndrome (a complex multisystem disorder which can include features of Myelodysplasia, recurrent Infections, Restriction of growth, Adrenal insufficiency, Genitourinary abnormalities, and Enteropathy) diagnosed due to concern regarding an underlying pathology when they were admitted for intensive care unit (ICU) support with life threatening SARS-CoV-2 pneumonitis.

Methods: These patients were receiving intensive care support for their SARS-CoV-2 pneumonitis. Although all three were born prematurely only one of the three had a supplemental oxygen requirement prior to the SARS-CoV-2 infection, and it was felt unusual that they had become so unwell with the infection. Immunology and Clinical Genetics Teams were consulted. MIRAGE syndrome is due to gain of function mutations is the sterile a motif domain-containing protein 9 (SAMD9) on the long arm of chromosome 7.

Results: On rapid trio sequencing (R14 panel) for acutely unwell children with a likely monogenic disorder all three patients were found to have SAMD9 variants consistent with MIRAGE syndrome. Their immunophenotyping with normal IgG in 2/3, lymphopenia with normal naïve T lymphocytes in 2/3, and normal responses to mitogen stimulation but alongside susceptibility to infections (including other respiratory viral infections, *Pneumocystis jirovecii,* and *Aspergillus fumigatus)* was consistent with previous descriptions.

Conclusions: Identifying their diagnosis has given all three patients the benefits of multi-disciplinary care (with increased experience of the teams caring for them and national/international collaborative working), individualised management, the opportunity of support from other MIRAGE families, monosomy 7 surveillance, and early interventions such as immunoglobulin replacement therapy and antimicrobial prophylaxis.

Disclosure: No.

Keyword: MIRAGE, SAMD9, covid

PD296

CHILDHOOD VASCULITIS UNMASKING INBORN ERRORS of IMMUNITY

POSTER DISPLAY 06: GENETICS IN IEI

Andreea Ioan, Alexis Virgil Cochino, Oana Maria Farkas
National Institute for Mother and Child Alessandrescu Rusescu, Immunology, Bucharest, Romania

Background and Aims: Non-infectious manifestations unmasking dysregulated immune responses are the new "red flags" of inborn errors of immunity (IEI). We retrospectively describe clinical and laboratory features of paediatric vasculitis cases, with a focus on those proven as IEI.

Methods: We reviewed medical records of paediatric vasculitis cases from 2004 to 2021. Patients with atypical clinical features, early onset, or familial aggregation underwent genetic testing through NGS panel testing.

Results: We included 160 children with a sex ratio of 1.02 (M/F) and a median age at diagnosis of 6.2 years (range 0.2 - 17.8). IgA vasculitis was the most common (52 patients, 32%), followed by Kawasaki disease (KD) (36 patients, 22%) and limited cutaneous vasculitis (27 patients, 16%). Median age in years was 2.3 in KD (95% CI 1.5-3.2), 7.1 in IgA vasculitis (95% CI 6-8.3) and 10 in cutaneous vasculitis (95% CI 8.1-11.90, $p<0.01$. We found ADA2 disease-causing mutations in 3/7 patients initially diagnosed as Behcet's disease (time from onset 1-14 years; one fatal outcome) and in two others with early systemic vasculitis (fever, strokes) and immunodeficiency.

Conclusions: Our recent increased access to genetic testing allowed the right diagnosis – ADA2 deficiency – in five paediatric vasculitis cases. Childhood vasculitis, particularly Behcet's disease, represents a rare entity that can prove to be an IEI. Early complete diagnosis and treatment of monogenic vasculitis are needed to prevent possible life losses.

Disclosure: No.

Keywords: DADA2, Inborn errors of immunity, immunodeficiency, Vasculitis, Adenosine deaminase 2

PD297

A TRIPLE NEWBORN SCREENING STRATEGY FOR INBORN ERRORS of IMMUNITY: A RETROSPECTIVE STUDY OVER 10-YEARS IN TUSCANY

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Valentina Guarnieri[1,2], Caterina Pelosi[1,2], Valeria Astorino[1,2], Clementina Canessa[1,2], Martina Cortimiglia[1,2], Elisa Calistri[1,2], Lorenzo Lodi[1,2], Francesca Lippi[1,2], Francesca Capitanini[2], Giancarlo La Marca[1,2], Chiara Azzari[1,2], Silvia Ricci[1,2]
[1]Meyer Children Hospital, Pediatrics, Florence, Italy, [2]University of Florence, Department of Health Sciences, Florence, Italy

Background and Aims: Inborn errors of Immunity (IEIs) are characterized by an increased susceptibility to life-threatening infectious diseases, severe autoimmunity/autoinflammation and high mortality rate in infancy. Early diagnosis through newborn screening (NBS) allow pre-emptive treatment and tailored follow-up. We aim to share our 10-years-experience (2011-2021) of a triple NBS strategy for IEIs started in Tuscany (Italy) as a pilot project in 2011 and become mandatory since October 2018.

Methods: T-cell receptor excision circles (TREC) and Kappa-deleting recombination excision circles (KREC) were quantified simultaneously by quantitative RT-PCR on dried blood spots; adenosine deaminase (ADA)/purine nucleoside phosphorylase (PNP) metabolites were detected by tandem mass spectrometry (TMS). Patients with abnormal values underwent clinical evaluation, lymphocyte subset and/or genetic analysis.

Results: ADA/PNP metabolites were tested in 349,788 newborns with a retest rate of 0.004% and a referral rate to clinician of 0.0006%. TREC/KREC were evaluated in 108,158 newborns with a retest rate of 0.41 % and 0.37% and a referral rate of 0.03% and 0.06% respectively. During the 10-year screening period, 10 IEIs were diagnosed (2 by TMS only, 6 by TREC only and 2 by KREC only): 2 ADA-SCID (1 late onset; 1 delayed onset), 1 JAK3-deficient severe combined immunodeficiency, 1 cartilage-hair hypoplasia with combined immunodeficiency, 4 severe lymphopenia (1 with Blackfan-Diamond syndrome; 3 DiGeorge syndrome), 2 agammaglobulinemia (1 NBAS deficiency; 1 Zellweger syndrome).

Conclusions: A triple strategy significantly enhances NBS sensitivity, driving up the incidence of IEIs to 1:12,018 in Tuscany.

Disclosure: No.

Keywords: IEI, newborn screening, tandem mass spectrometry, TREC, KREC

PD298

ASSESSING THE FUNCTIONAL RELEVANCE of CTLA4 VARIANTS: THE EXPERIENCE of THE CENTER FOR CHRONIC IMMUNODEFICIENCY IN FREIBURG, GERMANY

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Jessica Rojas Restrepo[1,2,3], Elena Sindram[1,2,3,4], Marie-Céline Deau[2,3], Andrés Caballero-Oteyza[2,3,5], Michele Proietti[2,3,5,6], Noriko Mitsuiki[2,3], Simon Zenke[2,3], Jan Rohr[2,3], Laura Gámez-Díaz[2,3], Bodo Grimbacher[2,3,5,7,8,9]
[1]Faculty of Biology, Albert-ludwigs-university of Freiburg, Freiburg, Germany, [2]Center for Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg, Germany, [3]Institute for Immunodeficiency, University Medical Center Freiburg, Freiburg, Germany, [4]Spemann Graduate School of Biology and Medicine (SGBM), Albert-ludwigs-university of Freiburg, Freiburg, Germany, [5]Resolving Infection Susceptibility (RESIST) - Cluster of Excellence 2155 to Hannover Medical School, Satellite Center Freiburg, Freiburg, Germany, [6]Department of Rheumatology and Clinical Immunology, Hannover Medical University, Hannover, Germany, [7]German Center for Infection Research (DZFI), Satellite Center Freiburg, Freiburg, Germany, [8]Center for Integrative Biological signaling Studies (CIBSS), Albert-ludwigs-university of Freiburg, Freiburg, Germany, [9]Department of Rheumatology and Clinical Immunology, University Medical Center Freiburg, Freiburg, Germany

Background and Aims: Heterozygous mutations in the human Cytotoxic T lymphocyte antigen 4 (CTLA4) result in an immune dysregulation syndrome known as CTLA4 insufficiency. CTLA4 is a negative immune regulator expressed on regulatory and activated T-cells. CTLA4 outcompetes CD28 for their shared ligands CD80 and CD86 to engulf them in a process called transendocytosis. Variants in CTLA4 are frequently identified in antibody deficiency and immune dysregulation cohorts. However, the functional relevance of each variant needs to be determined before a diagnosis can be made.

Methods: Here, we share our experience at the Center for Chronic Immunodeficiency in Freiburg, Germany, at assessing the impact of CTLA4 variants in CTLA4-mediated transendocytosis. Isolated CD4+ T-cells from CTLA4 carriers were co-cocultured with CD80-mScarlet or CD80-GFP expressing CHO (Chinese Hamster Ovarian) cells. The ability of T-cells to engulf CD80-fluorescent ligands was analyzed by flow cytometry.

Results: We have analyzed 42 healthy donors and 31 patients with heterozygous mutations in CTLA4. These mutations included 21 missense, four frameshift and two splice site variants. Nineteen were located in the ligand-binding domain, five in the transmembrane domain, one in the intracellular domain, and two at the splice site in intron 1. Transendocytosis was reduced for 22 CTLA4 variants, four tested normal, and for one results were inconclusive. The latter mutation (p.G109E) found in four different patients was measured reduced in one patients and normal in the other three patients.

Conclusions: Most but not all heterozygous mutations in CTLA4 reduced CD80-transendocytosis in our patient cohort, demonstrating the relevance of functional testing.

Disclosure: No.

Keywords: Transendocytosis, diagnostics, Immune Dysregulation, CTLA4

PD299

NEWBORN SCREENING FOR X-LINKEND AGAMMAGLOBULINEMIA: THE NEED FOR SECOND-TIER TESTING

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Maartje Blom[1], Ingrid Pico-Knijnenburg[1], Sandra Imholz[2], Dagmar Berghuis[3], Mirjam Van Der Burg[1]
[1]Leiden University Medical Center, Laboratory For Pediatric Immunology, Department of Pediatrics, Leiden, Netherlands, [2]National Institute for Public Health and the Environment, Department For Biologicals, Screening & Innovation, Bilthoven, Netherlands, [3]Leiden University Medical Center, Pediatrics, Leiden, Netherlands

Background and Aims: Newborn screening (NBS) for X-linked agammaglobulinemia (XLA) and other B-cell deficiencies is based on quantification of kappa-deleting recombination excision circles (KRECs). Early detection of these disorders might prevent severe infections by timely intervention with immunoglobulin substitution. Screening based on KREC-detection would result in a high number of false-positive referrals associated with high impact for parents and health care systems, indicating the need for a second-tier test.

Methods: KRECs were measured in 110.000 newborns with a multiplex TREC/KREC qPCR assay. qPCR with different primers was performed on NBS cards of newborns with low KRECs. Epigenetic immune cell counting was used for relative quantification of B-cells in these samples. Additionally, Sanger sequencing of the BTK gene and rapid next-generation sequencing (NGS) with a B-cell deficiency panel were explored as second-tier test options as well.

Results: In total, 136/110,000 newborns had KRECs below cut-off, leading to a referral rate of 0.12%. With the alternative KREC-qPCR, 15% of these newborns (16/110) had KRECs above cut-off and would not have been referred. With epigenetic qPCR, 17% (18/103) had relative B-cell counts in the range of healthy controls. Sanger sequencing had a relatively low overall success-rate while rapid NGS with targeted panels showed promising results.

Conclusions: Several second-tier tests can potentially reduce the number of false-positive referrals in NBS for XLA. Genetic analyses seem to have an important role in the future of NBS for inborn errors of immunity. Our results show promising first steps towards the implementation of NBS for XLA with potential health gain for XLA patients worldwide.

Disclosure: No.

Keywords: XLA, KRECs, NBS, B-cell deficiency, newborn screening, x-linked agammaglobulinemia

PD300

DEVELOPMENT of A SCREENING ALGORITHM FOR THE EARLY DETECTION of PRIMARY ANTIBODY DEFICIENCIES IN PRIMARY CARE

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Marianne Messelink[1], Roos Berbers[1], Joris Van Montfrans[1], Pauline Ellerbroek[2], Frank Van Genderen[3], Paco Welsing[1], Helen Leavis[1]
[1]University Medical Center Utrecht, Department of Rheumatology & Clinical Immunology, Utrecht, Netherlands, [2]UMC Utrecht, Department of Internal Medicine, Utrecht, Netherlands, [3]Takeda Netherland B.V, Medical Affairs, Hoofddorp, Netherlands

Background and Aims: Primary antibody deficiencies (PAD) are characterized by a heterogeneous clinical presentation and low prevalence, contributing to a median diagnostic delay of 3-10 years. This increases the risk of morbidity and mortality from undiagnosed PAD, which could be prevented with adequate therapy. To reduce diagnostic delay in PAD, we developed a screening algorithm that identifies high-risk patients in a primary care setting.

Methods: Primary care electronic health record (EHR) data on presenting signs and symptoms of PAD were extracted and compared between PAD patients and control groups. Inclusion of items in the algorithm was based on their discriminatory value and clinical rationale.

Results: We analyzed the primary care EHRs of 30 PAD patients, 26 non-specified immunodeficiency patients and 58,223 control patients. The median diagnostic delay of PAD patients was 9.5 years. Several candidate items showed a clear difference in prevalence between PAD patients and controls, most notably the mean number of antibiotic prescriptions in the 4 years prior to diagnosis (5.14 vs. 0.48). The final algorithm included antibiotic prescriptions, diagnostic codes for respiratory tract- and other infections, gastro-intestinal complaints, auto-immune symptoms, malignancies and lymphoproliferative symptoms, as well as laboratory values and visits to the general practitioner.

Conclusions: The primary care screening algorithm presented in this abstract has the potential to reduce diagnostic delay in PAD. In addition to the results above, we will present the preliminary results of a prospective validation study, in which the screening algorithm is applied to 60,000 EHRs and high-risk individuals undergo laboratory evaluation.

Disclosure: This study was funded by Takeda Pharmaceuticals. HL and JM received consulting fees for Advisory Boards with Takeda Pharmaceuticals. RB received personal fees from Takeda Pharmaceuticals.

PD301

UNEXPECTED INFANT DEATHS – POSSIBLE ROLE of SEVERE COMBINED IMMUNODEFICIENCY (SCID) AND INBORN ERROR of IMMUNITY (IEI)? A NATIONWIDE POPULATION STUDY, 2012-2017.

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Jintana Andersen[1], Janne Strand[2], Asbjørg Stray-Pedersen[2], Arne Stray-Pedersen[3,4], Tore Abrahamsen[1,5,6], Hans Christian Erichsen[1,5,6]
[1]Oslo University Hospital, Centre For Rare Disorders, Oslo, Norway, [2]Oslo University Hospital, Dept. of Newborn Screening, Oslo, Norway, [3]University of Oslo, Dept. of Forensic Medicine, Oslo, Norway, [4]Oslo University Hospital, Div. of Laboratory Medicine, Oslo, Norway, [5]Oslo University Hospital, Paediatric And Adolescent Medicine, Oslo, Norway, [6]University of Oslo, Inst. of Clinical Medicine, Oslo, Norway

Background and Aims: Babies born with SCID or IEI are seemingly healthy at birth, but may become fatally ill in early life and can presumably go on unrecognized until death. We aimed to unravel the role of SCID and IEI as the cause of unexpected infant deaths.

Methods: We identified all children in Norway <2 years old who died during 2012-17 through the Norwegian Cause of Death Registry (NCoDR). Next, we reviewed the medical records of the deceased children registered with an ICD-10 code in the NCoDR of infections, sepsis, or sudden infant death syndrome (SIDS). Finally, blood samples collected for newborn screening were analysed to determine T-cell receptor excision circle (TREC) levels, and sequenced for SCID and IEI (~370) genes (NGS panel).

Results: of 352,915 live births during 2012-17, 907 children <2 years died. 11% (n=101) fulfilled our inclusion criteria. of these, 36 died due to a recognized infection. In this period, two of total 14 children with established SCID, died. These were not included. Samples from 75% (n=76) of the eligible children were available for genetic analyses. NGS screening did not reveal pathogenic genetic variants. Lowest TREC detected was 21.9/µl (cut-off <25/µl). We did not identify any IEI among the children who died with a recognized infection, nor in the group of children with SIDS (n=52).

Conclusions: This nationwide study covering six years and >350,000 live births, did not reveal any missed cases of SCID or IEI. In the SIDS group, no cases of IEI were identified.

Disclosure: No.

Keywords: Genetics, Diagnostic, SIDS, Nationwide, SCID, IEI

PD302

THE DIAGNOSTIC YIELD of NEXT-GENERATION SEQUENCING INCLUDING NONCODING VARIANTS AND HIGH-RESOLUTION CNV ANALYSIS IN THE DIAGNOSIS of INBORN ERRORS of IMMUNITY

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Kimberly Gall, Mari-Liis Lukke, Christèle Du Souich, Zoe Powis, Julie Hathaway, Alicia Scocchia, Elina Hirvonen, Päivi Kokkonen, Inka Saarinen, Matias Rantanen, Pertteli Salmenperä, Massimiliano Gentile, Jennifer Schleit, Lotta Koskinen, Jussi Paananen, Samuel Myllykangas, Juha Koskenvuo
Blueprint Genetics, Blueprint Genetics, Espoo, Finland, Finland

Background and Aims: Primary immunodeficiencies, or inborn errors of immunity (IEIs), are a group of inherited disorders affecting the immune system. Historically, diagnosis was based on clinical and laboratory assessment. IEIs' clinical presentations are diverse and they also overlap. Given the challenges of clinical diagnosis and the value of a molecular diagnosis, genetic testing is essential for these patients. Here, we report results from over 4,800 patients who underwent testing with 1 of 11 immunology-related panels including high-resolution copy number variant detection (CNV) and clinically relevant noncoding variants for the indication of IEI.

Methods: We retrospectively examined deidentified genetic test results from consecutive patients tested for IEI. Panel target regions generally included all coding exons, 20 base pairs at intron-exon boundaries, and select clinically relevant non-coding variants. CNV analysis was performed bioinformatically with 2 pipelines, including a proprietary pipeline designed for the detection of small (4 or less), exon-level CNVs. Variant interpretation was performed using a point-based modification of the ACMG guidelines.

Results: A diagnosis was achieved in 547 patients (11.2%); however, the diagnostic rate varied by panel and age at testing. Diagnostic variants in 158 genes were reported. CNVs contributed to the diagnosis in 56 patients (10%), with 18 (32%) being 4 exons or smaller. Non-coding variants contributed to the diagnosis in 21 patients (4%).

Conclusions: The use of comprehensive panels including detection of small CNVs and non-coding variants are key in the IEI population. They account for over 10% of the diagnostic yield in this large, unselected IEI cohort.

Disclosure: No.

Keywords: Copy number variants, Molecular diagnosis, Non-coding variants, Inborn errors of immunity, Multigene panel testing

PD303

PREVALENCE of MALIGNANCIES IN AN ITALIAN COHORT of PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY (CVID): A SINGLE CENTER RETROSPECTIVE STUDY.

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Alessandro Dell'Edera, Helena Buso, Patrick Bez, Riccardo Scarpa, Marcello Rattazzi, Carlo Agostini, Francesco Cinetto
Ca' Foncello Hospital-Treviso (University of Padua), Rare Disease Referral Center-internal Medicine, Treviso, Italy

Background and Aims: Approximately 70% of CVID present non-infectious complications. A recent meta-analysis reported a prevalence of malignancies of 8.6%. The aim of this study was to investigate the prevalence of cancer and associated clinical, immunological and genetic factors in a cohort of CVID.

Methods: In this retrospective monocenter cohort study, we investigated the relation between different forms of cancer, immune-mediated co-morbidities and B-cell subsets.

Results: 45/130 (34%) CVID patients were diagnosed with at least one cancer, including 25 subjects with malignant tumors, 10 with T-cell large granular lymphocytic leukemia and 16 with benign cancers. Focusing on malignant cancers, we found: 11 lymphomas, 5 gastric, 2 intestinal tumors, 5 non-melanoma skin cancer, 2 breast, 1 endometrial, 1 pancreatic, 1 melanoma. 9/44 patients developed more than one malignancy. The median time from CVID to cancer diagnosis was 13 years; 15 patients had 7 years delay in CVID diagnosis after the malignancy. Granulomatous disease ($p<0.001$), autoimmune cytopenia ($p=0.039$) and bronchiectasis ($p=0.007$) were significantly prevalent in the overall cancer group. We found a significant reduction of naive ($p=0.007$) and IgM/IgD+CD27+ (MZ) B cells ($p=0.011$) in such group. Results of genetic screening were available for 13 of 45 cancer patients; two presented pathogenic monoallelic variants in TNFRSF13B, one in NFKB2 and one in C8b.

Conclusions: Lymphoma and gastric cancer are the most frequent CVID-associated cancers. Granulomatous disease, reduction of MZ may be associated with the increase risk of malignancies. Further studies are needed to better define the role of immunologic phenotype and monogenic variant in the risk of cancer development.

Disclosure: No.

Keywords: Malignancy, gastric cancer, CVID, cancer, PADs, Lymphoma

PD304

PATHOGENIC LANDSCAPE IN GENES of PRIMARY IMMUNODEFICIENCIES

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Daria Sviridova[1], Dmitry Kolobkov[1], Serikbai Abilev[1], Lubov Salnikova[1,2]
[1]Vavilov Institute of General Genetics, The Laboratory of Ecological Genetics, Moscow, Russian Federation, [2]Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, The Laboratory of Molecular Immunology, Moscow, Russian Federation

Background and Aims: Understanding of genotype-phenotype relationships is important for genetic counselling and treatment decisions. To summarize modern knowledge on genetic variability in primary immunodeficiencies (PID) genes, we performed an analysis of genetic variants in 403 PID genes presented in the 2019 Update International Union of Immunological Societies (IUIS)[1].

Methods: In silico analysis of ClinVar and HGMD® databases.

Results: ClinVar and HGMD® included, respectively, 97004 (19.2% pathogenic/likely pathogenic) and 34743 (77.2% disease-causing) variants in PID genes (Fig. 1a). The assessment of GnomAD[2] population allele frequencies as a predictor of variant pathogenicity showed that ClinVar used more stringent classification criteria than HGMD® (Fig.1b). In the joint ClinVar/HGMD database, 94.7% and 83.7% of classifications were concordant for pathogenic and benign variants (Fig. 1c). The largest number of variants (33.5%) was reported for a new group of genes 'Bone marrow failure', which was included in the last IUIS version. These genes were mainly associated with cancer phenotypes. The proportion of pathogenic variants in different IUIS categories varied from 19.8% ('Immunodeficiencies affecting cellular and humoral immunity') to 52.6% ('Complement deficiencies') (Fig 1d). In ClinVar/HGMD, non-synonymous, mainly missense variants accounted for 64% of all variants. Missense variants mapped within protein domains were more often classified as pathogenic than those occurring outside of protein domains (Fig. 1e).

Conclusions: Our report described data on variability in PID genes and might be useful for the interpretation of future genetic findings in the field. References. 1.Tangye et al. J Clin Immunol. 2020; 40(1):24-64. 2. https://gnomad.broadinstitute.org/

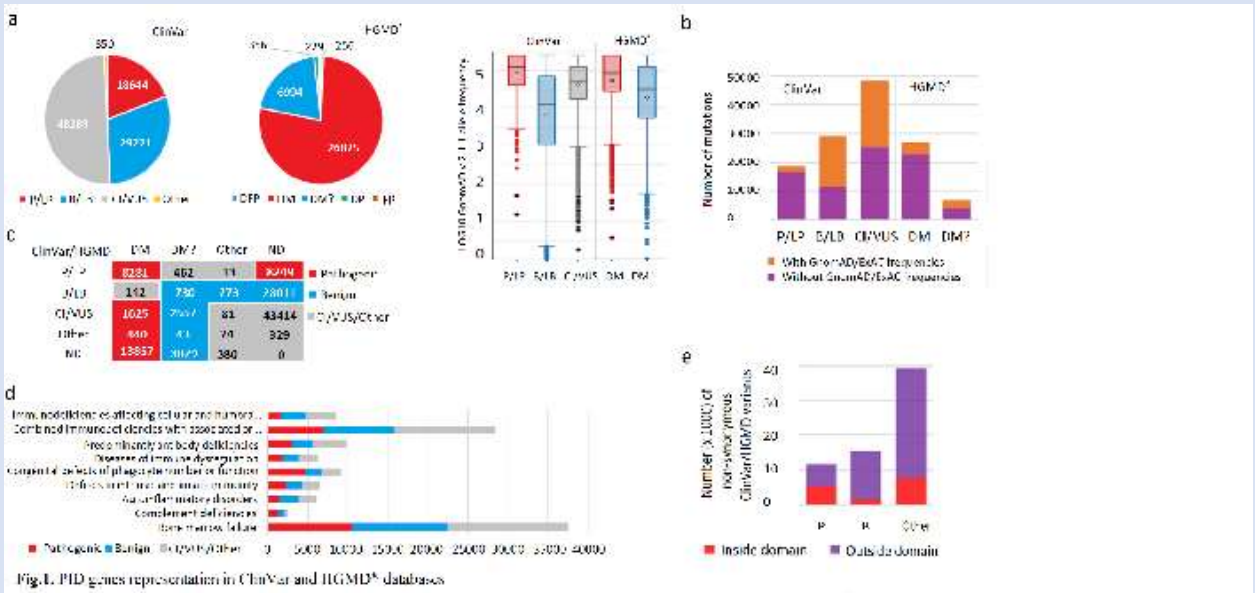


Fig.1. PID genes representation in ClinVar and HGMD® databases

Fig.1. PID genes representation in ClinVar and HGMD® databases

a Clinical significance of variations in ClinVar and HGMD® databases. **b** Proportion of variants with and without GnomAD /ExAC[2] frequencies in variant classes. **c** Classifications of variant in the joint ClinVar/HGMD database. **d** Total number and clinical significance of variants in genes assigned to IUIS categories. **e** Distribution of non-synonymous variants from ClinVar/HGMD inside/outside protein domains.
P/LP, pathogenic/likely pathogenic; B/LB, benign/likely benign; CI/VUS, conflicting evidence/variant with uncertain significance; DM, disease-causing mutation; DM?, likely disease-causing, but with questionable pathogenicity mutation; DP, disease-associated polymorphism; DFP, disease-associated polymorphism with additional functional evidence; FP, in vitro or in vivo functional polymorphism; ND, no data.

Disclosure: No.

PD305

ATRIP-DEFICIENT SECKEL SYNDROME PATIENT PRESENTS WITH IMMUNODEFICIENCY

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Lynn Backers[1], Simon Tavernier[2,3], Mattias Van Heetvelde[1], Bram Parton[1], Ria Roelandt[4], Evi Duthoo[5], Elien Beyls[5], Likun Du[6], Marieke De Bruyne[1], Kim De Leeneer[1], Levi Hoste[7], Victoria Bordon[8], Ans Baeyens[5], Anne Vral[5], Tessa Kerre[9], Qiang Pan-Hammarström[6], Filomeen Haerynck[10], Kathleen Claes[1]
[1]Ghent University, Biomolecular Medicine, Ghent, Belgium, [2]VIB, Vib-ughent Center For Inflammation Research, Laboratory of Molecular Signal Transduction In Inflammation, Ghent, Belgium, [3]Ghent University, Department of Biomedical Molecular Biology, Ghent, Belgium, [4]VIB-UGent Center for Inflammation Research, Vib Single Cell Core, Ghent, Belgium, [5]Ghent University, Human Structure And Repair, Ghent, Belgium, [6]Karolinska Institutet, Bionut, Huddinge, Sweden, [7]Ghent University Hospital, Pediatric Pulmonology, Infectious Diseases And Immunology, Ghent, Belgium, [8]Ghent University Hospital, Pediatric Hemato-oncology, Gent, Belgium, [9]Ghent University Hospital, Department of Hematology, Ghent, Belgium, [10]Ghent University Hospital, Department of Pediatric Pulmonology And Immunology And Pid Research Lab, Ghent, Belgium

Background and Aims: We report the second ATRIP-deficient patient clinically diagnosed with Seckel Syndrome (SS). The ATRIP protein is implemented in the DNA damage response pathway as the partner in crime of key player ATR. Besides the typical clinical SS characteristics (primary dwarfism, facial dysmorphia, skeletal abnormalities, microcephaly and mental retardation), our patient suffers from a combined immunodeficiency disorder. However a role for the ATR-ATRIP complex during the development or functioning of the immune system has not been thoroughly investigated and remains largely unclear.

Methods: Whole exome sequencing, transcriptomics, western blot, micronucleus assays, flow cytometry and single cell RNA-Sequencing.

Results: The patient was found to be homozygous for a splice variant (c.829+5G>T) in ATRIP leading to out-of-frame exon 5 skipping. RT-PCR showed no expression of the wild type allele, confirmed by Western blot that showed absence of the ATRIP protein. A micronucleus assay revealed defective DNA repair. The effect on downstream substrates of the ATR-ATRIP complex are currently being investigated. No other pathogenic variant was identified in 460 PID genes by WES, while peripheral blood analysis and immunophenotyping revealed CD4/CD8 inversion, decreased B and T cell maturation, IgG subclass deficiencies, T cell oligoclonality. First results of single cell RNA-Seq point towards a recombination deficiency during B and T cell development, as was published for ATR-deficient SS patients (doi:10.1084/jem.20050595), and allows to further elaborate the immune phenotype in great detail.

Conclusions: We expanded the molecular and clinical spectrum of Seckel syndrome and further validations will provide insights into the possible link between the ATR-ATRIP pathway and the immune system.

Disclosure: No.

Keywords: Seckel Syndrome, DNA Damage Response, VDJ Recombination, ATRIP-ATR pathway, Class Switch Recombination (CSR), Combined Immune Deficiency (CID)

PD306

INDETERMINATE INTERFERON GAMMA RELEASE TUBERCULOSIS ASSAY AS A WARNING SIGN FOR PID

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Marianna Tzanoudaki[1], Georgia Koltsida[2], Konstantinos Zachos[3], Elisavet Georgiadou[2], Eleni Christakou[4], Sofia Tantou[1], Rediona Kane[1], Virginia Polaki[1], Olga Vougiouka[5], Manolis Liatsis[1]
[1]"Aghia Sophia" Children's Hospital, Dept. of Immunology & Histocompatibility, Athens, Greece, [2]"Aghia Sophia" Children's Hospital, 1st Pediatric Clinic National And Kapodistrian University of Athens, Athens, Greece, [3]"Aghia Sophia" Children's Hospital, First Department of Pediatrics, Athens, Greece, [4]"Aghia Sophia" Children's Hospital, Pediatric Intensive Care Unit, Athens, Greece, [5]P & A Kyriakou Children's Hospital, Second Department of Pediatrics, National And Kapodistrian University of Athens, Athens, Greece

Background and Aims: Interferon-γ release assays (IGRAs) for M. tuberculosis (Mtb) are functional assays of antigen specific T cell immunity, based on T-cell stimulation with PMA or Mtb antigens. Indeterminate results due to failure of IFN-γ production post PMA stimulation may reflect underlying immune defects. However, this is often disregarded, as results are usually evaluated by non-immunologists. We aim to report a series of PID cases initially suspected by or related to non-interpretable IGRA results.

Methods: Among 821 in-tube IGRAs performed, 42 were indeterminate. In the absence of any known immunosuppression, repetition of the test was requested, when possible. 5 patients with persistently non interpretable results were investigated for PID. IL-12/IFN-γ axis was evaluated in 3 patients. Lymphocyte proliferation test (LPT) was performed in 2.

Results: of the total 42 cases with indeterminate in-tube IGRA, and the 5 highly suspicious cases, there were 4 PID diagnoses. 2 patients with abnormal IL-12/IFN-γ axis assay had heterozygous STING1:c.841C>T and STAT3:c.454C>T mutations respectively. 1 patient had homozygous TREX1:c.137dupC discovered independently by WES. 1 additional patient had abnormal LPT results and a final leaky SCID diagnosis.

Conclusions: There is an elevated frequency of PID underlying indeterminate IGRAs. Raising awareness of the above among non-immunologists may enhance early referral to specialists and timely PID diagnosis. Surprisingly, most detected defects were not directly related to IL-12/IFN-γ axis, but rather to other signaling pathways, possibly down-regulating IFN-γ production.

Disclosure: No.

PD307

WEIGHTING THE FREE CHAINS: CHARACTERIZATION of FREE LIGHT CHAINS IN A COMMON VARIABLE IMMUNODEFICIENCY COHORT

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Pedro Alves[1], Helena Pires Pereira[1], Jóni Carvalho[1], Ângela Maresh[2], Cláudia Fidalgo[2], Rosário Cunha[2], Artur Paiva[3], Ana Todo Bom[1], Emília Faria[1], Frederico Regateiro[1]
[1]Centro Hospitalar e Universitário de Coimbra, Allergy And Clinical Immunology, Coimbra, Portugal, [2]Centro Hospitalar e Universitário de Coimbra, Clinical Pathology, Coimbra, Portugal, [3]Centro Hospitalar e Universitário de Coimbra, Flux Cytometry Unit - Clinical Pathology, Coimbra, Portugal

Background and Aims: Serum free light chains (sFLC) are a proposed biomarker for Common Variable Immunodeficiency (CVID) diagnosis and may be associated with different clinical phenotypes. We aimed to explore this hypothesis in our CVID population.

Methods: Retrospective study with CVID patients (ESID criteria) evaluated at our Unit between January 2020 and March 2022. Demographic, clinical and laboratory data were collected from CVID patients and a control group. STATA 16.1 was used for statistical analysis.

Results: 36 CVID patients were included. The median age of disease onset was 36 years (IQR 27-41), 44.4% (n=16) were males. sFLC levels were measured in 30 patients (83.3%). Compared to the control group (n=190), CVID patients had lower levels of kappa (1.35 vs 17.80 mg/dL, p<0,001) and lambda sFLC (2.00 vs 16.15 mg/dL, p<0,001). Groups were similar in age, gender and sFLC ratio. Among CVID patients, low kappa (Rho 0.60, p<0.001) and lambda FLC (Rho 0.47, p=0.010) and their ratio (Rho 0.49, p=0.006) correlated with baseline IgG levels. FLC levels correlated with number of B Lymphocytes (k – Rho 0.53, p=0.005; l – Rho 0.49, p=0.009), but not with T Lymphocytes. Patients with a history of recurrent lower respiratory tract infections had lower levels of kappa (1.00 vs 3.45, p=0.029) and lambda sFLC (0.90 vs 2.20, p=0.023). No significant associations were observed with gender, age, microbial colonization, bronchiectasis, hepatosplenomegaly, rhinosinusitis, diarrhea, gastritis, colitis, arthritis, asthma/COPD, autoimmunity or neoplasia.

Conclusions: Our data suggests that sFLC may be promising markers to identify CVID subgroups at higher risk of lower respiratory tract infections.

Disclosure: No.

Keywords: primary, immunodeficiency, antibodies, free light chains, CVID

PD308

NEW AGE-MATCHED CRITERIA BETTER IDENTIFY LATE-ONSET COMBINED IMMUNODEFICIENCY AMONG PATIENTS WITH A DIAGNOSIS of COMMON VARIABLE IMMUNODEFICIENCY

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Martin Perez-Andres[1], Alba Torres Valle[1], Sonia De Arriba[2], Larraitz Aragon[3], Cristina Serrano[4], Susana Silva[5], Dolores Subira[6], Marta Ruiz Mercado[7], Miguel Marcos[8], Sandra Ines[8], Catarina Martins[9], Beatriz Albarran[10], Abelardo Barez[11], Guillermina Hurtado[12], Jana Neirinck[13,14], Pedro Pablo Arenas Cabo[3], Ignacio Madruga[8], Maria Jara[1], Carlos Prieto[15], Carolien Bonroy[13,14], Ana E. Sousa[5], Alvaro Prada[3], Jacques J.M. Van Dongen[1,16], Alberto Orfao[1]
[1]University of Salamanca (USAL), Cancer Research Centre (ibmcc, Usal-csic; Ciberonc Cb16/12/00400), Institute For Biomedical Research of Salamanca (ibsal), Department of Medicine And Cytometry Service (nucleus Research Support Platform), Salamanca, Spain, [2]Hospital Clin Univ Salamanca, Servicio De Pediatria, Salamanca, Spain, [3]Donostia University Hospital, Immunology Department, San Sebastian, Spain, [4]Fundacion Jimenez Diaz, Servicio De Inmunologia, Madrid, Spain, [5]Universidade de Lisboa, Instituto De Medicina Molecular João Lobo Antunes, Lisboa, Portugal, [6]Hosp Univ. Guadalajara, Flow Cytometry Unit, Guadalajara, Portugal, [7]Hospital Costa del Sol, Hematologia Y Hemoterapia, Marbella, Spain, [8]Hospital Clin Univ Salamanca, Servicio De Medicina Interna, Salamanca, Spain, [9]Faculdade de Ciências Médicas Universidade Nova de Lisboa, Nova Medical School, Lisboa, Portugal, [10]CAU Palencia, Hematology, Palencia, Spain, [11]Complejo Asistencial Avila, Servicio Hematologia, Avila, Spain, [12]Complejo Hospitalario de Navarra,, Servicio Hematologia, Pamplona, Spain, [13]Ghent University, Department of Diagnostic Sciences, Ghent, Belgium, [14]Ghent University Hospital, Department of Laboratory Medicine, Ghent, Belgium, [15]University of Salamanca, Bioinformatics Service (nucleus), Salamanca, Spain, [16]Leiden University Medical Cente, Department of Immunology, Leiden, Netherlands

Background and Aims: It has been suggested that a subset of common variable immunodeficiency (CVID) patients actually suffers from a more severe disease called late-onset combined immunodeficiency (LOCID). Several criteria based on naïve $CD4^+$ T-cell counts have been proposed for LOCID but without considering normal age-related ranges.

Methods: Ninety-seven CVID patients from eleven hospitals were studied by flow cytometry. Absolute naïve $CD4^+$ T-cell counts were normalized against the lower limit of normality (LLN) obtained from a cohort of 262 healthy donors (4-9y:359; 10-17y:249; 18-39y:127; 40-59y:112 and >60y:31 cells/µL). The new criteria, based on age-matched reference values, was compared to the DEFI (<20 naïve $CD4^+$ T-cells/µL) and Freiburg (<10% naïve $CD4^+$ T-cells) classifications.

Results: Overall, a greater percentage of patients was identified as LOCID with the new criteria (29%), compared to the DEFI (18%) and Freiburg (23%) criteria ($p<0.001$). This was due to the identification of significantly higher percentages of LOCID patients among the 18-39 (34% vs. 16% and 25%; $p<0.01$) and 40-59 age-groups (42% vs. 25% and 28%; $p<0.001$). A better discrimination of patients presenting with any of the three clinical complications typically associated with LOCID (autoimmune cytopenias, enteropathy and granulomas), when the new criteria was used (82% vs. 45%; $p=0.001$), as compared to the DEFI (73% vs. 49%; $p>0.05$) and Freiburg (77% vs. 49%; $p=0.02$) classifications.

Conclusions: Age-matched criteria for the identification of decreased naïve $CD4^+$ T-cell counts, among both children and adult CVID patients, results in a more sensitive diagnosis of LOCID, associated with worst clinical phenotypes, particularly for patients under 60 years.

Disclosure: No.

Keywords: CVID, Late onset combined immunodeficiency, naive CD4T-cells, age, Diagnostic, Cytometry

PD309

THE ROLE AND SIGNIFICANCE of FLOW CYTOMETRIC ANALYSIS IN THE EARLY DIAGNOSIS of INBORN ERRORS of IMMUNITY (IEI)

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Dilara Besli Celik[1], Sule Haskologlu[2], Deniz Guloglu[2], Dogan Kaymaz[1], Candan Islamoglu[2], Meltem Arikan[2], Avniye Baskin[2], Dugu Ugur[2], Nazli Deveci Demirbas[2], Figen Dogu[2], Aydan Ikinciogullari[2]
[1]Ankara University School of Medicine, Department of Pediatrics, Ankara, Turkey, [2]Ankara University School of Medicine, Department of Pediatrics, Division of Immunology And Allergy, Ankara, Turkey

Background and Aims: Flow cytometry (FC) is a technique of quantitative single-cell analyses serving as a diagnostic approach to inborn errors of immunity (IEI); mostly via phenotypic and functional assays or the evaluation of specific molecule expressions. In this study, we aimed to assess the usefulness of FC as an early and accurate diagnostic tool for IEIs.

Methods: The clinical and flow cytometric data of 1407 patients with IEI who were followed-up between 2010-2020, were evaluated retrospectively.

Results: Antibody deficiencies (67.8%), combined immunodeficiencies (CIDs) (12.2%), and combined immunodeficiencies with syndromic features (7.5%) were the most common PID subgroups among 1407 patients included in the study. FC analysis was performed in 996 (70.8%) of the patients. A definitive diagnosis achieved in 229 (23.0%) patients; mostly in severe combined immunodeficiencies (100%), phagocyte dysfunctions (95.6%) and CIDs (82.8%); via phenotypic cytometry in 16.2% (162/996), specific protein expression analysis in 50.9% (79/155), and functional analysis in 12% (101/836) of the patients. The median time between patient admission and flow cytometric diagnosis was found to be 4 days, ranging from 0 to 169.6 months whereas the median time between flow cytometric and genetic analysis was 12.4 (0.3-152.8) months.

Conclusions: The data revealed that FC is an invaluable diagnostic tool in IEI whereas early diagnosis is the most important factor for the curative treatment and prognosis. The abnormality detected by FC narrows the possible etiology and allows for a much quicker intervention in the disease process before the actual genetic abnormality can be specifically ascertained.

Disclosure: No.

Keywords: Inborn errors of immunity, flow cytometry, early diagnosis

PD310

VERY-EARLY ONSET INFLAMMATORY BOWEL DISEASE (VEO-IBD): A CLINICAL AND LABORATORY APPROACH

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Amanda Lima, Amanda Sobrinho, Amanda Machado, Larissa Said, Bruna Oliveira, Maria Gabriela Sá, Veridiana Verzignassi Fiorotte, Rafaela Guimarães, Carolina Sanchez Aranda, Dirceu Solé
Federal University of São Paulo, Division of Allergy, Clinical Immunology And Rheumatology - Department of Pediatrics, São Paulo, Brazil

Background and Aims: VEO-IBD is a rare presentation defined as the onset of inflammatory bowel disease (IBD) under 6 years of age, which may have an underlying monogenic etiology as well as inborn error of immunity associated. The study aimed to develop a clinical and laboratory investigation pilot Protocol (IPP) to guide the diagnosis of VEO-IBD.

Methods: The PPI was applied to 75 patients with IBD referred for evaluation at the reference Immunology center. The PPI had a clinical record standardized in a routine of exams such as blood count, lymphocyte subclasses, complement, vaccine response, DHR, and immunoglobulins, in addition to the investigation of the IL12/IFG-gamma axis and evaluation of the exome, when relevant because of the initial exams.

Results: of the 75 patients analyzed, 37 (49%) patients had symptoms before the age of six years. Within this group, 56% had changes in the blood count, predominantly anemia (95%), followed by lymphopenia (11%) and thrombocytopenia (5%). More than one class of immunoglobulins below the 3rd percentile was found in 13.5% of patients, only IgA or IgM appeared reduced in another 13.5%, and IgG alone was reduced in 11%. The protein response was not adequate in 13.5% of the patients. Two patients had altered DHR. In 46% of patients, the monogenic disease was confirmed with diagnoses such as SCID, IL-10 deficiency, XLP2, APDS, WAS, and CGD.

Conclusions: The protocol was a valuable tool. We agree that having a routine of exams helped us to clarify the diagnosis of most of our patients.

Disclosure: No.

Keyword: veo-ibd, inborn error of immunity, investigation protocol, diagnosis, monogenic disease, laboratory

PD311

CLINICAL AND GENETIC CHARACTERIZATION of JAPANESE PATIENTS WITH ARTEMIS DEFICIENCY

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Kento Inoue[1], Satoshi Miyamoto[1], Dan Tomomasa[1,2], Tomohiro Morio[1], Hirokazu Kanegane[1]
[1]Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Pediatrics And Developmental Biology, Tokyo, Japan, [2]Tokyo Medical and Dental University, Pediatrics And Developmental Biology, Tokyo, Japan

Background and Aims: Artemis is an exonuclease essential for repair of DNA double strands breaks. Pathogenic variants in DCLRE1C encoding Artemis cause $T^-B^-NK^+$ SCID, and Artemis deficiency (ART-SCID) is an indication for early allogeneic hematopoietic cell transplantation (HCT). Here we describe clinical and genetic characterization of Japanese patients with ART-SCID.

Methods: We collected the clinical data of the patients who was diagnosed from 2010-2022. Genetic analysis was performed using the target gene panel sequencing, and the large deletions were validated using MLPA method.

Results: Eight patients from seven families were diagnosed with ART-SCID due to severe infection within 6 months of life. They underwent HCT within 60 days after the diagnosis. Unfortunately, 2 patients with poor performance status (PS) died of complications within 2 years after HCT. The remaining 6 patients were well after HCT; however, 3 patients had growth retardation. Two patients had the missense variant, and 4 families had genomic large deletion. One patient had the combination of missense variant and large deletion. MLPA analysis revealed the deletions of exons 3-4 (n = 2) and exons 1-3 (n =3) of DCLRE1C including MEIG1 and DCLRE1CP (pseudogene).

Conclusions: In Japan, most patients with ART-SCID were caused by large deletion of DCLRE1C, MLPA analysis may be useful for detecting large deletion. To improve the outcome of HCT, we need the more reduced conditioning and early diagnosis with newborn screening for SCID.

Disclosure: No.

Keywords: ART-SCID, MLPA, large deletion, HCT, Artemis deficiency, DCLRE1C

PD312

MALIGNANCY AND CHROMOSOME INSTABILITY SYNDROMES

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Tatiana Volodashchik[1], Svetlana Sharapova[1], Svetlana Aleshkevich[2], Yulia Zharankova[2], Ekaterina Polyakova[1], Irina Guryanova[1], Mikhail Belevtsev[1]
[1]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Research Department, Borovlyany, Belarus, [2]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Outpatient Department, Borovlyany, Belarus

Background and Aims: Ataxia telangiectasia (A-T), Nijmegen breakage syndrome (NBS) and Bloom syndrome (BS) are a group of recessively inherited conditions associated with defects in DNA repair mechanisms that lead to chromosomal instability, chromosomal breakage and an array of phenotypic consequences, including an increased risk of developing malignancies.

Methods: We report the incidence of malignancy among 47 patients with chromosome instability syndromes (CIS), diagnosed from 1990 until 2022 in Belarus.

Results: 15/47 (31.9%) patients developed a malignancy in the age of 1-21 years with median of 8 years. Underlying diagnosis in 15 affected patients was NBS (n=4), A-T (n=4), BS (n=1). Ten patients with NBS developed T-cell lymphoblastic lymphoma (T-LBL) (n=2), peripheral T-cell lymphoma, unspecified (PTCL-US) (n=1), anaplastic large cell lymphoma (ALCL) (n=1), diffuse large B-cell lymphoma (DLBCL) (n=2), T-cell acute lymphoblastic leukemia (T-ALL) (n=2), mixed-phenotype acute leukemia (MPAL) (n=1), acute undifferentiated leukemia (AUL) (n=1). Four patients with A-T developed T-ALL (n=2), non-determined subtype of lymphoma (n=1), optic nerve glioma (n=1). A patient with BS was diagnosed with ALCL. In total two patients survived (13%) and malignancy was the main cause of death (7 – NBS, 1 – A-T, 1 – BS). Three patients with NBS underwent HSCT once the disease was in remission. One patient with A-T lost to follow-up.

Conclusions: Our results show that 31.9% of patients with CIS developed a malignancy. Hematological malignancies were prevalent (14/15, 93%). The study group is characterized by the predominance of T-cell neoplasms.

Disclosure: No.

Keywords: Bloom syndrome, Malignancy, chromosomal instability, Nijmegen breakage syndrome, Ataxia Telangiectasia

PD313

CLINICAL ASSAYS TO VALIDATE THE SIGNIFICANCE of UNKNOWN VARIANTS IN DNA REPAIR GENES IN PATIENTS WITH IMMUNODEFICIENCY.

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Ola Hammarsten[1], Anna Lyytikäinen[1,2], Sofia Thunström[3], Torben Ek[4], Anders Fasth[5], Olov Ekwall[6], Sara Cajander[7], Emilie Wahren Borgström[8], Carl Inge Edvard Smith[9], Pegah Johansson[1]
[1]Sahlgrenska University Hospital, Laboratory of Clinical Chemistry, Gothenburg, Sweden, [2]Sahlgrenska University Hospital, Clinical Chemistry, Gothenburg, Sweden, [3]Sahlgrenska University Hospital, Clinical Genetics, Gothenburg, Sweden, [4]Queen Silvia Children's Hospital, Childrens Cancer Center, Gothenburg, Sweden, [5]Institute of Clinical Sciences, Sahlgrenska Academy, Department of Pediatrics, Gothenburg, Sweden, [6]Univ Gothenburg, Dept Pediatrics, Gothenburg, Sweden, [7]Örebro University, Infectious Diseases, Örebro, Sweden, [8]Karolinska Institutet, Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden., Huddinge, Sweden, [9]Karolinska Institutet, Department of Laboratory Medicine, Biomolecular And Cellular Medicine,, Stockholm, Sweden

Background and Aims: DNA repair deficiency disorders are rare inherited diseases arising from variants in genes involved in DNA repair. The DNA repair proteins involved in the repair of double-strand breaks (DSBs) are also involved in V(D)J recombination and immunological development. Consequently, defects in these pathways leads to varying levels of immunodeficiency as well as cellular hypersensitivity to DSB inducing agents such as radiation. There are no clinical assays for the investigation of pathological significance of unknown variants in DNA repair genes. We aimed to develop clinical assays for measuring patient cell hypersensitivity to DNA damaging agents used to establish the pathological significance of unknown variants in DNA repair genes.

Methods: We used the cell division assay (CDA) and γ-H2AX assay that were developed by us, to measure patient white blood cell hypersensitivity in response to ionizing radiation, and other DNA damaging agents. Five patients with variants in DNA repair genes PRKDC (two siblings), DCLRE1C (two siblings), and NBN were included. The patients presented with varying levels of immunodeficiency.

Results: Radiation hypersensitivity was detected in the two patients with variants in PRKDC and the two patients with DCLRE1C. The cells from the patients with PRKDC variant were also deficient in removing γ-H2AX. The cells from the patient with variants in the NBN gene were hypersensitive to mitomycin C and deficient in both induction and removal of γ-H2AX in response to radiation.

Conclusions: The CDA and the γ-H2AX assay are useful in investigating the significance of unknown variants in some DNA-repair genes in patients with immunodeficiency.

Disclosure: No.

Keywords: Cell division assay, gamma-H2AX assay, Functional diagnosis, DNA repair deficiency disorders, immunodeficiency, Radiation sensitivity

PD314

INITIAL PRESENTING MANIFESTATIONS of PAEDIATRIC-ONSET COMMON VARIABLE IMMUNODEFICIENCY DISORDERS: A 20-YEAR EXPERIENCE of TWO GREEK REFERRAL CENTRES

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Konstantina Charisi[1], Antonios Gkantaras[1], Eleni Papadimitriou[1], Anna Taparkou[1], Androniki Kapousouzi[2], Vasiliki Sgouropoulou[1], Matthaios Speletas[2], Evangelia Farmaki[1]
[1]Aristotle University of Thessaloniki, Paediatric Immunology And Rheumatology Referral Center, 1st Department of Paediatrics, Thessaloniki, Greece, [2]University of Thessaly, School of Health Sciences, Faculty of Medicine, Department of Immunology And Histocompatibility, Larissa, Greece

Background and Aims: Data demonstrating the initial presenting manifestations of paediatric-onset Common Variable Immunodeficiency (CVID) are limited. Hence, we sought to determine the phenotypic spectrum of CVID in Greek patients with disease onset before adulthood.

Methods: We retrospectively reviewed a group of children and young adults with established diagnosis of CVID, who had disease onset before adulthood and minimum 5-year follow-up after diagnosis. X-linked agammaglobulinaemia and CD40L deficiency had been excluded. A statistical analysis was conducted to identify differences between early-onset (<10 years) and adolescent-onset (11-18 years) CVID.

Results: Among the 51 CVID subjects (M:F=2:1) included in our analysis, 19 patients (37.3%) had early-onset disease. According to clinical manifestations at and before diagnosis, 28 patients (54.9%) presented with predominantly recurrent infections [infections-only:15 (29.4%)], 11 (21.6%) with infections and chronic lung disease (including 4 with concurrent non-infectious manifestations), 3 (5.9%) with infections combined with autoimmunity and/or lymphoproliferation, and 9 (17.6%) with non-infectious manifestations only (autoimmune cytopenias:5, lymphoma:2, enteropathy:2). We observed a tendency of male predominance (84.2% vs 56.2%;p=0.065) and higher frequency of autoimmune cytopenias during follow-up (47.4% vs 21.9%;p=0.058) in the early-onset group. Patients with lymphoproliferation during follow-up had lower IgG values at diagnosis (p=0.003), whereas patients with cytopenias during follow-up had higher IgM values at diagnosis (p=0.034).

Conclusions: Non-infectious manifestations are frequently the only or predominant clinical feature of paediatric-onset CVID, requiring high awareness and periodic evaluation of immunoglobulin levels. The observed male predominance and immune dysregulation in early-onset disease may suggest distinct genetic and pathophysiologic mechanisms in CVID.

Disclosure: No.

Keywords: Common variable immunodeficiency, Paediatric-onset CVID, Clinical Phenotypes, Immune Dysregulation, Non-infectious manifestations

PD315

FACS-BASED EVALUATION of T-CELL FUNCTION IN CHILDREN WITH STIMULI BEYOND MITOGENS

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Emma Schumann[1], Livia Schulze[2], Manuela Rejzek[2], Julia Körholz[1], Eva Jacobsen[3], Axel Roers[4], Catharina Schuetz[1]
[1]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Pediatric Immunology, Dresden, Germany, [2]Institute of Immunology, Medical Faculty Carl Gustav Carus, Dresden, Germany, [3]University Medical Center Ulm, Germany, Department of Pediatrics And Adolescent Medicine, Ulm, Germany, [4]University Hospital Heidelberg, Institute For Immunology, Heidelberg, Germany

Background and Aims: FACS-based testing of T-cell proliferation with specific antigens is rarely offered as routine diagnostics. Where the traditional radioactive lymphocyte transformation (LTT) assay is not available, clinical laboratories generally offer T-cell function to mitogens only. We here discuss a T-cell proliferation assay using a variety of specific antigens providing a more in-depth insight into T-cell functionality. This has the potential to detect more subtle T-cell defects.

Methods: The proliferation assay was performed on cryopreserved peripheral blood mononuclear cells (PBMCs) in healthy donors between 6 months to 18 years and in a broad spectrum of patients. PBMCs were labeled with the fluorescent dye CellTrace Violet (CTV) to visualize cell division. Antigens used are tetanus toxoid (TT), CMV, candida, and adenovirus. Data generated from cryopreserved PBMCs were compared with those of fresh PBMCs from the same healthy donors.

Results: Proliferation upon stimulation with CMV and adenovirus antigens was regularly observed in older age groups of healthy donors. In contrast, there was a robust proliferation upon candida in healthy donors of all ages including infants. Results using cryopreserved PBMCs compared to fresh PBMCs from the same donor did not show a reduced proliferation, suggesting that cryopreserved PBMCs can be used for diagnostic purposes.

Conclusions: This study highlights the potential of FACS-based evaluation using specific antigens for T-cell proliferation assays for routine diagnostics. Performing this laborious assay for multiple parallel samples is feasible and reliable due to use of cryopreserved PBMCs. This assay may perspectively replace the ^{3}H Thymidine LTT.

Disclosure: No.

Keywords: FACS, T-cell proliferation, CellTrace Violet (CTV), Functional assay

PD316

AN ATYPICAL LYMPHOMA PRESENTATION IN SCID

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Helena Pires Pereira[1,2], Isabel Carrapatoso[1], Sonia Lemos[3]
[1]Centro Hospitalar e Universitário de Coimbra, Allergy And Immunology, Coimbra, Portugal, [2]Centro Hospitalar e Universitário de Coimbra, Immunoallergology, Coimbra, Portugal, [3]Centro Hospitalar e Universitário de Coimbra, Pediatrics, Coimbra, Portugal

Background and Aims: Individuals with primary immunodeficiencies are at higher risk to develop not only infections but also neoplastic diseases.

Methods: We report an unclear presentation of malignancy in a patient with severe combined immunodeficiency (SCID).

Results: Case report: A 4 month-old male patient was hospitalized with acute respiratory failure requiring mechanical ventilation for Pneumocystis jirovecii pneumonia, after presenting with vomiting, diarrhea and prostration, following rotavirus vaccine. Due to a significant left unilateral swelling of the malar region, a CT-guided bone biopsy was performed, revealing destruction of the left zygomatic bone, initially attributed to a fungal osteomyelitis, but with poor response to amphotericin. A sustained low lymphocyte count, including near absence of T cells and NK and low B cell count, and an absent thymic shadow led to genetic testing which confirmed SCID with a c.562C>T variant p.(Gln188*), in hemizygosity in the IL2RG gene encoding the common Y chain. The zygomatic lesions were later diagnosed as bone involvement of diffuse large B cell lymphoma, which was treated with rituximab. The patient was submitted to an allogeneic bone marrow transplant showing clinical improvement.

Conclusions: This case illustrates the association between inborn errors of immunity and malignancy serving as an example of an atypical lymphoma presentation.

Disclosure: No.

Keywords: SCID, Lymphoma, Inborn errors of immunity

PD317

OUR EXPERIENCES WITH CLINICAL MANIFESTATION of PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY FROM SPECIALISED CENTRE FOR PRIMARY IMMUNODEFICIENCIES IN MARTIN, SLOVAKIA

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Adam Markocsy[1], Peter Banovcin[1], Otilia Petrovicova[1], Lenka Kapustova[1], Anna Bobcakova[2], Milos Jesenak[1]
[1]University Teaching Hospital in Martin, Centre For Primary Immunodeficiences - Esid Registry Site, Department of Children And Adolescents, Jessenius Faculty of Medicine, Comenius University In Bratislava, Martin, Slovak Republic, [2]Jessenius Faculty of Medicine, Comenius University in Bratislava, Centre For Primary Immunodeficiencies, Department of Pulmonology And Phthisiology, Martin, Slovak Republic

Background and Aims: Common variable immunodeficiency (CVID) is heterogeneous group of disorders that belongs to Predominantly antibody deficiencies with various clinical and immunological features. There are four classification systems based on B cell phenotypic profiling. The genetics supplies clinical diagnostic criteria and often changes the definite diagnosis.

Methods: This is the retrospective clinical study of clinical manifestation, laboratory findings, autoimmune, granulomatous, lymphoproliferative complications of patients followed up with the diagnosis of CVID. It also compares the clinical manifestation of patients in different groups according to EuroCLASS classification and tries to find some correlations and perspective diagnostic markers. We also study the genotype-phenotype correlations in patients with confirmed causal pathogenic variant in genes associated with Primary immunodeficiencies.

Results: We follow up 59 patients (27 males, 32 females) with CVID diagnosis. The mean age of patients is 41 years. Infectious complications are present in 91,1 % (n=51) of patients. Autoimmune complications are present in 39 % (n=23) of patients. Lymphoproliferative disease is found in 8,5 % (n=5), splenomegaly in 17 % (n=10) and granulomatous complications in 17 % (n=10) of patients of our cohort. We perform molecular-genetic testing in 17 % (n=10) of patients and find causal pathogenic variant in 30 % (n=3) of this group.

Conclusions: Clinical diagnostic criteria for CVID and classification systems are still not sufficient to predict clinical manifestation and complications. Genetic testing can be helpful in this issue.

Disclosure: No.

Keywords: Common variable immunodeficiency, predominantly antibody deficiency, EuroCLASS, retrospective clinical study

PD318

DIAGNOSIS of IMMUNODEFICIENCY USING TYPHIM VI IN CHILDREN IMMUNISED WITH PNEUMOCOCCAL CONJUGATE VACCINE

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Jesmeen Maimaris[1,2], Elizabeth Mapazire[2,3], Helen Lock[2], Tasneem Rahman[2], Sofia Grigoriadou[2], Chris Scott[2], Andrew Prendergast[3,4], Sarah Brown[2,3], Sorena Kiani-Alikhan[2]
[1]University College London, Institute of Immunity And Transplantation, London, United Kingdom, [2]Barts Health NHS Trust, Department of Immunology, London, United Kingdom, [3]Barts Health NHS Trust, Department of Paediatric Medicine, London, United Kingdom, [4]Queen Mary University of London, Centre For Genomics And Child Health, Blizard Institute,, London, United Kingdom

Background and Aims: The evaluation of a child with suspected primary immunodeficiency should include the measurement of polysaccharide vaccination responses to evaluate T-cell-independent Type II antigen-specific antibody production. However, due to successful infant vaccination programmes with Prevenar 13 (Pfizer, Inc.) and endemic exposure to pneumococci, antibodies to pneumococcal serotypes are often present in protective quantity. To overcome this difficulty, our clinic has established a Salmonella typhi Vi polysaccharide vaccine (Typhim Vi™) diagnostic challenge. We conducted a retrospective observational study of patients in our paediatric immunology clinic to assess the diagnostic capability of Typhim Vi test vaccination in children with suspected PID.

Methods: Clinical history and laboratory investigations such as Typhim Vi responsiveness, IgG and baseline pneumococcal serotype specific antibodies at presentation and post-vaccination were analysed.

Results: 11 out of 56 patients (19.6%) were categorised as having not responded to Typhim Vi vaccination. Typhim Vi non-responders were more likely to be diagnosed with a PID at 1 year follow-up (p-value =0.0006). 4 of 11 patients (36.3%) with low Typhim Vi responsiveness in our study had protective baseline pneumococcal serotypes.

Conclusions: Our study demonstrates Typhim Vi vaccination as a feasible and useful tool in diagnosis of PID in children. The use of Typhim Vi circumvents the challenge of interpreting pneumococcal-specific IgG responses in early life. Indeed, baseline pneumococcal responses did not predict Typhim Vi responsiveness in our study, and further vaccination with the polysaccharide Pneumovax 23 did not elicit a sufficient fold-increase to distinguish between responsiveness and unresponsiveness to pneumococcal vaccine challenge.

Disclosure: No.

Keywords: Typhim, DIAGNOSIS, immunodeficiency, Vaccination, paediatrics

PD319

THE EUROFLOW PID ORIENTATION TUBE (PIDOT) IN THE DIAGNOSTIC WORK-UP of PRIMARY IMMUNODEFICIENCY: DAILY PRACTICE PERFORMANCE IN A TERTIARY UNIVERSITY HOSPITAL

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Jana Neirinck[1,2], Annelies Emmaneel[3,4], Malicorne Buysse[2], Jan Philippé[1,2], Sofie Van Gassen[3,4], Yvan Saeys[3,4], Xavier Bossuyt[5], Stefanie De Buyser[6], Mirjam Van Der Burg[7], Martin Perez-Andres[8,9], Alberto Orfao[8,9], Jacques J.M. Van Dongen[9,10], Bart N. Lambrecht[11], Tessa Kerre[12], Mattias Hofmans[2], Filomeen Haerynck[13], Carolien Bonroy[1,2]
[1]Ghent University, Department of Diagnostic Sciences, Ghent, Belgium, [2]Ghent University Hospital, Department of Laboratory Medicine, Ghent, Belgium, [3]VIB Center for Inflammation Research, Data Mining And Modelling For Biomedicine Group, Ghent, Belgium, [4]Computer Science and Statistics, Department of Applied Mathematics, Ghent, Belgium, [5]KU Leuven, Clinical And Diagnostic Immunology, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [6]Ghent University, Department of Public Health And Primary Care, Ghent, Belgium, [7]Leiden University Medical Center, Laboratory For Pediatric Immunology, Department of Pediatrics, Leiden, Netherlands, [8]University of Salamanca (USAL), Cancer Research Centre (ibmcc, Usal-csic; Ciberonc Cb16/12/00400), Institute For Biomedical Research of Salamanca (ibsal), Department of Medicine And Cytometry Service (nucleus Research Support Platform), Salamanca, Spain, [9]University of Salamanca (USAL), Translational And Clinical Research Program, Centro De Investigación Del Cáncer And Instituto De Biología Molecular Y Celular Del Cáncer, Consejo Superior De Investigaciones Científicas (csic)), Salamanca, Spain, [10]Leiden University Medical Center, Department of Immunology, Leiden, Netherlands, [11]VIB-UGhent Center for Inflammation Research, Laboratory of Mucosal Immunology, Ghent, Belgium, [12]Ghent University Hospital, Department of Hematology, Ghent, Belgium, [13]Ghent University Hospital, Department of Pediatric Pulmonology And Immunology And Pid Research Lab, Ghent, Belgium

Background and Aims: Multiparameter flow cytometry (FCM) is an important tool in the diagnostic screening of primary immunodeficiency (PID). The EuroFlow consortium developed the PID Orientation Tube (PIDOT) as a universal screening tool to identify lymphoid-PID in suspicious patients. Although PIDOT can identify different lymphoid-PIDs with high sensitivity, clinical validation in a broad spectrum of patients is missing. We investigated the PIDOT diagnostic performance in a daily routine practice.

Methods: PIDOT was tested in 887 consecutive patients suspicious of PID at the Ghent University Hospital, Belgium. Patients were classified into lymphoid-PID subgroups vs. non-PID disease controls (DCs). Comprehensive characterization of lymphoid defects and identification of the most discriminative features to distinguish lymphoid-PID from non-PID DCs, was performed. Next, a decision tree was designed to guide subsequent FCM analyses.

Results: The mean number of lymphoid defects detected by PIDOT was 2.82 times higher in lymphoid-PID patients compared to non-PID DCs ($p<0.001$), resulting in an overall sensitivity and specificity of 83% and 68% to detect Severe Combined Immunodeficiency, Combined immunodeficiency with associated/syndromic features, Immune dysregulation disorder and Common Variable ImmunodeficiencY. The most discriminative populations were total memory and switched memory B-cells, total T-cells, (naive) $TCD4^+$-cells, together with serum Ig levels. The decision tree resulted in an increased overall sensitivity and specificity for lymphoid-PID of 91% and 73%, respectively.

Conclusions: Altogether, our findings document that PIDOT is a powerful tool for diagnostic screening of lymphoid-PID. The combination of PIDOT and serum Ig levels provides an efficient guide for further diagnostic work-up.

Disclosure: No.

Keywords: flow cytometry, immunophenotyping, EuroFlow, primary immunodeficiencies, standardization, clinical validation

PD320

THE NEUROLOGICAL SPECTRUM of ADULT GRISCELLI SYNDROME

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

François Rodrigues[1], Anouk Le Goueff[2], Philippe Kerschen[3], Lionel Galicier[1], Sophie Georgin-Lavialle[4], Alain Lefèvre-Utile[5], Angela Daher[6], Frédéric Vandergheynst[2], David Boutboul[1]
[1]Hopital Saint Louis, Université de Paris Cité, Clinical Immunology, Paris, France, [2]Hôpital Erasme, Internal Medicine, Brussels, Belgium, [3]Centre Hospitalier de Luxembourg, Neruology Department, Luxembourg ville, Luxembourg, [4]Hôpital Tenon, Internal Medicine, Paris, France, [5]Hôpital Jean Verdier, General Pediatrics, Bondy, France, [6]Abou Jaoude Hospital, Internal Medicine And Clinical Immunology, Jal El Dib, Lebanon

Background and Aims: Type 2 Griscelli syndrome (GS) is an autosomal recessive disorder characterized by silver-grey hair, skin hypomelanosis and immunodeficiency including hemophagocytic lymphohistiocytosis (HLH). Neurological involvement of HLH is of particular concern and severity in patients with GS and is associated with high early mortality without hematopoietic stem cell transplantation (HSCT). Easy access to Next Generation Sequencing have allowed the diagnosis of atypical and late forms of primary immune deficiencies. We here describe 3 adults diagnosed with GS and prominent neurological involvement.

Methods: Three patients with an adult diagnosis of GS were reported.

Results: Patients were diagnosed with type 2 GS at 19, 30 and 22, respectively. WES identified previously reported biallelic RAB27A mutations. P1 and P3 carried the same homozygous mutation without pigmentation disorder, explaining the normal hair phenotype. P2 harbored compound heterozygous mutations and only had focal hair abnormalities. Only P3 met HLH criteria. The three patients presented with various forms of neuroinflammatory syndromes, including neuromyelitis optica (NMO), CNS vasculitis, and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). These disorders were incompletely controlled after immunosuppressive treatments and WES allowed proper diagnosis and treatment. P1 and P2 are alive and well after HSCT. P3 died from refractory HLH following COVID-19.

Conclusions: We report 3 cases of type 2 GS diagnosed in adult patients with prominent life-threatening neurological disease. Type 2 GS should be emphasized as a cause of adult inflammatory demyelinating disease, even in the absence of hypopigmentation and/or HLH. Adult clinicians should be aware of the possibility of such a diagnosis in this clinico-radiological setting.

Disclosure: No.

Keywords: Griscelli Syndrome, Hemophagocytic Lymphohistiocytosis, Late diagnosis, Neurological involvement

PD321

COMBINED IMMUNODEFICIENCY (CID) IS MISSED BY NEWBORN SCREENING FOR T CELL RECEPTOR EXCISION CIRCLES (TREC) IN IMMUNODEFICIENCY CENTROMERIC INSTABILITY AND FACIAL ANOMALIES (ICF)

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Olga Staudacher[1], Jeanette Klein[2], Jan Ullrich[1], Anna Stittrich[3], Nadine Unterwalder[4], Stephanie Thee[1], Sarah Dinges[1], Cinzia Dedieu[1], Mirjam Völler[1], Johannes Schulte[5], Uwe Kölsch[6], Renate Krüger[1], Jörn-Sven Kuehl[7], Christian Meisel[4], Oliver Blankenstein[2], Horst Von Bernuth[1,4]
[1]Charité-Universitätsmedizin Berlin, Pediatric Respiratory Medicine, Immunology And Critical Care Medicine, Berlin, Germany, Berlin, Germany, [2]Charité-Universitätsmedizin Berlin, Newbornscreening Laboratory, Berlin, Germany, [3]Labor Berlin Charité-Vivantes GmBH, Human Genetics, Berlin, Guatemala, [4]Labor Berlin Charité-Vivantes GmBH, Immunology, Berlin, Germany, [5]Charité-Universitätsmedizin Berlin, Pediatric Hematology And Oncology, Berlin, Germany, [6]Labor Berlin Charité-Vivantes GmBH, Human Genetics, Berlin, Germany, [7]University of Leipzig, Pediatric Oncology, Hematology And Hemostaseology, Leipzig, Germany

Background and Aims: Severe combined immunodeficiency (SCID) comprises a heterogeneous group of inborn conditions with low values (T cells < 300/ml) and/ or low T-cell function at birth. Most patients seem healthy, yet are at risk to die in infancy due to severe infections and/ or immune dysregulation. Outcome improves vastly, if early recognition leads to treatment, before the age of 3.5 months. T cell receptor excision circles (TRECs) can be measured in dried blood spots of newborn screening for the detection of severe T lymphopenia. The sensitivity of TREC screening for the detection of bona fide SCID is supposed to be almost 100%. In addition, TREC newborn screening also allows the identification of combined immunodeficiency (T cells > 300, yet < 1500/ml) due to further inborn errors of immunity (IEI). Yet, despite sensitivity of TREC-screening for SCID being high, it becomes increasingly obvious that a relevant number of patients with (S)CID may pass undetected.

Methods: We therefore retrospectively analyzed the amount of TRECs in archived dried blood spots of Guthrie cards in children with diagnosed IEI who were born in the Berlin-Brandenburg area before 2018.

Results: Among the patients with diagnosed (S)CID one patient with Immunodeficiency centromeric instability and facial anomalies type 2 (ICF2) and one with ICF3 had TREC levels above cut-off at birth, results from a third patient were inconclusive.

Conclusions: In conclusion, ICF2 and ICF3 are presumably not detected by TREC newborn screening although these patients would also benefit from early stem cell transplantation.

Disclosure: No.

PD322

INFLAMMATORY BOWEL DISEASE (IBD) IN PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA (XLA) RECEIVING INTRAVENOUS IMMUNOGLOBULIN (IVIG) THERAPY

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Daria Yukhacheva, Yulia Rodina, Anna Shcherbina
Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation

Background and Aims: XLA is a primary immunodeficiency, manifesting mainly by bacterial infections and less frequently by autoimmune/autoinflammatory complications, which are usually controlled by regular IVIG therapy.

Methods: We report two unrelated patients, who were diagnosed with XLA at the age of 3 years via BTK gene mutations identification (P1 - deletion of exons 2-3, P2 - c.1700A>C p.Glu567Ala), and developed IBD after 4 years of regular IVIG therapy.

Results: While on the regular IVIG therapy P1 at the age of 7 years developed recurrent fever, diarrhea with weight loss of 5 kg, high inflammatory activity. Low trough IgG was noted (2.25 g/l). Antibacterial therapy was ineffective. Abdomen CT shown severe intestinal wall thickening, yet no macroscopic changes were found via colonoscopy. 2 weeks of steroids therapy (budesonide) led to resolution of all symptoms. However, after 2 months of steroids, videocapsule enteroscopy showed signs of ulcerative erosive duodenitis, jeunitis, ileitis with multiple lymphangiectasias. Fecal calprotectin was elevated (707 mcg/kg). P2 was asymptomatic (including normal pre-infusion IgG level), but at the age of 7 years fecal calprotectin was measured as part of the screening and found to be elevated (1012 mcg/kg). Despite the absence of macroscopic changes on colonoscopy, the histological changes included active ileitis, active total colitis with structural changes and Paneth cell metaplasia. Both patients were started on anti-TNF treatment (adalimumab).

Conclusions: Development of IBD in XLA despite regular IVIG treatment demonstrates the need of regular screening to detect IBD even without obvious clinical symptoms, which should include at least assessment of a fecal calprotectin.

Disclosure: No.

Keywords: x-linked agammaglobulinemia, Inflammatory bowel disease, autoimmune/autoinflammatory complications, fecal calprotectin

PD323

NBS EXPERIENC - KNOWING THE INCIDENCE of SCID IN BRAZIL

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Larissa Said[1], Carolina Sanchez Aranda[1], Barbara Ramos[1], Amanda Sobrinho[1], Amanda Lima[1], Amanda Machado[1], Lara Teixeira[1], Mariana Gouveia-Pereira[1], Dirceu Solé[1], Antonio Condino-Neto[2]
[1]Federal University of São Paulo, Division of Allergy, Clinical Immunology And Rheumatology - Department of Pediatrics, São Paulo, Brazil, [2]University of São Paulo, Institute of Biomedical Sciences, Department of Immunology., São Paulo, Brazil

Background and Aims: The implementation of newborn screening (NBS) started in early 2021 and will take place in five stages, with SCID screening in phase 4. As of March 2021, the city of São Paulo expanded the NBS with the quantification of TRECs and KRECs. Our study aimed to analyze the first year of screening.

Methods: A retrospective analysis of the charts was conducted. All exams with a cutoff value of fewer than 25 copies/uL were considered abnormal and thus referred to a single Immunology Center until March 2022.

Results: We received 75 infants (one baby with abnormal tests for every 1700 live births). 13 babies had TREC<25. of these three SCIDs were diagnosed, and four DGS were suspected. Regarding the KREC below the cutoff, we had 62 infants, which reflects a wider range of possible diagnoses and tests with false positives. Only ten infants showed CD19<1%. After 3 months, B lymphocytes recovered (two are children of a mother with SLE, three are children of kidney transplant mothers, and five, mothers had gestational hypertension). There was one result that showed an elevated KREC which culminated in the diagnosis of juvenile myelomonocytic leukemia.

Conclusions: NBS is still a revolutionary test providing a rapid diagnosis of treatable diseases. This year, after the implementation of NBS in Sao Paulo we were able to make 3 SCIDs diagnoses (1 for every 43,000 live births). Furthermore, it was possible to make a diagnosis of leukemia from the NBS, which infers new possibilities of knowledge in the development of lymphocytes.

Disclosure: No.

Keywords: newborn screening, TRECs, KREC, Severe combined immunodeficiency

PD324

IN-DEPTH PHENOTYPING of THE T-CELL SYSTEM of A ZAP-70-DEFICIENT PATIENT POST-HSCT IN CONTEXT of MIXED CHIMERISM

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Thomas Weitering[1], Monique Van Ostaijen-Ten Dam[1], Danielle Brinkman[2], Petra Hissink Muller[2], Janine Melsen[1], Marco Schilham[1], Arjan Lankester[3], Mirjam Van Der Burg[1]
[1]Leiden University Medical Center, Laboratory of Pediatric Immunology, Leiden, Netherlands, [2]Leiden University Medical Center, Pediatric Rheumatology, Leiden, Netherlands, [3]Leiden University Medical Center, Department of Pediatrics, Stem Cell Transplantation Program, Leiden, Netherlands

Background and Aims: ZAP-70 is an important protein involved in T-cell receptor-signaling. Autosomal recessive ZAP-70-deficiency results in combined immunodeficiency characterized by a specific absence of CD8 T-cells. The clinical presentation is variable, but often includes recurrent respiratory infections and dermatitis. Here, we present a case of a 17-year-old ZAP-70-deficient female who received a matched unrelated donor hematopoietic stem-cell transplantation (HSCT) 11 years ago. She was diagnosed at age 6, after suffering from recurrent pulmonary and chronic EBV infections, resulting in broncho-obstruction and interstitial lung disease. After reduced-intensity conditioning, the HSCT resulted in the resolution of EBV and lung disease, but with poor donor-cell chimerism (12% of blood mononuclear cells). At 7 years post-HSCT, she developed recurrent idiopathic uveitis requiring treatment with diverse biologicals. Considering this suboptimal HSCT-outcome, our aim was to study in-depth the quality, sustainability and chimerism of her current T-cell system.

Methods: We developed a 27-color Spectral flowcytometry panel, including a ZAP-70-specific antibody.

Results: The absolute T-cell subset counts were normal-low. Based on ZAP-70 expression, high donor chimerism was observed 11 years post-HSCT in the early naïve (89.9%), stem-cell-memory (95.3%) and central-memory (78%) CD8 T-cell subsets. However, within the effector-memory CD8 T-cells (39.9% donor), a patient-derived population with an ambiguous phenotype (CD27+CD28+CD56+) was identified, that was absent pre-SCT. Moreover, her current CD4 T-cell subsets were 50-70% of patient origin.

Conclusions: This ZAP-70 expression based in-depth subset chimerism approach allowed us to discriminate donor- from patient-derived T-cells. The persistent ZAP-70-deficient T-cells could be responsible for the refractory uveitis, which is important in consideration of re-transplantation.

Disclosure: No.

Keywords: Hematopoietic Stem Cell Transplantation (HSCT), ZAP-70-deficiency, chimerism, Spectral flowcytometry, immune reconstitution

PD325

DOUBLE HETEROZYGOUS RAB27A MUTATIONS IN A YOUNG MAN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS – THE ROLE of GENETIC TESTING FOR THE GRISCELLI SYNDROME

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Ciprian Jurcut[1], Alexandru Bardas[2], Mihaela Bataneant[3], Anca Manolache[1], Augustin Serban[1], Daniel Coriu[2]
[1]Dr. Carol Davila Central University Emergency Military Hospital, Internal Medicine, Bucharest, Romania, [2]Fundeni Clinical Institute, Carol Davila University of Medicine and Pharmacy, Hematology Clinic, Bucharest, Romania, [3]Louis Turcanu Clinical Emergency Hospital for Children, Victor Babes University of Medicine and Pharmacy, Pediatrics, Timisoara, Romania

Background and Aims: The diagnostic of patients with Griscelli syndrome might be challenging in daily clinical practice.

Methods: We present the case of a young man diagnosed with Griscelli syndrome in our clinic, highlighting the role of genetic testing.

Results: A 26 years old man was referred to our clinic with the suspicion of primary immunodeficiency. The history began 10 years ago with an episode of Epstein-Barr virus infection. Low levels of IgG, IgA and IgM were noted at this time. During the follow-up the patients developed skin (cutaneous lupus at biopsy) and nasal (epistaxis, nasal septum perforation) manifestations. The new nasal and skin biopsies showed granulomatous lesions. CVID was suspected and the supplementation with IVIg was initiated. The clinical aspect (partial albinism) and microscopical examinations of the hair were suggestive for Griscelli syndrome. The genetic testing revealed two heterozygous mutations for RAB27A [pathogenic c.460A>T (p.Lys154*) mutation and c.227C>T (p.Ala76Val), considered initially as being of uncertain significance and reclassified as pathogenic; the genetic testing of the parents showed that these mutations are in opposite chromosomes]. During the follow up the patient presents with fever, cytopenia, high ferritin, low fibrinogen, high levels of soluble interleukin 2 receptor and the hemophagocytic lymphohistiocytosis (HLH) was confirmed at bone marrow examination. The 2004 HLH protocol was initiated and bone marrow transplant is considered.

Conclusions: This case of double heterozygous Griscelli syndrome emphasize the role of genetic testing and early recognition of HLH, the most severe complication of this clinical condition.

Disclosure: No.

Keyword: Griscelli syndrome, RAB27A mutations

PD326

IMMUNOLOGICAL AND CLINICAL CHARACTERIZATION of GASTRIC PATHOLOGY IN COMMON VARIABLE IMMUNODEFICIENCY (CVID) PATIENTS: A SINGLE CENTRE RETROSPECTIVE STUDY.

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Claudia Discardi[1], Stefania Nicola[2], Helena Buso[1], Vera Bonato[1], Alessandro Dell'Edera[3], Riccardo Scarpa[4], Carla Felice[4], Marcello Rattazzi[4], Carlo Agostini[4], Francesco Cinetto[4]
[1]University of Padova, Specialisation School in Allergology and Clinical Immunology, Department of Medicine—dimed, Treviso, Italy, [2]Ordine Mauriziano Turin Hospital, Medical Sciences - University of Turin, Torino, Italy, [3]University of Padua, Dimed, Treviso, Italy, [4]University of Padua, Department of Medicine, Treviso, Italy

Background and Aims: The predisposition to bacterial infections is the hallmark of CVID. Patients with CVID also have a high risk of gastric cancer and Helicobacter pylori (Hp) infection is a well-known risk factor in gastric carcinogenesis. This study focuses on the correlation between gastric pathology, Hp infection, B-cell subsets and T-cell large granular lymphocyte (TLGL).

Methods: We retrospectively analysed a cohort of 77 CVID patients with at least 5yrs of follow-up and full data availability. Each patient was screened for Hp infection and underwent upper GI endoscopy with biopsies. B-cell typing was made according to the EUROclass study and TLGL by CD3, CD16, CD56, CD57 expression.

Results: 43/77 patients (56%) complained of GI symptoms: mostly abdominal pain/diarrhoea (36/43, 84%), and dyspepsia/heartburn (49%). The most frequent histopathological findings were gastritis (64/77, 84%) – chronic (44/64), atrophic (11/64), and erosive (9/64) – intestinal metaplasia (20/77, 26%) and dysplasia (3/77, 4%). Hp infection was observed in 20/77 (26%) patients. Five developed gastric cancer, of which 3 Hp+. In the Hp positive group we observed higher prevalence of chronic active (p=0.038) and atrophic gastritis (p=0.009), intestinal metaplasia (p=0.003). No correlation was found with B-cells subsets, but a significant increase of TLGL was detected in the Hp positive group (26.5 vs 15%, p=0.037).

Conclusions: Regular upper endoscopy and Hp treatment are fundamental during the follow-up of CVID. Further studies are needed to understand the role of TLGL in Hp positive group, particularly in terms of cancer risk.

Disclosure: No.

Keywords: CVID, hpylori, EuroCLASS, gastric-cancer, Enteropathy

PD327

X-LINKED CHRONIC GRANULOMATOUS DISEASE SECONDARY TO SKEWED X CHROMOSOME INACTIVATION IN FEMALE PATIENTS

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Yue Zhang[1], Zhou Shu[1], Yan Li[1], Yurong Piao[1], Tongxin Han[1], Tianyou Wang[2], Huawei Mao[1]
[1]Beijing Children's Hospital, Capital Medical University, Department of Immunology, Beijing, China, [2]Beijing Children's Hospital, Capital Medical University, Department of Hematology And Oncology, Beijing, China

Background and Aims: Chronic granulomatous disease (CGD) is a heterogeneous primary immunodeficiency characterized by severe bacterial and fungal infections early in life and tissue granuloma formation. XL-CGD caused by gene defects of CYBB is the most prevalent type of CGD. We aim to understand the clinical and molecule features of XL-CGD secondary to skewed XCI in female.

Methods: We retrospectively reviewed the medical records of a female patient diagnosed with XL-CGD in Beijing Children's Hospital and summarized the previously published female XL-CGD cases secondary to skewed XCI in the literature.

Results: Clinical data were available for 15 female subjects. The median age of onset was 10 years and the median diagnosis age was 16 years. Consist with XL-CGD in males, infection was the most frequent manifestation in the female patients, especially in lung, mucocutaneous, urogenital system and liver. Catalase-positive pathogens including Serratia marcescens and Staphylococcus aureus infections were the most common pathogens. Autoimmune/autoinflammation manifestations were observed in 5 patients. DHR assay showed that median %DHR^+ values were 7% and the values varying with age were observed in two patients. All patients had a skewing XCI and there was no consistency between the daughter and carrier mother. No data about the mortality was reported in XL-CGD female patients, and most of them were responsive to anti-infections treatment.

Conclusions: XL-CGD should not be neglected in female patients presenting with CGD phenotype. It is necessary to make periodic clinical evaluation of XL-CGD female carriers as the neutrophil oxidative function may decline with aging and increase the risk for infection.

Disclosure: No.

Keywords: Dihydrorhodamine, Chronic Granulomatous Disease, Female gene carrier, Skewed X-chromosome inactivation

PD328

CHARACTERISTICS of THE CYTOKINE STATUS IN NEWBORNS WITH INTRAUTERINE INFECTIONS.

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Gulnara Nasrullayeva, Nushaba Mollayeva, Vafa Mammadova
Azerbaijan Medical University, Research Immunology Laboratory, Baku, Azerbaijan

Background and Aims: Cytokines are substances that regulate the body's response to infection, inflammation and injury. The levels of cytokines in the blood serum reflect the current state of the immune system, provide information on the functional activity of immunocompetent cells; the ratio of T-helper types-1 and 2. Pro-inflammatory cytokines are intensively synthesized during illness and provoke local reactions, anti-inflammatory cytokines are able to reduce inflammation. A decrease in cytokine production may be a sign of a lack of cellular immunity.

Methods: Under observation there were 56 newborns aged from 1 to 30 days, born from mothers with intrauterine infection. Intrauterine infection was detected by the specific IgM, IgG in serum of mothers and newborns. Cytokines IL-1, IL-6 and TNFα were measured in 14 children with intrauterine infections by ELISA.

Results: 44% of mothers treated intrauterine infection during pregnancy. The largest number of sick children born from mothers infected with an associated intrauterine infection: herpes + cytomegalovirus was detected in 11.6% of cases, toxoplasmosis + cytomegalovirus in 38.3% of cases. Only one type of maternal infection was rare: CMV-16 - 6%, toxoplasmosis - 20%, herpes - 6.6%, rubella - 3.3%, chlamydia - 3.3%. Our results revealed significantly high of TNFα (34.5±0.2 pg/ml) and IL-6 had some tendency to increase (19.3 ±2.8 pg/ml). The levels of serum cytokines IL-6 and TNFα compared with the severity of intrauterine infection in newborns and Th1/Th2 reaction.

Conclusions: An advantage of measuring serum cytokines in neonates is the ability to analyze the cytokine profile when the immune response is more specific.

Disclosure: No.

Keyword: cytokines, infection, diagnostics

PD329

NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY (SCID) IN EUROPE: FIVE-YEARS´ EXPERIENCE IN CATALONIA

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Andrea Martín-Nalda[1], Jacques Rivière[1], Ana Argudo Ramírez[2], Jm González De Aledo[2], Jl Marín Soria[2], Rm López Galera[2], S Pajares García[2], A Paredes Fuentes[2], A Ribes Rubio[2], J García[2], Roger Colobran[3], Clara Franco Jarava[4], Marina Garcia-Prat[4], A Parra Martínez[4], M Martinez-Gallo[4], M Hernandez-Gonzalez[4], B Prats[5], L Asso[5], L Alonso García[6], C Díaz De Heredia[6], Pere Soler-Palacin[1]
[1]Vall d´Hebron Hospital, Pediatric Infectious Diseases And Immunodeficiencies Unit, Hospital Universitari Vall D'hebron (huvh), Vall D'hebron Research Institute (vhir), Universitat Autònoma De Barcelona, Catalonia, Spain. Jeffrey Modell Excellence Centre, Barcelona, Spain, [2]Hospital Clínic, Barcelona, Catalonia, Spain, Newborn Screening Laboratory. Section of Inborn Errors of Metabolism, Biochemistry And Molecular Genetics Department, Barcelona, Spain, [3]Hospital Universitari Vall d'Hebron (HUVH, Barcelona, Catalonia, Spain, Immunology Department.department of Clinical And Molecular Genetics, Barcelona, Spain, [4]Hospital Universitari Vall d'Hebron (HUVH, Barcelona, Catalonia, Spain, Immunology Department, Barcelona, Spain, [5]Departament de Salut. Generalitat de Catalunya, Spain, Public Health Agency of Catalonia, Barcelona, Spain, [6]Hospital Universitari Vall d'Hebron (HUVH), Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Catalonia,, Spain, Pediatric Oncology And Hematology Department, Barcelona, Spain

Background and Aims: Severe combined immunodeficiency (SCID) can be screened at birth through T cell receptor excision circles (TRECs) in dried blood spot. We describe the results of the first 5 years of the SCID newborn screening (NBS) program in Catalonia, Spain

Methods: All samples between January 2017- December 2021 were analyzed. TRECs quantification was carried out with Enlite-Neonatal TREC kit from PerkinElmer® (cutoff 20 copies/µL). T, B and NK cell flow cytometry (CD45RO/RA, T CD4+ and CD8+ HLA-DR, TCR repertoire αβ/γδ TCR, recent thymic emigrants) and lymphocyte mitogen proliferation were performed. Genetic testing was performed by a custom NGS targeted gene panel containing 323 genes (including all SCID-causing genes). Case definitions were those proposed by Blom et al

Results: of 314.509 newborns screened, 77 tested positive (0.02%). Five SCID patients were detected; with an incidence of 1:62.901 (median TRECs value=1 copy/µL): RAG-2 (n=2), PNP (n=1), IL2RG (n=1) deficiencies, and one with no mutation found. Four underwent early stem cell transplantation (median age of 78 days, IQR=35.5) with good outcome. The IL2RG deficiency patient is ready for a gene therapy trial. Other case definitions: 25 non-SCID T-cell lymphopenia (11/25 22q11.2 deletion syndrome, 2/25 Down syndrome, 2/25 ataxia telangiectasia, 5/25 reversible conditions, 5/25 idiopathic T-cell lymphopenia), 6 preterm, 32 false positive and 9 inconclusive

Conclusions: SCID patients incidence in Catalonia is 1:62.901 births. NBS program for SCID led to 100% OS and 75% EFS reinforcing the usefulness of this approach. Other encountered diagnoses were similar to those described in larger SCID NBS programs

Disclosure: No.

Keywords: primary immunodeficiency, T cell receptor excision circle (TREC), severe combined immunodeficiency (SCID), lymphopenia, newborn screening

PD330

CHRONIC SALMONELLA MENINGOENCEPHALITIS REVEALING AN EXPRESSION DEFICIT of HLA -DR MOLECULES

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Kahina Ouahbi[1], Ourida Gacem[2], Nacera Hammadouche[2], Hanifa Benmekhlouf[1], Fatiha Boukandoura[1], Nadia Mehaba[1], Moussa Achir[1], Mohamed.Samir Ladj[2]
[1]university of algiers - faculty of medecine, Eph Djilali Belkhenchir (ex Birtraria), ALGER, Algeria, [2]EPH Djilali Belkhenchir (ex Birtraria), Department of Pediatric Djillali Belkhenchir Hospital Algiers Algeria, ALGER, Algeria

Background and Aims: Combined immunodeficiency associated with a defect in the expression of major histocompatibility complex (HLA) class II molecules is an autosomal recessive inherited disease leading to increased susceptibility to infections.

Methods: A case with HLA DR deficiency revealed by a chronic meningoencephalitis has been reported

Results: A 3-month-old infant hospitalized for severe sepsis and generalized hypertonic convulsive seizure disorder preceded by a 20-day history of watery diarrhea. The post-critical examination revealed consciousness disorders, horizontal nystagmus and opistotonos attitude. Laboratory tests revealed neutrophil hyperleukocytosis, positive CRP and DIC. The lumbar puncture returned a turbid fluid with altered elements and a positive culture for salmonella spp. He was put on triple antibiotic therapy and anticonvulsant treatment. On the 4th day, the neurological examination was disturbed with several generalized hypertonic seizures. Brain MRI: active tetra ventricular hydrocephalus. He was discharged after 45 days of treatment with sterilization of the CSF. 48 hours later, he was readmitted for recurrent meningitis with the same germ, put on ciprofloxacin and cefotaxime. The immunological assessment revealed a combined immune deficiency due to a lack of expression of HLA DR molecules. In spite of antibiotic prophylaxis and monthly infusion of immunoglobulins, the evolution was unfavorable with 3 other episodes of meningitis with salmonella spp, to die at the age of 1 year.

Conclusions: The case of our patient illustrates the seriousness of this disease. Bone marrow transplantation remains the only curative treatment.

Disclosure: No.

Keyword: HLA DR deficiency,Immunodeficiency , Consanguinity, infections, bone marrow transplantation

PD331

JOB-LIKE PHENOTYPE ASSOCIATED TO PHOSPHOGLUCOMUTASE 3(PGM3) COMPOUND HETEROZYGOUS MUTATIONS IN MONOZYGOTIC TWINS

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Ana Lucia Jimenez Portillo, Maikel Bravo Gonzales, Cinthya Fusi, Sergio Mora, Francisco Marco De La Calle
General University Hospital of Alicante Dr. Balmis, Immunology, Alicante, Spain

Background and Aims: Phosphoglucomutase 3 (PGM3) deficiency (Immunodeficiency 23, OMIM: 615816) is a rare congenital disorder of glycosylation that can lead patients to a hyper-IgE syndrome (HIES). PGM3 is an enzyme responsible for the conversion of N-acetyl-glucosamine (GlcNAc)-6-phosphate involved in GlcNAc-1-phosphate, which is converted to uridine diphosphate (UDP)-GlcNAc, that is a common substrate of multiple glycosylation pathways and is an essential glycosylation precursor. We aimed to characterize clinical phenotype, immunological profile, and genetic outcome of a 37-years-old monozygotic twins with PGM3 deficiency.

Methods: We selected the twin with more severe clinical presentation as the index case, performing a whole-exome sequencing. Sanger sequencing of PGM 3 was performed on the other twin and both parents. Patients were studied with a panel of immunological tests that included the detection of TH17 populations, lectin-based by flow cytometry (L-PHA) and other tests oriented to HIES.

Results: Both twins showed dysmorphic facial features, micrognathia, severe atopic disease, recurrent skin abscesses, and severe respiratory infections (viral and bacterial) and cognitive impairment different grade of severity. Exome sequencing identified a PGM3 compound heterozygous variants c.1438_1442del and c.1475C>T. Sanger sequencing of PGM3 performed to the other twin, identified the same genetic variant. Each parent carried one of the variants confirming the inheritance pattern. L-PHA analysis of peripheral Blood Mononuclear Cell showed a reduced binding of lectin when compared to healthy controls. Both patients showed increased expression of Th17 population.

Conclusions: Our patients present a Job-like syndrome, we considered that the PGM3 gene mutation should be considered among the possible diagnoses in individuals with HIES.

Disclosure: No.

Keyword: PGM3 deficiency; glycosylation deficiency; Hyper-IgE syndrome; compound heterozygous variants

PD332

REAL-TIME PCR BASED QUANTITATIVE EPIGENETIC IMMUNE CELL PROFILING of PATIENTS WITH PRIMARY AND SECONDARY IMMUNE DEFECTS

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Janika Schulze[1], Neftali Ramirez[2], Steffi Walter[1], Pavla Mrovecova[2], Christoph Sachsenmaier[1], Bodo Grimbacher[2], Ulrich Salzer[2]
[1]Epimune GmbH, Research & Development, Berlin, Germany, [2]University Medical Center Freiburg, Center For Chronic Immunodeficiency, Freiburg, Germany

Background and Aims: Early detection and monitoring of patients with primary and secondary immune defects requires quantitative determination of their cellular immune system. The current standard of care requires patients to provide a fresh blood sample followed by flow cytometry analysis on the same day. By contrast, epigenetic immune cell quantification allows broad immune cell profiling from a drop (40µl) of fresh, frozen, or dried blood. Here, we demonstrate the utility of epigenetic immune cell quantification for patients with a wide variety of primary and secondary immune defects.

Methods: We determined epigenetic immune cell profiles in frozen blood samples of 265 patients with different primary and secondary immune defects using a 13- immune cell marker panel (CD3+, CD4+, CD8+ T-, B, NK, TFH, PD-1, memory B, Th17, CCR6, Treg, monocytes, granulocytes). We grouped the patients according to their immune defect as well as their respective genetic diagnosis.

Results: While differences in immune profiles between groups can be observed, the inter-individual immune cell profiles - even within the same diagnosis group - vary substantially. Analysis is ongoing linking strong individual immune cell dysregulation to genetic diagnosis and/or therapy. Selected cases will be presented.

Conclusions: Epigenetic immune cell quantification is suitable for broad immune cell profiling in patients. Since the approach allows self-collection of a dried blood spot (DBS) sample, this enables patient management over long distances and in cases where a visit to a doctor’s office is not possible or very far away.

Disclosure: JS, SW and CS are full-time employees of Epimune GmbH

Keywords: Real-time PCR, Self-sampling, Epigenetics, Immune Cell Quantification, Dried Blood Spots (DBS), Screening

PD333

A PECULIAR DIAGNOSTIC PATTERN IN AN ADA SCID CHILD

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Alessandra Beghin[1], Marta Comini[1], Federica Bolda[1], Stefano Rossi[2], Elena Soncini[2], Giulia Baresi[2], Fulvio Porta[2], Arnalda Lanfranchi[1]
[1]ASST Spedali Civili di Brescia, Stem Cell Laboratory, Section of Hematology And Blood Coagulation, Clinical Chemistry Laboratory, Diagnostic Department, Brescia, Italy, [2]Children's Hospital, Spedali Civili, Brescia, Italy, Oncohematology And Bone Marrow Transplant (bmt) Unit, Brescia, Italy

Background and Aims: Adenosine Deaminase (ADA) deficiency is a common form of Severe Combined Immunodeficiency (SCID). The diagnosis is established by demonstrating an absent or very low ADA activity and by high levels of toxic metabolites (dATP, dAdo, dAXP) in red blood cells (RBC).

Methods: We report on a patient with ADA deficiency and surprisingly nearly normal level of ADA activity.

Results: The patient is an Italian female infant referred to our Clinic at the age of 6 months because of recurrent respiratory infections, failure to thrive, profound lymphopenia and positivity for infection by Covid Omicron variant. Additional laboratory tests revealed high levels of toxic metabolites (AXP: 1.08 µmol/ml RBC (range 0.8-1.6 µmol/ml RBC; dAXP: 0.37 µmol/ml RBC (range<0.005 µmol/ml RBC), %dAXP: 25.9 (range<0.5%), that lead to a diagnosis of ADA SCID. On the other hand, surprisingly, ADA activity in RBC lysates was abnormally high for ADA SCID (0.85 U/g Hb, range: 0.8-2.5 U/g Hb), whilst the patient had never received RBC transfusions. To confirm the diagnosis by molecular analysis, the sequencing of exon 2 revealed the mutation: NM_000022.2:c.43C>G(p.His15Asp), while the sequencing of exon 5 showed the mutation NM_000022.2:c.367delG(p.Asp123Thrfs*10). Both mutations were previously reported. After 4 months of enzyme replacement therapy (PEG-ADA, 0.2 mg/kg/twice weekly), the patient showed a decrease of toxic metabolites: AXP: 0.882 µmol/ml RBC; dAXP: 0.003 µmol/ml RBC; %dAXP: 0.36, Covid virus cleared and CD4+ lymphocyte started to normalize their count.

Conclusions: Dosage of ADA toxic metabolites is a reliable method and is more sensitive to pose diagnosis of ADA then enzyme activity.

Disclosure: No.

Keywords: SCID, ADA SCID, DIAGNOSIS

PD334

EARLY WISKOTT-ALDRICH SYNDROME DIAGNOSIS DUE TO INCREASED AWARENESS of PID IN A GENERAL PEDIATRIC CLINIC

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Flora Tzifi[1], Marianna Varsou[1], Marianna Tzanoudaki[2], Sofia Tantou[2], Afroditi Sakellaropoulou[1], Christina Karastathi[1], Anastasia Konidari[1], Manolis Liatsis[2]
[1]CHILDREN'S HOSPITAL "P.&AGLAIA KYRIAKOU", 2nd Department of Pediatrics, ATHENS, Greece, [2]"Aghia Sophia" Children's Hospital, Dept. of Immunology & Histocompatibility, Athens, Greece

Background and Aims: Early diagnosis of Wiskott-Aldrich syndrome (WAS), within the first months of life, in the absence of family history, is rare. However, timely diagnosis is crucial for Hematopoietic Stem Cell Transplantation (HSCT) success and overall survival.

Methods: A one-month old infant with severe thrombocytopenia since birth was admitted to our pediatric clinic. It was the first sibling of a non-consanguineous couple with unremarkable family history for inherited disorders. Clinical evaluation of the infant showed severe facial eczema, oral ulcers causing severe dysphagia and bloody stools. Laboratory evaluation displayed thrombocytopenia (PLTs: 23.000 mm^3 with MPV 5 fL), eosinophilia, low serum IgM (31 mg/dl) and marginal CD8+ lymphopenia. A strong suspicion of WAS led to assessment of WAS-protein expression by flow cytometry, in which WAS-P was undetectable. Immediate treatment with intravenous gamma-globulin and antibiotics was initiated, avoiding platelet transfusions. Subsequent HLA analysis was performed, while waiting for genetic confirmation.

Results: Sequence analysis and deletion/duplication testing of the WAS gene revealed the mutation c.631C>T (pArg211*) at exon 7, hemizygous, which results in a disrupted protein product or in an absent protein. This genetic result matches with the WAS protein absence detected in flow cytometry analysis. The patient has been transferred to a HSCT clinic.

Conclusions: Early WAS diagnosis due to enhanced awareness of primary immunodeficiencies (PID) in general pediatric clinic, led to patient's successful evaluation of clinical and laboratory findings. Therefore, training pediatricians in PID reference centers and continuous education on PID is of utmost importance.

Disclosure: No.

Keywords: PID awareness, DIAGNOSIS, Wiskott-Aldrich Syndrome

PD335

ANTIVIRAL ANTIBODIES IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY (CVID)

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Zita Chovancova[1], Jiri Litzman[1], Monika Dvorakova Heroldova[2]
[1]St. Anne´s University Hospital in Brno and Medical Faculty of Masaryk University, Department of Clinical Immunology And Allergy, Brno, Czech Republic, [2]St. Anne´s University Hospital in Brno and Medical Faculty of Masaryk University, Department of Microbiology, Brno, Czech Republic

Background and Aims: Common variable immunodeficiency (CVID) is characterized by hypogammaglobulinemia and impaired specific antibody production which is usually determined after vaccination with protein and polysaccharide bacterial antigens. Nevertheless, the benefit of measuring antiviral antibody levels at the time of diagnosis is unclear.

Methods: The serum concentration of IgG antibodies against cytomegalovirus (anti-CMV), Epstein-Barr virus viral capsid antigen (anti-EBV VCA), Epstein-Barr virus nuclear antigen (anti-EBV EBNA), herpes simplex virus (anti-HSV), varicella-zoster virus (anti-VZV), rubella virus (anti-RuV), mumps virus (anti-MuV) and measles virus (anti-MoV) was measured in 50 adult patients with CVID at the time of diagnosis and 20 patients (hypoIg) with IgG levels < 6 g/l not meeting the diagnostic criteria for CVID. Patients with secondary hypogammaglobulinemia were excluded.

Results: Presence of antiviral antibodies was in CVID group: IgG anti-CMV in 11/50 (22%), anti-EBV VCA in 12/50 (24%), anti-EBV EBNA 18/50 (36%), anti-HSV 25/49 (51%), anti-VZV 14/50 (28%), anti-RuV 12/50 (24%), anti-MuV 6/50 (12%) and anti-MoV 4/42 (10%); and in hypoIg group: IgG anti-CMV in 13/20 (65%), anti-EBV VCA in 14/20 (70%), anti-EBV EBNA 14/20 (70%), anti-HSV 15/20 (75%), anti-VZV 14/19 (74%), anti-RuV 12/20 (60%), anti-MuV 7/20 (35%) and anti-MoV 5/14 (36%). Decreased frequency of antiviral antibodies in CVID compared to hypoIg group was statistically significant in all measured types of antiviral antibodies ($p < 0,05$; Fischer exact test) except for IgG anti-HSV antibodies.

Conclusions: Antiviral antibodies were present in a significant proportion of CVID patients. Presence of antiviral antibodies in hypogammaglobulinemic patients has only limited value in determination of specific antibody production defect.

Disclosure: No.

Keyword: antiviral antibodies, CVID, antibody deficiency, specific antibody production, diagnostics

PD336

THE DARK SIDE of APDS2: A STORY TOLD THROUGH FDG-PET

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Arianna Catelli[1], Cristina Nanni[2], Rita Mulè[3], Andrea Pession[4], Francesca Conti[4]
[1]Specialty School of Paediatrics, Alma Mater Studiorum-university of Bologna, Bologna, Italy, [2]Nuclear Medicine, Irccs Azienda Ospedaliero-universitaria Di Bologna, Bologna, Italy, [3]Rheumatology Unit, Azienda Ospedaliero-universitaria Di Bologna, Bologna, Italy, [4]Pediatric Unit, Irccs Azienda Ospedaliero-universitaria Di Bologna, Bologna, Italy

Background and Aims: Lymphoproliferation and increased risk of malignancy are key features of activated phosphoinositide 3-kinase-δ syndrome 2 (APDS2). We report the use of FDG-PET/CT as a helpful diagnostic tool for accurate identification of inborn errors of immunity (IEI), especially among lymphoproliferative disorders.

Methods: Activating mutation of PIK3R1 was found in a 30-year-old woman with refractory systemic lupus erythematosus, autoimmune cytopenia, and diffuse lymphoproliferation.

Results: Ten years before, our patient was diagnosed with Hodgkin's lymphoma, although atypical aspects emerged: FDG-PET/CT at baseline showed several hot supra and subdiaphragmatic lymph nodes with a very symmetrical distribution, associated to inhomogeneous increased tracer uptake in axial and appendicular bone marrow and slight and diffuse increase of the spleen metabolism. Several scans repeated after chemotherapy and autologous stem cell transplantation revealed incomplete resolution, with persistent diffuse increased FDG uptake at multiple supradiaphragmatic nodes and axial and appendicular bone marrow. One year after APDS2 diagnosis and rapamycin treatment, FDG-PET/CT confirmed remission of lymphoproliferation, showing a complete metabolic normalization of all sites.

Conclusions: FDG-PET/CT has a crucial role in differentiating malignant proliferation from immune dysregulation phenotypes. In our case, inadequate response to lymphoma treatment was due to diffuse lymphoproliferation, and numerous imaging studies could be avoided. Therefore, the presence of atypical patterns and unusual metabolic uptake at FDG-PET/TC should be interpreted as a red flag for the need of an early immunological evaluation, especially in patients with other features of immune dysregulation.

Disclosure: No.

Keywords: APDS2, PI3K-AKT-mTOR, FDG-PET/CT, LYMPHOPROLIFERATION, Lymphoma

PD337

CHRONIC GRANULOMATOSIS DISEASE WITH AN UNUSUAL DHR PATTERN AND NBT RESULT

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Kasra Jahankhani[1], Abdollah Karimi[2], Samin Sharafian[3], Zahra Chavoshzadeh[3], Mehrnaz Mesdaghi[1,3]
[1]Shahid Beheshti University of Medical Sciences, Department of Immunology, School of Medicine, Tehran, Iran, [2]Shahid Beheshti University of Medical Sciences, Pediatric Infections Research Center, Mofid Children Hospital, Tehran, Iran, [3]Shahid Beheshti University of Medical Sciences, Department of Allergy And Clinical Immunology, Mofid Children's Hospital, Tehran, Iran

Background and Aims: Chronic granulomatosis disease (CGD) is a heterogeneous defect leading to insufficient phagocytic function. Several mutations have been reported to be responsible for this disorder, among which NADPH oxidase complex subunits of neutrophils and monocytes are the most common.

Methods: In a 3-month old boy with disseminated BCG infection, NBT and DHR tests were performed to diagnose or rule out CGD. Whole exome sequencing (WES) was done to confirm the diagnosis.

Results: The diagnosis of disseminated BCG infection was confirmed by PCR. The first NBT was reported 0 and the second NBT was reported 100. DHR mean fluorescence intensity was reported 10 (in the range of CGD), but 60% of the granulocytes were in positive region and DHR pattern was consistent with CGD carrier. WES confirmed CGD diagnosis and a deletion in exon 2 of CYBC1 gene (a pathogenic mutation) was reported. Both parents were carriers for this mutation.

Conclusions: NBT and DHR results might be misleading in some cases, in whom genetic studies can be helpful. The reported mutation in this patient is a novel mutation. This DHR pattern maybe relevant to this novel mutation and studying further cases is needed to conclude.

Disclosure: No.

Keywords: Chronic granulomatosis disease, DHR, NBT, Whole Exome Sequencing, primary immunodeficiency

PD338

STUDY of IMMUNOGLOBULIN SUBCLASS EXPRESSION ON B CELLS: INITIAL EXPERIENCE FROM ITS IMPLEMENTATION IN CLINICAL PRACTICE

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Marianna Tzanoudaki, Sofia Tantou, Rediona Kane, Virginia Polaki, Manolis Liatsis
"Aghia Sophia" Children's Hospital, Dept. of Immunology & Histocompatibility, Athens, Greece

Background and Aims: Laboratory markers are needed to predict the clinical course of Primary Antibody Deficiencies. IgG and IgA subclass expression on B cells has been recently used for further classification of this heterogeneous group. We aimed to evaluate its applicability in clinical practice.

Methods: B cell subsets of 5 CVID patients (4-42y), 4 with selective IgA deficiency (IgAdef, 14-43y), 2 with CID/SCID (1.5 – 13y), and 4 with normal serum immunoglobulins (4-42y), were studied by multicolor Flow Cytometry, using CD19, CD20, CD27, CD38, IgD, IgM, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. Results were expressed as % on switched memory B cells (smB: CD27+IgD-CD38med) and compared to clinical data.

Results: In 3 CVID patients with autoimmunity IgA1/2+ smB were undetectable, whereas the 2 CVID patients with favorable clinical course had IgA1+ 0.2-0.6% on smB (compared to median 1.1% in controls). IgA2 was detectable in 2 asymptomatic IgAdef patients. All symptomatic patients had undetectable IgA2+ smB. IgG subclass expressing smB were low in all CVID patients (median 1% for IgG1+). Remarkably, elevated % of IgG1+ smB was noticed in IgAdef (median 16.9%) compared to controls (median 5.8%). As expected, IgG+ and IgA+ smB were extremely low (max 0.5% for IgG1+) in PID/SCID and IgG2+ and IgG4+ smB were undetectable in the respective selective deficiency.

Conclusions: IgG and IgA subclass expression is easily implemented in the clinical lab. Results are consistent with diagnosis. Lack of mucosa associated IgA2+ smB seems to correlate with autoimmunity, needing further studies for confirmation.

Disclosure: No.

Keywords: primary antibody deficiencies, B cell immunophenotyping

PD339

LIFE-CHANGING TREATMENT AFTER A LATE DIAGNOSIS of CHAPLE SYNDROME. CASE REPORT.

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Mariana Villa[1], Andrea Bernasconi[1], Jimena Messina[2], Natalia Pabon[2], Laura Busquet[3], Carolina Bouso[1], Luciano Urdinez[1], Matias Oleastro[1], Silvia Danielian[1], Adriana Bottero[3]
[1]Hospital Nacional de Pediatría Prof. Dr. Juan P. Garrahan, Immunology, Ciudad Autónoma de Buenos Aires, Argentina, [2]Hospital Nacional de Pediatría Prof. Dr. Juan P. Garrahan, Paediatrics, Ciudad Autónoma de Buenos Aires, Argentina, [3]Hospital Nacional de Pediatría Prof. Dr. Juan P. Garrahan, Gastroenterology, Ciudad Autónoma de Buenos Aires, Argentina

Background and Aims: Mutations in the gene encoding CD55, the decay-accelerating factor, leads to CHAPLE syndrome (hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy (PLE)). We describe a patient with a long history of gastrointestinal complications, mesenteric thrombosis and antibody immunity compromise with final diagnosis of CHAPLE syndrome.

Methods: The patient, a 14 year-old- Bolivian male was the 3rd child of non-consanguineous parents. The diagnosis was based in protein detection by Flow cytometry and genetic identification by Next Generation Sequencing.

Results: Our patient presented with chronic diarrhea, severe abdominal pain and intermittent subocclusive episodes since he was 8 months old. He also had failure to thrive, pubertal delay and digital hypocratism, without a respiratory cause. Besides he had hypoalbuminemia (1.6g/dl), hypogammaglobulinemia (0.24 g/dl) and elevated α1-anti-trypsin clearance (1060 ml/24h). Enterotomography evidenced thrombosis of the superior mesenteric vein. Small Intestine Transit showed distension and thickness of yeyunal and ileon handles, whereas exploring laparotomy showed thickened and strapped areas of stenosis. Biopsy revealed severe ulcerated enteritis with lymphangiectasia. These findings led to discard PNH which detected an exclusively lack of CD55. Molecular analysis detected a homozygous deletion in CD55: c.1039_1042 del AAAG (p.Lys347GlufsTer74). A specific therapy protocol with human monoclonal antibody against complement factor C5 was implemented that improved all the symptoms.

Conclusions: A monogenic defect should be considered in a patient with an early starting PLE and thrombosis. The lack of CD55 expression by flow cytometry, with the following molecular diagnosis, guided the therapeutic approach.

Disclosure: No.

Keywords: CHAPLE, hypogammaglobulinemia, CD55 deficiency, losing protein enteropathy, complement hyperactivation, thrombosis

PD340

FROM THE CLINICAL PHENOTYPE TO THE MOLECULAR DIAGNOSIS: FIRST YEAR of EXPERIENCE IN A PEDIATRIC HOSPITAL IN EL SALVADOR WITH MOLECULAR DIAGNOSIS IN PID

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Wendy Venavides, Hector Guidos, Carmen Bermudez
Hospital Nacional de Niños Benjamin Bloom, Immunology Department, San Salvador, El Salvador

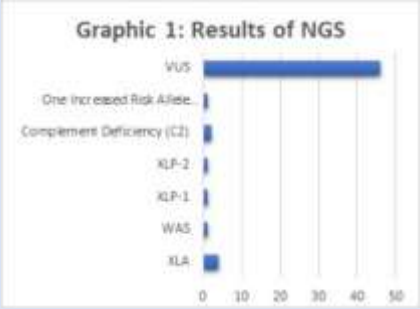
Background and Aims: IEI are progresive field of research specially in diagnosis and treatment; genetics test are an important tools to provide molecular confirmation of disease in a patient with a suspected; In El Salvador the diagnosis throug the last 20 years had been limited for: blood leukocyte count, flow cytometry and Ig leves, recently we had the chance to send samples to laboratories in other countries.

Methods: The study included 57 patients who were suspected to have IEI. The clinical suspicion of IEI was based on clinical and laboratory parameters table 1.

Table 1 Suspicius previus to molecular test

SCID	2
CID with associated or syndromic features	4
Antibody deficiencies	15
Diseases of immune dysregulation	3
Congenital defects of phagocyte	8
Defects in intrinsic and Innate immunity	7
AI disorders	4
Complement deficiencies	8
Bone marrow failure	6
	57

Results: 56 patients were tested by NGS and in 1 patient WES. NGS: XLA: 4 patients 2 genes mutations for BTK , 1 in WAS gene, 1 patient to XLP-1 and other XLP-2; 2 complement deficiency (C2) and other results are showing in graphic 1; in one patient by WES was detected mutation N159S gen IKZF1 positive for IKAROS disease.



Conclusions: These results represent our first experience with the use of molecular diagnostic tools in IEI, exposing the growing need for access to greatly improve the diagnostic and approach treatment in developing countries.

Disclosure: No.

Keywords: Next-generation sequencing technology, Whole genome sequencing, inborn error of immunity

PD341

NIJMEGEN SYNDROME IN AN ADULT PATIENT - THE ROLE of EARLY DIAGNOSTIC

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Anca Manolache[1], Mihaela Bataneant[2], Augustin Serban[1], Diana Preda[3], Iulia Ursuleac[3], Daniel Coriu[3], Ciprian Jurcut[1]
[1]Dr. Carol Davila Central University Emergency Military Hospital, Internal Medicine, Bucharest, Romania, [2]Louis Turcanu Clinical Emergency Hospital for Children, Victor Babes University of Medicine and Pharmacy, Pediatrics, Timisoara, Romania, [3]Fundeni Clinical Institute, Carol Davila University of Medicine and Pharmacy, Hematology Clinic, Bucharest, Romania

Background and Aims: The diagnostic of adult patients with Nijmegen syndrome might be challenging in daily clinical practice.

Methods: We present the case of a man diagnosed with Nijmegen syndrome in the context of B-cell lymphoma.

Results: The patient was diagnosed with hypogammaglobulinemia at the age of 7, during an episode of severe pneumonia. He was lost to follow-up but multiple upper respiratory tract infection and pneumonia were diagnosed. No constant IVIg supplementation. At the age of 24, a large laterocervical adenopathy was noted and the biopsy revealed B cell non-Hodgkin's lymphoma. The CT scan at the time of the diagnosis revealed: multiple diffusely distributed adenopathies, hepatomegaly, severe splenomegaly, and multiple splenic nodules. The treatment of lymphoma was started and, in the context of clinical examination revealing microcephaly, proeminent nose, sloping forehead, small jaw and severe hypogammaglobulinemia, the genetic testing was performed. It showed pathogenic homozygous mutation (c.657_661del (p.Lys219Asnfs*16) in the NBN gene. The supplementation with immunoglobulins (IVIg, followed by facilitated subcutaneous immunoglobulins) was initiated. Despite the adequate Ig treatment infectious episodes were diagnosed during the follow-up, related to to primary immunodeficiency in Nijmegen syndrome and secondary immunodeficiency related to lymphoma and its treatment.

Conclusions: We present a case report of a patient with Nijmegen syndrome, emphasizing the role of early diagnosis and genetic testing in patients with hypogammaglobulinemia and specific phenotype.

Disclosure: No.

Keyword: Nijmegen syndrome, B cell non-Hodgkin's lymphoma

PD342

ADA DEFICIENCY DIAGNOSED IN AN ADULT WOMEN – THE IMPORTANCE of THE GENETIC TESTING

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Anca Manolache[1], Mihaela Bataneant[2], Augustin Serban[1], Ciprian Jurcut[1]
[1]Dr. Carol Davila Central University Emergency Military Hospital, Internal Medicine, Bucharest, Romania, [2]Louis Turcanu Clinical Emergency Hospital for Children, Victor Babes University of Medicine and Pharmacy, Pediatrics, Timisoara, Romania

Background and Aims: The diagnostic patients with ADA deficiency syndrome might be challenging in daily clinical practice, especially in adult patients.

Methods: We present the case of a woman diagnosed with ADA deficiency syndrome highlighting the role of genetic testing in this context.

Results: A 32 years old women was referred to our clinic for persistent lymphopenia and high levels of IgE. The onset started at the age of 1 year with type 1 diabetes mellitus and recurrent severe respiratory infections, followed by the diagnostic of autoimmune thyroiditis and asthma. At this time, the CT scan of the lung revealed bilateral bronchiectasis. During the follow-up, the patient developed influenza and pneumonia with Enterobacter Kobei and Pseudomonas Putida and erythematous skin lesions but the skin biopsy showed nonspecific chronic dermatitis. An episode of hypersensitivity pneumonitis was diagnosed and high levels of IgE were noted during this episode (3876 U/ml). Allergies, allergic bronchopulmonary aspergillosis and cystic fibrosis were excluded. Multiple tests for autoimmune diseases and hematological diseases were negative. Immunological investigations showed severe lymphopenia (296/µL) with absent B cells and low naïve CD4+ cells, high LTCD3+HLADR+ and hypo IgG3 and IgG4. We performed the genetic testing that showed the pathogenic homozygous mutation c.302G>T (p.Arg101Leu) in the ADA gene; this mutation is known to be a mild mutation.

Conclusions: Recurrent infections with early onset autoimmunity, high IgE and lymphopenia is suggestive for ADA deficiency even in adult patients, the genetic testing being crucial for the diagnosis and treatment decision.

Disclosure: No.

PD343

CARD11 – ONE GENE, MORE DISEASES

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Mihaela Bataneant[1], Svetlana Sciuca[2], Adela Chirita Emandi[3], Patricia Urtila[1], Mihaela Baica[4], Estera Boeriu[1]
[1]"Victor Babeș" University of Medicine and Pharmacy, Iiird Pediatric Clinic, Timisoara, Romania, [2]Nicolae Testemitanu State University of Medicine and Pharmacy, Pediatrics, Chisinau, Moldova, [3]"Victor Babeș" University of Medicine and Pharmacy, Genetics, Timisoara, Romania, [4]Louis Turcanu Children Hospital, Laboratory, Timisoara, Romania

Background and Aims: Primary immunodeficiencies are complex diseases, mutations in more genes causing the same clinical picture but also different mutations in the same gene can lead to different diseases. An example is the CARD11 gene that regulates cellular apoptosis. Clinically, biallelic mutations in the CARD11 gene cause severe combined immunodeficiency, germline GOF mutations cause BENTA syndrome, and LOF germline mutations are manifested by atopy, immunodeficiency and autoimmunity.

Methods: To exemplify the clinical diversity of CARD11 gene mutations with 3 cases.

Results: Patient 1. A boy with a family history of cancer had recurrent and prolonged infections, recurrent diarrhea, malnutrition since infancy. Digestive causes are excluded. At the age of 11 years, he was diagnosed with hypogammaglobulinemia and the genetic investigation revealed a double heterozygous mutation c.572A>G/c.490_492del in the CARD11 gene. Patient 2. A 16-year-old girl developed recurrent and persistent infections from the infancy, hepatosplenomegaly and then massive laterocervical lymphadenopathy. Investigations identify hypogamaglobulinemia with elevated IgM, B lymphocytosis, and decreased memory B lymphocytes. Genetic investigation reveals heterozygous mutation p.Gly123Ser in the CARD11 gene, confirming BENTA syndrome. Immunoglobulin treatment reduced lymphadenopathy, splenomegaly and the frequency of infections. Patient 3 is a 4 years old girl, who developed universal alopecia from 1year, atopic dermatitis, recurrent wheezing, allergy. Investigations rule out the endocrinological cause and reveal leukopenia with neutropenia, IgA and IgG4 deficiency with hyperIgE, poor vaccination response, and genetic investigation showed heterozygous mutation R974C in the CARD11 gene.

Conclusions: Mutations in CARD11 gene cause different phenotypes, and genetic investigation is essential in the diagnosis of any primary immunodeficiency.

Disclosure: No.

Keywords: Immunodeficiencies, child, CARD11

PD344

ANALYSIS of THE DIHYDRORHODAMINE ASSAY IN THE DIAGNOSIS of CHRONIC GRANULOMATOUS DISEASE

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Asmaa Drissi Bourhanbour[1], Asmaa Dably[2], Bouchra Ifegh[1], Hind Ouair[3], Ibtihal Benhsaien[4,5], Fatima Ailal[5,6], Ahmed Aziz Bousfiha[3,5], Jalila El Bakouri[6,7]
[1]IBN Rochd University Hospital, 1. immunology Laboratory, CASABLANCA, Morocco, [2]IBN Rochd University Hospital, Immunology Laboratory, CASABLANCA, Morocco, [3]Faculty of Medecine and Pharmacy, University Hassan II, Casablanca, Laboratory of Clinical Immunology, Inflammation And Allergy (licia), CASABLANCA, Morocco, [4]Faculty of Medicine and pharmacy of Casablanca, 1) research Laboratory In Clinical Immunology And Inflammation (licia), Casablanca, Morocco, [5]Abderrahim El Harouchi Children Hospital, University Hospital Center Ibn Rochd, Casablanca, Morocco., Clinical Immunology Unit, Department of Infectious Diseases, Casablanca, Morocco, [6]Faculty of Medicine and pharmacy of Casablanca, Research Laboratory In Clinical Immunology And Inflammation (licia), Casablanca, Morocco, [7]IBN Rochd University Hospital,, Immunology Laboratory, Casablanca, Morocco

Background and Aims: A retrospective study includes all patients followed up in the Pediatric Infectious Diseases Department of the Ibn Rochd University Hospital of Casablanca, in whom a dihydrorhodamine (DHR) assay was requested. The aim of the study is to analyse the importance of the different parameters provided by the DHR assay in the diagnosis and characterization of CGD.

Methods: DHR assay was performed using three stimulants; E.coli bacteria, N- formylMetLeuPhe and phorbol 12-myristate 13- acetate. We collected and analysed data from 2016 to 2019.

Results: A total of 398 patients with suspected GSD were tested during the study period. Twenty patients had abnormal DHR assay. The mean age of the patients was 4 years with a male predominance. An absence of oxidase activity in stimulated phagocytes was detected in 17 patients, consistent with a phenotype observed in X-linked CGD. A reduction of oxidase activity was detected in two patients. In these cases the reduction may be due to the neutropenia observed in both patients. One patient had a normal response to PMA but reduced response to E. coli. This case can be explained by a myeloperoxidase deficiency. The fluorescence histogram of two female patients showed two peaks of fluorescence indicating two populations of neutrophils; this result is consistent with the X-linked female carriers of the disease. These patients had a normal response to PMA.

Conclusions: In countries with limited resources, the use of the DHR assay may provide a solution to assist in the classification of CSD subtypes

Disclosure: No.

Keywords: assay, Chronic Granulomatous Disease, Dihydrorhodamine

PD345

EVALUATION of TOTAL SERUM IGE LEVELS AMONG A COHORT of ATOPIC PATIENTS WITH PRIMARY ANTIBODY DEFICIENCY

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Francesco Muscianisi[1], Alessandro Dell'Edera[1], Franco Borghesan[1], Riccardo Scarpa[2], Marcello Rattazzi[2], Carlo Agostini[2], Francesco Cinetto[2]
[1]Ca' Foncello Hospital-Treviso (University of Padua), Rare Disease Referral Center-internal Medicine, Treviso, Italy, [2]University of Padua, Department of Medicine, Treviso, Italy

Background and Aims: Specific antibody production is impaired in Primary Antibody Deficiencies (PADs). Only few studies analysed the prevalence of IgE-mediated disorders in such patients. We investigated the prevalence of atopic manifestations in a cohort of patients with PADs and compared serum IgE levels between the different groups.

Methods: We retrospectively analysed a monocentric PADs cohort composed by 128 Common Variable Immunodeficiency (CVID) and 33 IgG subclass deficiencies (IgSD). As a control group, we selected 39 immunocompetent subjects mono-sensitized to Hymenoptera venom. We compared serum IgE levels between groups by Kruskal-Wallis test.

Results: A total of 44/161 (27%) PADs patients presented history of atopy: rhinitis/polyposis (12/44), asthma (7/44), sensitization to inhalants (8/44), to drugs (24/44), to hymenoptera venom (1/44). 5/44 had polysensitization. 7 of 161 patients reported adverse reactions related to immunoglobulin replacement therapy, with 3 cases of anaphylaxis. No differences were found in atopic manifestations between CVID and IgSD, while a statistically significant difference was observed in median IgE levels (2 vs 198, $p=0.04$). When comparing IgE levels of PADs patients with controls, only CVID patients showed a significant difference (2 vs 141, $p<0.001$).

Conclusions: Total serum IgE seems not to be a suitable parameter in the diagnostic work-up of allergies in patients affected by PADs, especially in those ones with CVID, where the total serum IgE are frequently undetectable. Further studies are needed to investigate the possible presence of allergen specific IgE or other more accurate markers of allergies in PADs patients.

Disclosure: No.

Keywords: allergy, Inborn errors of immunity, Primary Antibody Deficiency, IgE

PD346

SEVERE IMMUNE DEFICIENCY DISCOVERED FOLLOWING BILATERAL PNEUMOPATHY: A CASE REPORT

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Fatiha Boukandoura, Kahina Ouahbi, Hanifa Benmakhlouf, Nacera Hamadouche, Ourida Gacem, Mohamed.Samir Ladj
Alger, University of Medecine Algiers, Algeria, Eph Birtraria, Algiers, Algeria

Background and Aims: We report a case of T-B-NK+ severe combined immunodeficiency (SCID) discovered following bilateral lung disease.

Methods: We report a 13-month-old female case of severe combined immunodeficiency (SCID) T-B-NK+.

Results: 13-months-old female infant born, from a consanguineous marriage, brother died at the age of 6 months due to severe septicaemia. Personal history of bcgitis; hospitalized several time for recurrent infections. At the age of 1 year, the patient was admitted to the hospital of Tiaret for 15 days for respiratory distress with high fever, put on antibiotic therapy. In view of the unfavourable evolution and the aggravation of her respiratory distress, she was referred to our department On admission, the clinical examination found a hypotrophic infant in a poor general state, with severe respiratory distress and hepatomegaly. The chest X-ray on the patient's bed showed multiple diffuse reticulo-nodular opacities in both lung fields, a correct cardio-thoracic index with the presence of a thymic shadow. Biologically, the leukocyte count returned to 6500/mm3 with lymphopenia at 657/mm3 neutrophils 5701/mm3 CRP positive at 40 mg/l. Chest CT scan showed diffuse bilateral lung condensation with frosted glass and mosaic appearance. Given the family history, repeated infections and lymphopenia, a primary immune deficiency was strongly suspected, confirmed by the immunological work-up, which showed a severe combined immune deficiency with T-B-NK+ in favour of a leaky SCID. Despite management with immunoglobulin and triple antibiotic therapy, the patient died.

Conclusions: In the absence of an early diagnostic and treatment with bone marrow transplantation, all children with SCID die in infancy

Disclosure: No.

Keyword: severe combined immunodeficiency (SCID), Cansanguinity, bone marrow transplantation

PD347

INTERPRETATION of HETEROGENEOUS TNFRSF13B MUTATION POSES A CHALLENGE IN THE CLINICAL SETTING

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Laura Koumas[1], Rafaella Gavrielidou[1], Elena Socratous[1], Andri Miltiadous[2], Petroula Gerasimou[2], Evangelia Karaoli[3], Eleni Papachristodoulou[3], Paul Costeas[2]
[1]Karaiskakio Foundation, Cellular Pathology- Immunology, Nicosia, Cyprus, [2]Karaiskakio Foundation, Molecular Pathology And Genetics, Nicosia, Cyprus, [3]Makarios Hospital, Paediatric Oncology, Nicosia, Cyprus

Background and Aims: Described herein is a case involving a family with triplets, two males and one female, where at 4 years old, the female and one male presented at the clinic with EBV infection, AIHA, recurrent urticaria and episodes of bronchitis requiring antibiotics. The female died from fulminant EBV pneumonopathy and pericarditis. The male, with chronic asthmatic and allergic manifestations since infancy, was pale, non-febrile, without lymphadenopathy or hepatosplenomegaly, with normal ECG, HSV skin infection, onychodystrophia post severe fungal infection, enamel and dental abnormalities.

Methods: Multi-parametric flow cytometry was used for lymphocyte immunophenotyping and exome sequencing performed on an Illumina platform.

Results: Flow cytometry showed decreased absolute lymphocyte counts, decreased NK cell percentage but no decrease in memory B or T cells. Exome sequencing revealed presence of heterozygous TNFRSF13B c.418G>Ap.Glu140LysNM_012452.2 mutation with uncertain significance in the male, but not female patient.

Conclusions: Mutations in TNFRSF13B pose a challenge in how we interpret their association as possible risk of developing CVID. It remains unknown if the mutation identified in this patient can be considered as a risk factor for CVID, since heterogeneous TNFRSF13B mutations have been observed in a significant proportion of the normal population. Functional effects of heterogeneous TACI variants should be studied to better understand mechanisms involved and their contribution to CVID. This case is posing a diagnostic challenge as a rare clinical situation with no current definitive diagnosis, despite the fact that symptoms reflect an unexplained immune deficiency. Poodt et al.Clinical and Experimental Immunology,2009,156:35-39. Pan-Hammarstrom et al.,Nat Genet, 2007,39(4):429-430. Leonardi et al.,Frontiers in Pediatrics, 2019,7(418);1-5.

Disclosure: No.

Keywords: TNFRSF13B gene, CVID

PD348

LYMPHOPROLIFERATION AT THE ONSET of PID PATIENTS IN THE REPUBLIC of BELARUS

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Yulia Zharankova[1], Tatiana Volodashchik[2], Svetlana Aleshkevich[1], Ekaterina Polyakova[2], Irina Guryanova[2], Yulia Skibo[3], Mikhail Belevtsev[2]
[1]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Outpatient Department, Borovlyany, Belarus, [2]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Research Department, Borovlyany, Belarus, [3]Kazan Federal University, Institute of Fundamental Medicine And Biology, Kazan, Russian Federation

Background and Aims: PID-associated non-malignant lymphoproliferation is more common than malignant and represents a serious diagnostic problem, especially when it comes to the onset of the disease.

Methods: We analyzed the clinical data of Belarusian patients with PID with a lymphoproliferation as a manifestation of the disease.

Results: Lymphoproliferative syndrome in the initial stage of the disease in 29 patients with PID (4.7% of total PIDs). The diagnostic period ranged from 1m to 20yrs (mean 7.8yrs). The following genetic defects were identified in 27 patients: FAS-TNFRSF6 (8), PIK3CD GOF (6), STAT3 GOF (3), LRBA (2), SH2D1A (2), XIAP (2), NFkB1 (1), NFkB2 (1), CTLA4 (1), C2 (1), CVID (2). The median age of manifestation in ALPS-FAS patients is 3yrs, in patients with T-reg defects (STAT3 GOF, LRBA, CTLA4) - 2.3yrs, in XLPI/II patients - 1.8yrs, in APDS patients - 0.6yrs. Treatment options and outcomes: mTOR inhibitor therapy was successfully applied in 7 patients ((FAS-TNFRSF (3), PIK3CD GOF (4)), inosine-monophosphate dehydrogenase inhibitor - 1 patient (STAT3 GOF (1)), Rituximab - 1 patient (STAT3 GOF (1), Abatacept - 1 patient (CTLA4 (1)), 6 patients receive IG replacement therapy (SH2D1A (1), NFkB1 (1), NFkB2 (1), CVID (2) (1)), one ALPS patient developed B-cell lymphoma (age of onset 45yrs), HSCT was performed in 3 patient (LRBA (2), XLPII (1) - alive 1, dead 2), XLPI (SH2D1A (1)) died before diagnosis.

Conclusions: Genetic analysis demonstrates the possibility of similar clinical manifestations in patients with various PID mutations. Establishing a genetic diagnosis in PID patients provides genotype-specific management.

Disclosure: No.

Keyword: non-malignant lymphopriliferation

PD349

DIFFERENT CLINICAL PRESENTATION of CHRONIC GRANULOMATOUS DISEASE - INTRICATE PATHWAYS TO DIAGNOSIS

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Justyna Błach[1,2], Iwona Rywczak[1], Anna Pituch-Noworolska[1], Anna Szaflarska[1], Karolina Bukowska-Strakova[3], Jarosław Baran[3], Monika Mach-Tomalska[1]
[1]University Children Hospital, Department of Clinical Immunology, Cracow, Poland, [2]Medical University of Lublin, Department of Clinical Immunology, Lublin, Poland, [3]Jagiellonian University Medical College, Department of Clinical Immunology, Cracow, Poland

Background and Aims: CGD patients struggle with life-threatening infections and excessive inflammatory responses. It's perceived as a well defined disease with determined genetic background, however it may turn out a diagnostic and therapeutic challenge.

Methods: Chemiluminescence, NBT, phagoburst.

Results: Case1: A 8-yo boy, with history of MAS, liver abscess, serous effusions, recurrent fevers. Despite CGD suggestive symptoms, the implemented tests (chemiluminescence for ROS production, myeloperoxidase expression) failed twice to confirm the diagnosis. Subsequently, because of MAS history and an impaired NK cells activity, the boy was diagnosed toward HLH. Due to negative HLH genetics and high suspicion of CGD, a phagoburst test was performed. An impaired ROI production with the absence of $gp91^{phox}$ were confirmed. The patient is awaiting HSCT. Case2: A 5-yo boy, with lymphadenopathy, recurrent fevers, chronic anemia, eosinophilia. Mediastinal lymph node biopsy suggested tuberculosis or another contagious disease. Finally, after excluding of infectious agents, tests (chemiluminescence, NBT, phagoburst, lack of $gp91^{phox}$) confirmed X-CGD with CYBB mutation. Recently, HSCT has been performed with non-complicated post-transplant short-term observation. Case3: A 2-yo boy with recurrent fevers, erythema papulosum, dysplastic nails. After exclusion of fungal infection, tests (chemiluminescence, phagoburst test) made diagnosis possible. There was a $gp91^{phox}$ expression, no mutation in the coding part of the CYBB gene was detected, other genetic tests are pending. The boy needed a second HSCT due to first graft rejection.

Conclusions: The clinical CGD features can be highly diversified. Although there are many laboratory test, each of them has it’s limitations, It makes the diagnosis not only difficult but also time-consuming.

Disclosure: No.

Keywords: phagoburst test, Chronic Granulomatous Disease, chemiluminescence, CYBB mutation, NBT

PD350

MYCOBACTERIUM ABCESSUS IN A PATIENT WITH ARPC1B MUTATION

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Noemi Gomez Hernandez[1], Marco Yamazaki-Nakashimada[2], Eduardo Torres Rojo[1], Margarita Ortega Cisneros[3]
[1]Centro Medico Nacional de Occidente Instituto Mexicano Seguro Social. Hospital Especialidades, Allergy And Clnical Immunology, Guadalajara, Jalisco., Mexico, [2]National Institute of Pediatrics, Immunology, Mexico City, Mexico, [3]Hospital de Especialidades, Instituto Mexicano del Seguro Social, Departamento De Inmunología Clínica Y Alergia, Guadalajara, Jalisco, Mexico

Background and Aims: Introduction: ARPC1B plays a critical role in supporting T cell and thrombocyte development. Objectives: Report of a patient with ARPC1B mutation with a renal abscess secondary to Mycobacterium Abcessus.

Methods: Clinical and laboratory features of the patient were described.

Results: 28-year-old male, originally from Michoacan Mexico, his parents are consanguineous. .The patient began with a history of childhood eczema and recurrent abscesses from one year of age, multiple episodes of otitis media sinusitis and infectious gastroenteritis. Initially was diagnosed with HIES with elevated IgE levels, but the sequencing study documented mutation ARPC1B. In January 2022, he presented pneumonia with a negative SARS COV2 study. One month later, he returned with fever of 40 C, pain in right renal fossa. Abdominal CT scan: Shows right renal mass compatible with an abscess, lung disease associated with a bulla in the left base. Required a nephrectomy, 10 days later return due to fever 39 C, dehiscence on the surgical wound and abundant purulent secretion . The PCR in renal tissue, resulting positive for Mycobacterium Abcessus. Was indicated therapy with imipenem ,tigecycline, azithromycin, and linezolid , after 3 weeks he presented hematological toxicity with plaquetopenia so linezoid was discontinued and he continued with meropenem , tigecycline, azithromycin with adequate evolution . bibliography DOI 10.1111/imcb.12243

Conclusions: Host factors that predispose to infection for Mycobacterium Abcessus include genetic disorders such as cystic fibrosis or bronchiectasis. ARPC1B deficiency viral and bacterial infections observed in many of the patient, but the presence of atypical mycobacteria has not been previously reported.

Disclosure: No.

Keywords: Mycobacterium Abscessus, immunodeficiency, ARPC1B

PD351

A NOVEL MUTATION IN CD40LG GENE CAUSING HYPER IGM SYNDROME IN VIETNAMESE FAMILY

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Thi Phuong Mai Nguyen
National Children's Hospital, Human Genetic Department, Hà Nội, Viet Nam

Background and Aims: The X-linked hyper IgM syndrome is a rare disorder with a prevalence of 1:1,000,000 males because mutations in the CD40LG gene (CD40 ligand gene) lead to CD40 ligand deficiency. In this study, we have two patients who are siblings in the same family. Both patients have clinical symptoms of recurrence of severe pneumonia, diarrhea, mouth ulcers, and sepsis in the first year of life.

Methods: We used whole-exome sequencing (WES) was carried out on the Illumina sequencing machine (Illumina, CA, USA). DNA sequencing was performed in both directions, initiated from the forward and the reverse primers, which had been used in the initial PCR reaction. The sequencing data were analyzed using BioEdit 7.2.5 software. The novel nucleotide change was evaluated with the in silico analysis tools: PROVEAN, SIFT, PolyPhen-2, and Mutation Taster.

Results: Both the two patients carried the c.760delA (p.Thr254fs, exon 5) mutation inherited from their mother. The c.760delA mutation resulted in a frameshift mutation (p.Thr254fs) and extended the polypeptide chain by 51 amino acids compared to the original protein. This mutation is located in the TNF domain of the CD40LG protein.

Conclusions: Our results contribute to the general understanding of the etiology of the disease and can help diagnose the different forms of PID

Disclosure: No.

Keywords: Hyper IgM, CD40LG gene, Primary immunodefciency

PD352

ATAXIA TELANGIECTASIA: ABOUT TWO BROTHERS

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Kahina Ouahbi, Fatiha Boukandoura, Mohamed Aouiz, Hanifa Benmakhlouf, Nacera Hammadouche, Ourida Gacem, Naziha Mehaba, Mohamed.Samir Ladj
university of algiers - faculty of medecine, Eph Djilali Belkhenchir (ex Birtraria), ALGER, Algeria

Background and Aims: Evoke ataxia telangiectasia in the presence of characteristic clinical manifestations and a primary immune deficiency

Methods: We report the case of 2 brothers aged 2 and 4 years respectively from a consanguineous couple.

Results: T.H, a 2-year-old infant with a history of recurrent ENT and pulmonary infections since the first months of life, was admitted for measles complicated by macrophagic activation syndrome. The clinical examination revealed staturo-ponderal growth retardation, prominent blood vessels on the bulbar conjunctiva and several milk coffee spots on different parts of the body. The immunological investigation revealed a combined immune deficiency with a near absence of IgA, elevated serum IgM levels, frank T and B lymphopenia and a strong expansion of memory B cells and CD21 B cells (low). Examination of the older brother T.I, aged 4 years, revealed cerebellar ataxia, ocular telangiectasia and milk coffee spots on the body. The immunological assessment revealed the same disturbances as his brother. the association of cerebellar ataxia in one and a combined immune deficiency with telangiectasia and milk coffee spots in both; ataxia telangiectasia or louis barr syndrome is strongly evoked, confirmed by the significant increase in alpha-fetoprotein in the two brothers After the management by polyvalent immunoglobulin substitution and prophylactic antibiotic therapy, T.H had fewer infectious episodes. Following the development of thrombocytopenia during follow-up, the myelogram revealed dysmyelopoiesis requiring regular checks.

Conclusions: Ataxia telangiectasia is a chronic disabling disease with a severe prognosis linked particularly to the neurodegenerative syndrome and the risk of infections and malignant degeneration.

Disclosure: No.

Keyword: Ataxia telangiectasia, immune deficiency, recurrent infections, malignant degeneration

PD353

DEFICIENCY of ADENOSINE DEAMINASE IN CHILDREN: THE FIRST CASE SERIES FROM CHINA

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Yue Zhang[1], Wei Liu[2], Zhou Shu[1], Yan Li[1], Fei Sun[1], Zhigang Li[3], Tongxin Han[1], Huawei Mao[1], Tianyou Wang[4]
[1]Beijing Children's Hospital, Capital Medical University, Department of Immunology, Beijing, China, [2]Zheng Zhou Children's Hospital, Hematology Oncology Center, Zheng Zhou, China, [3]Beijing Children's Hospital, Capital Medical University, Hematology And Oncology Laboratory, Beijing, China, [4]Beijing Children's Hospital, Capital Medical University, Department of Hematology And Oncology, Beijing, China

Background and Aims: Adenosine deaminase (ADA) is a key enzyme in purine salvage pathway. Genetic defects of the ADA gene cause a subtype of severe combined immunodeficiency. So far, few Chinese cases have been reported. We describe the first case series of ADA deficieny in China.

Methods: We retrospectively reviewed the medical records of patients diagnosed with ADA deficiency in Beijing Children's Hospital and summarized the previously published ADA deficiency from China in the literature.

Results: Eight children from China with ADA deficiency were included. Three novel mutations were reported including a synonymous mutation that affected pre-mRNA splicing. Early-onset infection, thymic abnormalities and failure to thrive were the most common manifestations. One patient developed language and fine motor regression and had blurred vision in the third year after diagnosis. Cerebral aneurysm was identified in the patient by cranial angiography. Laboratory studies revealed cellular and humoral immune deficiency in all patients. Immune repertoire analysis in one patient demonstrated decreased TCR and BCR diversity, and oligoclonal T cell expansion. In total, 5 patients died, and the median age at death was 4 months.

Conclusions: We described the first case series of Chinese ADA deficieny. Early-onset infection, thymic abnormalities and failure to thrive were the most common manifestations of our patients. We identified a synonymous mutation that affected pre-mRNA splicing in ADA gene, which had never been reported in ADA deficiency. Furthermore, we reported cerebral aneurysm in the delayed-onset patient for the first time. The impaired purine metabolism and accumulation of substrates would contribute to the vascular inflammation.

Disclosure: No.

Keywords: Deficiency of adenosine deaminase, Severe combined immunodeficiency, Cerebral aneurysm, China, synonymous mutation

PD354

A CASE of LATE DİAGNOSIS IMMUNODEFICIENCY: GOOD'S SYNDROME

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Ezgi Sönmez, Fevzi Demirel, Özgür Kartal
University of Health Sciences , Gülhane Training and Research Hospital, Clinic of Immunology And Allergic Diseases, ANKARA, Turkey

Background and Aims: Good's syndrome (GS), composed of thymoma, hypogammaglobulinemia and immunodeficiency is a late onset primary immune deficiency diseases (PIDDs) . Here we mentioned a case with GS diagnosed 5 years after thymectomy.

Methods: Case Presentation A 49 year-old male patient referred to our cilinic due to the history of frequent respiratory tract infections continuing for 3 years. He underwent thymectomy after thymoma was incidentally detected in the thorax CT 5 years ago. When the patient was evaluated in our clinic, he was diagnosed GS with his medical history, clinical findings and laboratory results (Table 1 and 2) and he was started on intravenous immunoglobulin (IVIG) therapy.
Table 1: Lymphocyte subgroups

	%
CD 19(+) B	0 (7 - 23)
CD 3(+) T	97.3(62,8 - 85)
CD 4(+) T	13.9(34 - 63,8)
CD 8(+) T	81.25 (19 - 48)
CD 4/CD 8	0,17 (0,8 – 3,3)

Table 2 : Immunoglobulin Levels

	g/L
Ig G	0,013 (7,51 – 15,6)
Ig A	0,004 (0,82 – 4,53)
Ig M	0,003(0,46 – 3,04)

Results: GS was described by Good in 1954 first and is one of the rare causes of adult PIDDs. Owing to the defects in both humoral and cellular immunity and infectious, autoimmune and hematological complications the prognosis is quite bad in patients with GS.

Conclusions: Therefore early diagnosis and treatment is vital for patients with GS. Our patient's delay in diagnosis is 5 years. At present he has been receiving IVIG treatment for 5 months and his complaints were almost decreased.

Disclosure: No.

Keyword: Good's Syndrome, thymoma, immune deficiency, intravenous immune globuline

PD355

PERITONEAL PSEUDO TUMOR TUBERCULOSIS COMPLICATING HLA-DR DEFICIENCY

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Kahina Ouahbi[1], Ourida Gacem[2], Hanifa Benmekhlouf[2], Nacera Hammadouche[1], Nadia Mehaba[1], Moussa Achir[3], Mohamed.Samir Ladj[3]
[1]university of algiers - faculty of medecine, Eph Djilali Belkhenchir (ex Birtraria), ALGER, Algeria, [2]university of algiers - faculty of medecine, Department of Pediatric Djillali Belkhenchir Hospital Algiers Algeria, ALGER, Algeria, [3]university of algiers - faculty of medecine, Eph Djilali Belkhenchir (ex Birtraria), Algiers, Algeria

Background and Aims: Deficient expression of major histocompatibility complex class II (MHC-II) molecules is a rare inherited disorder characterised by a combined immune deficiency To illustrate the difficulty of diagnosis and management of peritoneal tuberculosis in primary immune deficiency

Methods: A case of peritoneal pseudo tumor tuberculosis in an infant with HLA-DR deficiency was reported.

Results: S.R., a male infant from a young consanguineous couple, with a sister and a brother, died in a severe pulmonary infection, hospitalized at the age of 3 months for bilateral broncho-pneumopathy. The investigation revealed an HLA DR deficiency. He was put on immunoglobulin infusion and antibiotic prophylaxis. Readmitted at the age of 13 months for malnutrition and moderate ascites, the puncture of which brought back a serous hematic exudative fluid with 1200 ele/ml of lymphocytes. Abdominopelvic CT scan showed a hypodense solid intraperitoneal mass projecting from the left flank, poorly enhanced after injection of contrast medium with multiple confluent coeliac-mesenteric adenopathies.The anatomopathological study of biopsy was in favour of an inflammatory myofibroblastic tumour without major nuclear anomalies.Peritoneal tuberculosis was strongly suspected.Antituberculosis treatment was initiated. Mycobacteria in the culture of the ascites fluid on day 28 came back positive. After 8 months of treatment, an abdominal CT scan revealed L1 spondyloarthritis with disappearance of the mass.

Conclusions: MHC-II molecule deficiency is a serious pathology for which marrow transplantation remains the only curative TRT. The prognosis for our patient is poor due to the occurrence of an invasive infection that is difficult to diagnose and sterilise.

Disclosure: No.

Keyword: Immune deficiency, HLA-DR, Peritoneal pseudotumor tuberculosis, Bone marrow transplant

PD356

IMMUNOPHENOTYPIC ABERRANCIES IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Saniya Sharma, Ankur Jindal, Rahul Tyagi, Manpreet Dhaliwal, Amit Rawat, Surjit Singh
Post Graduate Institute of Medical Education and Research, Chandigarh, Allergy-immunology Unit, Dept of Paediatrics, Chandigarh, India

Background and Aims: Common variable immunodeficiency (CVID) is characterized by the failure of B-cells to undergo class-switching, with a reduction in switched memory B-cells. The present study aimed to detect immunophenotypic aberrancies in different lymphocyte subsets in CVID patients

Methods: Clinical, flow cytometry, and genetic data were analyzed in 20 patients with CVID phenotype.

Results: Lymphopenia and lymphocytosis were found in 2 (10%) of cases each. B-cells were reduced in 7 (35%), and increased in 2 (10%) cases. T-cells were reduced in 2 (10%), and increased in 5 (25%) cases. NK-cells were reduced in 5 (25%), and increased in 1 (5%) cases. Naïve B- cells were increased in 10 (58.8%), and reduced in 2 (11.7%). Unswitched memory B- cells were increased in 5 (29.4%), and decreased in 5 cases (29.4%). Switched memory B-cells were reduced in 14 (82.4%), and increased in 2 cases (11.7%). Helper T-cells were increased in 7 (53.8%) and reduced in 2 (15.4%). Cytotoxic T-cells were increased in 11 (84.6%). CD4:CD8 ratio was reversed in 4 (30.7%) cases. γδ T-cells were increased in 8 cases (61.5%) of cases. of 4 cases evaluated, naïve CD4+ T cells were reduced in 3 (75%) and naïve CD8+ T cells were reduced in 2 (50%).

Conclusions: B-cell class-switching defect was the predominant defect. Aberrancies in T/NK-cells were also detected including reduced NK-cell counts, reduced naïve T-cells, increased γδ T-cells, and reversed CD4:CD8 ratio. A comprehensive flow cytometry panel evaluating all lymphocyte subsets reveals clinically useful information in CVID patients.

Disclosure: No.

Keywords: predominantly antibody deficiency, Inborn errors of immunity, Class-switching defect, CVID, flow cytometry, primary immunodeficiency

PD357

DIFFERENTIAL DIAGNOSIS of COUGH AND DYSPNOEA IN GATA2 DEFICIENCY - A CASE REPORT

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Mark Kacar[1], Marko Kavčič[2], Saša Šetina Šmid[3], Tina Srovin[4], Izidor Kern[5], Malena Aldeco[3], Simona Avcin[2], Maruša Debeljak[6], Tadej Avcin[7], Gasper Markelj[7]
[1]University Clinic Golnik, Allergy Unit, Golnik, Slovenia, [2]University Children's Hospital, University Medical Center Ljubljana, Ljubljana, Slovenia, Department of Haematology, Ljubljana, Slovenia, [3]University Children's Hospital, University Medical Center Ljubljana, Ljubljana, Slovenia, Department of Pneumology, Ljubljana, Slovenia, [4]University Medical Center Ljubljana, Department of Infectious Diseases, Ljubljana, Slovenia, [5]University Clinic Golnik, Department of Pathology, Golnik, Slovenia, [6]University Children's Hospital, University Medical Center Ljubljana, Department of Genetics, Ljubljana, Slovenia, [7]Children's Hospital, University Medical Center Ljubljana, University of Ljubljana, Department of Allergology, Rheumatology And Clinical Immunology, Ljubljana, Slovenia

Background and Aims: GATA2 haploinsufficiency manifests as bone marrow failure syndrome. The manifestations of GATA2 deficiency are varied and include B-cell, NK-cell lympohopenia and monocytopenia with recurrent infections (nontuberculous mycobacteria, HPV and fungi), myelodysplasia with or without progression to acute myeloid leukaemia. Impaired pulmonary diffusion is evident in the majority of reported patients, with pulmonary alveolar proteinosis diagnosis reported in up to one fifth.

Methods: A 15-year-old girl with known neutropenia was admitted with dyspnoea, cough, weight loss and febrile pancytopenia. B-,T-,NK-cell lymphopenia and monocytopenia were observed.

Results: Mycobacterium avium was confirmed in lymph node, bone marrow, and blood. Heterozygous GATA2 mutation was confirmed(p.Ala30Glyfs*50). Pulmonary function testing(PFT) revealed reduced DLCO whilst HRCT and bronchoscopy were normal. Bronchoalveolar lavage(BAL) microscopy revealed CD4+lymphocytic alveolitis. Transbronchial biopsy(TBB) revealed granulomatosis without evident protein deposition. Microbiology of both samples was negative. Treatment of haemophagocytosis(anaemia, thrombocytopenia, hyperferritinaemia, elevated solubleCD25)with methylprednisolone and cyclosporin resulted in clinical, laboratory and PFT improvement. Repeat bronchoscopy and TBBwere normal, BAL showed reduction in alveolar lymphocyte counts. microbiology were negative. Further BAL/TBB prior to HSCT showed further improvement of lymphocytic alveolitis and resolution of granulomatosis, respectively.

Conclusions: Our patient presented with dyspnoea and cough with reduced lung diffusion capacity. Microbiology was persistently negative however, CD4+lymphocytic alveolitis with macrophage activation were noted. Early initiation of immunomodulatory therapy improved the patient's symptoms and diffusion capacity and might have served to prevent the progression to PAP, a mostly irreversible pulmonary complication. The patient's specific mutation in GATA2 has never been described and might be responsible for the respiratory and haemophagocytosis-predominant phenotype.

Disclosure: No.

Keywords: GATA2, haemophagocytosis, pulmonary alveolar proteinosis, monoMAC, immunosuppression

PD358

GOOD'S SYNDROME A PHENOCOPY of A COMPLEX PRESENTATION

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Patricia O Farrill Romanillos[1], Diana Herrera Sánchez[1], Maura Noyola García[2]
[1]Mexican Institute of Social Security, Hospital Especialidades, XXI Medical Center, Allergy And Clinical Immunology, Mexico, Mexico, [2]Mexican Institute of Social Security, Hospital Especialidades, XXI Medical Center, Internal Medicine, Mexico, Mexico

Background and Aims: Introduction : Good's Syndrome is an Innate Inborn Errornsfrom the group of Phenocopies, characterized by the presence of thymoma, hypogammaglobulinemia, invasive infections by bacteria, opportunistic agentes and autoimmunity. It occurs in adults 40–60 years. It is rare, in the Latin American registry of IIE, there are only 12 reported.
objetive: to describe the characteristics of patients with Good syndrome

Methods: we presented a series of 3 cases with Good Syndrome and diferents outcomes.

Results: Resulta: 66% men, mean age at diagnosis 50 years. In 66% the thymoma was initially documented, in 33% hypogammaglobulinemia. 100% > 2 autoimmune diseases: lichen planus 33%, immune thrombocytopenia 66%, inflammatory bowel disease 66%, rheumatoid arthritis 33%. 66% with Thymoma AB according to the WHO classification and 33% A. 100% with mixed bronchiectasis and use of macrolide prophylaxis. All with IVIg replacement therapy. Mortality 66%: Bacterial pneumonia and severe COVID-19

Conclusions: Good's syndrome is an IIE without an identified genetic defect, presenting in adulthood. Its early diagnosis is important, since it allows the timely detection of complications: autoimmune and infectious. It is important to take into account that it should be considered as a combined defect due to the alterations it presents in T and B cells and to consider, in addition to replacement therapy with IVIg, the use of prophylaxis for opportunists.

Disclosure: No.

Keyword: Phenocopy, Good's syndrome, thymoma

PD359

BALLER-GEROLD SYNDROME – RECQL4 PATIENT IDENTIFIED BY TREC NEWBORN SCREENING

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Sujal Ghosh[1], Luisa Averdunk[2], Katharina Gössling[1], Katja Hüwe[3], Franka Köster[3], Reinhard Kalb[4], Jörg Schaper[5], Hans-Jürgen Laws[1], Arndt Borkhardt[1]
[1]Center of Child and Adolescent Health, Medical Faculty, Heinrich Heine University, Department of Pediatric Oncology, Hematology And Clinical Immunology, Düsseldorf, Germany, [2]University, Department of General Pediatrics, Neonatology And Pediatric Cardiology, Duesseldorf, Germany, [3]Matthias-Spital, Klinikum Rheine, Department of Pediatrics, Rheine, Germany, [4]University of Würzburg, Department of Human Genetics, Biocenter, Würzburg, Germany, [5]Medical Faculty, Heinrich Heine University Düsseldorf, Centre For Rare Diseases, Duesseldorf, Germany

Background and Aims: We report on a female infant with a pathological TREC newborn screening.

Methods: The second child of Syrian consanguineous parents was born at 36+6 wog after suffering from IUGR. Beside postnatal respiratory distress requiring ventilation the patient showed syndromic features with absent thumbs, bilateral radial aplasia / hypoplasia, sparse hair, craniosynostosis, exophthalmos, anal atresia, hypothyroidism and bilateral hearing loss. Furthermore, she had systemic infections whilst being admitted at the primary NICU. Oral feeding was insufficient to achieve weight gain.

Results: TREC newborn screening (repeatedly 0 TRECs) indicated severe combined immunodeficiency. Flow cytometry showed lymphopenia with low CD3 T cells (total 200 / µl) – with absent CD8s and decreased CD4s (naive 75%), low NK cells (total 17/µl), but normal B cells (418 / µl). TCR Vbeta Repertoire in CD4 cells was broad and not skewed. Chromosomal analysis did not show any numerical abnormalities, however suggested increased chromosomal breakage. Exome based panel sequencing revealed a known biallelic mutation in RECQL4 suggesting Baller-Gerold / Rothmund-Thomson syndrome.

Conclusions: RECQL4 encodes a DNA helicase that belongs to the RecQ helicase family. Mutations in three of the five human helicase genes (BLM, WRN and RECQL4) are associated with disease with increased cancer predisposition, immunodeficiency and premature aging. Due to the clinical condition with poor weight gain and syndrome-associated clinical challenges we have refrained from HSCT in the first months of life. The patient has been put on prophylaxis, regular IVIG substitution and parenteral nutrition. A multidisciplinary approach needs to be in place before considering a curative strategy.

Disclosure: No.

Keywords: Helicase, combined immunodeficiency, Rothmund-Thomson, TREC, SCID

PD360

NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY: FIRST PILOT STUDY IN UKRAINE

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Oksana Boyarchuk[1], Halyna Makukh[2,3], Nataliya Yarema[1], Volodymyr Kravets[2], Tatyana Hariyan[1], Liubov Volianska[1], Iryna Chornomydz[1], Maria Kinash[1], Ivanna Shymanska[2]
[1]I.Horbachevsky Ternopil National Medical University, Department of Children's Diseases And Pediatric Surgery, Ternopil, Ukraine, [2]Scientific Medical Genetic Center LeoGENE, LTD, Rt-pcr, Lviv, Ukraine, [3]Institute of Hereditary Pathology of the Ukrainian National Academy of Medical Sciences, Laboratory of Genetic Investigations, Lviv, Ukraine

Background and Aims: Severe combined immunodeficiency (SCID) is a group of inborn errors of immunity (IEI) characterized by severe T- and / or B-lymphopenia. Timely diagnosis and treatment play a crucial role in patient survival.

Methods: For the first time in Ukraine, we initiated a pilot study on newborn screening for SCID and T-cell lymphopenia by determining T cell receptor excision circles (TRECs) and kappa-deleting recombination excision circles (KRECs). The analysis of TREC and KREC was performed by real-time polymerase chain reaction (RT-PCR) followed by analysis of melting curves in neonatal dry blood spots (DBS). In total, 10,350 newborns were screened between May 2020 and January 2022. Sixty-five blood DNA samples were used for control: 25 from patients with ataxia-telangiectasia, 37 - from patients with Nijmegen breakage syndrome, 1 – with X-linked agammaglobulinemia, 2 – with SCID (JAK3 deficiency and DCLRE1C deficiency).

Results: There were 608 (5.87%) premature babies. Cut-off level below 5,000 copies per 10^6 cells for TREC/KREC was used on the first stage, and below 2,000 copies per 10^6 cells –during the next stage. Referral to confirm or rule out the diagnosis was used in 3 cases. CID ($T^{low}B+NK+$) was confirmed in a patient with the urgent abnormal value. Approbation of the method in the control group showed a greater sensitivity and efficiency of TREC assay.

Conclusions: TREC and KREC assay using RT-PCR followed by analysis of melting curves is effective for the detection of severe T- and B-lymphopenia. In resource-limited settings, the detection of TRECs only will be efficiently effective for SCID screening.

Disclosure: No.

Keywords: newborm screening, TREC, KREC, SCID

PD361

IMMUNOLOGICAL AND CLINICAL ANALYSIS IN PATIENTS WITH SEVERE COMBINED IMMUNODEFICIENCY IN MOROCCO

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Fouad Seghrouchni[1], Aicha El Allam[2], Sara El Fakihi[1], Hicham Tahoun[1], Karima Sahmoudi[1], Houria Bouserhane[1], Youssef Bakri[3], Naima Elhafidi[4]
[1]Institut National d'Hygiène, Immunology, Rabat, Morocco, [2]national institue of hygiene, Cellular Immunology, SALE, Morocco, [3]FacultSciences, University Mohammed V, Centre of Human Pathology Genomic, Rabat, Morocco, [4]children hospital, Ibn Sina university hospital, Pediatrics, rabat, Morocco

Background and Aims: The severe combined immunodeficiency (SCID) is characterized by a severe abnormality of combined cellular and humoral immune system. It is considered the severe form of primary immunodeficiency disease (PID) . An early diagnosis is required to improve the vital prognosis of young children with SCID. The objective of this study is to analyze cytometric measurements and clinical features within our Moroccan SCID cohort compared to children with non-PID affections.

Methods: In this retrospective study, biological and clinical data from 35 confirmed SCID patients were analyzed, as well as those from the 622 young patients initially suspected as suffering from PID but was later confirmed to be affected non-PID diseases.

Results: As expected, T cell count was less than 300 cells/ml in most patients with SCID (85.5%). Unexpectedly, patients with T cell counts in the range between 300 and 500 cells/ml (5.7%), as well as even higher than 500 cells/ml (8.7%) were also clinically diagnosed as SCID. Furthermore, flow cytometry demonstrated that the proportion of the B cell deficiency was highly represented in our cohort. 71.4% of Moroccan SCID patients were B cell deficient. 40% of the patients had a T-B-NK+ profile and 31.4% had a T-B-NK- profile. The most common clinical manifestations observed in our SCID cohort were pneumonia, failure to thrive, candidiasis, diarrhea, bronchitis and urinary tract infections.

Conclusions: Our results highlight the incidence pattern of common SCID subtypes in the Moroccan population including the finding of atypical SCID, which may help the clinician to make an early diagnosis of the SCID in Morocco.

Disclosure: No.

Keywords: DIAGNOSIS, Severe combined immunodeficiency, lymphocytes subpopulation counts, flow cytometry, primary immunodeficiency, Morocco

PD362

HRCT SCREENING FOR AIRWAY DISEASE IN PATIENTS WITH PRIMARY ANTIBODY DEFICIENCY: A 10-YEARS PERSPECTIVE FROM A DUTCH TERTIARY CENTER

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Sharisa Boland[1], Bas Smits[1], Marjolein Hol[2], Anke Bruns[3], Michiel Van Der Flier[1], Helen Leavis[4], Jan Jelrik Oosterheert[3], Annette Van Royen-Kerkhof[1], Firdaus Mohamed Hoesein[2], Joris Van Montfrans[1], Pauline Ellerbroek[3]
[1]UMC Utrecht, Pedriatric Immunology, Utrecht, Netherlands, [2]UMC Utrecht, Radiology, Utrecht, Netherlands, [3]UMC Utrecht, Department of Internal Medicine, Utrecht, Netherlands, [4]University Medical Center Utrecht, Utrecht University, Department of Rheumatology & Clinical Immunology, Utrecht, Netherlands

Background and Aims: Airway disease (AD) is a frequent complication in primary antibody deficiency (PAD). It is associated with chronic cough, dyspnea and end-stage pulmonary failure. This study aims to gain better insight in predictive factors for the presence and progression of AD in PAD.

Methods: Data were retrospectively extracted from patient records. HRCT scans were analyzed using the Hartmann scoring system. AD-scores >7 and an increase in AD-score >0.5/year were considered clinically relevant. Risk factors were identified using univariate analysis and logistic regression.

Results: Preliminary analysis of 10 XLA, 54 CVID, 18 SPAD/IGSD and 7 unclassified PAD (unPAD) patients showed higher AD scores in XLA patients (p=0.04). In the remaining cohort (n=79), median time since PAD diagnosis was 17 years. Risk factors for high AD-scores were age (p<0.01) and CD19+ B cell counts (p=0.01). AD progression was detected in 15/79 cases; 10 of these 15 cases had pre-existent AD-scores >7 (p=0.02), the other 5 cases had a longer disease history compared to cases without disease progression (p=0.04). The presence of AD and/or clinical signs of PAD for >20 years were predictive for AD progression (93% sensitivity and 45% specificity).

Conclusions: For IGSD/SPAD, CVID and unPAD patients, predictive risk factors for AD progression were identified, suggesting that screening frequencies could be reduced for low-risk patients. However, XLA patients more often showed CT signs of severe AD and should be studied as a distinct subgroup. Future research should focus on the risk factors within PAD subgroups for further optimization of clinical management of AD.

Disclosure: No.

Keywords: Airway Disease, Hartmann Score, Risk Factor, Primary Antibody Deficiency, CVID, XLA

PD363

FAILURE TO MOUNT A DETECTABLE HUMORAL VACCINE RESPONSE – A NEW DIAGNOSTIC TOOL TO SUPPORT DIAGNOSIS of HYPOGAMMAGLOBULINAEMIA?

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Mark Ponsford[1,2], Daniel Farewell[3], Usman Khalid[2,4], Georgios Koimtzis[4], Laszlo Szabo[4], Chris Chalklin[4], Aled Richards[5], Chris Brown[5], Soma Meran[6], Kathryn Bramhall[1], Leanne Grant[1], Ian Humphreys[2], Argiris Asderakis[2,4], Stephen Jolles[1]
[1]Immunodeficiency Centre for Wales, University Hospital For Wales, Cardiff, United Kingdom, [2]Cardiff University, Institute For Infection & Immunity, Cardiff, United Kingdom, [3]Cardiff University, Division of Population Medicine, Cardiff, United Kingdom, [4]University Hospital for Wales, Cardiff Transplant Unit, Cardiff, United Kingdom, [5]Swansea Bay University Health Board, Haemodialysis Unit, Swansea, United Kingdom, [6]Cardiff University, Wales Kidney Research Unit, Cardiff, United Kingdom

Background and Aims: Kidney transplant recipients (KTRs) are at heightened risk of hypogammaglobulinaemia and infection, but immunoglobulin surveillance is not routinely conducted. This study addresses if failure to mount a detectable humoral vaccine response could support the diagnosis of hypogammaglobulinaemia.

Methods: Anti-SARS-CoV-2-Spike-S1-IgG responses were determined in 680 KTRs participating in the COVID-19 ENLIST study (REC: 20/YH/0309), at least 7-days following ≥3 COVID-19 vaccinations. Calculated globulin and immunoglobulin results were extracted between 1-January-2020 and 09-June-2022. Total IgG, IgA, and IgM levels were determined in 20 seropositive and 20 seronegative individuals, blinded to wider clinical and laboratory details.

Results: Historical immunoglobulin results were available in 79/680 (11.6%) of the cohort . Calculated globulin, IgG, IgA, and IgM were consistently depressed within seronegative kidney transplant recipients relative to seropositive individuals. 35% of seronegative KTRs had an IgG <6g/L, compared to only 3% of seropositive KTR (odds ratio: 20.3; 95% CI: 2.33 to 176.4, p=0.001). Reflex immunoglobulin testing in 20 seronegative KTRs identified one individual with previously undiagnosed severe hypogammaglobulinaemia (IgG=3.1 g/L; IgA=1.17 g/L ; IgM=0.31g/L).

Conclusions: Antibody deficiency is a treatable cause of infection susceptibility, however delays in recognition can lead to irreversible end-organ damage. In this pilot study, reflex immunoglobulin testing of seronegative KTRs despite serial COVID-19 immunisation achieved a positive predictive value for hypogammaglobulinaemia (IgG<6g/L) of 35% and 5% for severe hypogammaglobulinaemia (IgG<4g/L), exceeding the National Institute for Clinical Excellence threshold to trigger investigation for life-threatening illness. This simple approach may hasten the diagnosis and treatment of antibody deficiency.

Disclosure: A.A. has received grants from Sanofi (France) for work related to thymoglobulin and from Novartis (United Kingdom) as part of various trials. He also serves as a board member of Kidney Wales. S.R.J. reports advisory board, speaker, conference, drug safety

Keywords: diagnostics, Renal transplantation, Secondary Immunodeficiency, Hypogammaglobulinaemia, Vaccine response, SARS-CoV-2

PD364

HYPER IGE SYNDROME (JOB SYNDROME) IN ROMANIA: A CASE REPORT

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Brindusa Capilna[1], Erika Dee[1], Tudor Capilna[2]
[1]EMERGENCY COUNTY HOSPITAL TARGU MURES, Pediatric Clinic/allergology Immmunology Department, TARGU MURES, Romania, [2]GEORGE EMIL PALADE UNIVERSITY MEDICINE, PHARMACY, SCIENCE AND TECHNOLOGY of TARGU MURES, Faculty of Medicine, TARGU MURES, Romania

Background and Aims: Autosomal dominant hyper IgE syndrome resulting from STAT3 mutation is a primary immunodefficiency which was originally described as a triad of extreme elevation of serum IgE level (>2000 UI/ml), recurrent staphylococcal abscesses and recurrent cyst-forming pneumonias. In addition, it has nonimmunologic characteristics, that include gastrointestinal, vascular or skeletal abnormalities. Here, we present a patient with STAT3 hyper IgE syndrome who was diagnosed before the age of 2.

Methods: A 1-year-and-9-months old male pacient was born prematurely at 36 weeks and hospitalised for two more weeks in Neonatal Intensive Care Unit in Stockholm Sweden. At the age of 2 months he had coronavirus disease (treated with immunoglobulins) and spastic hemiparesis of the left side. Also, he was hospitalised several times for bacterial respiratory and mucocutaneous infections.

Results: Laboratory findings revealed eosinophilia, neutropenia , ALP elevation and IgE elevation. Chest imaging demonstrates structural damage of the lungs: shows a gas-filled cystic space/ pneumatocele. Computed tomography of the brain revealed a porencephalic cyst with intralesional calcification. Sequence analysis and deletion/duplication testing of the 574 genes in Inborn Errors of Immunity and Cytopenias Invitae Panel identified a Pathogenic variant, c.1144C>T (p.Arg382Trp) in STAT3.

Conclusions: HIES is a rare disease, a multisystemic disorder with a broad constellation of clinical manifestations and is a great challenge for clinicians in establishing a diagnosis in suspected cases. Our case having many typical HIES features and require interdisciplinary care. To the best of our knowledge, this is the first such case diagnosed early in our country.

Disclosure: No.

Keyword: Hyper-IgE syndrome, HIES, STAT3, Primary immunodeficiency, PID, pneumatocele

PD365

FAST AND COST-EFFECTIVE FLOW CYTOMETRIC METHOD TO DISCRIMINATE PATIENTS WITH ATOPIC DERMATITIS AND HYPER-IGE SYNDROME

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Edyta Heropolitanska-Pliszka[1], Katarzyna Tkaczyk[2], Urszula Grycuk[2], Barbara Piątosa[2]
[1]CMHI, Immunology, warsaw, Poland, [2]CMHI, Histocompatibility Laboratory, Warsaw, Poland

Background and Aims: Atopic dermatitis (AD) overlaps with STAT3 hyper-IgE syndrome (STAT3-HIES) in terms of eczema, eosinophilia, and increased serum IgE. Discrimination between both conditions is of utmost importance, as treatment and prognosis are completely different. Molecular identification of STAT3 mutations is not widely available but also time and cost-consuming. HIES patients have significantly reduced Th17 cells, whereas AD patients demonstrate elevated Th2 cells. Cytokine measurement in plasma is not sufficient do identify cytokine producing cells. Effector cytokine producing T helper cells are characterized by specific combinations of surface markers. Therefore, we intended to verify usefulness of this approach for diagnostic purposes.

Methods: Peripheral blood was drawn from 13 STAT3-deficient and 21 AD patients, and 41 healthy controls. Eight-color flow cytometry was used to identify Th1, Th2, Th9, Th17, Th17.1, Th22, ThG, follicular TFH1-like, TFH2- like, TFH17-like and TFH17.1-like cell populations based on differential expression of CD3/CD4/CD45RA/CCR10/CD183/CD185/CD194/CD196. Results for individual cell populations within T helper cells and relationship between them were compared to age-related normal control ranges.

Results: Significant differences between HIES and AD patients found for Th17 (reduced Th17 - 12/13 HIES vs 1/21 AD) and Th2 (elevated 13/21 AD vs 3/13 HIES) confirmed the diagnoses. HIES patients demonstrated significantly more frequently reduced Th9 (12/13 vs 3/21) and Th2-like cells (11/13 vs 4/21).

Conclusions: Flow cytometric evaluation of cytokine producing effector helper cells is fast method to discriminate patients with HIES from healthy controls and AD patients. Identification of elevated proportions of Th2 cells is not sufficient to diagnose AD patients.

Disclosure: No.

Keywords: hyper-IgE syndrome, Atopic dermatitis, Cytometry, Effector T cells

PD366

PEDIATRIC REFERENCE RANGES IN THE MOROCCAN POPULATION

POSTER DISPLAY 07: GENETICS DIAGNOSTICS

Aicha El Allam[1], Sara El Fakihi[1], Hicham Tahoun[1], Karima Sahmoudi[1], Houria Bouserhane[1], Naima Elhafidi[2], Youssef Bakri[3], Fouad Seghrouchni[1]
[1]Institut National d'Hygiène, Immunology, Rabat, Morocco, [2]children hospital, Ibn Sina university hospital, Pediatrics, rabat, Morocco, [3]FacultSciences, University Mohammed V, Centre of Human Pathology Genomic, Rabat, Morocco

Background and Aims: The presence and distribution of the lymphocyte subset vary in several diseases. Therefore, their number and distribution are used for several clinical diagnoses, The interpretation requires a comparison of patient results with reference values. Best practice reference values should be established in a representative population of healthy subjects, to date no specific reference value for the Moroccan population is available and a comparison is made with the Caucasian population. Unfortunately, any difference between the two populations may affect the diagnosis of diseases and disorders such as (PID). The objective of this study is to establish age-stratified normal reference values of lymphocyte subsets for the Moroccan population.

Methods: We measured the concentration of lymphocyte subpopulations by flow cytometry from 83 Moroccan healthy subjects stratified into 5 age groups of 0–1, 1–2, 2–6, 6–12, and > 12–18.

Results: The lymphocyte subsets T, B, and NK cells were measured and compared with other countries. An age-related variation has been observed. Decrease of T lymphocytes with age, with both CD4+ and CD8+, as well as B lymphocytes, were also decreased. Finally, we compared the values of our Moroccan study group with results from other countries and observed significant differences in Moroccan values.

Conclusions: The results of this study have a significant impact on improving the threshold values of the reference intervals routinely used in the diagnosis of pediatric diseases such as PIDs or mother-to-child transmitted HIV within the Moroccan population.

Disclosure: No.

Keywords: reference values, pediatric population, Morocco, Primary Immunodeficiency Diseases, DIAGNOSIS, blood leucocytes

PD367

IMMUNE RECONSTITUTION (IR) AFTER HSCT PERFORMED WITH AN INNOVATIVE METHOD of GRAFT MANIPULATION IN CHILDREN WITH PRIMARY IMMUNODEFICIENCIES (PIDS) AND PRIMARY IMMUNE DYSREGULATION DISEASES (PIRDS)

POSTER DISPLAY 08: THERAPY

Alison Lanciarotta[1], Elena Soncini[2], Marianna Maffeis[2], Vincenzo Pintabona[2], Fulvio Porta[2], Raffaele Badolato[3]
[1]University of Padua-Ca' Foncello Hospital Treviso, Specialty School of Allergology And Clinical Immunology, Treviso, Italy, [2]Spedali Civili di Brescia, Bone Marrow Transplant Unit 'monica E Luca Folonari', Brescia, Italy, [3]Specialty School of Paediatrics, University of Brescia, Spedali Civili di Brescia, Paediatrics Clinic, Brescia, Italy

Background and Aims: HSCT is a valid approach to treat and ameliorate quality of life of PIDs and PIRDs. New graft manipulation techniques are under investigation to improve engraftment and IR, without increasing GvHD rates.
We evaluated IR after HSCT manipulated with positive selection of CD34+cells and CD3+cells addback of $30x10^6$/kg of recipient.

Methods: We retrospectively studied 66 children affected by PIDs and PIRDs, treated with HSCT from Matched Unrelated Donors from 2001 to 2021 with this specific graft manipulation.

Results: 43 patients underwent BM-HSCT (Bone Marrow) and 23 PBSC-HSCT (Peripheral Blood Stem-Cells). These patients were affected by SCID/CID, WAS, CGD and other phagocyte deficiencies, Hyper-IgE and -IgM Syndrome, MHC-II deficiency and PIRDs.
Engraftment timing and rates of OS, graft failure, GvHD and post-HSCT autoimmunity (mostly represented by cytopenia and thyroiditis) were comparable between the two subgroups and with literature. Chimerism was total in most cases, or at least sufficient to restore the impaired immune function. TRECs and KRECs were considered possible markers of T/B-cell recover.
Lymphocyte subsets reconstitution was similar in both subgroups, except for a faster CD3+ cell recover after PBSC-HSCT. Mitogen-induced T-cell proliferative response was restored in both subgroups. Most patients discontinued IgRT by 6 months after HSCT and presented an efficient humoral response to vaccinations.

Conclusions: In PIDs and PIRDs, PBSC-HSCT with this specific manipulation represents an innovative therapy with comparable (or even superior) efficiency and safety to BM-HSCT. However, further studies are needed to find the ideal dose of CD3+cells addback and to correct other factors affecting IR and transplant outcomes.

Disclosure: No.

Keywords: Immune-reconstitution, HSCT, CD3+addback, IEI, PID, PIRD

PD368

REPURPOSING DRUGS FOR ORPHAN DISEASES: DUPILUMAB FOR AD HIES-RELATED DERMATITIS AND BENRALIZUMAB FOR SEVERE EOSINOPHILIC CYSTITIS IN CGD

POSTER DISPLAY 08: THERAPY

Malena Perez-Lorenzo[1,2,3], Andrea Martín-Nalda[1,2,3], Aurora Fernández-Polo[4], Pere Soler-Palacin[1,2,3], Roger Colobran[3,5,6,7], Romy Gander[8], Vicente Garcia-Patos[9,10], Jacques Rivière[1,2,3]
[1]Vall d'Hebron Barcelona Hospital Campus, Pediatric Infectious Diseases And Immunodeficiencies Unit, Barcelona, Spain, [2]Vall d'Hebron Barcelona Hospital Campus, Infection In Immunocompromised Pediatric Patients, Barcelona, Spain, [3]Jeffrey Modell Foundation, Diagnostic And Research Center For Primary Immunodeficiencies, Barcelona, Spain, [4]Vall d'Hebron Barcelona Hospital Campus, Children's Hospital / Proa-nen, Barcelona, Spain, [5]Vall d'Hebron Institute of Research (VHIR), Translational Immunology, Barcelona, Spain, [6]Vall d'Hebron Barcelona Hospital Campus, Department of Clinical And Molecular Genetics, Barcelona, Spain, [7]Hospital Universitari Vall d'Hebron (HUVH), Barcelona, Catalonia, Spain, Immunology Department. Department of Clinical And Molecular Genetics, Barcelona, Spain, [8]Vall d'Hebron Barcelona Hospital Campus, Pediatric Urology And Pediatric Kidney Translplant Unit. Pediatric Surgery Department, Barcelona, Spain, [9]Vall d'Hebron Barcelona Hospital Campus, Department of Dermatology, Barcelona, Spain, [10]Universitat Autònoma de Barcelona, Facultat De Medicina, Barcelona, Spain

Background and Aims: Biological therapy is widely used in daily allergist practice for common diseases such as atopic dermatitis or asthma. Inborn errors of immunity (IEI) are rare diseases with less targeted treatments due to low frequency. We report potentially game-changer repurposing of two broadly used biological drugs in non-orphan disease setting in IEI patients.

Methods: P1, a 6-year-old boy (STAT3 heterozygous loss-of-function mutation) presented severe dermatitis and recurrent skin infections refractory to all standard treatments. P2, a 4-year-old boy (chronic granulomatous disease (CYBB)) presented with severe eosinophilic cystitis refractory to steroids, antihistamines and local therapy requiring prolonged suprapubic percutaneous catheter. Dupilumab is a monoclonal antibody targeting IL-4Rα, inhibiting the main drivers of type 2 inflammation: IL-4 and IL-13. Benralizumab is a monoclonal antibody that blocks the binding of IL-5 to its receptor, inhibiting eosinophil differentiation and maturation in bone marrow and inducing cell-mediated cytotoxicity in eosinophils. Family consent and centre approval was obtained for this use.

Results: Based on scarce published data, expert opinion and extrapolation of IEI physiopathology, we used Dupilumab (P1) and Benralizumab (P2). P1 was treated for the last 21 months with complete response at 6 months (initial/final SCORAD 60/5). P2 was treated 8 months along with oral steroids initially and showed partial response after 2 months (removal of vesical catheter) and complete remission after 6 months. Benralizumab was then discontinued with no further relapse.

Conclusions: The effective treatment of IEI with Dupilumab and Benralizumab, broadly used in daily allergist practice, emphasizes the real potential of drug repurposing for orphan diseases.

Disclosure: No.

Keywords: STAT3LOF, Dupilumab, HIES, CGD, Benralizumab, IEI

PD369

ALLOGENEIC HAEMATOPOIETC STEM CELL TRANSPLANTATION OUTCOME IN OLDEST KNOWN SURVIVING PATIENTS WITH WISKOTT ALDRICH SYNDROME IN THE UK.

POSTER DISPLAY 08: THERAPY

Navdeep Nath[1], Siobhan Burns[2,3], Arian Laurence[2,3,4], Susan Tadros[2], Eleni Thalouli[5], Yadanar Lwin[6], Nicolas Martinez-Calle[6], Prashantha Vaitla[7], Ariharan Anantharachagan[1], Emma Morris[2,3,4]
[1]Preston Royal Hospital, Immunology & Allergy, Preston, United Kingdom, [2]The Royal Free London NHS Foundation Trust, Immunology, London, United Kingdom, [3]UCL, Institute of Immunity And Transplantation, London, United Kingdom, [4]UCL, Department of Haematology, London, United Kingdom, [5]Manchester University NHS Foundation Trust, Department of Haematology, Manchester, United Kingdom, [6]Nottingham University Hospitals, NHS Trust, Department of Haematology, Nottingham, United Kingdom, [7]Nottingham University Hospitals, NHS Trust, Immunology, Nottingham, United Kingdom

Background and Aims: Wiskott Aldrich Syndrome (WAS) is a rare, X-linked combined immune deficiency. Clinical features include eczema, thrombocytopenia, life-threatening infections and malignancy. The median survival of untransplanted patients lacking WASp expression is < 20 years. The only potentially curative treatments are haematopoietic stem cell transplantation (HSCT) and gene therapy. In the largest HSCT series published to date the median age at transplant was < 5 years. Here we describe the early outcomes for the two oldest WAS patients reported to have undergone HSCT. Patient 1 was 39 years at HSCT and had a prior history of thrombocytopenia, eczema, DLBCL (treated to CR with 6 cycles of R-CHOP), inflammatory arthropathy and mild bronchiectasis. Patient 2 was 43 years at transplant with a prior history of hypogammaglobulinaemia, bronchiectasis, chronic sinusitis, thrombocytopenia (<10) with a subdural haemorrhage and mild eczema. Both underwent Fludarabine, treosulfan, thiotepa conditioned MUD allografts (9/10 and 10/10, respectively). They received in vivo T cell depletion (alemtuzumab), ciclosporin and MMF as GVHD prophylaxis.

Methods: Case Series

Results: Both are alive at 8.5 months and 8 months post-HSCT respectively with tri-lineage 100% donor chimerism, and correction of thrombocytopenia. Patient 1 has had multiple infectious complications (recurrent HSV2 and adenoviraemias) together with GVHD of skin and gut (now resolved). Patient 2 developed adenoviraemia, chronic renal impairment and mild GVHD of the skin, now resolved. Both remain on systemic immunosuppression.

Conclusions: HSCT is possible in older patients and should be considered for those where a donor is available. Longer follow-up is required to provide evidence of definitive benefit.

Disclosure: No.

Keywords: Wiskott, Aldrich, Syndrome, allogeneic, HSCT, Adults

PD370

STUDY DESIGN AND BASELINE CHARACTERISTICS of A SINGLE ARM, OPEN-LABEL, MULTICENTER, US REGISTRY STUDY of ELAPEGADEMASE TREATMENT IN PATIENTS WITH ADA-SCID

POSTER DISPLAY 08: THERAPY

Morna Dorsey[1], Manish Butte[2], Jolan Walter[3], Fernando Tricta[4], Caroline Fradette[5], Joseph Wiley[6], Luke Wall[7]
[1]University of California San Francisco Medical School, Pediatric Immunology And Allergy Center, San Francisco, United States of America, [2]UCLA, Department of Pediatrics, Division of Immunology, Los Angeles, United States of America, [3]Johns Hopkins All Children's Hospital, St. Petersburg, Division of Allergy/immunology, Department of Pediatrics, St.Petersburg, United States of America, [4]Chiesi Canada Corporation, Head of Strategic Innovation, Toronto, Canada, [5]Chiesi Canada Corporation, Clinical Program Leader, Hematology/immunology, Toronto, Canada, [6]Leadiant Biosciences, Inc., Medical Affairs, Gaithersburg, United States of America, [7]Louisiana State University Health Sciences Center and Children's Hospital, Department of Pediatrics, Section of Allergy Immunology, New Orleans, United States of America

Background and Aims: Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) is a metabolic condition that is usually fatal if left untreated. Elapegademase, a PEGylated recombinant bovine ADA-replacement therapy, is the first-line treatment for metabolic detoxification and immune recovery in patients with ADA-SCID. Owing to the ultra-rare nature of ADA-SCID, real-world clinical experience with elapegademase is limited. Here, we present registry design and baseline characteristics of patients with ADA-SCID from the elapegademase registry (NCT03878069).

Methods: US patients with ADA-SCID receiving elapegademase (dosed and monitored per the USPI), regardless of treatment status, will be followed ≥2 years or until undergoing allogeneic hematopoietic stem cell transplant (HSCT). Patients are assessed for deoxyadenosine nucleotide levels, ADA activity, clinical and immunological status, quality of life, and safety. Patients undergoing HSCT will be evaluated 1 and 6 months after last elapegademase dose to assess safety and survival.

Results: As of December 2021, 22 patients were enrolled at 11 US sites. For 20 patients with available information, mean age at enrollment was 17.6y (range: 0–47y; 12 (60%) ≥18y); 13 (65%) were female. Six (30%) patients were enrolled soon after diagnosis: 1 (5%) 1 month after birth, 4 (20%) 1–2y after birth, and 1 (5%) 3y after birth. Fifteen (75%) patients identified as White (n=3 Hispanic/Latino); 5 (25%) identified as Black (n=1 Hispanic).

Conclusions: The elapegademase registry is ongoing. Results from this registry will provide real-world data regarding ADA-SCID progression on treatment, long-term elapegademase safety, efficacy, effect of dosage adjustment based on biochemical assessments, and outcomes of HSCT.

Disclosure: This retrospective registry analysis was previously sponsored by Leadiant and is now sponsored by Chiesi USA, Inc. Medical writing support was provided by Melissa Victoria Fernandez, PhD, of Oxford PharmaGenesis Inc., Newtown, PA, USA and was funded by Ch

Keywords: ADA-SCID, Severe combined immunodeficiency, enzyme replacement therapy, elapegademase, metabolic detoxification, lymphocyte counts

PD371

INTERFERON GAMMA (IFNG) INHIBITOR EMAPALUMAB IS EFFECTIVE AND SAFE IN TREATMENT of PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (P-HLH) IN CHILDREN

POSTER DISPLAY 08: THERAPY

Yulia Rodina[1], Anna Roppelt[1], Vasiliy Burlakov[1], Nelly Kan[1], Varvara Kallinina[2], Elena Raykina[3], Alexey Maschan[4], Galina Novichkova[5], Anna Shcherbina[1]
[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [2]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation, Laboratory of Molecular Laboratory, Moscow, Russian Federation, [3]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Laboratory of Molecular Biology, Moscow, Russian Federation, [4]Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, Department of Pediatric Hematology And Oncology, Moscow, Russian Federation, [5]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Medical Director, Moscow, Russian Federation

Background and Aims: P-HLH is a group of genetically determined disorders with multi-organ damage due to systemic inflammation with high IFN-g production, and high mortality rate, despite extensive immunosuppressive treatment

Methods: We retrospectively analyzed 7 patients with P-HLH (XLP2 – 3, FHLH3 – 2, FHLH1 – 2), treated with emapalumab. Precedingconcurrent immunosuppressive therapy included HLH-2004 protocol variations, with addition of tocilizumab in 3/7, JAKinibs - 4/7, kineret - 1/7. Emapalumab was administrated twice weekly for a median of 6.3 weeks (2-13 weeks), at an average dose of 1.7 mg/kg in 3 patients, and 7.2 mg/kg in 4 patients. The severity of the disease was assessed using adapted H-score, remission was registered at H-score<90

Results: Significant clinical and laboratory improvement was documented after 2 weeks of emapalumab therapy in both groups ($p<0.05$), all patients reached remission by the end of the treatment. Yet, in high-dose group 2/4 patients reached remission by day 14, and 1/4 by day 28. In the low-dose group no remission was noted at day 14, 1/3 reached remission by day 28. In the whole cohort addition of emapalumab allowed to reduce dexamethasone dose from 10±2 at baseline to 0.7± 0.4 mg/kg/day by week 4. No side effects or new infections were noted during the treatment. 6/7 patients underwent HSCT at the end of the treatment period, without relapse of HLH in the post-transplant period

Conclusions: We demonstrate efficacy and safety of Emapalumab in treatment of severe P-HLH in a group of children. The optimal doses of emapalumab require further investigation

Disclosure: No.

Keywords: Emapalumab, HLH, Children, treatment

PD372

SURVEY of COMPLEX MULTI-SYSTEM COMMON VARIABLE IMMUNODEFICIENCY PRESENTATION, INVESTIGATION AND TREATMENT IN 15 CENTRES IN THE UNITED KINGDOM

POSTER DISPLAY 08: THERAPY

Sarah Goddard[1], Heba Bintalib[2], Manisha Ahuja[3], Tomaz Garcez[4], Mark Gompels[5], Alexandros Grammatikos[5], Sofia Grigoriadou[6], Elizabeth Drewe[7], Sadia Noorani[8], Smita Patel[9], Sinisa Savic[10], Adrian Shields[11], Kavitha Sooriyakumar[11], Cathal Steele[12], Prashantha Vaitla[13], Patrick Yong[14], John Hurst[2], Siobhan Burns[15], Shuayb Elkhalifa[16], K Townsend[6], Neil Halliday[15], Matthew Buckland[17]
[1]University Hospitals of North Midlands NHS Trust, Immunology And Allergy, Stoke-on-Trent, United Kingdom, [2]Universiry College london, Respiratory Medicine, London, United Kingdom, [3]Newcastle Upon Tyne Hospitals NHS, Immunology, Newcastle, United Kingdom, [4]Manchester university NHS Foundation Trust, Greater Manchester Immunology Service, Manchester, United Kingdom, [5]North Bristol NHS Trust, Clinical Immunology And Allergy, Bristol, United Kingdom, [6]Barts Health NHS Trust, Department of Immunology, London, United Kingdom, [7]Nottingham University Hospitals, Immunology, Nottingham, United Kingdom, [8]Sandwell and West Birmingham Hospitals NHS Trust, Department of Immunology, Birmingham, United Kingdom, [9]University of Oxford, Nihr Brc Oxford Biomedical Research Centre, Oxford, United Kingdom, [10]St James's University Hospital, Clinical Immunology And Allergy, Leeds, United Kingdom, [11]University of Birmingham, Clinical Immunology Service,, Birmingham, United Kingdom, [12]Aberdeen Royal Infirmary, Immunology, Aberdeen, United Kingdom, [13]Nottingham University Hospitals, NHS Trust, Immunology, Nottingham, United Kingdom, [14]NHS Frimley Foundation trust, Immunology, Frimley, United Kingdom, [15]UCL, Institute of Immunity And Transplantation, London, United Kingdom, [16]University of Manchester, Immunology, PL, United Kingdom, [17]Great Ormond Street Hospital for Children, Immunology, London, United Kingdom

Background and Aims: A significant proportion of people with common variable immunodeficiency develop a multi-system disease. Complications involving, the liver, gut and other systems occur and management of these rare patients with multi-system presentation is challenging in the clinic. We have developed a nationwide multi-specialty panel for discussion of patients, highlighting problems in management of these rarer patients and development of assessment and management.

Methods: Patients with multi-system common variable immundeficiency (CVID) were identified using 'granulomatous' as a search term on the national immunodeficiency database. We contacted the centres involved and also invited them to submit data for any other patients who had complex multi-system CVID. 15 centres submitted data.

Results: We collected data on 140 patients. 75 had genetics investigation and 9 had a gene defect identified. 125 patients had lung disease, and 75 -GLILD. 75 -lymphadenopathy, 94 -splenomegaly (13 splenectomy), 52 -skin disease, 13 -renal disease, 61 -gastrointestinal disease and 14 -neurological disease. 52 -ITP, 21 -autoimmune haemolytic anaemia. 80% were taking antibiotic prophylaxis, most common was azithromycin. 88% of patients had either had prednisolone or were currently taking it. Rituximab was the next most common agent followed by MMF. The most common cause of death was respiratory, but liver disease was the next commonest cause of death.

Conclusions: The multi-specialty approach to management of CVID is very difficult, especially for smaller centres. However by taking a national approach we have been able to engage with enthusiastic specialists from other disciplines and highlight under-recognised causes of morbidity and mortality in CVID.

Disclosure: No.

Keyword: complex multi-system common variable immunodeficiency

PD373

TO CURE LUNG DISEASE IN STAT3-HYPER IGE SYNDROME (STAT3-HIES)

POSTER DISPLAY 08: THERAPY

Beate Hagl[1], Renate Effner[1], Verena Häfner[1,2,3], Christian Birk[1,4], Theresa Mittweg[1], Andreas Eberherr[1], Anica Lechner[1], Miriam Kastlmeier[2], Christine Wolf[1], Ricardo Berutti[5], Carolin Kröner[3,6], Gudrun Schopper[4], Alena Buyx[7], Florian Giesert[8], Jens Neumann[9], Adam Chaker[10], Ulrich Zissler[3,11], Carola Voss[2], Tobias Stoeger[2,3], Ellen Renner[1,4,12,13]

[1]_Technical University Munich & Helmholtz Zentrum Munich, Translational Immunology In Environmental Medicine, Munich, Germany, [2]Helmholtz Zentrum Munich, Lung Health And Immunity, Neuherberg, Germany, [3]German Center for Lung research, (dzl), Munich, Germany, [4]TUM, Department of Pediatrics, Munich, Germany, [5]TUM, Institute of Human Genetics, Munich, Germany, [6]LMU, Department of Pediatrics, Dr. Von Hauner Children's Hospital, Munich, Germany, [7]TUM, Institute For History And Ethics of Medicine, Munich, Germany, [8]Helmholtz, Institute of Developmental Genetics, München Neuherberg, Germany, [9]Ludwig Maximilian University, Department of Pathology, School of Medicine, Munich, Germany, [10]TUM, Department of Otorhinolaryngology And Head And Neck Surgery, Munich, Germany, [11]TUM & Helmholtz Center Munich, Center of Allergy & Environment (zaum), Munich, Germany, [12]Technical University of Munich, Department of Pediatrics, School of Medicine, Klinikum Rechts Der Isar, Munich, Germany, [13]Technical University Munich & Helmholtz Zentrum Munich, Translational Immunology In Environmental Medicine, Neuherberg, Germany

Background and Aims: Destructive lung disease is a frequent finding in patients with STAT3 hyper-IgE syndrome (STAT3-HIES). To date no curative treatment of this chronic lung disease is available. Here, we report steps towards our vision to cure lung disease in STAT3-HIES.

Methods: To follow clinical courses of STAT3-HIES patients, to address immune responses, lung pathology in human, lung organoids, and mouse models, and to develop CRISPR-Cas guided adenine base editors (ABEs) applications towards a cure of lung disease.

Results: Recurrent infections of the lung were a major risk for our STAT3-HIES patients to develop chronic destructive lung disease presenting as pneumatoceles, scar tissue, and abscess formation. With age, patients developed an increasing restrictive and obstructive lung disease, particularly affecting peripheral airways. We not only identified reduced numbers of alveolar type 2 (AT2) cells identified in post mortem histology investigations in STAT3-HIES patients (Kröner et al. Allergy 2019), but also in our lung injury mouse model. Along with reduced levels of VEGFA and altered immune responses in our fibroblast infections models, we expect these findings to explain impaired wound healing. While we were successful in the functional repair of the hotspot mutation STAT3 p.R382W (Eberherr et al. CRISPR J 2021) in fibroblasts and induced pluripotent stem cells (iPSC) of patients, there are various remaining questions to be solved to advance to lung therapy of STAT3-HIES.

Conclusions: In a translational approach we are addressing lung pathology, immune responses, and treatment options to develop a causative treatment for chronic lung diseases in STAT3-HIES.

Disclosure: No.

Keywords: STAT3-HIES, lung disease, organoids, base editing, CRISPR/Cas

PD374

REVERSAL of SEZARY SYNDROME AND PML THROUGH HEMATOPOIETIC STEM CELL TRANSPLANTATION IN A YOUNG ADULT WITH DOCK8 DEFICIENCY

POSTER DISPLAY 08: THERAPY

Alexandra Freeman[1], Anita Fletcher[2], Daniele Avila[3], Heidi Kong[4], Irene Cortese[2], Corina Gonzalez[3]
[1]NIAID, Laboratory of Clinical Immunology And Microbiology, Bethesda, United States of America, [2]NIH, Ninds, Bethesda, United States of America, [3]NIH, Nci, Bethesda, United States of America, [4]NIH, Niams, Bethesda, United States of America

Background and Aims: A 21-year-old male with DOCK8 deficiency was referred for hematopoietic stem cell transplant (HSCT). Patient's history included eczema, oto-sinopulmonary infections with bronchiectasis, and warts. Sezary syndrome (SS) was diagnosed from skin and node biopsies, and peripheral blood flow cytometry. Asymptomatic progressive multifocal leukoencephalopathy (PML) was diagnosed from brain MRI, CSF JC virus and biopsy.

Methods: Review of instructional patient case.

Results: HSCT was accepted given the lack of neurologic symptoms and a matched sibling donor. To avoid progression of PML with chemotherapy, bexarotene was initiated for SS, achieving a partial response, and HSCT donor polyomavirus-specific T cells were infused twice pre-HSCT. HSCT conditioning with busulfan and fludarabine was followed by peripheral blood stem cell infusion. Graft versus host disease prophylaxis included one dose of cyclosphosphamide, one month of MMF and 6 months of tacrolimus. Patient had neutrophil engraftment day +13, followed by worsening neurologic status day +29. Brain MRI showed florid enhancement of lesions, and CSF had increased pleocytosis with decreased JC viral load. Corticosteroids were initiated for presumed immune reconstitution syndrome, with gradual neurologic improvement. Six months post HSCT, the patient has 100% donor chimerism including CSF white cells, is in remission from SS, and only trace neurologic defects remain with negative JC viral load in CSF and improved brain imaging.

Conclusions: PML is fatal without immune reconstitution, and HSCT is contraindicated. Due to the lack of neurologic symptoms, HSCT was performed following polyomavirus specific T lymphocyte infusions and resulted in PML and SS remission, and presumed cure for DOCK8 deficiency.

Disclosure: No.

Keywords: DOCK8 deficiency, Sezary syndrome, PML, Hematopoetic stem cell transplantation, Polyomavirus-directed T cell therapy

PD375

SUCCESSFUL TREATMENT of DRUG-RESISTANT CHRONIC COLITIS WITH TGF-BETA2-CONTAINING HYDROLYSATE FORMULATION IN A PATIENT WITH X-LINKED LYMPHOPROLIFERATIVE SYNDROME TYPE 1 FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION

POSTER DISPLAY 08: THERAPY

Francesca Cillo, Giuliana Giardino, Roberta Romano, Elisabetta Toriello, Antonio De Rosa, Emma Coppola, Emilia Cirillo, Claudio Pignata
University of Naples Federico II, Translational Medical Sciences, Section of Pediatrics, Naples, Italy

Background and Aims: cGVHD (Chronic Graft Versus Host disease) with gastrointestinal involvement is a rare complication of hematopoietic stem cell transplantation (HSCT).

Methods: We present the case of a pediatric patient with X-linked Lymphoproliferative Syndrome type 1 (XLP1), who underwent HSCT from a matched unrelated donor. The procedure was complicated by the development of cutaneous and hepatic aGVHD (at + 32 days) and of cutaneous cGVHD (at + 5 months), successfully treated.

Results: 1 year after HSCT, the patient developed fever, diarrhea and failure-to-thrive, associated with macrocytic anemia, hypoalbuminemia and persistent elevation in inflammatory markers. Abdominal CT and colonoscopy showed a macroscopic and histological picture of active chronic colitis. Histological findings were not clearly conclusive for a cGVHD with intestinal localization. The patient was started on Ruxolitinib and Prednisone 1mg/kg/day for two months, with poor response. Due to the persistence of active chronic colitis, exclusive enteral nutrition (EEN) with TGF-β2-containing hydrolysate formulation was started. Following the EEN introduction, a reduction in inflammatory markers, malabsorption resolution, weight gain and regression of diarrhea were observed. For the maintenance of remission, off-label therapy with Ibrutinib, was started as second line in the treatment of steroid-resistant cGVHD.

Conclusions: This case suggests that EEN with TGF-β2-containing hydrolysate formulation may represent a safe and efficacious therapeutic option to induce the remission of chronic active colitis in cGVHD. This efficacy, due to the anti-inflammatory effect of TGF-β2 on the intestinal mucosa and to the modulatory action on the intestinal microflora, should be proven on a larger cohort.

Disclosure: No.

Keyword: XLP1, HSCT, cGVHD, colitis, exclusive enteral nutrition

PD376

PRETRANSPLANT USE of VIRUS SPECIFIC T CELLS FOR EBV+ LYMPHOPROLIFERATION IN AN ARPC1B DEFICIENT PATIENT

POSTER DISPLAY 08: THERAPY

Gasper Markelj[1], Primož Poženel[2], Tomaž Prelog[3], Tina Srovin[4], Spela Markelj[5], Urban Švajger[2], Barbara Jezeršek Novaković[6], Tadej Avcin[1]
[1]University Children's Hospital, University Medical Center Ljubljana, Department of Allergology, Rheumatology And Clinical Immunology, Ljubljana, Slovenia, [2]Blood Transfusion Center of Slovenia, Department For Therapeutic Services, Ljubljana, Slovenia, [3]University Children's Hospital, University Medical Centre Ljubljana, Department of Oncology And Haematology, Ljubljana, Slovenia, [4]University Medical Centre Ljubljana, Department of Infectious Diseases, Ljubljana, Slovenia, [5]University Medical Centre Ljubljana, University Eye Hospital, LJUBLJANA, Slovenia, [6]Institute of Oncology, Division of Medical Oncology, Ljubljana, Slovenia

Background and Aims: Homozygous mutations in the ARPC1B cause an autosomal recessive syndrome of combined immune deficiency with impaired T-cell immunity, defective phagocyte function and abnormal thrombocytes. Virus specific T cells (VST) have been used successfully to combat resistant virus infections predominantly after HSCT. In only rare cases VST was used before allogeneic stem cell transplantation for primary immunodeficiency to control the viral infection.

Methods: We present a case of a patient with ARPC1B deficiency who received several infusions of VST for uncontrolled EBV lymphoma in the pretransplant period. Family donors were typed for HLA at allelic level and screened for EBV seropositivity (VCA IgG and EBNA1 IgG). Mononuclear cell collection was performed the day before immunoselection with EBV Peptivator Select to isolate EBV specific lymphocytes with IFN gamma secretion. Positive cell fraction from target cell bag was taken to flow cytometry for lymphocyte subpopulations analysis and was released for clinical use.

Results: 28y old male patient with several complications of ARPC1B deficiency presented with EBV+ lymphoma after 10 years of mild clinical course of his disease. We were able to control his disease with antiviral therapy and anti-CD20 monoclonal antibodies for the first year. After SARS-CoV2 infection his disease relapsed, we combined chemotherapy with VST as method to control the disease while we were preparing him for HSCT.

Conclusions: In our case we have had a partial response in controlling EBV+lymphoproliferation with pretransplant VSL. We have observed neurological and ophthalmological complication after VSL infusions. ARPC1B deficiency exhibits several immune-dysregulation manifestations which could lead to strong alloreactive anti-lymphocyte responses.

Disclosure: No.

Keyword: ARPC1B, T Cell immunity, EBV+ lymphoma, virus specific cell therapy

PD377

TEN-YEAR TRENDS of IMMUNOGLOBULIN USE, BURDEN of ADULT ANTIBODY DEFICIENCY AND FEASIBILITY of SUBCUTANEOUS IMMUNOGLOBULIN (SCIG) REPLACEMENT IN HONG KONG

POSTER DISPLAY 08: THERAPY

Andy Ka Chun Kan, Chak Sing Lau, Philip Li
The University of Hong Kong, Division of Rheumatology And Clinical Immunology, Department of Medicine, Hong Kong, Hong Kong PRC

Background and Aims: The real-world situation of immunoglobulin use and antibody deficiency among Chinese patients remains unclear. We studied the burden of adult antibody deficiency and feasibility of subcutaneous immunoglobulin (SCIg) replacement in Hong Kong (HK).

Methods: Patients from the entire HK population who received human immunoglobulin between 2012 and 2021 were identified. Longitudinal clinical data of adult immunodeficiency patients at the Immunology Clinic of the HK West Cluster were obtained and analysed.

Results: There was an increasing trend of gross immunoglobulin use, from 175,512 grams in 2012 to 298,514 grams in 2021. Throughout the years, majority (64.8% – 76.6%) of the patients were recurrent users (≥2 doses within a year), and this was on a rising trend (from 886 in 2012 to 1,435 in 2021). Antibody deficiency accounted for 43% of adult immunodeficiency patients. Twenty-two adult antibody deficiency patients on immunoglobulin replacement were identified; 8 (36.4%) and 14 (63.6%) were on SCIg and intravenous immunoglobulin (IVIg) replacement respectively. Patients on SCIg required a lower dose (0.52 vs 0.66 g/kg/month, p=0.046) while having less frequent immunodeficiency-related hospitalisations within one year (0.50 vs 13.0 episodes, p<0.001). Patients on SCIg had significantly better health-related quality of life, reflected by the 'Physical Component Summary' of SF-36v2 (54.5 vs 45.8, p=0.016), as well as the 'Treatment Interference' (88.9 vs 64.3, p=0.004) and 'Therapy Settings' (94.4 vs 63.9, p=0.024) domains of Life Quality Index.

Conclusions: There was an increasing burden of adult antibody deficiency in HK. Patients on SCIg had better outcomes compared to those on IVIg.

Disclosure: No.

Keywords: immunodeficiency, Antibody, immunoglobulin replacement, Hospitalisation, quality of life, Subcutaneous

PD378

SUCCESSFUL TREATMENT WITH HAPLOIDENTICAL STEM CELL TRANSPLANTATION AFTER TCRAB/CD19 DEPLETION IN AN ICOS-DEFICIENT PATIENT

POSTER DISPLAY 08: THERAPY

Nazli Deveci Demirbas[1], Sule Haskologlu[1], Avniye Baskin[1,2], Hasret Erkmen[2], Sevgi Kostel Bal[3], Kaan Boztug[3], Figen Dogu[1,2], Aydan Ikinciogullari[2]
[1]Ankara University School of Medicine, Department of Pediatric Immunology And Allergy, Ankara, Turkey, [2]Ankara University School of Medicine, Department of Pediatric Immunology And Allergy, ANKARA, Turkey, [3]Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, Department of Genetics, vienna, Austria

Background and Aims: Inducible T cell co-stimulator (ICOS) deficiency has been categorized as a combined immunodeficiency often complicated by enteropathies, autoimmunity, lymphoproliferation, and malignancy.

Methods: Here, we report an ICOS case that was transplanted twice due to secondary graft failure which was effectively treated by haplo-HSCT after TCRαβ/CD19 depletion.

Results: 19 years-old-male patient initially administered to our clinic at 4 years old with bronchiectasis, chronic diarrhea, failure to thrive, and hypogammaglobulinemia. In follow up severe infections, autoimmune hypothyroidism, GCSF-resistant neutropenia, and refractory thrombocytopenia have occurred. Genetic analysis revealed a homozygous mutation in the ICOS gene. After a reduced-intensity conditioning regimen (RIC), he underwent HSCT from a MUD. Myeloid and thrombocyte engraftment were achieved on the 25th and 39th days, respectively, and T cell chimerism was detected in 55%. Thrombocytopenia and neutropenia occurred at the +58th day. Donor chimerism also declined over time; thus the patient was diagnosed as secondary graft failure. Due to the Covid-19 pandemic, HSC's could not be obtained from MUD for the second time. TCR αβ/CD19 depleted HSCT from his haploidentical father was performed with RIC regimen consisting of treosulfan, fludarabine, thiotepa, and ATG. Cyclosporine was given as GvHD prophylaxis. Myeloid engraftment and full donor chimerism were achieved on the day of 22 post-HSCT. Grade-1 acute skin and gut GvHD was developed and treated with steroids. There were no additional complications 9 months after the HSCT.

Conclusions: We conclude that haploidentical HSCT followed by a TCRαβ/CD19 depletion may be considered in PID patients when a MRD is unavailable.

Disclosure: No.

Keyword: ICOS deficiency, Haploidentical HSCT, TCR αβ/CD19 depletion

PD379

USE of TOFACITINIB IN THE TREATMENT of THREE ADULT PATIENTS WITH GAIN-OF-FUNCTION MUTATIONS IN STAT-1

POSTER DISPLAY 08: THERAPY

Susan Tadros[1], Ally Speight[2], Stephen Boag[3], Sadia Noorani[4], Siobhan Burns[1,5]
[1]The Royal Free London NHS Foundation Trust, Department of Immunology, London, United Kingdom, [2]The Newcastle Upon Tyne NHS Foundation Trust, Department of Gastroenterology, Newcastle, United Kingdom, [3]The Newcastle Upon Tyne NHS Foundation Trust, Department of Immunology, Newcastle, United Kingdom, [4]Sandwell and West Birmingham Hospitals NHS Trust, Department of Immunology, Birmingham, United Kingdom, [5]University College London, Institute of Immunity And Transplantation, London, United Kingdom

Background and Aims: Gain-of-function (GOF) mutations in signal transducer and activator of transcription 1 (STAT1) present with a broad clinical phenotype including chronic mucocutaneous candidiasis (CMC) and immune dysregulation. Disease manifestations respond to treatment with JAK inhibitors with most experience with Ruxolitinib. Here we report our experience of using tofacitinib in adults with STAT1 GOF.

Methods: We performed a retrospective case review for adults with STAT1 GOF at our center, established on tofacitinib for 3 months or more. We collected data for clinical outcomes and adverse events.

Results: 3 patients were identified. Patient 1 (Pt1) a 19-year-old male, with a Lys344Gln STAT1 GOF mutation, respiratory infections, CMC, massive splenomegaly and severe anaemia. Pt2, a 21-year-old female with a Thr385Met STAT1 GOF mutation, CMC and small bowel enteropathy causing weight loss requiring parenteral nutrition. Pt 3 a 35-year-old male, with a Phe404Val STAT1 GOF mutation with bronchiectasis and azole resistant CMC. Tofacitinib 5mg BD was commenced then increased to 10mg twice daily with regular blood monitoring. Haemoglobin increased, spleen size reduced, and candidiasis resolved with treatment in Pt1. After 3 weeks of treatment, diarrhoea resolved, weight increased by 5kg and parenteral nutrition was stopped in Pt2. Pt 3 is clinically stable on amphotericin lozenges. ALT increased after initiation of tofacitinib in Pt2. Antifungal prophylaxis was stopped with close monitoring of liver function but tofacitinib continued. No patient experienced significant side effects.

Conclusions: We present three cases demonstrating tofacitinib to be an effective and well tolerated treatment in STAT1 GOF.

Disclosure: No.

Keywords: Tofacitinib, STAT1 gain-of-function, JAK inhibitors

PD380

CORTICOSTEROID-INDUCED REMISSION, AND MYCOPHENOLATE MAINTENANCE THERAPY IN GLILD: LONG-TERM, LONGITUDINAL CHANGE IN LUNG FUNCTION IN A SINGLE CENTRE COHORT

POSTER DISPLAY 08: THERAPY

Heba Bintalib[1], David Lowe[2], Gaia Mancuso G[3], Georgia Gkrepi[4], Suranjith Seneviratne[5], Siobhan Burns[2], John Hurst[1]
[1]Universiry College london, Respiratory Medicine, London, United Kingdom, [2]UCL, Institute of Immunity And Transplantation, London, United Kingdom, [3]Vita-Salute San Raffaele University, Unit of Immunology, Rheumatology, Allergy, And Rare Diseases, Milan, Italy, [4]University Hospital of Ioannina, Respiratory Medicine Department, Ioannina, Greece, [5]Royal Free London NHS Foundation Trust, Department of Immunology, London, United Kingdom

Background and Aims: Granulomatous lymphocytic interstitial lung disease (GLILD) is rare non-infectious complication in patients with common variable immunodeficiency disorders (CVID) which significantly impacts morbidity and mortality. Aim is to evaluate the response of lung function to different treatment regimens.

Methods: This is a longitudinal retrospective cohort study.Patients were divided into three groups. To assess the response to different treatments, we compared baseline lung function to post-treatment.

Results: 14 patients with GLILD were included. 7 patients were treated with acute corticosteroids for a mean duration of 4 months. The spirometry results were unchanged, but there was a significant improvement in DLCO% and KCO% (median change in DLCO% =5%, P=0.04, and KCO%= 12%, P= 0.02). Relapse occurred in 5/7 patients. 5 patients were treated with long-term MMF with/out corticosteroids for a mean duration of 3.8 years. Two had relapsed after multiple courses of acute steroids. No changes were found in spirometry. However, there was a significant increase in DLCO% and KCO% (mean change in DLCO% = 10%, P=0.04, and KCO%= 11%, P=0.04). 4 patients on steroids with MMF successfully weaned the Prednisone dose over 12 months. 4 patients had never received immunosuppression therapy. A significant decline was found in lung function over 7.8 years. The median reduction in the FVC%, FEV1%, and DLCO% were 20%, 10%, and 11%, respectively.

Conclusions: Corticosteroids improve gas transfer, but patients often relapse. The use of MMF was associated with long-term effectiveness in GLILD and permits weaning of corticosteroids. A delay in initiating and continuing maintenance treatment could lead to disease progression.

Disclosure: No.

Keywords: Common variable immunodeficiency, GLILD, treatment, corticosteroids, mycophenolate mofetil

PD381

ABATACEPT: A SUCCESSFUL OPTION IN A CHILD WITH LRBA DEFICIENCY

POSTER DISPLAY 08: THERAPY

Lucia Baselli[1], Claudia Ballerini[2], Elena Trombetta[3], Catarina Granjo Morais[4], Sofia Torreggiani[1], Maria Carrabba[5], Laura Porretti[3], Rosa Dellepiane[1]
[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlnico, Pediatric Department, Milano, Italy, [2]Università degli Studi di Milano, Paediatric Department, Milano, Italy, [3]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlnico, Flow Cytometry Laboratory, Clinical Laboratory, Milano, Italy, [4]Centro hospitalar e universitário de São João, Department of Pediatrics, Maia, Portugal, [5]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, UOS Malattie Rare, Dipartimento Di Medicina Interna, Milano, Italy

Background and Aims: Abatacept has been shown to be effective in improving immune-dysregulation in LPS-responsive beige-like anchor (LRBA) deficiency. However, there is no agreement on the most appropriate dosing and therapeutic scheme in these patients, especially in paediatric age.

Methods: We report the case of a 7-year-old girl diagnosed with LRBA deficiency with focus on treatment of immune dysregulation with abatacept.

Results: She presented at the age of 19 months with hemolytic anemia, immune thrombocytopenia, splenomegaly and lymphadenopathy. She was treated with systemic steroids, with good control of cytopenia, but not of lymphoproliferation. The patient came to our attention at the age of 5 years and 10 months. LRBA deficiency was diagnosed with an NGS gene panel showing a novel homozygous frameshift mutation in LRBA (c.4134dupG;p.Leu1379Alafs*10). Due to severe hypogammaglobulinemia she was started on intravenous immunoglobulin replacement therapy. Given the worsening of pulmonary lymphoid infiltrates, abatacept therapy was started with an intravenous loading dose of 10mg/kg followed by subcutaneous administration of 125mg every two weeks (10-15mg/kg/month). The patient showed a dramatic clinical improvement. Systemic steroid was tapered and stopped with no relapsing of cytopenia. No adverse effects were reported in one year of therapy.
CXCR5+PD1+Follicular T helper cells (cTfh) were increased at baseline (42,8% of CD3+CD4+), as expected in LRBA deficiency patients. The percentage dropped with abatacept therapy, then reached a plateau at around 30%. No significant change was observed in naïve T cells percentage.

Conclusions: Abatacept therapy is safe and effective in LRBA patients. CXCR5+PD1+cTfh could be useful in monitoring the response to treatment.

Disclosure: No.

Keywords: LYMPHOPROLIFERATION, Autoimmune cytopenia, LRBA deficiency, Abatacept, Immune Dysregulation

PD382

POPULATION PHARMACOKINETICS of IMMUNOGLOBULIN G AFTER INTRAVENOUS, CONVENTIONAL SUBCUTANEOUS OR FACILITATED SUBCUTANEOUS ADMINISTRATION IN IMMUNOGLOBULIN-NAÏVE PATIENTS WITH PRIMARY IMMUNODEFICIENCIES

POSTER DISPLAY 08: THERAPY

Zhaoyang Li[1], Ed Freshwater[2], Frank Engler[2], Leman Yel[3]
[1]Takeda Development Center Americas, Inc., Clinical Pharmacology & Early Clinical Development, Cambridge, United States of America, [2]Certara Strategic Consulting, Clinical Pharmacology, Princeton, United States of America, [3]Takeda Development Center Americas, Inc., Pdt Bu Research And Development, Cambridge, United States of America

Background and Aims: We simulated immunoglobulin G (IgG) pharmacokinetics for different immunoglobulin therapies with varied dosing regimens in IgG-naïve patients with primary immunodeficiencies (PID) to characterize IgG pharmacokinetics and the impact of patient factors as potential covariates.

Methods: An integrated population pharmacokinetic model was previously developed using data from eight clinical trials (each ≥1-year duration; n=384 patients), which characterized serum IgG pharmacokinetics for intravenous (IVIG), conventional (cSCIG) and facilitated subcutaneous (fSCIG) immunoglobulin in patients with PID. Model-based simulations assessed IgG pharmacokinetics following different dosing regimens of IVIG, cSCIG and fSCIG (400 and 600 mg/kg 4-weekly [Q4W] for IVIG and fSCIG; weekly equivalent for cSCIG) in IgG-naïve patients with PID of varying age (2–<6, 6–<12, 12–<18 and ≥18 years) and baseline total serum IgG levels (1.5 or 4.0 g/L), representing differing disease severities.

Results: In IgG-naïve patients with baseline IgG 1.5 or 4.0 g/L receiving 400 mg/kg doses, mean steady-state IgG trough levels ($C_{min,ss}$) ranged between 2.47–5.02 g/L and 4.97–7.52 g/L, respectively, across ages following IVIG, cSCIG or fSCIG. For 600 mg/kg doses mean $C_{min,ss}$ values were 2.92–6.66 g/L and 5.42–9.16 g/L, respectively, across age categories and IVIG, cSCIG or fSCIG. In most patients, mean $C_{min,ss}$ was higher after IVIG than cSCIG or fSCIG, and $C_{min,ss}$ increased slightly with age.

Conclusions: To achieve protective serum IgG levels, IgG-naïve patients with PID may require loading doses and individualized dosing guided by serum IgG monitoring, clinical status, endogenous IgG levels and age. Study/writing support funder: Takeda Development Center Americas, Inc.

Disclosure: ZL and LY are employees of Takeda Development Center Americas, Inc., and are Takeda shareholders. EF and FE are employees of Certara USA, and have received research grants from Takeda Development Center Americas, Inc. for this study.

Keywords: primary immunodeficiencies, Facilitated subcutaneous immunoglobulin, Immunoglobulin-naïve, Immunoglobulin G, Subcutaneous immunoglobulin, Population pharmacokinetic modelling

PD383

RITUXIMAB MONOTHERAPY FOR GRANULOMATOUS-LYMPHOCYTIC INTERSTITIAL LUNG DISEASE IN COMMON VARIABLE IMMUNE DEFICIENCY: A CASE SERIES

POSTER DISPLAY 08: THERAPY

Helena Buso[1], Valentina Soccodato[2], Cinzia Milito[2], Riccardo Scarpa[1], Marcello Rattazzi[1], Carlo Agostini[1], Francesco Cinetto[1]
[1]University of Padua, Department of Medicine, Treviso, Italy, [2]Università La Sapienza, Department of Molecular Medicine "sapienza" University of Rome, Italy, Rome, Italy

Background and Aims: Granulomatous and Lymphocytic Interstitial Lung Diseases (GLILD) is one of the most severe complications in Common Variable Immunodeficiency (CVID). There is currently no consensus on a standardized treatment protocol for GLILD. The aim of our study is to explore the use of Rituximab (RTX) for GLILD treatment.

Methods: We retrospectively reviewed data of 5 GLILD patients treated with at least one cycle of RTX at a dose of 375 mg/m^2 weekly for 28 days (to a maximum of 4 cycles with a six-to-nine-months interval). The treatment's efficacy was evaluated using FDG-positron emission tomography and computed tomography (PET-CT) at baseline and after one cycle of RTX.

Results: The baseline PET-CT of the 5 patients documented areas of hypermetabolism in both lungs and above and below diaphragm lymph nodes. The PET-CT performed after one cycle of RTX showed an almost complete resolution of the pathological hypermetabolism with a reduction of lymph nodes size and an improvement or normalization of lung architecture in all patients. Interestingly, 2 patients performed a second PET-CT after the third cycle, showing maintenance of treatment response. Moreover, 4 patients had a baseline and after-RTX spirometry and 3 of them had improvement greater than 10% in the lung diffusion capacity (DLCO). Furthermore, 3 patients with baseline splenomegaly had a documented reduction up to 40% in the spleen size. None had a clinical or radiological relapse (median follow-up 16 months).

Conclusions: Our study supports a possible role of Rituximab monotherapy in GLILD treatment. Further clinical studies with larger samples and standardized assessment protocols are needed.

Disclosure: No.

Keywords: GLILD, CVID, RITUXIMAB, ILD, PET-CT

PD384

IMPACT of EARLY DIAGNOSIS of CONGENITAL ATHYMIA ON THE EUROPEAN THYMUS TRANSPLANTATION PROGRAMME.

POSTER DISPLAY 08: THERAPY

Evey Howley[1], Alexandra Kreins[2], Zainab Golwala[2], Matthew Buckland[2], Austen Worth[3], Graham Davies[2]
[1]Great Ormond Street Hospital for Children, Immunology, London, United Kingdom, [2]Great Ormond Street Hospital, Immunology, London, United Kingdom, [3]Great Ormond Street Hospital, Department of Immunology And Gene Therapy, London, United Kingdom

Background and Aims: Thymus transplantation has become the treatment of choice for congenital athymia associated with DiGeorge syndrome and other genetic causes[1,2]. Patients may present with syndromic characteristics, features of Omenn syndrome, recurrent or opportunistic infections. The last may compromise the outcome of thymus transplantation (TT). In recent years, diagnosis through newborn screening (NBS) programmes for severe T-cell deficiency has also increasingly occurred. We postulated that earlier diagnosis and treatment might result in better outcomes.

Methods: Patient characteristics, clinical presentation, and early outcomes in patients receiving TT were compared between those treated before January 2019 (Group A, n=37) and those since (Group B, n=19).

Results: Nine of 19 patients in Group B were diagnosed through NBS. Median (range) age (months) at transplantation were 10 (2-25) and 5 (1.5-19) respectively. There was no difference between the groups in the presence of Omenn syndrome (68% v 62%). The prevalence of life-threatening viral or mycobacterial infections at the time of transplantation tended to be lower in Group B (32% v 43%). In patients more than 18 months after TT, median time (range) in months to achieving a minimal level of thymic output of 50 x 10^6 naïve T-cells/uL was 6 (3-57) in those transplanted <6 months of age (n=11) compared to 10 (5-23) in those >6months (n=24).

Conclusions: Earlier diagnosis and treatment of athymia, through NBS programmes and increased awareness of appropriate treatment may result in quicker immune reconstitution after thymus transplantation. References: 1. Markert et al, 2022. 2. Davies et al, 2017.

Disclosure: No.

Keywords: Transplantation, DiGeorge, athymia, DIAGNOSIS, thymus

PD385

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PRIMARY IMMUNODEFICIENCIES

POSTER DISPLAY 08: THERAPY

Monia Ouederni[1,2], Nessrine Zekri[1], Samya Rekaya[1,2], Ilhem Benfraj[1,2], Takwa Lamouchi[1], Mohamed Bejaoui[1], Fethi Mellouli[1], Monia Ben Khaled[1,2]
[1]University Tunis El Manar, Facuty of Medecine, Tunis, Tunisia, [2]Bone Marrow Transplant Center, Departement of Pediatrics, TUNIS, Tunisia

Background and Aims: Primary immunodeficiencies (PID) are frequent in Tunisia. Hematopoietic stem cell transplantation (HSCT) is the only effective therapy for lethal forms in Tunisia. We aimed to report our experience and describe the results of HSCT in PIDs children.

Methods: We report clinical data from 62 children undergoing HSCT for PIDs at the Pediatric HSCT Unit in Tunis including severe combined immunodeficiency disease(14), CMH-II deficiency(18) OMMEN syndrome(05), LFA-1 deficiency(04), Wiskott-Aldrich syndrome(04), hereditary lymphohistiocytosis(03), Severe congenital neutropenia(03), osteopetrosis(04) and other PIDs(07). The mean age at HSCT was 31.7 months(2 months-16.9 years). Five patients were unconditioned. Myeloablative conditioning containing Busulfan (Bu) was used in all remaining patients, with Cyclophosphamide in 17 patients, and Fludarabine in 40 patients.

Results: Primary engraftment was achieved in 93.4% of patients (57/62) using Granulocyte-colony stimulating factor (GCSF) in 47.4% of cases. Hepatic Veno-occlusive disease was documented in 39.3% of patients, acute GVHD in 51.6% of patients, and chronic GVHD in 16.1% (10 patients). Viral infections occurred in 61.3% of patients. Transplant-related mortality was 33.87%. The death occurred 72.82 days after HSCT (9-246). It was due mainly to viral infections (28.6%), veno-occlusive disease (14.3%), and GVHD (9.5%). The overall survival of the whole group was 66.1% at five years. 40/62 patients are alive at median follow-up 46.26 months (2.7-144) after HSCT.

Conclusions: HSCT has markedly improved the prognosis of PID patients in our country over the last few years. However, transplant-related toxicity and mortality should be reduced through an early diagnosis and prompt management.

Disclosure: No.

Keywords: primary immunodeficiencies, Hematopoietic stem cell transplantation, T cell deficiencies, GVHD

PD386

TWO NOVEL VARIANT MUTATIONS of CD3E IN UNRELATED PATIENTS BOTH of WHITCH UNDERWENT HEMATOPOIETIC STEM CELL TRANSPLANT WITH INFUSION ONLY

POSTER DISPLAY 08: THERAPY

Manar Alghamdi[1], Reem Mohammed[2]
[1]King Faisal Hospital and Research Center, Pediatric Allergy And Immnology, .Riyadh, Saudi Arabia, [2]King Faisal Hospital and Research Center, Pediatric Allergy And Immunology, .Riyadh, Saudi Arabia

Background and Aims: CD3 complex is crucial for T-cell regulation.CD3E gene mutations particularly have been associated with rare forms of autosomal recessive immunodeficiencies.Until now there are fifteen CD3E gene mutation analysis.

Methods: We report the outcome of two different Novel Variant Mutations of CD3E in patients who underwent unconditioned stem cell transplantation.

Results: First patient presented with recurrent infections,Diarrhea,and failure to thrive.His markers showed lymphopenia and hypogammaglobulinemia with a flow cytometry of surface markers showing T- B+ NK+ phenotype.Whole exome sequence(WES)test revealed a novel pathogenic homozygous variant mutation in CD3E gene on chromosome 11 on the nucleotide c.521-1G>A and confirmed by sanger sequencing.He underwent hematopoietic stem cell transplantation(HPSCT)through infusion from a full matched sibling.Complications post transplantation including reactivation of localized BCGitis was managed successfully.Last chimeric post-transplant profile showed 100% T lymphocyte and 0% myeloid cell engraftment.He is still having poor B cell engraftment requiring monthly intravenous immunoglobulins(IVIG).Second patient presented as Omenn syndrome Phenotype.His markers showed lymphocytosis.flowcytometry revealed positive T Cells,negative B and NK cells in addition to hypogammaglobulinemia.WES revealed a different Novel pathogenic homozygous variant mutation in the CD3E gene on the nucleotide c.281G>C and confirmed by sanger sequencing. He underwent HPSCT through infusion from a fully matched sibling.Complication of grade two liver Graft versus host disease was managed successfully. He required IVIG for two years post-transplant.Last chimeric post-transplant profile showed 79% T lymphocyte and 0% myeloid cell engraftment.Both families underwent segregation test and found to be heterozygous carriers of the mutations.

Conclusions: CD3E mutations cause rare forms of immunodeficiencies.Unconditioned transplantations can show excellent results.

Disclosure: No.

Keywords: primary immunodeficiency, CD3ε deficiency, HPSCT, Severe combined immunodeficiency, Stem Cell Transplant, CD3ε Novel Variant Mutation

PD387

A CLINICAL TRIAL DATA REVIEW of TOLERABILITY TO SUBCUTANEOUS IMMUNOGLOBULIN PRODUCTS USED TO TREAT PRIMARY IMMUNODEFICIENCY

POSTER DISPLAY 08: THERAPY

James Jordan[1], Michael Runken[1], Elisabet Viayna[2]
[1]Grifols, Global Health Outcomes Research, Research Triangle Park, United States of America, [2]Grifols, S.A., Global Health Outcomes Research, Barcelona, Spain

Background and Aims: Though marketed subcutaneous immunoglobulins (SCIgs) are chemically different, they are viewed as clinically interchangeable. The tolerability of different immunoglobulins is not well reported. This study reviews clinical trial-reported tolerability of SCIg products in patients with primary immunodeficiency.

Methods: US and EU single-arm, open-label, pivotal trial adverse event (AE) data deemed by treating physician to be study SCIg-related for Xembify (BrX), Cuvitru (BrC), and Hizentra (BrH) were analyzed. AE rates with an absolute difference ≥5% between any SCIgs were identified. Baseline characteristics, trial designs and treatment parameters were compared across trials to identify potential confounders.

Results: Analyzed AE data included 49-to-74 patients per trial. EU study designs and patient characteristics were similar across all three SCIg trials, with the exception of BrH having lower infusion rates. The situation was similar with US trials of BrX and BrH. BrC's US trial had differences in design and infusion rate compared to the others, potentially creating opposing confounders that make AE comparison more difficult. There was a ≥5% difference in AE rates within the US trials for injection-site reactions (BrX=26.5%, BrC=24.3%, BrH=100%), headache (BrX=0%, BrC=10.8%, BrH=24.5%), pain (BrX=2%, BrC=6.9%, BrH=18.4%), nausea (BrX=0%, BrC=6.8%, BrH=4.1%), fatigue (BrX=0%, BrC=6.8%, BrH=6.1%) and vomiting (BrX=0%, BrC=0%, BrH=6.1%). Among EU trials, differences in AE rates ≥5% between SCIgs were observed for injection-site reactions (BrX=26.2%, BrC=35.4%, BrH=49%), headache (BrX=1.6%, BrC=6.3%, BrH=11.8%), fever (BrX=0%, BrC=0%, BrH=5.9%), and pruritis (BrX=0%, BrC=0%, BrH=7.8%).

Conclusions: Though SCIg products are viewed as interchangeable, pivotal trial adverse event data reflects tolerability differences between SCIg products.

Disclosure: The authors are research scientists employed at Grifols, the manufacturer of one of the immunoglobulin products included in this research.

Keywords: Subcutaneous, Immunoglobulin, immunodeficiency, adverse event, tolerability

PD388

THREE ADULT CASES of STAT1 GAIN-OF-FUNCTION WITH CHRONIC MUCOCUTANEOUS CANDIDIASIS TREATED WITH JAK INHIBITORS

POSTER DISPLAY 08: THERAPY

Emilie Wahren Borgström[1], Marie Edvinsson[2], Lucía Peña-Pérez[3], Anna Carin Norlin[4], Sara Lind Enoksson[5], Susanne Hansen[1], Anders Fasth[6], Vanda Friman[7], Olle Kämpe[8], Robert Månsson[3], Hernando Yesid Velasquez[9], Qing Wang[3], Tan Ziyang[10], Tadepally Lakshmikanth[11], Carl Inge Edvard Smith[3], Petter Brodin[12], Peter Bergman[13]
[1]Karolinska Institutet, Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden., Huddinge, Sweden, [2]Section of Infectious Diseases, Uppsala University Hospital, Epartment of Medical Sciences, Uppsala, Sweden, [3]Karolinska Institutet, Department of Laboratory Medicine, Biomolecular And Cellular Medicine,, Stockholm, Sweden, [4]Karolinska Institutet, Department of Clinical Immunology, Huddinge, Sweden, [5]Karolinska Institutet, Department of Clinical Immunology And Transfusion Medicine, Stockholm, Sweden, [6]Institute of Clinical Sciences, Sahlgrenska Academy, Department of Pediatrics, Gothenburg, Sweden, [7]Sahlgrenska Academy, University of Gothenburg, Department of Infectious Diseases, Gothenburg, Sweden, [8]Karolinska Institutet, Department of Medicine, Stockholm, Sweden, [9]arolinska Institutet, Department of Laboratory Medicine, Clinical Research Center, Stockholm, Sweden, [10]Karolinska Institutet, Department of Women And Childrens Health, Stockholm, Sweden, [11]Karolinska Institutet, Head of Cellular Immunomonitoring Facility - Scilifelab, Stockholm, Sweden, [12]Department of Women's and Children's Health, Karolinska Institutet, Science For Life Laboratory, Stockholm, Sweden, [13]Karolinska Institutet, Department of Clinical Microbiology, Huddinge, Stockholm, Sweden

Background and Aims: The aim of this study was to characterize clinical effects and biomarkers in three patients with chronic mucocutaneous candidiasis (CMC) caused by gain-of-function (GOF) mutations in the STAT1 gene during treatment with Janus kinase (JAK) inhibitors.

Methods: Mass cytometry (CyTOF) was used to characterize mononuclear leukocyte populations and Olink assays to quantify 265 plasma proteins. Flow-cytometric Assay for Specific Cell-mediated Immune-response in Activated whole blood (FASCIA) was used to quantify the reactivity against Candida albicans.

Results: Overall, JAK inhibitors improved clinical symptoms of CMC, but caused side-effects in two patients. Absolute numbers of neutrophils, B and T-lymphocytes and NK-cells were sustained during JAK inhibitor baricitinib treatment. Detailed analysis of cellular subsets using CyTOF, revealed increased expression of CD45, CD52 and CD99 in NK-cells, reflecting a more functional phenotype. Conversely, monocytes and eosinophils downregulated CD16, consistent with reduced inflammation. Moreover, B- and T-cells showed increased expression of activation markers during treatment. In one patient with a remarkable clinical effect of baricitinib treatment the immune response to C. albicans increased after 7 weeks of treatment. Alterations in plasma biomarkers involved downregulation of cellular markers CXCL10, annexin A1, granzyme B, granzyme H and oncostatin M, whereas FGF21 was the only upregulated marker after 7 weeks. After 3 months, IFN-ɣ and CXCL10 were downregulated.

Conclusions: The clinical effects of JAK inhibitor treatment of CMC is promising. Several biological variables were altered during baricitinib treatment demonstrating that lymphocytes, NK-cells, monocytes and eosinophils were affected. In parallel, the cellular reactivity against C. albicans was enhanced.

Disclosure: No.

Keyword: JAK inhibitor, chronic mucocutaneous candidiasis, STAT1, mass cytometry, Olink.

PD389

PATIENT AND PARENTS UNDERSTANDING AND COMPLIANCE WITH IMMUNOGLOBULIN REPLACEMENT THERAPY FOR ANTIBODY DEFICIENCIES

POSTER DISPLAY 08: THERAPY

Eito Asano[1], Walaa Al Qudah[2], Paula Shevlin[2], Archana Herwadkar[3], Stephen Hughes[2], Shuayb Elkalifa[3], Peter Arkwright[2]
[1]University of Manchester, Medical School, Manchester, United Kingdom, [2]Royal Manchester Children's Hospital, Paediatric Allergy & Immunology, Manchester, United Kingdom, [3]Salford Royal Foundation Trust, Immunology, Manchester, United Kingdom

Background and Aims: Patient education and compliance is essential in the management of patients with antibody deficiency on immunoglobulin treatment (IGRT). This Manchester-based multi-centred service evaluation survey aimed to investigate patients and parents understanding of immunoglobulin replacement therapy.

Methods: Patients or parents of children with antibody deficiencies (XLA 36%, CVID 16%, 48% other) on IGRT from the regional paediatric (RMCH) and adult (Salford Royal) immunology centres were invited to complete an online survey by telephone call, email, or in-person during clinics. The survey explored four knowledge domains: diagnosis, treatment, prognosis, and the availability of support networks.

Results: Thirty-one patients, 52% children under 18 years old took part in the survey. 81% had their antibody deficiency diagnosed before the age of 5 years old, 75% had been on treatment (77% SCIG, 23% IVIG) for 5 years or more. Three patients approached refused to take part in the survey. 94% were having their treatment at home. 87% never or rarely missed at dose and 13% said they missed a dose once a month. 84% found the treatment easy. 94% of patients understood that IGRT protected them from bacterial sepsis and 64% understood that their life expectancy was the same as the general population. All were happy to continue with the treatment. 10% had previously been in contact with patient support groups. There were no significant differences in the views of children vs adults / patients vs parents.

Conclusions: Most patients and parents of children with antibody deficiencies on IGRT are knowledgeable and compliant with IGRT.

Disclosure: No.

Keywords: immunoglobulin replacement, patient education, antibody deficiency, patient compliance, XLA, CVID

PD390

LONG-TERM-OUTCOME of GROWTH IN PATIENTS WITH MALIGNANT INFANTILE OSTEOPETROSIS (MIOP) AND SEVERE COMBINED IMMUNODEFICIENCY (SCID) AFTER HUMAN STEM CELL TRANSPLANTATION - SINGLE-CENTRE STUDY

POSTER DISPLAY 08: THERAPY

Matthias Baiker[1], Martin Wabitsch[2], Manfred Hönig[1], Ansgar Schulz[1]
[1]University Medical Center Ulm, Department of Pediatrics And Adolescent Medicine, Pediatric Immunology, Rheumatology And Stem Cell Transplantation, Ulm, Germany, [2]University Medical Center Ulm, Department of Pediatrics And Adolescent Medicine, Pediatric Endocrinology And Diabetes, Ulm, Germany

Background and Aims: Only few long-term data are available on the physical development after HSCT in MIOP and SCID.

Methods: Retrospective data after HSCT in the first months of life (9.5 ±11.93) from n=42 (52.4% female) MIOP and n=80 (41.3% female) SCID patients were studied. All patients with MIOP and 51.3% with SCID received myeloablative conditioning. The calculation was based on z-score of WHO growth charts.

Results: The mean follow-up was 9.2 ±4.5 (MIOP) and 14.5 ±6.4 (SCID) years.
Birth measurements were normal. Patients with MIOP show predominantly percentile parallel growth one year after HSCT. z-scores of final heights were significantly reduced (-1.55 ±1.08); with no sex difference. z-score of BMI was normal (-0.26; ± 1.12). 54% patients achieve a final z-score of height below the 95%CI of the genetic target height. Patients with SCID showed impaired growth with height z-sore of -0.79 ±1.3. Patients without conditioning had a height of -0.53 ±1.23, with no significant sex difference. With conditioning, the height of female patients (-1.90 ± 1.39) and male patients (-0.44 ±1.00) differed significantly ($p<0.001$). No significant group differences could be demonstrated between different forms of SCID or the medication used for conditioning.

Conclusions: For the first time, we present longitudinal growth data of patients with MIOP after HSCT, showing a normal growth velocity. Height z-scores in SCID and MIOP patients were significantly reduced. Greatest growth retardation was seen in patients with osteopetrosis and in girls with SCID after conditioning. Larger studies are needed to clarify possible influencing factors.

Disclosure: No.

Keywords: SCID, HSCT, Long-term outcome, Growth, MIOP

PD391

CHARACTERIZATION of IMMUNOGLOBULIN G ANTIBODIES AGAINST HUMAN CRIMEAN CONGO HEMORRHAGIC FEVER VIRUS IN INTRAVENOUS IMMUNOGLOBULINS SAMPLES

POSTER DISPLAY 08: THERAPY

Aida Herrerias, Berta Pons, Núria Marzo, Maite Lopez, Salvador Grancha
Grifols, Research And Development, Barcelona, Spain

Background and Aims: Crimean Congo hemorrhagic fever (CCHF) is a tick-borne disease caused by CCHF virus (CCHFV). WHO has identified CCHFV as one of the emergent pathogens with epidemic potential. Intravenous immunoglobulins (IVIGs) contain antibody specificities against a broad spectrum of pathogens, which result from plasma donors vaccination or natural exposure to pathogens. IVIG composition could be an indicative of spread worldwide emergent pathogens. This study was aimed to evaluate the levels of IgG antibodies against CCHFV in IVIG samples obtained from plasma of different origins manufactured by Grifols.

Methods: Antibodies against antigens from CCHFV were analyzed by using two quantitative (MyBiosource and Creative Diagnostics) and one qualitative (VectoCrimean) commercial ELISA tests. In the qualitative test, samples were considered positive/negative respect to a cut-off tested in the same assay.

Results: In the quantitative tests, detectable antibody levels against CCHFV were observed in all IVIG samples (ranges: 1048.1–3133.5 U/mL and 139.6–547.3 pg/mL in 10% IVIG, and 506.6-1754.5 U/mL and 71.5-346.6 pg/mL in 5% IVIG). Plasma collected in Germany showed higher levels compared to that collected in the USA and Spain. Despite the presence of antibody evidenced by quantitative tests, qualitative test resulted negative.

Conclusions: All plasmas showed some reactivity against CCHFV. As expected, antibody levels were below those that could be detectable in plasma from individuals with active infection or recovered from the CCHF disease. This finding is in agreement with the low exposure to CCHFV expected in the evaluated donors' population.

Disclosure: The authors of the study are full-time employees of Grifols, a manufacturer of intravenous immunoglobulins.

Keywords: intravenous immunoglobulins, plasma, IgG antibodies, Crimean Congo hemorrhagic fever virus

PD392

SCHIMKE IMMUNO-OSSEOUS DYSPLASIA: ANALYSIS of A COHORT of RUSSIAN PATIENTS.

POSTER DISPLAY 08: THERAPY

Anna Mukhina[1], Yulia Rodina[1], Marina Aksenova[2], Diana Khalikova[3], Alexander Rumyantsev[3], Elena Machneva[4], Elena Skorobogatova[4], Natalia Kuzmenko[1], Vasiliy Burlakov[1], Nelly Kan[1], Anna Khoreva[1], Daria Yukhacheva[1], Viktoriya Bludova[1], Victoria Vedmedskaya[1], Dmitry Pershin[1], Igor Miloserdov[5], Mikhail Kaabak[6], Anna Shcherbina[1]
[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [2]Y.Veltischev Research Clinical Institute of Pediatrics at Pirogov Russian National Research Medical University, Nephrology, Moscow, Russian Federation, [3]Russian Children's Clinical Hospital of the N.I. Pirogov Russian National Research Medical University, Ministry of Health of Russia, Nephrology, Moscow, Russian Federation, [4]Russian Children's Clinical Hospital of the N.I. Pirogov Russian National Research Medical University, Hematopoietic Stem Cell Transplantation, Moscow, Russian Federation, [5]Shumakov Federal Research Center of Transplantology And Artificical Organs, Nephrology, Moscow, Russian Federation, [6]Medical university Reaviz, Nephrology, Moscow, Russian Federation

Background and Aims: SIOD is a rare autosomal recessive inborn error of immunity (IEI) caused by mutations in SMARCAL1 gene, with multisystem involvement, early mortality mainly due to kidney disease and infections.

Methods: We retrospectively analyzed data of 19 Russian patients with SIOD from 18 families.

Results: Genetic data was available for 15 patients. SMARCAL1 variant c.2542G>T p.Glu848Term was found in 4/15 (31%) in homozygous and in 6/15 – in the compound-heterozygous state, resulting in the allele frequency of 46,7%. In all patients studied TREC values were extremely low or absent, KREC values were normal. All patients (100%) had severe CD3+ lymphopenia. Mean CD19+ counts were 389±203cell/ul, with reduced numbers of switched B-cells (23±12cell/ul). Mean NK-cell numbers were 173±132 cell/mkl, with moderate expansion of CD56+^{bright}population (mean 18,5%) in 3 of 8 studied patients. IgG was low in 82% of patients (median 2,24g/l), IgM and IgA were normal. Six patients received kidney transplantation (mean age 6,7 years). Two of them also underwent HSCT (at 4,5 and 6 years). Overall, 10 children are currently alive with the median age 5 (2-10) years; 9 are deceased with the median age of death 8 years (5-12 years), including 5 who had HSCT/renal transplantation.

Conclusions: Our data demonstrates high rate of SMARCAL1 variant c.2542G>T in the Russian SIOD cohort and increased CD56^{bright} cell subset in some patients as reported previously. New therapeutic options including a combination of HSTC and kidney transplantation should be discussed. Newborn screening might improve outcomes in SIOD patients.

Disclosure: No.

Keywords: newborn screening, IEI, Schimke immuno-osseous dysplasia, kidney transplantaion, HSCT, TREC/KREC

PD393

A NOVEL APPROACH TO CUSTOMIZING THE FLOW PROFILE FOR THE ADMINISTRATION of SUBCUTANEOUS IMMUNOGLOBINS TO MINIMIZE OR ELIMINATE SITE REACTIONS – A CASE STUDY

POSTER DISPLAY 08: THERAPY

Melody Bullock, Andrew Sealfon, Paul Baker
Innovative Health Sciences LLC, Clinical, Chester, United States of America

Background and Aims: Site reactions have been considered “common and expected”. This system determines the dynamic equilibrium of sites for SC infusions and enables real-time flow rate adjustment. The objective of this case study was to confirm the theoretical prediction that the system could minimize or stop site reactions before they start.

Methods: An experienced SCIg patient was selected to deliver 50ml using three 26G needles. Infusion began at the highest flow rate and was monitored during the procedure. After setting controller, patient noted the volume in the syringe, and a stopwatch was started. The remaining volume was noted after 10 and 20 minutes consecutively. Actual flow rates calculated: 67ml/hr after 10mL and 50ml/hr after 20mL. After infusing 35ml, the flow rate was manually decreased to 25ml/hr and continued to the end without further impairment of flow rate or evidence of tissue saturation.

Results: Total time of infusion for 50ml was 24.26 minutes. Patient commented that he could “feel” improvement in the reduced flow rate. At the end of the infusion, when the needles were removed, there was no redness, pain, leaking or any other site sequalae.

Conclusions: To deliver the fastest flow rates possible in the least amount of time, it is possible to begin the infusion at the highest rate and manually decrease as the sites begin to fill. This new approach has the capability to revolutionize SCIg administrations providing infusions in minimal time with little or no adverse site reactions.

Disclosure: No.

Keywords: Optimizing the infusion, Selectable Rate Flow Control, Dynamic Equilibrium, Pain-free infusions, Custom Flow Control, Subcutaneous Immunoglobulin Infusion

PD394

THE RESPIRATORY INFECTIOUS BURDEN of A LARGE COHORT of ANTIBODY DEFICIENT PATIENTS ON IMMUNOGLOBULIN REPLACEMENT THERAPY

POSTER DISPLAY 08: THERAPY

Jonathan Cutajar[1], Effrossyni Gkrania-Klotsas[2], Andres Floto[3], Anita Chandra[4], Ania Manson[4], Clare Sander[5], Dinakantha Kumararatne[4]
[1]Wycombe Hospital, Department of Medicine, High Wycombe, United Kingdom, [2]Addenbrooke's Hospital, Infectious Diseases, Cambridge, United Kingdom, [3]Royal Papworth Hospital, Cambridge Centre For Lung Infection, Cambridge, United Kingdom, [4]Addenbrooke's Hospital, Clinical Immunology, Cambridge, United Kingdom, [5]Addenbrooke's Hospital, Respiratory Medicine, Cambridge, United Kingdom

Background and Aims: Antibody deficiencies result in reduced immunoglobulin levels and function, increasing susceptibility to, primarily, bacterial infection. Primary antibody deficiencies (PAD) comprise of intrinsic defects in B cell physiology, often due to inherited errors. Haematological malignancies or B cell suppressive therapy, used in the treatment of autoimmune diseases, are mostly responsible for secondary antibody deficiency (SAD). Although immunoglobulin replacement therapy (IGRT) reduces infectious burden in antibody deficiency, respiratory tract infections remain a significant health burden in these patients. Objective: To review the respiratory infectious burden, and the impact of lung pathologies and gastro-oesophageal reflux disease (GORD) on this, in PAD and SAD patients.

Methods: The electronic medical records of 231 patients on IGRT at a tertiary referral centre, from 26/10/2014 to 19/02/2021, were reviewed to determine microbial isolates from sputum samples. The prevalence of common lung pathologies and GORD in these patients was collected.

Results: Haemophilus species and Pseudomonas species were identified in 30.2% and 21.4% of sputum samples showing growth respectively, representing a large segment of the infectious burden; filamentous fungal and mycobacterial infections were rare. Lung pathology increased the proportion of patients with Pseudomonas, Candida, Klebsiella and Stenotrophomonas species isolated in their sputum, and GORD increased the proportion with Enterobacter and Candida species isolated.

Conclusions: Significant bacterial lower respiratory infection burden remains in PAD and SAD despite IGRT. Lung pathology and GORD are associated with statistically significant changes to the microbiome of patients' sputum samples. Specialist respiratory medicine input is indicated to optimise respiratory outcomes in antibody deficiency patients.

Disclosure: No.

Keywords: immunoglobulin replacement therapy, antibody deficiency, Lung pathology, Gastro-oesophageal reflux disease, Microbiology, Sputum culture

PD395

EXPERIENCE IN PATIENTS WITH INBORN ERRORS of IMMUNITY (IEI) WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

POSTER DISPLAY 08: THERAPY

Amanda Sobrinho[1], Amanda Lima[1], Barbara Ramos[1], Amanda Machado[1], Larissa Said[1], Luiza Schmid[1], Juliana Folloni[2], Antonio Condino-Neto[3], Dirceu Solé[1], Carolina Sanchez Aranda[1]
[1]Federal University of São Paulo, Division of Allergy, Clinical Immunology And Rheumatology - Department of Pediatrics, São Paulo, Brazil, [2]Institute for the Treatment of Childhood Cancer, Bone Marrow Transplant, São Paulo, Brazil, [3]University of São Paulo, Institute of Biomedical Sciences, Department of Immunology., São Paulo, Brazil

Background and Aims: IEI corresponds to a group of heterogeneous diseases with more than 400 identified genetic defects. HSCT is currently the only well-established curative treatment for patients with severe forms of EII such as Severe Combined Immunodeficiency (SCID). This study aims to analyze the outcome of patients with IIE referred for HSCT.

Methods: A retrospective cross-sectional study based on an analysis of medical records at a referral center in Brazil from January 2020 to May 2022.

Results: Nine patients were referred for HSCT (five boys; 55.5%) aged 0 to 16y. Six patients with SCID (ADA, JAK3, NOD2, ILR7), one Leaky SCID (RAG1), one Wiskott Aldrich Syndrome (WAS), and one XIAP. Eight underwent haploidentical related transplantation and one with a fully identical donor. of the nine patients, four (44%) died, all over two years of age (one in conditioning and three after transplantation). Three (33%) patients were discharged from the hospital and are in good clinical condition (performed before the age of two), and two were still being hospitalized in the immediate post. The conditionings performed were: Thymoglobulin plus Fludarabine plus Busulfan (FB) or FB or Alemtuzumab plus Fludarabine plus Melphalan. Among six SCID patients, three were referred before six months of life, with diagnoses made at 1 month of life by NBS - two of them have already been discharged, and one remains in hospital with bone marrow engraftment.

Conclusions: It is correct to say that the survival of patients with IEI submitted to HSCT was higher the earlier this treatment was performed.

Disclosure: No.

Keywords: Inborn errors of immunity, Hematopoietic stem cell transplantation, Severe combined immunodeficiency, Wiskott-Aldrich Syndrome, Leaky SCID, XIAP

PD396

SAFETY, TOLERABILITY AND IMMUNOGENICITY of FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN IN PEDIATRIC PATIENTS WITH PRIMARY IMMUNODEFICIENCIES: FINAL RESULTS FROM A EUROPEAN POST-AUTHORIZATION STUDY

POSTER DISPLAY 08: THERAPY

Peter Ciznar[1], Marion Roderick[2], Helena Schneiderova[3], Milos Jesenak[4], Gergely Krivan[5], Nicholas Brodszki[6], Stephen Jolles[7], Charles Atisso[8], Katharina Fielhauer[9], Shumyla Saeed-Khawaja[10], Barbara Mccoy[11], Leman Yel[12]
[1]Children's University Hospital Bratislava, National Institute of Children's Diseases, Clinical Immunology Service, Pediatric Department, Bratislava, Slovak Republic, [2]Bristol Royal Hospital for Children, Department of Paediatric Immunology, Bristol, United Kingdom, [3]Faculty of Medicine, Masaryk University, Department of Pediatrics, Brno, Czech Republic, [4]Jessenius Faculty of Medicine, Comenius University in Bratislava, Department of Pediatrics, Martin, Slovak Republic, [5]Szent László Hospital, Department of Pediatric Hematology & Stem Cell Transplantation, Budapest, Hungary, [6]Skane University Hospital, Department of Pediatric Onocology/hematology/immunology, Lund, Sweden, [7]University Hospital of Wales, Immunodeficiency Center For Wales, Cardiff, United Kingdom, [8]Takeda Development Center Americas, Inc., Pharmacometrics & Pre-clinical Biostatistics, Cambridge, United States of America, [9]Baxalta Innovations GmbH, a Takeda company, Clinical Medicine Ig/pid, Vienna, Austria, [10]Takeda Development Center Americas, Inc., Clinical Medicine Ig/pid, Cambridge, United States of America, [11]Baxalta Innovations GmbH, a Takeda company, Pdt Clinical Medicine, Vienna, Austria, [12]Takeda Development Center Americas, Inc., Pdt Bu Research And Development, Cambridge, United States of America

Background and Aims: We assessed the safety, tolerability and immunogenicity of facilitated subcutaneous immunoglobulin (dual-vial unit of human immunoglobulin 10% and recombinant human hyaluronidase [rHuPH20]; fSCIG) in European pediatric patients with primary immunodeficiencies (PID).

Methods: Patients aged 2 to <18 years with PID who had received immunoglobulin G (IgG) therapy for ≥3 months were eligible for this phase 4, post-authorization, prospective, non-controlled, multicenter (n=16) study (NCT03116347). New fSCIG starters received a fSCIG dose ramp-up for ≤6 weeks (Epoch 1), before receiving fSCIG for ≤3 years (Epoch 2); pre-treated patients entered Epoch 2 directly. fSCIG safety (adverse events [AEs]), tolerability, immunogenicity, administration and IgG trough-level data were summarized using descriptive statistics; AEs were categorized using the Medical Dictionary for Regulatory Activities.

Results: Overall, 42 patients were enrolled (median [range] age 11.5 [3–17] years, 81% male; 23 new starters, 19 pre-treated). of 49 related, non-infectious, treatment-emergent AEs (TEAEs) reported in 15 patients, 87.8% were mild. One patient reported two severe related TEAEs (infusion site pain, emotional distress); no serious treatment-related AEs were reported. No patients developed binding anti-rHuPH20 antibodies (defined as titer ≥160). Patients received a median of 1.2 infusions/month; median infusion volume was 120.0 mL/site and median dose across all patients was 0.13 (Epoch 1) and 0.12 g/kg/week (Epoch 2). Median serum IgG trough levels were 8.9 g/L at baseline and 8.7 g/L at Epoch 2 Month 12.

Conclusions: These data support the long-term safety of fSCIG in children with PID. Funding: Baxalta US Inc., a Takeda company (study); Takeda Development Center Americas, Inc. (writing support).

Disclosure: Peter Čižnár has received speaker honoraria from Ewopharma and Takeda. Marion Roderick, Helen Schneiderova and Gergely Kriván have nothing to disclose. Miloš Jeseňák has received honoraria, consultancy and speaker fees from ALK, CSL Behring, Ewopharma, GS

Keywords: Facilitated subcutaneous immunoglobulin application, pediatrics, Primary Immunodeficiency Diseases, Recombinant human hyaluronidase, Safety, immunoglobulin replacement therapy

PD397

REAL-WORLD UTILIZATION, SAFETY AND PATIENT EXPERIENCE of 20% SUBCUTANEOUS IMMUNOGLOBULIN IN PATIENTS WITH PRIMARY IMMUNODEFICIENCIES: FINAL DATA FROM THE CORE STUDY

POSTER DISPLAY 08: THERAPY

Maria Fasshauer[1], Michael Borte[1], Michaela Bitzenhofer[2], Christine Pausch[3], David Pittrow[4], Michelle Park[5], Andre Gladiator[6], Peter Jandus[7]
[1]Hospital for Children & Adolescents, St. Georg Hospital, Leipzig, Academic Teaching Hospital of The University of Leipzig, Immunodeficiency Center Leipzig (idcl),leipzig, Leipzig, Germany, [2]University Hospital of Berne, Division of Allergy And Clinical Immunology, Berne, Switzerland, [3]GWT-TUD GmbH, Clinical Research/pharmacoepidemiology, Dresden, Germany, [4]GWT-TUD GmbH, Innovationszentrum Real-world Evidence, Dresden, Germany, [5]Takeda Development Center Americas, Inc., Pdt Medical Affairs, Cambridge, United States of America, [6]Takeda Pharmaceuticals International AG, Pdt Medical Affairs, Zurich, Switzerland, [7]University Hospitals and Medical Faculty, Division of Immunology And Allergy, Department of Medicine, Geneva, Switzerland

Background and Aims: CORE aimed to provide a detailed understanding of real-world immune globulin subcutaneous (human) 20% solution (Ig20Gly) utilization in patients with primary immunodeficiencies (PID) in Germany and Switzerland.

Methods: Patients with PID receiving a stable dose of any subcutaneous immunoglobulin for ≥3 months before enrollment were eligible for this multicenter (n=5), phase 4, non-interventional, prospective, longitudinal cohort study (DRKS00014562). Besides baseline demographics and clinical characteristics, Ig20Gly utilization and safety data, and patient-reported outcomes (Life Quality Index/Treatment Satisfaction Questionnaire for Medication) were collected at baseline, 6 and 12 months. Statistical analysis was descriptive.

Results: Overall, 36 patients provided data at baseline (69.4% female; mean age: 41.6 years [range: 7–78 years]). Twenty-three and 26 patients attended 6- and 12-month visits, respectively; 16 attended all three visits. One patient withdrew consent before 6-month follow-up. Median maximum infusion rates at baseline, 6 and 12 months were 26.7, 24.5 and 40.0 mL/h, respectively (range: 10–60 mL/h). Infusion and dosing parameters remained consistent across time points: patients used a median of two infusion sites; all but one infused at home and most self-administered Ig20Gly (80.8–83.3%) at once-weekly intervals (69.2–73.9%). During follow-up, 10 adverse events were reported: none was rated serious; two were considered probably related to Ig20Gly. Total patient-reported outcome scores remained high throughout the study.

Conclusions: This study provides real-world evidence of the feasibility and tolerability of Ig20Gly infusions, at mostly weekly intervals, over 1 year in patients with PID. Funding: Baxalta Innovations GmbH, a Takeda company (study); Takeda Development Center Americas, Inc. (writing support).

Disclosure: Michael Borte’s institution has received research grant support from Baxalta, CSL Behring and Octapharma; and he has participated in advisory boards for CSL Behring, Octapharma and Shire. Maria Fasshauer has participated in advisory boards for Baxalta/Shi

Keywords: Ig20Gly, immunoglobulin replacement therapy, primary immunodeficiencies, Real-world, Subcutaneous immunoglobulin

PD398

IKAROS- GLIDING THROUGH AN EASY TRANSPLANT COURSE

POSTER DISPLAY 08: THERAPY

Julia Körholz[1], Maria Prazenicova[2], Björn Lange[2], Oliver Tiebel[3], Eva Jacobsen[4], Joachim Roesler[1], Julia Hauer[5], Catharina Schuetz[1]
[1]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Pediatric Immunology, Dresden, Germany, [2]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Pediatrics, Dresden, Germany, [3]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Laboratory Medicine And Clinical Chemistry, Dresden, Germany, [4]University Medical Center Ulm, Germany, Department of Pediatrics And Adolescent Medicine, Ulm, Germany, [5]München Klinik, Department of Pediatrics, München, Germany

Background and Aims: Inborn errors of immunity (IEI) manifest with susceptibility to infection, but may also present with autoinflammation, au[1]toimmunity or malignancies. In certain IEI hematopoietic stem cell transplant (HSCT) is a curative therapeutic option. Choosing the optimal point in time and weighing the benefit for the patient is challenging due to the rareness of single IEI entities. IKZF1 germline variants (IKAROS disease) are associated with different phenotypes: haploinsufficiency is predominantly linked to CVID-like phenotypes, dominant negative forms are predicted to cause CID like phenotypes, dimerization deficiency predominantly generates hematologic dysfunction. Only few patients with IKAROS disease have undergone HSCT so far.

Methods: We performed trio WES revealing a de novo pathological variant in IKZF1. The patient was transplanted with stem cells (HSCT) from his HLA-identical sister. Conditioning comprised Thiotepa, Fludarabin, Treosulfan.

Results: The 13-year old patient presented with chronic recurrent upper airway infections, osteomyelitis and streptococcal bacteremia at age 7. Diagnostic workup revealed absent immunoglobulin titers and B- and T-cellular maturation dysfunction. A pathological variant in IKZF1 was located in the DNA-binding domain of the encoded protein leading to haploinsufficiency. The boy is perfectly well 20 months after uneventful HSCT and off immunoglobulin substitution.

Conclusions: Clinical presentation of IKAROS is highly variable. Considering a possible poor outcome of the underlying disease including lymphoma, curative HSCT was performed. We confirm previous reports, and suggest HSCT as curative treatment option for selected IKAROS patients.

Disclosure: No.

Keywords: HSCT, IKAROS, IKZF1, CID

PD399

OUTCOMES of DIFFERENT THERAPEUTIC APPROACHES FOR ADA-SCID: A SINGLE CENTER EXPERIENCE

POSTER DISPLAY 08: THERAPY

Andrea González-Torbay[1], Elisabet Matas Pérez[1], Ricardo Cuesta Martín De La Cámara[1], Laura Miguel Berenguel[1], María Bravo García-Morato[1,2,3], Carla Gianelli[1,3], Teresa Del Rosal Rabes[4], Ana Méndez Echevarría[4], Claire Booth[5,6], Yadira Bravo Gallego[2,3,7], Eduardo López Granados[1,2,3], Rebeca Rodríguez Pena[1,2,3]
[1]La Paz University Hospital, Department of Immunology, Madrid, Spain, [2]Rare Diseases Network Research Center, Ciberer U767, Madrid, Spain, [3]Hospital La Paz Institute for Health Research (IdiPAZ), Lymphocyte Pathophysiology In Immunodeficiencies Group, Madrid, Spain, [4]La Paz University Hospital, Department of Pediatric Infectious Diseases, Madrid, Spain, [5]University College London, Division of Infection And Immunity, London, United Kingdom, [6]Great Ormond Street Hospital, Department of Immunology & Gene Therapy, London, United Kingdom, [7]ERN Transplantchild, Medical Advisor And Clinical Audits. Wg Coordinator, Madrid, Spain

Background and Aims: Adenosine deaminase (ADA) is a key enzyme in purine metabolism and its deficiency can lead to a T-B-NK- severe combined immunodeficiency (ADA-SCID). There are currently three therapeutic options available for ADA-SCID: hematopoietic stem cell transplantation (HSCT), gene therapy (GT) and enzyme replacement therapy (ERT). The first two are intended to be curative, while ERT partially corrects the deficiency. The aim of this review is to describe our single center experience.

Methods: We performed a retrospective analysis of the six patients with ADA-SCID followed at La Paz University Hospital since 1998.

Results: All patients presented with classical SCID symptoms in the first six months of life. The p.Leu107Pro variant was found in five patients (two were homozygous). Three of them underwent HSCT (diagnosed in 2002, 2016, and 2017); the others had no optimal donors found. Two are still on ERT therapy (since 2003 and 2005, respectively), and one (diagnosed in 2018) was included in a gene therapy trial at Great Ormond Street Hospital. Absence of infectious susceptibility has been achieved by all, but complete immunologic reconstitution is found just for 2 HSCT and the GT patients. Neurological symptoms are the main concern for four patients, regardless of the treatment option.

Conclusions: ADA-SCID is the most common form of autosomal recessive SCID. Fortunately, definitive and bridge therapeutic options are available and have allowed 100% survival in our series. Our current main challenges are the management of patients on long-term ERT and the address of the neurological manifestations present in most of our patients.

Disclosure: No.

Keywords: adenosine deaminase deficiency, ADA-SCID, enzyme replacement therapy, Severe combined immunodeficiency, HSCT, gene therapy

PD400

THE VERY FIRST PATIENT of IL-21 DEFICIENCY SUCCESSFULLY TREATED WITH HEMATOPOETIC STEM CELL TRANSPLANTATION

POSTER DISPLAY 08: THERAPY

Nazli Deveci Demirbas[1], Sule Haskologlu[1], Avniye Baskin[1], Hasret Erkmen[1], Kaan Boztug[2], Figen Dogu[1], Aydan Ikinciogullari[1]
[1]Ankara University School of Medicine, Department of Pediatric Immunology And Allergy, Ankara, Turkey, [2]Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, Department of Genetics, Vienna, Austria

Background and Aims: IL-21 has emerged as a critical cytokine that regulates multiple immune system arms. IL-21 deficiency is a novel primary immunodeficiency, which associates a CVID-like B-cell deficiency with early-onset IBD and was first described with this patient in 2014.

Methods: Here, we present the successful hematopoietic stem cell transplantation performed the first case of IL-21deficiency in the world.

Results: The 18-year-old male patient was born of consanguineous parents. Two siblings died of severe diarrhea before reaching the age of one year. The patient was admitted to the hospital at the age of two months with suspicion of primary immunodeficiency due to recurrent respiratory infections, chronic diarrhea, and failure to thrive. Immunological testing revealed the CVID-like immunodeficiency phenotype. IVIG replacement therapy and trimethoprim-sulfamethoxazole prophylaxis was started then a homozygous mutation in the IL-21 gene was discovered. HSCT was performed in 10/10 HLA matched sibling donor with reduced toxicity regimen consisting of fludarabine, treosulfan, thiotepa and received methotrexate and tacrolimus as GvHD prophylaxis. Myeloid and trombocyte engraftment were achieved at +14 and +22 days, respectively. Except for the pulmonary hemorrhage, which was treated with prednisolone, no other complications occurred. The patient is now at +5 months after transplantation with full donor chimerism and is in good condition without receiving any immunosuppressive treatments.

Conclusions: As our knowledge, this is the first patient with IL-21 deficiency who was successfully treated by HSCT.

Disclosure: No.

Keyword: IL-21 deficiency, immunodeficiency, HSCT

PD401

TREATMENT of CAMPYLOBACTER ENTERITIS IN COMMON VARIABLE IMMUNODEFICIENCY - A MONOCENTRIC EXPERIENCE

POSTER DISPLAY 08: THERAPY

Sigune Goldacker[1], Lucia Peirano.[2], Bodo Grimbacher[3], Valentina Strohmeier[3], Klaus Warnatz[4]
[1]Medical Center – University of Freiburg, Faculty of Medicine, Department of Rheumatology And Clinical Immunology,, Freiburg, Germany, [2]Hospital Italiano Buenos Aires- CIC BEZRODNIK., Internal Medicine- Immunology., Buenos Aires., Argentina, [3]Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany, [4]Institute for Immunodeficiency, Center for Chronic Immunodeficiency (CCI), Faculty of Medicine, Medical Center - University of Freiburg, Department of Rheumatology And Clinical Immunology, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

Background and Aims: Campylobacter enteritis is a well-known infection amongst patients with common variable immunodeficiency (CVID). Due to the underlying immunodeficiency, antibiotic treatment usually is recommended. However, persistent or chronic-recurrent courses are common and require solid diagnostics in order to direct antibiotic stewardship especially in case of repetitive treatment. Especially in patients with concomitant autoimmune enteropathy with need for immunosuppression treatment strategies to achieve sustained remission of the infection are needed.

Methods: Here, we report a retrospective analysis of clinical records from our adult outpatient clinic from 2015 until 2020.

Results: 29 patients had a history of Campylobacter enteritis. Four of these had no recorded antibiotic treatment with assumed self-limited disease in three cases. 11 out of 12 patients who received treatment with macrolides or quinolones once remained without relapse over a median observation time of 45 months, one patient with recurrence was not retreated because of lack of symptoms. 13 patients suffered from recurrent infection. Recurrent standard treatment finally achieved long-lasting remission in only three patients and two additional patients after either prolonged therapy with oral erythromycin or additional oral gentamycin. In 7 patients intravenous application of ertapenem or imipenem was introduced because of severe symptoms or short relapse-free intervals. All patients responded and remained without relapse for a median of 24 months of follow up.

Conclusions: Our observations support the use of penems in recurrent Campylobacter infection in CVID patients refractory to standard therapy.

Disclosure: No.

Keywords: CVID, Campylobacter, penem, infectious enteritis

PD402

QUALITY of LIFE EVALUATION IN 26 SAUDI ARABIAN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES RECEIVING SUBCUTANEOUS IGG INFUSIONS AT HOME

POSTER DISPLAY 08: THERAPY

Bandar Al Saud[1], Nora Alrumayyan[2], Areej Alfattani[3], Sawsan Abu Awwad[4], Dema Al Saud[3], Reem Mohammed[1], Sultan Albuhairi[1], Sahar Elshorbagi[1], Sakra S. Balhareth[5], Hasan Al-Dhekri[1], Rand Arnaout[1], Edward De Vol[3], Hamoud Al-Mousa[1]
[1]King Faisal Specialist Hospital & Research Centre, Pediatric Allergy And Immunology, Riyadh, Saudi Arabia, [2]King Faisal Specialist Hospital & Research Centre, Pediatric Allergy And Immunology, RIYADH, Saudi Arabia, [3]King Faisal Specialist Hospital & Research Centre, Department of Biostatistics, Epidemiology And Scientific Computing Department, RIYADH, Saudi Arabia, [4]King Faisal Specialist Hospital & Research Centre, Nursing Affairs, RIYADH, Saudi Arabia, [5]King Faisal Specialist Hospital & Research Centre, Pharmaceutical Care Division, Riyadh, Saudi Arabia

Background and Aims: Subcutaneous immunoglobulin (SCIG) home infusion is widely used as an alternative to intravenous immunoglobulin (IVIG). The aim of this study is to determine the quality of life (QoL) in primary immunodeficiency patient's after switching to home based SCIG.

Methods: QoL was determined using a validated Child Health Questionnaire (CHQ) (HealthActCHQ, Boston, MA, USA) in Arabic at baseline, 3 and 6 months after switching from IVIG to SCIG.

Results: From July 2018 to August 2021, 26 patients were recruited: 15 females and 11 males. The median age was 5 years old (Range 0 – 15 years). The patients' diagnoses were 11 severe combined immunodeficiency, 3 combined immunodeficiency, 3 agammaglobulinemia, 2 Omenn syndrome, 2 immunodysregulation, 2 hyper-IgE syndrome, 1 common variable immunodeficiency, 1 bare lymphocyte syndrome, and 1 chronic granulomatous disease. The median time on IVIG was 57 months (Range 3 – 125 months). The baseline mean serum IgG trough levels was 8.8 mg/dL ± 2.1. The mean serum IgG level was significantly higher on SCIG at 11.7 ± 2.3 and 11.7 ± 2.5 at 3 months and 6 months respectively. The QoL score showed a significant improvement in the child's global health at 3 and 6 months compared to baseline (P-value 0.001 and 0.001 respectively) and a significant improvement in the child general health in the 3 and 6 months compared to the baseline (P-value 0.01 and 0.03 respectively).

Conclusions: First study in an Arab population showing improvement in the QoL for PID patients after switching from hospital based IVIG to home based SCIG.

Disclosure: No.

Keywords: immunoglobulin replacement therapy, hypogammaglobulinemia, Intravenous immunoglobulin replacement, Primary Antibody Deficiency, Severe combined immunodeficiency, Subcutaneous immunoglobulin replacement

PD403

HAPLOIDENTICAL STEM CELL TRANSPLANTATION WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE IN A SEVERE COMBINED IMMUNE DEFICIENCY PATIENT: THE FIRST MOROCCAN CASE

POSTER DISPLAY 08: THERAPY

Ibtihal Benhsaien[1], Maria El Kababri[2], Asmaa Quessar[3], Jalila El Bakouri[4,5], Naima Elhafidi[6], Hind Ouair[7], Fatima Ailal[7,8], Laila Hssissen[2], Ahmed Aziz Bousfiha[8,9]
[1]Ibn Rochd hospital university, faculty of medecine of Casablanca, Hassan II university, Pediatrics, casablanca, Morocco, [2]pediatric hemato-oncolgy center (SHOP), Children hospital, Ibn Sina hospital university, Pediatrics, casablanca, Morocco, [3]Ibn Rochd hospital university, Hematology, casablanca, Morocco, [4]Faculty of Medicine and pharmacy of Casablanca, Research Laboratory In Clinical Immunology And Inflammation (licia), Casablanca, Morocco, [5]IBN Rochd University Hospital,, Immunology Laboratory, Casablanca, Morocco, [6]children hospital, Ibn Sina university hospital, Pediatrics, rabat, Morocco, [7]Faculty of Medecine and Pharmacy, University Hassan II, Casablanca, Laboratory of Clinical Immunology, Inflammation And Allergy (licia), CASABLANCA, Morocco, [8]Abderrahim El Harouchi Children Hospital, University Hospital Center Ibn Rochd, Casablanca, Morocco., Clinical Immunology Unit, Department of Infectious Diseases, Casablanca, Morocco, [9]Faculty of Medicine and pharmacy of Casablanca, 1) research Laboratory In Clinical Immunology And Inflammation (licia), Casablanca, Morocco

Background and Aims: Haploidentical stem cell transplantation (haplo SCT) has emerged as an acceptable alternative to matched family donor transplantation for children diagnosed to have primary immune deficiency disorders (PIDs). We present the first Moroccan case of unmanipulated T cell replete haplo SCTs with post-transplant cyclophosphamide (PTCy).We present the first Moroccan case of unmanipulated T cell replete haplo SCTs with post-transplant cyclophosphamide (PTCy) in children diagnosed to have SCID (severe combined immunodeficiency) . The diagnosis was made at the age of 8 months when the baby was admitted for severe pneumonia and was confirmed by immunology work up. The genetic study shows homozygous mutation of Jak3 gene. The donor was the mother and the source of stem cells was bone marrow. The conditioning regimen was based on busulfan and fludarabin and GvHD prophylaxis consist on PTCy, ciclosporine and mecophenolate mofetil (MMF).

Methods: The donor was the mother and the source of stem cells was bone marrow. The conditioning regimen was based on busulfan and fludarabin and GvHD prophylaxis consist on PTCy, ciclosporine and mecophenolate mofetil (MMF).

Results: Engraftment occurred by day 12 post hematopoietic stem cell transplantation. The patient is 3 months post-transplant with no complication either GvH or infection.

Conclusions: . In resource limited settings, PTCy has the potential to provide a cost-effective advantage in terms of accessibility of this curative procedure among children with PIDs especially in SCID when the transplant is urgent .

Disclosure: No.

Keyword: primary immune deficiency . haploidenticel post-transplant cyclophospha

PD404

HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN AS A PROTOCOL FOR LONG-TERM SURVIVAL AFTER LUNG TRANSPLANTATION IN COMMON VARIABLE IMMUNODEFICIENCY

POSTER DISPLAY 08: THERAPY

Ana Paulina Moncayo Muñoz[1], María Mejía[2], Mercedes Díaz-Luna[1], Javier Carbone[3]
[1]Hospital General Universitario Gregorio Marañón, Immunology, Madrid, Spain, [2]Hospital General universitario Gregorio Marañón, Immunology, Madrid, Spain, [3]Hospital General Universitario Gregorio Marañon, Immunology, Madrid, Spain

Background and Aims: HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN AS A PROTOCOL FOR LONG-TERM SURVIVAL AFTER LUNG TRANSPLANTATION IN COMMON VARIABLE IMMUNODEFICIENCY Objetive: Describe the case of a CVID patient treated with a high-dose IVIG protocol before and after lung transplantation (LT).

Methods: High-dose IVIG protocol: Reconditioning phase before the LT: 1.2g/kg/month. Immediate post-LT phase (first month): 2.3g/kg/month. Maintenance period after LT (from the first month after LT until December 2009): 1.1g / kg / month. Long-term maintenance period after 5 years of LT until now: 650mg - 1g / kg / month. The doses were calculated assuming the patient's high IgG catabolism, expecting to have IgG levels over 1000mg/dL of the time.

Results: A 56-year-old male who was diagnosed in 1988 with CVID. CVID related complications: upper and lower respiratory tract infections, toxoplasmosis, possible tuberculosis, bronchiectasis with destruction of lung parenchyma, severe respiratory failure, chronic leukopenia and thrombopenia, chronic liver-associated disease, lymphoid hyperplasia (with splenomegaly > 20 cm). He evolved into terminal pulmonary disease with 24-hour oxygen requirement and prognosis of 6 months of life. He had a double lung transplant in 2004 in the Puerta de Hierro-Majadahonda Hospital in Madrid. 18 years after LT, he still receives 30g of IVIG every 21 days. The patient is still having a good quality of life, with independency for all activities.

Conclusions: The presentation of this case report is relevant because the intensification of IVIG therapy could be one of the keys for the successful and prolonged survival and acceptable quality of life in a CVID patient after LT.

Disclosure: No.

Keywords: Intravenous immunoglobulin, lung transplantation, Common variable immunodeficiency, high-dose IVIG protocol

PD405

MONOMAC SYNDROME PATIENT WITH NOVEL GATA2 MUTATION SUCCESSFULLY TREATED BY ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION- A CASE REPORT

POSTER DISPLAY 08: THERAPY

Ewa Karakulska-Prystupiuk[1], Ewa Bernatowska[2], Piotr Boguradzki[1], Grzegorz Basak[1], Wiesław Jędrzejczak[1]
[1]Medical University of Warsaw, Department of Hematology, Transplantation And Internal Medicine, Warszawa, Poland, [2]Children Memorial Health Institute, Department of Immunology, Warszawa, Poland

Background and Aims: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) represents the only curative therapy in patients with GATA2 mutation. There are no published studies regarding the fertility of transplanted males with GATA2 deficiency. Here, we report a case of an allo-HSCT performed on a man with this syndrome.

Methods: This is a retrospective case report. The patient gave informed consent.

Results: The proband, a 32-year-old man with de novo mutation showed mutation of the GATA2 gene. Target DNA sequencing identified a novel Gata2 (NM_032638.4):N/c.1075_1081delTTATGGC mutation. He presented congenital hearing loss and history of recurrent infections, with granulomatous lung disease, mediastinal and abdominal lymphadenopathy, hepatosplenomegaly, cholestatic jaundice, diabetes, and pancytopenia with monocytopenia. Myelodysplastic syndrome criteria were not met. Allo-HSCT was performed from the HLA-identical, healthy brother after a reduced-intensity conditioning regimen with fludarabine and cyclophosphamide. The post-transplant course was complicated by the occurrence of moderate veno-occlusive disease. Transplant engraftment was achieved on day 30 and complete chimerism on 49 days after allo- HSCT. Complete hematological recovery and normal counts of lymphocyte subpopulations were obtained gradually over 19 months. Currently, 4.5 years after allo- HSCT, he remains in complete chimerism and has no recurrent infections. He is still receiving immunosuppressive therapy (tacrolimus) because of hepatitis, possibly related to chronic GvHD (liver biopsy was non-conclusive). This year he became father of a son.

Conclusions: Allo-HSCT provides a cure for a novel GATA 2 mutation. Its success has shown that reduced intensity conditioning is sufficient for engraftment and is not associated with loss of fertility.

Disclosure: No.

Keywords: allogeneic hematopoietic stem cell transplantation, Gata2 mutation, primary deficiency, monoMAC syndrome

PD406

CLINICAL CONDITION DETERIORATION IN A LIKELY DOCK8 DEFICIENCY IRANIAN PATIENT WHO UNDERWENT A DONOR RELATED-HSCT COMPLICATED IN CHRONIC GRAFT VERSUS HOST DISEASE (GVHD)

POSTER DISPLAY 08: THERAPY

Marcelo Teocchi, Irene Ridolfi, Luisa Brussino
AO Ordine Mauriziano Hospital, Allergy And Clinical Immunology Unit, Turin, Italy

Background and Aims: DOCK8 mutations are associated with autosomal recessive hyper IgE syndrome (AR-HIES), an extremely rare syndrome showing highly elevated serum IgE levels, recurrent pneumonia and staphylococcal skin abscesses. This syndrome is further characterized by extreme hypereosinophilia; viral infections susceptibility; central nervous system abnormalities; T-cell defects; and a high mortality.

Methods: We present the case of a 29-year-old Iranian man. Data were acquired from medical records. Diagnostic reasoning was established on patient's story, clinical features and suggestive immunologic laboratory findings but without a confirmatory genetic analysis.

Results: Patient's childhood was distinguished by several skin infections, two episodes of pneumonia requiring hospitalization, severe meningitis, and a chickenpox infection. He also had basal (mouth and nose) and squamous (scrotum) cell carcinomas. Related donor HSCT was performed at the age of 20 years old. Resolution of clinical manifestations persisted for about 16 months, when a lichenoid eruption-associated chronic GVHD was diagnosed and treated with four sessions of IVIG. Currently, he has asthma, onychomycosis, repeated conjunctivitis, ulcers (lower lip), gingivitis, xerophthalmia and xerostomia. Spirometry reveals severe airway obstruction and alveolar hyperinflation with a slight DLCO reduction. HRTC shows bronchiectasis. Lymphocytes and switched memory B-cells count at normal values, but CD8 T-cells are slightly increased, transitional B-cells slightly reduced (0.6%), and marginal memory B-cells decreased (1.6%). IgE level is 1156 UI/mL.

Conclusions: Although our patient has benefited from HSCT, his condition has required constant screening for infections, neoplasms and autoimmunity. His molecular diagnosis is being studied and, considering his deteriorating clinical situation, a more resolute treatment will be needed.

Disclosure: No.

Keywords: Graft versus Host Disease, Job syndrome, Immunoglobulin E, Hematopoietic stem cell transplantation

PD407

MATERNAL T CELL INTERFERS IN HLA TYPING IN SEVERE COMBINED IMMUNODEFICIENCY

POSTER DISPLAY 08: THERAPY

Ibtihal Benhsaien[1], Jalila El Bakouri[2], Fatima Ailal[3], Ahmed Aziz Bousfiha[4]
[1]Ibn Rochd hospital university, faculty of medecine of Casablanca, Hassan II university, Pediatrics, casablanca, Morocco, [2]IBN Rochd University Hospital,, Immunology Laboratory, Casablanca, Morocco, [3]Abderrahim El Harouchi Children Hospital, University Hospital Center Ibn Rochd, Casablanca, Morocco., Clinical Immunology Unit, Department of Infectious Diseases, Casablanca, Morocco, [4]Faculty of Medicine and pharmacy of Casablanca, 1) research Laboratory In Clinical Immunology And Inflammation (licia), Casablanca, Morocco

Background and Aims: Human leukocyte antigens (HLA) typing is an important step of the laboratory assessment. Maternal T cell engreftment can interfere with HLA typing then be a challenging task.

Methods: The aim of the study is to report the interference of human leukocyteantigen (HLA) typing by engraftment of maternal T cells in a two infants diagnosed as severe combined immunodeficiency (SCID) awaiting for hematopoietic stem cell transplantation (HSCT). HLA typing was performed with sequence-specific oligonucleotide (SSO) then on molecular biology in a second time on peripheral blood leukocytes from the patient and peripheral blood leukocytes from the parents and their families.

Results: First case: a boy of 6 month-old was diagnosed SCID T-B+NK- with T cell maternal engraftment based on the presence of 40% lymphocyte (XX) . Second case: A girl of 8 months diagnosed as a SCID T-B-NK+ with high rate of memory T cell (CD45RO). HLA typing of the patients were unable to resolve the genotypes at HLA loci due to a hybridization pattern that could not be accounted for by one or two alleles. This ambiguity is due probably to the presence of maternal T cell. An HLA typing from the child's buccal cells was performed in order to solve this interference problem. Effectively,

Conclusions: Maternal T-cell engraftment may interfere with HLA typing in patients with SCID. Selection of the appropriate specimens is critical for accurate HLA typing and immunologic assessment before allogeneic hematopoietic stem cell transplantation.

Disclosure: No.

Keyword: maternal T cell, HLA typing, SCID

PD408

COMPARISON of FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN USE BETWEEN PATIENTS WITH PRIMARY OR SECONDARY IMMUNODEFICIENCIES: RESULTS FROM THE FACILITATED IMMUNOGLOBULIN ADMINISTRATION REGISTRY AND OUTCOMES STUDY (FIGARO)

POSTER DISPLAY 08: THERAPY

Michael Borte[1], Leif G Hanitsch[2], Nizar Mahlaoui[3], Maria Fasshauer[1], Dorte Huscher[4], Matthaios Speletas[5], Maria Dimou[6], Marta Kamieniak[7], David Pittrow[8], Cinzia Milito[9]
[1]Hospital for Children & Adolescents, St. Georg Hospital, Leipzig, Academic Teaching Hospital of The University of Leipzig, Immunodeficiency Center Leipzig (idcl),leipzig, Leipzig, Germany, [2]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Institute of Medical Immunology, Berlin, Germany, [3]French National Reference Center for Primary Immune Deficiencies (CEREDIH), Necker Children's University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Pediatric Immuno-hematology & Rheumatology Unit, Paris, France, [4]Institute of Biometry and Clinical Epidemiology, Charité Universitätsmedizin, , Berlin, Germany, [5]University of Thessaly, School of Health Sciences, Faculty of Medicine, Department of Immunology And Histocompatibility, Larissa, Greece, [6]National & Kapodistrian University of Athens Medical School, General Hospital "LAIKO,", First Department of Propaedeutic Internal Medicine, Athens, Greece, [7]Takeda Pharma Sp.z.o.o, Pdt Medical Affairs, Warsaw, Poland, [8]GWT-TUD GmbH, Innovationszentrum Real-world Evidence, Dresden, Germany, [9]Università La Sapienza, Department of Molecular Medicine "sapienza" University of Rome, Italy, Rome, Italy

Background and Aims: The FIGARO study (NCT03054181) assessed facilitated subcutaneous immunoglobulin (fSCIG) usage and tolerability in routine clinical practice, comparing patients with primary (PID) and secondary immunodeficiencies (SID).

Methods: FIGARO was a European multicenter (n=14), prospective, observational study of patients with ≤3 years of follow-up. Included patients had received or were due to receive ≥1 infusion of fSCIG for PID/SID. Data were analyzed according to indication (PID/SID) at baseline and visits at approximately 6-month intervals.

Results: In total, 125 patients with PID (mean age 37.7 years; 50.4% male) and 31 with SID (mean age 61.4 years; 61.3% male) were included. Median fSCIG dose was initially lower in PID than SID (25.0g vs 30.0g) and increased over 3 years to 35.0g in PID while remaining unchanged in SID. Across all visits, 84.6–97.7% of all patients received their full infusion at one infusion site and 78.7–95.7% of all patients self-administered fSCIG. At baseline, 6.4% and 32.3% of patients with PID and SID, respectively, reported acute severe bacterial infections (ASBIs). During follow-up, 28 ASBIs were reported in PID only, most commonly respiratory-related infections (n=22). At baseline, adverse drug reactions (ADRs) were reported in 22.4% and 6.5% of patients with PID and SID, respectively; during follow-up, serious local and/or systemic ADRs were reported in 4.8% and 12.9%, respectively.

Conclusions: This real-world study confirms the feasibility and tolerability of fSCIG utilization in patients with PID or SID. Funding: Baxalta Innovations GmbH, a Takeda company (study); Takeda Development Center Americas, Inc. (writing support). Study sponsor: GWT-TUD GmbH.

Disclosure: MB's institution has received research grant support from Baxalta, CSL Behring and Octapharma. He has participated in advisory boards for CSL Behring, Octapharma and Shire. LGH has participated in advisory boards from Shire. NM, MD and CM have nothing to

Keywords: Facilitated subcutaneous immunoglobulin, Real-world study, primary immunodeficiencies, Secondary immunodeficiencies

PD409

OTHER USES IMMUNOGLOBULIN INTRAVENOUS IN PATIENT WHIT GATA 2 DEFICIENCY .

POSTER DISPLAY 08: THERAPY

Noemi Gomez Hernandez[1], Nayeli Servin Suarez[2], Margarita Ortega Cisneros[2]
[1]Centro Medico Nacional de Occidente Institute Mexican Secure Social, Allergy And Clnical Immunology, Guadalajara, Jalisco., Mexico, [2]Hospital de Especialidades, Instituto Mexicano del Seguro Social, Departamento De Inmunología Clínica Y Alergia, Guadalajara, Jalisco, Mexico

Background and Aims: Introduction and Objectives: Here we report of a patient with GATA 2 Deficiency with IgG IV human for wound healing.

Methods: Clinical features of the patient were described.

Results: A 30-year-old female patient from Michoacán, Mexico. At 17 years, she presented chickenpox complicated with sepsis , after she developed warts on all the pads of her hands and in the vulvar-vaginal region. In October 2017, she presented Medullary Hypoplasia. By sequencing she performs genetic diagnosis of GATA2 mutation, the biopsy of the labium major was documented: a high-grade malignant intrapithelial squamous lesion due to HPV, and later cervical cancer in situ. Required hysterectomy in 2018, in addition to cancer in situ in the vulva, received radiotherapy for two months . However, development a severe radioepithelitis, in the entire vulvar, and perianal area, which required hospitalization and treatment with anti-inflammatories and antibiotics for added infection without improvement. Intravenous human immunoglobulin therapy mensual was started with notable improvement of skin lesions throughout the vulva with gradual healing of the genital area.

Conclusions: The function of granulocytes in wound healing has been extensively studied. In aseptic wound healing, very few B cells migrate to the wound site. The importance of immunoglobulin in wound healing antibodies bound to damaged tissues might induce phagocytosis by Fcc receptors present on neutrophils and macrophages. In mice, the topical administration of a neutralizing antibody recognizing aminopeptidase-N, an enzyme implicated in the regulation of epidermal–dermal interaction and expression of adhesion molecules, led to acceleration of wound closure. Immunol Res (2015) 61:260–268

Disclosure: No.

Keywords: GATA 2 deficiency, inmunoglobulin intravenous, wound healing

PD410

A CHARACTERISATION of CHRONIC CAMPYLOBACTER INFECTION IN COMMON VARIABLE IMMUNODEFICIENCY PATIENTS.

POSTER DISPLAY 08: THERAPY

Adriel Roa-Bautista[1,2], Li-An Brown[3,4], Susan Tadros[2], Elena González-López[1], Siobhan Burns[5,6,7], Gauri Godbole[3,8], David Lowe[2,4]
[1]Hospital Universitario Marques De Valdecilla., Immunology Department, Santander, Spain, [2]The Royal Free London NHS Foundation Trust, Immunology, London, United Kingdom, [3]University College London Hospitals NHS Foundation Trust., Division of Infection And Immunity, London, United Kingdom, [4]UCL, Institute of Immunity And Transplantation, University College London., London, United Kingdom, [5]UCL, Institute of Immunity And Transplantation, London, United Kingdom, [6]University College London, Division of Infection And Immunity, London, United Kingdom, [7]University, University College London Hospitals Nhs Foundation Trust, Uk, London, United Kingdom, [8]Health Security Agency, Gastrointestinal Bacteria Reference Unit, London, United Kingdom

Background and Aims: Campylobacter infection usually causes a self-limited clinical illness lasting 5-7 days, resolving without antimicrobial treatment in immunocompetent subjects. However, an inadequate immune response can lead to a prolonged and severe disease requiring antibiotics and more aggressive therapeutic approaches.

Methods: A retrospective cohort of 17 common variable immunodeficiency (CVID) patients with Campylobacter infection and 109 CVID controls attending the Immunology clinic at the Royal Free Hospital was assessed. Immunological, clinical and microbiological parameters were measured. Patients were treated according to a novel algorithm for Campylobacter in antibody deficient patients.

Results: Immunological parameters: Flow cytometry evaluation of peripheral B lymphocytes demonstrated a lower long-term average CD19+ count with a higher proportion of $CD21^{LOW}CD38^{LOW}$ B cells in Campylobacter patients versus controls. Furthermore, a reduction in CD4+ T cell and NK cell counts over time was observed in Campylobacter patients. Treatment response: Patients were treated according to our novel algorithm. Clinical improvement and bacterial clearance were obtained after a median of 21 and 169 days for acute Campylobacter (ACP) and chronic Campylobacter (CCP) infections respectively. Ten received first-line of treatment [Azithromycin or Chloramphenicol], four second-line [Neomycin], and three received third-line [Tigecycline, Chloramphenicol and Ertapenem (one received Gentamicin due to resistance to carbapenems)].

Conclusions: Our study highlights immunological and clinical characteristics of recurrent Campylobacter infections in patients with CVID. Our treatment algorithm was successful and should be evaluated in a larger cohort.

Disclosure: No.

Keywords: Campylobacter infection, CVID, treatment, antibody deficiency, Chronic infection, Novel antibiotic algorithm

PD411

SAFETY ANALYSIS of ALLOGENEIC PROCESSED THYMUS TISSUE-AGDC TREATMENT IN PATIENTS WITH CONGENITAL ATHYMIA

POSTER DISPLAY 08: THERAPY

Christine Steinhart[1], Elizabeth Mccarthy[2], Eveline Wu[3]
[1]Enzyvant Therapeutics, Inc., Department of Medical Affairs, Cambridge, United States of America, [2]Duke School of Medicine, Department of Pediatrics, Division of Allergy And Immunology, Durham, United States of America, [3]University of North Carolina School of Medicine, Division of Rheumatology, Department of Pediatrics, Chapel Hill, United States of America

Background and Aims: Congenital athymia is an ultra-rare condition characterized by severe immunodeficiency that puts patients at risk for life-threatening infections and autoimmunity. Allogeneic processed thymus tissue-agdc is approved for immune reconstitution in patients with congenital athymia. This analysis assessed safety of allogeneic processed thymus tissue-agdc administration over time after treatment.

Methods: Safety was evaluated in 105 patients who received allogeneic processed thymus tissue-agdc in a retrospective analysis of 10 clinical trials from 1 site. Assessments included incidence of adverse events (AEs), serious AEs (SAEs; per the investigator), and deaths within the first year (Y1) and second year (Y2) after administration.

Results: In Y1 after allogeneic processed thymus tissue-agdc administration, all 105 patients experienced ≥1 AE, 86 experienced an SAE, and 23 died. In Y2, 39 patients experienced ≥1 AE, 33 experienced an SAE, and 2 died. The most common AE class was infections. In Y1, there were infections reported for 96 patients, serious infections for 68 patients, and infection-related deaths for 13 patients. In Y2, there were infections reported for 39 patients, serious infections for 26 patients, and 1 infection-related death (375 days post-treatment). Autoimmunity-related AE incidence also decreased over time. Thrombocytopenia was reported for 24 patients in Y1 (considered serious for 8 patients) and 1 patient in Y2 (considered serious).

Conclusions: The number of AEs, SAEs, and deaths decreased over time (Y1 to Y2) after allogeneic processed thymus tissue-agdc treatment. Similar patterns were observed for AE categories of particular relevance to congenital athymia, such as infections and autoimmunity.

Disclosure: CS is a full-time employee of Enzyvant. Portions of EAM’s salary were paid for by funding from Enzyvant. EYW has received consulting and/or advisory board fees from Pharming Healthcare and has received grants as an investigator from AstraZeneca, Bristol-M

Keywords: Congenital athymia, thymus, complete DiGeorge syndrome, CHARGE syndrome, 22q11.2 deletion, primary immunodeficiency

PD412

GENE THERAPY FOR ADENOSINE DEAMINASE DEFICIENCY: LONG-TERM OUTCOME AND POST-MARKETING EXPERIENCE.

POSTER DISPLAY 08: THERAPY

Maria Pia Cicalese[1,2,3], Maddalena Migliavacca[1,3], Daniela Cesana[3], Federica Barzaghi[1,3], Claudia Fossati[3], Paola Mv Rancoita[4], Michela Gabaldo[5], Francesca Dionisio[3], Stefania Giannelli[3], Federica Salerio[3], Francesca Ferrua[1,3], Francesca Tucci[1,3], Valeria Calbi[1,3], Vera Gallo[1,3], Salvatore Recupero[1,3], Giulia Consiglieri[1,3], Maria Sambuco[1,3], Alessio Priolo[1,3], Chiara Ferri[2], Vittoria Garella[2], Ilaria Monti[3], Paolo Silvani[6], Silvia Darin[3], Miriam Casiraghi[3], Ambra Corti[3], Stefano Zancan[5], Margherita Levi[5], Dalia Abdelaziz[7], Ulrich Baumann[8], Andrea Finocchi[9,10], Caterina Cancrini[9,10], Saverio Ladogana[11], Andrea Meinhardt[12], Isabelle Meyts[13,14], Davide Montin[15], Lucia Dora Notarangelo[16], Fulvio Porta[17], Marlene Pasquet[18], Carsten Speckmann[19], Polina Stepensky[20], Alberto Tommasini[21], Marco Rabusin[22], Zeynep Karakas[23], Miguel Galicchio[24], Lucia Leonardi[25], Marzia Duse[25], Sukru Nail Guner[26], Luigi Naldini[2,3], Marco Tartaglia[27], Clelia Di Serio[4], Fabio Ciceri[2,3,28], Maria Ester Bernardo[1,2,3], Eugenio Montini[3], Franco Locatelli[29], Alessandro Aiuti[1,2,3]
[1]IRCCS Raffaele Scientific Institute, Pediatric Immunohematology And Bone Marrow Transplantation Unit, Milano, Italy, [2]Vita-Salute San Raffaele University, ., Milano, Italy, [3]IRCCS San Raffaele Scientific Institute, San Raffaele Telethon Institute For Gene Therapy (sr-tiget), Milano, Italy, [4]Vita-Salute San Raffaele University, University Centre For Statistics In The Biomedical Sciences (cussb), Milan, Italy, [5]Fondazione Telethon, ., Milan, Italy, [6]IRCCS San Raffaele Scientific Institute, Department of Anesthesia And Critical Care, Milan, Italy, [7]Faculty of Medicine, Cairo University, Department of Pediatrics, Cairo, Egypt, [8]Hannover Medical School, Department of Paediatric Pulmonology, Allergy And Neonatology, Hannover, Germany, [9]Tor Vergata University, Department of Systems Medicine, Rome, Italy, [10]IRCCS Bambino Gesù Children Hospital, Academic Department of Pediatrics (dpuo), Unit of Clinical Immunology And Vaccinology,, Roma, Italy, [11]"Casa Sollievo della Sofferenza" Hospital, IRCCS, Paediatric Onco-haematology Unit, San Giovanni Rotondo, Italy, [12]University Hospital Giessen, Department of Pediatric Hematology And Oncology, Giessen, Germany, [13]KU Leuven, Laboratory of Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [14]University Hospitals Leuven, Department of Pediatrics, Jeffrey Modell Diagnostic And Research Network Center, Leuven, Belgium, [15]Ospedale Infantile “Regina Margherita", Pediatria Ad Indirizzo Infettivologico, Torino, Italy, [16]Spedali Civili di Brescia, Direzione Sanitaria, Brescia, Italy, [17]Children’s Hospital, Spedali Civili, Brescia, Italy,, Oncohematology And Bone Marrow Transplant (bmt) Unit, Brescia, Italy, [18]Hospital Center University De Toulouse, Hemato-immunology, Toulouse, France, [19]University of Freiburg, Division of Pediatric Hematology And Oncology, Department of Pediatrics And Adolescent Medicine, Medical Center - University of Freiburg, Faculty of Medicine, Freiburg, Germany, [20]Hadassah Hebrew University Medical Centre, Department of Bone Marrow Transplantation And Cancer Immunotherapy, Jerusalem, Israel, [21]IRCCS Burlo Garofolo, Department of Pediatrics, Trieste, Italy, [22]IRCCS Burlo Garofolo, Department of Oncohematology, Institute For Maternal And Child Health, Trieste, Italy, [23]Istanbul University, Istanbul School of Medicine, Department of Pediatrics, Hematology/oncology Unit, Istambul, Turkey, [24]Hospital de Niños VJ Vilela, Allergy And Immnunology Service, Rosario, Argentina, [25]La Sapienza University of Rome, Department of Pediatrics, Rome, Italy, [26]Meram Medical School, Necmettin Erbakan University, Division of Pediatric Allergy And Immunology, Konya, Turkey, [27]IRCCS Bambino Gesù Children’s Hospital, Genetics And Rare Diseases Research Division, Rome, Italy, [28]IRCCS San Raffaele Scientific Institute, Hematology And Bone Marrow Transplantation Unit, Milano, Italy, [29]Bambino Gesù Children Hospital, IRCCS,, Department Onco-haematology, And Cell And Gene Therapy, Rome, Italy

Background and Aims: Adenosine-deaminase (ADA) deficiency leads to severe combined immunodeficiency (SCID), treatable by enzyme replacement, allogeneic hematopoietic stem cell transplantation (HSCT) or autologous CD34+ cell gene therapy (GT). GT with bone marrow-derived CD34+ cells transduced with γ-retroviral vector (Strimvelis) was approved in 2016 in the EU.

Methods: We describe initial post-marketing experience of 12 subjects (STRIM cohort) with up to 24 months follow-up (F-U), provide extended F-U on the 22 subjects treated in clinical development/named patient program (CDP+NPP cohort, #NCT00598481) and report on 2 patients who received mobilized peripheral blood CD34+ cell GT.

Results: At data-cut, all 36 patients were alive with 8.8 years (interquartile range 1.8-13.3 years) median F-U and 2 years intervention-free survival (IFS) (no need for ERT or HSCT) of 85.4% (95% CI: 74.3%-98.1%). Most adverse events/reactions were related to disease background, busulfan conditioning or immune-reconstitution. Long-term persistence of gene-corrected cells and immune-reconstitution were observed in the CDP+NPP cohort. IFS, transduced-cell engraftment, ADA-detoxification, immune-reconstitution and safety of the STRIM cohort were in line with CDP. After data-cut, one NPP patient developed a drug-related T-cell acute lymphoblastic leukemia (T-ALL) 4.7

years post-GT. Blast cells contained a single vector activating insertion near *LMO2* and a variety of somatic mutations contributed to leukemic development. The patient underwent chemotherapy and, after remission, HLA-haploidentical HSCT, and is in molecular remission 14 months after HSCT.

Conclusions: At 2 years post-GT, 85.4% of all patients treated as CDP/NPP or commercially remain intervention free and all are alive. Due to the risk of genotoxicity, long-term safety monitoring remains important (#NCT03478670).

Disclosure: A. Aiuti was the PI of pilot and pivotal SR-TIGET clinical trial of gene therapy for ADA SCID. M.P. Cicalese is the PI of the Strimvelis Registry, RIS and RMMs studies. All authors declare no other competing interests.

Keywords: ex vivo gene therapy, Hematopoietic stem cell transplantation, retroviral vector, Immune-reconstitution, ADA-SCID, immunodeficiency

PD413

SAFETY AND EFFICACY of PAXLOVID IN CHILDREN WITH PRIMARY IMMUNODEFICIENCY AFFECTED BY SARS-COV-2 INFECTION: A CASE SERIES.

POSTER DISPLAY 08: THERAPY

Veronica Santilli[1], Emma Concetta Manno[1], Carmela Giancotta[1], Donato Amodio[1], Paola Zangari[1], Nicola Cotugno[1,2], Stefania Bernardi[3], Lorenza Romani[3], Maia De Luca[3], Laura Lancella[3], Laura Cursi[3], Sara Chiurchiu[3], Andrea Gioacchino Rotulo[1], Lucia Pacillo[1], Beatrice Rivalta[1], Leonardo Vallesi[4], Tiziana Corsetti[4], Paolo Rossi[3], Andrea Finocchi[1,2], Caterina Cancrini[1,2], Paolo Palma[1,2]
[1]IRCCS Bambino Gesù Children Hospital, Unit of Immunology And Vaccinology, Roma, Italy, [2]Tor Vergata University, Department of Systems Medicine, Rome, Italy, [3]Bambino Gesù Children's Hospital, IRCCS, 00165 Rome, Italy, Infectious Disease Unit, rome, Italy, [4]Ospedale Pediatrico Bambino Gesù, IRCSS, Rome, Italy., Hospital Pharmacy, rome, Italy

Background and Aims: Primary Immunodeficiency patients are often at the top of the list to be prescribed antiviral treatment in order to avoid progression to severe COVID disease. To date,the safety and effectiveness of Paxlovid have not yet been directly established in pediatric patients and experience of administering Paxlovid for COVID treatment in this populations is still limited. We report our experience in the administration of nirmatrelvir/ritonavir(Paxlovid) as a treatment for COVID in 9 immunocompromised children.

Methods: Paxlovid was administrated once we obtained a parent's consent, and off-label use was prescribed according to the Hospital's policy. All patients were hospitalized for the entire course of administration to monitoring adverse event, laboratory values and drug to drug interaction.

Results: In the present study we describe 9 patients aged from 1.7 to 14.9 years. The median age was 9,6years, with 7 of 9 being female. Four of them had humoral defect, three had T-cells defect, one had asplenia and one had congenital neutropenia. The major symptoms were fever (7of9) and cough (4of9). There were no significant severe adverse effects or reactions. One patients presented headache that required the cessation of the drug.We observed mild transient hypetriceridemia and hyperCKPemia respectly in two and one patient.One patient showed transient elevation of amilase/lipase. The median duration of viral clearance was estimated to be 9.5 days.

Conclusions: Based on the current small sample size study, Paxlovid is a feasible potential option for preventing disease deterioration in high risk pediatric patients. However further large scale-studies are needed to confirm and further these results.

Disclosure: No.

PD414

ALLOGENIC HSCT IN PID PATIENTS IN UKRAINE

POSTER DISPLAY 08: THERAPY

Anastasiia Bondarenko[1], Anna Hilfanova[2], Oleksandr Lysytsia[3], Nataliia Kavardakova[4], Oleh Ryzhak[5], Oleksandr Istomin[3], Alina Volkova[3], Olha Dashchakovska[3], Andriy Budzyn[3], Oksana Leontieva[3], A Horiachevska[3], Halyna Brudna[3], Dariia Zabara[6], Yaryna Romanyshyn[7], Olesja Zlotnykova[8], Larysa Kostuchenko[9], Stepan Beglaryan[10], Alla Volokha[11], Oksana Malko[12], Iryna Grabovska-Mykytuk[13], Roman Kuts[14], Liudmyla Chernyshova[1]
[1]Shupyk National Healthcare University of Ukraine, Pediatric Infectious Diseases And Pediatric Immunology Department, Kyiv, Ukraine, [2]Shupyk National Healthcare University of Ukraine, Department of Pediatric Infectious Diseases And Pediatric Immunology, Kyiv, Ukraine, [3]National Specialized Childrens Hospital "Ohmtadyt", Bone Marrow Transplantation & Immunotherapy Dep., Kyiv, Ukraine, [4]NATIONAL RESEARCH CENTER FOR RADIATION MEDICINE of THE NATIONAL ACADEMY of MEDICAL SCIENCES of UKRAINE (NRCRM), Hematologyc Department, Kyiv, Ukraine, [5]Biopharma Plasma, Medical Adviser, Kyiv, Ukraine, [6]National Academy of Medical Sciences of Ukraine, Institute of Pediatrics, Obstetrics And Gynecology Named After Academician O.m. Lukyanova, Kyiv, Ukraine, [7]Western-Ukrainian Specialized Children's Medical Centre, Clinic of Pediatric Immunology And Rheumatology, Lviv, Ukraine, [8]Kyiv Municipal Children's Hospital №1, Immunology Department, Kyiv, Ukraine, [9]West-Ukrainian Specialized Children's Medical Center, Pediatric Department, Lviv, Ukraine, [10]Smart Medical Centre, Immunology Departmentgy, Kyiv, Ukraine, [11]Shupyk National Healthcare University of Ukraine, Pediatric Infectious Diseases And Pediatric Immunology, Kyiv, Ukraine, [12]Regional Rivne Children's Hospital, Endocrinology Department, Rivne, Ukraine, [13]Volynsk Regional Children's Hospital, Immunology Department, Lutsk, Ukraine, [14]Ukrainian Bone Marrow Donor Registry, Ukrainian Bone Marrow Donor Registry, Ternopil, Ukraine

Background and Aims: Background. HSCT is lifesaving treatment option in some PID, however it may be challenging as it requires financial, organizational and legislative support and medical experience, which has been limited in Ukraine for a long time. **Aim**: to evaluate the HSCT needs and treatment outcomes in patients with PID in Ukraine.

Methods: Materials and methods: assessment of the needs and performed HSCT are based on 1360 patients from the Ukrainian National Registry of PI. Results of HSCT performed in Ukraine represent a one center experience of National Specialized Childrens Hospital "Ohmatdyt"

Results: Results. Taking into account the estimated and real indicators of PID diagnostics 2010-2020, country's annual need for HSCT is 12-25 PID patients per year. 50 patients received HSCT (23% of needed), 39 abroad (2000-2021) and 11 in Ukraine (2012-2021), the overall survival rate is 83,7%. *HSCT in Ukraine.* Diagnoses of 11 patients aged 1-6 y.o. included WAS (4), CGD (2), DOCK8 deficiency (1), SCID (3), STAT1 GOF (1). Bone marrow sourse: MSD-7, MUD-3 (since 2020), haplo-1. All patients are alive, the observation time is 10-56 months. uneventful – 1 patient, 10 had GVHD of varying severity or infectious complications.

Conclusions: Conclusions: Improvement of the legislative framework, creation of the Ukrainian Bone Marrow Donor Registry together with the coordinated work of immunologists and transplantologists have contributed to increased accessibility for HSCT for Ukrainian patients during the last 2 years, which has improved the survival rate due to the shortening the path to treatment.

Disclosure: No.

PD415

ROLE of BOOSTER DOSE IN A X-LINKED AGAMMAGLOBULINEMIA ADOLESCENT SARS-COV-2 INFECTED

POSTER DISPLAY 08: THERAPY

Marta Stracuzzi[1], Claudia Vanetti[2], Mario Clerici[3], Gianvincenzo Zuccotti[4], Daria Trabattoni[2], Vania Giacomet[1]
[1]università degli studi di milano, Pediatric Infectious Disease, Luigi Sacco Hospital, milan, Italy, [2]Università degli studi di MIlano, Chair of Immunology - Department of Biomedical And Clinical Sciences, Milan, Italy, [3]Università degli studi di MIlano, Chair of Immunology - Department of Pathophysiology And Transplantation, Milan, Italy, [4]Università degli studi di MIlano, Department of Pediatrics, Vittore Buzzi Hospital, Milan, Italy

Background and Aims: A very limited amount of data is present in literature on SARS-CoV-2 infection in X-Linked Agammaglobulinemia (XLA) patients. Moreover, it remains unclear the role of vaccination against SARS-CoV-2 in these subjects.

Methods: We investigated immune response of a mild symptomatic SARS-CoV-2 strain BA.2 (B.1.1.529.2) infected XLA 12 years old male, vaccinated with booster dose during acute infection (AI) and after one month post COVID-19 diagnosis (PI).

Results: B cell compartment was compromised (CD19+ 0,004*103/mL, 0,2%). No NTA was found against Omicron. No significant differences in CD4+ and CD8+ T effector memory (CD4+/CCR7-/CD45RA-, CD8+/CCR7-/CD45RA-) and central memory (CD4+/CCR7+/CD45RA-, CD8+/CCR7+/CD45RA-) lymphocytes were observed in unstimulated compared to SARS-CoV-2-specific cells at AI. In contrast with these data, SARS-CoV-2-specific IFNg-producing CD8+ T lymphocyte were increased compared to the unstimulated condition. We treated our patient with Xevudy (Sotrovimab) monoclonal antibodies. According to the monoclonal antibodies infusion, at PI high level of NTA was found against Omicron (1:60) variants. A moderate increment of SARS-CoV-2-specific IFNg-producing CD8+ T lymphocyte and degranulating CTL were detected when compared to the unstimulated condition. Notably, a robust increment in CD4+ and CD8+ central memory T lymphocytes was detected at PI compared to AI.

Conclusions: Due to the lack of the NTA in AI and the observation that virus-specific memory T cell was only seen at PI, we conclude that the booster dose of COVID-19 vaccine was unable to trigger a relevant immunological protection in this patient. The absence of BTK have a role in mitigate symptoms by impairing IL-6 production.

Disclosure: No.

Keywords: vaccine, SARS-CoV-2, Neutralizing antibody, x-linked agammaglobulinemia

PD416

WHAT DO WE KNOW SO FAR ABOUT THE SAFETY AND EFFICACY of THE IGE-TARGETED BIOLOGIC OMALIZUMAB FOR CHRONIC URTICARIA? A META-ANALYSIS

POSTER DISPLAY 08: THERAPY

Zouina Sarfraz[1], Azza Sarfraz[2], Miguel Felix[3], Karla Robles-Velasco[4], Ivan Cherrez-Ojeda[5]
[1]Fatima Jinnah Medical University, Research And Publications, Lahore, Pakistan, [2]Aga Khan University, Pediatrics And Child Health, Karachi, Pakistan, [3]New York City Health + Hospitals, Lincoln, Bronx, NY, USA, Department of Medicine, Bronx, United States of America, [4]Karla Robles-Velasco, MD; Universidad Espíritu Santo, Samborondón, Ecuador, Department of Medicine, Samborondon, Ecuador, [5]Universidad Espíritu Santo, Allergy And Pulmonology, Samborondon, Ecuador

Background and Aims: Recent guidelines for the treatment of chronic urticaria (CU) recommend using the IgE-targeted biologic omalizumab in patients who are refractory to antihistamines. The aim of this meta-analysis is to assess the efficacy of omalizumab in weekly itching scores and response rates to therapy.

Methods: Post conducing a systematic search across PubMed, Scopus, Embase, and ClinicalTrials.Gov, studies were located through August 21, 2022. Adhering to PRISMA Statement 2020 guidelines, the statistical analysis was conducted in RevMan 5.4.1 to compute i) standardized mean difference reported as Cohen's d and ii) risk ratio (RR) applying 95% confidence intervals (CI) and the random-effects model for weekly itching scores and response rate.

Results: 11 RCTs were included pooling in 2441 participants. Weekly itch score prognostic outcomes, post administering 75 mg omalizumab, had a small effect direction favoring intervention: -0.29 (95%CI: -0.54, -0.04, P<.05). On 150 mg dosage, the strongest effect direction was ascertained among all dosages (Cohen's d=-2.6, 95%CI: -4.75, -0.46, P<.05); 300 mg dosage strongly favored weekly itch score reductions (Cohen's d=-2.21, 95%CI=-3.36, -1.07, P<.05); 600 mg had medium effect direction in favor of omalizumab (Cohen's d=-0.55, 95%CI=-1.04, -0.05, P<.05). Omalizumab increased response rates and risks: 150 mg (RR=2.32), 300 mg (RR=6.27) and 600 mg (RR=11.67), all P<.05.

Conclusions: We report improved responder rates and clinical symptomatology (i.e., itching score) strongly favoring omalizumab treatment for CU, influencing immunological prognosis by downregulating IgE secretion and decreasing B-cell populations.

Disclosure: No.

Keywords: biologics, Therapeutics, Omalizumab, Chronic Urticaria, Meta Analysis

PD417

CASE REPORT: USE of PROPHYLACTIC SUBCUTANEOUS C1 ESTERASE INHIBITION FOR HEREDITARY ANGIOEDEMA IN PREGNANCY

POSTER DISPLAY 08: THERAPY

Natalya Ellis, Patrick Yong
Frimley Park Hospital, Immunology Department, Camberley, United Kingdom

Background and Aims: Hereditary angioedema, a condition resulting from deficiency or reduced function of plasma C1 inhibitor, causes episodes of mucosal and subcutaneous oedema. With a prevalence of 1 in 50,000, affected females experience greater frequency of clinical episodes, often with further increases in pregnancy, complicated by limited licensed management options[2]. We present a case report of successful use of subcutaneous plasma-derived C1-inhibitor concentrate (pdC1-INH) during pregnancy.

Methods: A 33-year-old patient with hereditary angioedema taking prophylactic tranexamic acid became pregnant. Tranexamic acid was stopped during early pregnancy, resulting in increasing clinically significant flares of angioedema. Intravenous pdC1-INH was started at nine weeks gestation. Due to challenging intravenous access, this was switched to twice weekly subcutaneous administration.

Results: Prophylactic twice weekly pdC1-INH 1500 units significantly reduced frequency of angioedema attacks, from weekly flares to only two mild episodes at the start of pdhC1-INH prophylaxis and no attacks for the remainder of pregnancy. She delivered a healthy baby at term without complication.

Conclusions: This case demonstrates successful use of subcutaneous pdC1-INH during pregnancy, supporting existing data. The use of subcutaneous pdC1-INH offers an easier form of administration to patients. The case also demonstrates that lower doses of subcutaneous pdC1-INH can be very effective in pregnancy. There is limited data on treatments for hereditary angioedema in pregnancy and further research would be beneficial. Citations Caballero T, Canabal J, Rivero-Paparoni D, Cabañas R. Management of hereditary angioedema in pregnant women: a review. Int J Womens Health. 2014 Sep 9;6:839-48. doi: 10.2147/IJWH.S46460. PMID: 25228822

Disclosure: Dr Patrick Yong has received consulting fees, honoraria and/or support for attending meetings from Biocryst, CSL Behring, Pharming and Takeda.

Keywords: C1 esterase inhibition, pregnancy, Hereditary Angioedema

PD418

PASSIVE IMMUNISATION AGAINST SARS-COV-2 BY IMMUNOGLOBULIN REPLACEMENT THERAPY

POSTER DISPLAY 08: THERAPY

Isobel Ramsay[1,2], Anne Boulton[1], Pehuén Pereyra Gerber[2], Rainer Doffinger[3], Ania Manson[4], Rachel Dale[1], Effrossyni Gkrania-Klotsas[5], Marie Fordham[1], Anna Mayhew[4], James Thaventhiran[1], Dinakantha Kumararatne[1], Nicholas Matheson[2]
[1]Cambridge University Hospital, Cambridge, UK, Clinical Biochemistry And Immunology, cambridge, United Kingdom, [2]Jeffrey Cheah Biomedical Centre, University of Cambridge, Cambridge, UK, Cambridge Institute For Therapeutic Immunology And Infectious Disease (citiid), cambridge, United Kingdom, [3]Cambridge University Hospitals, Clinical Immunology, Cambridge, United Kingdom, [4]Addenbrooke's Hospital, Clinical Immunology, Cambridge, United Kingdom, [5]Addenbrooke's Hospital, Infectious Diseases, Cambridge, United Kingdom

Background and Aims: Early in the COVID-19 pandemic an increased risk of adverse outcomes amongst patients with primary and secondary antibody deficiency (PID/SID) was observed. Immunoglobulin replacement therapy (IRT) passively protects against infectious agents, but antibodies against SARS-CoV-2 were initially absent from the donor population. Here, we measured neutralising antibodies against SARS-CoV-2 in therapeutic immunoglobulin preparations currently in use in the UK, and examined up-to-date clinical outcomes in patients with PID/SID.

Methods: We quantified neutralising antibodies against authentic wildtype (WT) and Omicron BA.2 variants of SARS-CoV-2 in 11 preparations of therapeutic human immunoglobulin in use in the UK in June 2022: Privigen (5 lots), Gammunex (3 lots), Intratect (2 lots) and Cutaquig (1 lot). Concomitantly, we retrospectively determined outcomes of COVD-19 amongst 79 patients with PID and 85 patients with SID at a UK tertiary hospital (between March 2020 and June 2022).

Results: All immunoglobulin preparations tested demonstrated strong neutralising activity against WT SARS-CoV-2 (median IC50 0.015mg/ml). Activity against the Omicron BA.2 variant was markedly reduced (median 18-fold lower), but still quantifiable for 10/11 preparations. The predicted neutralising antibody titres in sera for preparations dosed to 10mg/ml were comparable to those in immunocompetent individuals following SARS-CoV-2 vaccination. Poor outcomes from COVID-19 were rare amongst patients with immunodeficiency receiving IRT, with case fatality rates of 3% and 15% amongst the PID and SID cohorts, respectively.

Conclusions: Passive immunisation by IRT is likely to provide at least some protection against SARS-CoV-2 infection and/or severe COVID-19 disease, and may improve outcomes amongst patients with immunodeficiency.

Disclosure: No.

Keyword: antibody deficiency; SARS-CoV-2;Immunoglobulin therapy; passive immunity

PD419

CYCLIC NEUTROPENIA IN A PATIENT WITH SRP54 DEFICIENCY SUCCESSFULLY TREATED WITH G-CSF

POSTER DISPLAY 08: THERAPY

Oksana Boyarchuk[1], Melinda Erdős[2], Oleksandra Shulhai[1], Lesya Dobrovolska[1], Yulia Polyhach[3], László Maródi[2,4]
[1]I.Horbachevsky Ternopil National Medical University, Department of Children's Diseases And Pediatric Surgery, Ternopil, Ukraine, [2]Semmelweis University, Faculty of Medicine, Department of Dermatology, Venereology And Dermatooncology, Primary Immunodeficiency Clinical Unit And Laboratory, Budapest, Hungary, [3]Ternopil Regional Children Hospital, Hematology Department, Ternopil, Ukraine, [4]Rockefeller University, Laboratory of Human Genetics of Infectious Diseases, New York, United States of America

Background and Aims: Recently, de novo dominantly inherited mutations in the signal recognition particle (SRP) 54 genes were described and found to represent the second most common cause of congenital neutropenia with maturation arrest.

Methods: The patient and her family members were interviewed, examined, treated and monitored. Blood cell analysis was performed by routine hematological assays. Lymphocyte subsets were determined by flow cytometry. Genetic tests included whole exome sequencing, immunodeficiency panel sequencing and targeted gene sequencing.

Results: We report here a patient with *SRP54* mutation who developed cyclic neutropenia showing cycles of approximately 21-days interval. The first disease manifestations at 10 months of age include stomatitis, gingivitis and cervical lymphadenomegaly. During the second year of life she had recurrent stomatitis, impetigo and skin abscesses. At 2 years of age, she was evaluated for anemia, recurrent episodes of fever, mucositis and urinary tract infections. Ulcerative stomatitis recurred in every 2 to 4 weeks with fever, gingivitis, painful cervical lymphadenomegaly and angular cheilitis. Later on, exacerbations have been observed in every 3 weeks and lasted for 4-6 days. From the age of 3 years, the patient was treated with chronic constipation and radiology examination revealed dolichocolon. G-CSF treatment was initiated at the age of 10 years resulted in ANC counts above 1.000/μL and reduced the frequency and severity of infections.

Conclusions: We provided data on successful treatment of a SRP54 deficient patient by administration of G-CSF, in contrast to nearly all previously reported patients with *SRP54* mutations who presented with a poor or no response to G-CSF therapy.

Disclosure: No.

Keywords: SRP54 deficiency, cyclic neutropenia, G-CSF

PD420

PROLONGED REMISSION of AZOLE-RESISTANT LUNG ASPERGILLOSIS WITH OLOROFIM, IN AN ADOLESCENT WITH X-LINKED CHRONIC GRANULOMATOUS DISEASE

POSTER DISPLAY 08: THERAPY

Victor Michel[1], Nizar Mahlaoui[2], Emma Harvey[3], Laureline Berteloot[4], Despina Moshous[1], Athina Fouriki[1], Martin Castelle[1], Benedicte Neven[1], Marie-Elisabeth Bougnoux[5], Stephane Blanche[1], Fanny Lanternier[6], Romain Lévy[1]
[1]Hôpital Necker-Enfants Malades, Pediatric Immunology-hematology And Rheumatology Unit, Paris, France, [2]HOPITAL NECKER, Ceredih & Uihr, PARIS, France, [3]F2G Ltd, F2g, Manchester, United Kingdom, [4]Hôpital Necker-Enfants Malades, Pediatric Radiology Department, Paris, France, [5]Hôpital Necker-Enfants Malades, Parasitology-mycology Unit, Paris, France, [6]Hôpital Necker-Enfants Malades, Department of Infectious Diseases And Tropical Medicine, Paris, France

Background and Aims: X-linked Chronic Granulomatous Disease (XL-CGD) is responsible for life-threatening aspergillosis. Itraconazole prophylaxis improved patients prognosis, but breakthrough resistant aspergillosis can emerge with limited therapeutic options. Development of new antifungal class is a major need.

Methods: We report the efficacy of Olorofim (F2G Ltd), the first member of orotomides, a novel class of antifungals in clinical development, which inhibits pyrimidine synthesis resulting in fungal cell death.

Results: A 14-year-old XL-CGD patient (36kg), had breakthrough azole-resistant *Aspergillus fumigatus* lung aspergillosis while under itraconazole prophylaxis, within correct plasma levels (1540ug/mL). Lung-CT showed consolidation of the upper right lobe contoured by ground glass opacities, and costal osteolysis. Lung biopsy documented *Aspergillus fumigatus* mutated in *CYP51A* gene, conferring pan-azole resistance. Evolution at 3-months treatment with caspofungine and liposomal amphotericin B (L-AmB; 3mg/kg/d), showed partial remission, but was marked by tubulopathy and episodes of acute renal failure, due to L-AmB. After 9-months bi-therapy, lung-CT found progression of lesions while patient presented hemoptysis requiring urgent partial lobectomy. L-AmB was stopped 2 months after surgery, due to renal failure and replaced with oral Olorofim monotherapy (3 mg/kg/d), thanks to compassionate access. Plasma residual level on day 7 was within target ranges (1.241mg/mL), allowing complete and sustained remission by month 2, maintained on repeated lung-MRI after 18 months follow-up, and restored kidney function. No adverse effects were reported on routine monitoring including liver parameters.

Conclusions: We describe the first pediatric case of resistant aspergillosis, rescued with Olorofim. Pediatric pharmacokinetic and safety studies of Olorofim are needed, to allow routine use in children.

Disclosure: No.

Keywords: CGD, Innate Immunity, therapy, Olorofim, Aspergillosis

PD421

DO CVID PATIENTS ON SCIG HAVE MORE AUTOIMMUNE THROMBOCYTOPENIC EVENTS THAN CVID PATIENTS ON IVIG?

POSTER DISPLAY 08: THERAPY

Nadezhda Camacho-Ordonez[1], Aleksandra Hirsch[2], Sigune Goldacker[3], Siobhan Burns[4,5], Luiza Campos[5], Fernando Moreira[5], Klaus Warnatz[6], Bodo Grimbacher[7,8,9,10,11]
[1]Medical Center, University of Freiburg, Germany, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [2]Department of Rheumatology and Clinical Immunology, Center For Chronic Immunodeficiency (cci), Medical Center, Faculty of Medicine, Albert-ludwigs-university of Freiburg, Freiburg, Germany, [3]Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Center For Chronic Immunodeficiency (cci), Freiburg im Breisgau, Germany, [4]UCL, Institute of Immunity And Transplantation, London, United Kingdom, [5]The Royal Free London NHS Foundation Trust, Department of Immunology, London, United Kingdom, [6]Medical Center - University of Freiburg, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany, [7]Medical Center - University of Freiburg, Institute for Immunodeficiency, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany, [8]Satellite Center Freiburg, German Center For Infection Research (dzfi), Freiburg, Germany, [9]University Medical Center Freiburg, Department of Rheumatology And Clinical Immunology, Freiburg, Germany, [10]Satellite Center Freiburg, Resolving Infection Susceptibility (resist) - Cluster of Excellence 2155 To Hannover Medical School, Freiburg, Germany, [11]Center for Integrative Biological signaling Studies (CIBSS), University of Freiburg, Freiburg, Germany

Background and Aims: Autoimmune thrombocytopenia (AITP) is a frequent manifestation in patients with common variable immunodeficiency (CVID). The aim of this study was to prospectively assess the safety and efficacy of subcutaneous immunoglobulin (SCIG) and intravenous immunoglobulin (IVIG) treatment in patients with both CVID and AITP.

Methods: Patients with both CVID and AITP were enrolled at the Centre for Chronic Immunodeficiency in Freiburg, Germany and at the Royal Free Hospital, London, UK. Clinical and laboratory features of patients were monitored over a 64-month period.

Results: In this prospective study, we enrolled 55 adult patients.This analysis is based on the curated data on 40 patients, 26 on SCIG and 14 on IVIG. During the observation period, seven patients had an AITP bout, and platelet counts of additional four patients dropped below 50Tsd/uL without bleeding. of these 11 patients, 8 patients were on SCIG (31% of the SCIG cohort) and 3 patients were on IVIG (21% of the IVIG cohort), p-value=0.1. All patients received corticosteroids as treatment for the AITP bout. In our cohort, 37% of patients receiving SCIG and 33% of the IVIG-group had mean IgG trough levels < 7g/L at the time of the thrombocytopenic event.

Conclusions: We did not find a higher occurrence of AITP bouts in CVID patients who received SCIG compared to IVIG. However, one third of the patients with a thrombocytopenic event had an IgG through level <7g/l at the time of the event. Hence, similar to IVIG, keeping IgG trough levels >7 g/l is important for patients with AITP under SCIG replacement therapy.

Disclosure: This study was supported by grant #ZVS20140211c from CSLBehring.

Keywords: Common variable immunodeficiency, Intravenous immunoglobulin, Subcutaneous immunoglobulin, immunoglobulin replacement therapy, autoimmune thrombocytopenia

PD422

THE GAIN REGISTRY – A NEW PROSPECTIVE STUDY FOR PATIENTS WITH MULTI-ORGAN AUTOIMMUNITY

POSTER DISPLAY 09: OTHER

Paulina Staus[1], Stephan Rusch[2], Sabine El-Helou[3], Gabriele Müller[1], Mate Krausz[4], Ulf Geisen[5], Andrés Caballero Garcia De Oteyza[6], Renate Krüger[7], Shahrzad Bakhtiar[8], Maria Fasshauer[9], Ulrich Baumann[10], Bimba Hoyer[11], João Farela Neves[12], Michael Borte[13], Maria Carrabba[14], Fabian Hauck[15], Stephan Ehl[1], Peter Bader[8], Horst Von Bernuth[16], Faranaz Atschekzei[17], Esid Registry Working Party[18], Klaus Warnatz[19], Alexandra Nieters[1], Gerhard Kindle[1], Bodo Grimbacher[20]
[1]Medical Center - University of Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Faculty of Medicine, Freiburg, Germany, [2]Medical Center - University of Freiburg, Freiburg, Institute For Immunodeficiency, Center For Chronic Immunodeficiency (cci), Faculty of Medicine, Freiburg, Germany, [3]Institute for Immunodeficiency, Center for Chronic Immunodeficiency (CCI), Faculty of Medicine, Medical Center - University of Freiburg, Department of Rheumatology And Immunology, Hannover Medical School, Hanover, Germany. Hannover Medical School, Cluster of Excellence Resist (exc 2155), Freiburg, Germany, [4]University Hospital Freiburg, Institute For Immunodeficiency, Freiburg, Germany, [5]University Medical Center Schleswig-Holstein Campus Kiel, Comprehensive Center For Inflammation Medicine, Medical Department I, Rheumatology And Clinical Immunology, Kiel, Germany, [6]Institute for Immunodeficiency, Center for Chronic Immunodeficiency (CCI), Faculty of Medicine, Medical Center - University of Freiburg, Freiburg, Department of Rheumatology And Immunology, Hannover Medical School, Hanover, Germany. Hannover Medical School, Cluster of Excellence Resist (exc 2155), Freiburg, Germany, [7]Charité - Universitätsmedizin Berlin, Department of Pediatric Respiratory Medicine, Immunology And Critical Care Medicine, Berlin, Germany, [8]Hospital for Children and Adolescents, University Hospital, Goethe University, Division For Stem Cell Transplantation, Immunology And Intensive Care Medicine, Frankfurt am Main, Germany, [9]Hospital for Children & Adolescents, St. Georg Hospital, Leipzig, Academic Teaching Hospital of The University of Leipzig, Immunodeficiency Center Leipzig (idcl),leipzig, Leipzig, Germany, [10]Hannover Medical School, Department of Paediatric Pulmonology, Allergy And Neonatology, Hannover, Germany, [11]University Hospital Schleswig-Holstein, Campus Kiel, Excellence Center For Inflammation Medicine, Clinic For Rheumatology And Clinical Immunology, Kiel, Germany, [12]Primary Immunodeficiencies Unit, Hospital Dona Estefânia, Centro Hospitalar de Lisboa Central, EPE, Cedoc, Chronic Diseases Research Center, Nova Medical School, Lisboa, Portugal, [13]Hospital for Children & Adolescents, St. Georg Hospital, Leipzig, Academic Teaching Hospital of The University of Leipzig, Immunodeficiency Center Leipzig (idcl), Leipzig, Germany, [14]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, UOS Malattie Rare, Dipartimento Di Medicina Interna, Milano, Italy, [15]Dr von Hauner Children's Hospital, University Hospital, Ludwig Maximilians Universität München, Division of Pediatric Immunology And Rheumatology, Department of Pediatrics, Munich, Germany, [16]Charité Berlin, Department of Pediatric Pneumology And Immunology Head of Pediatric Immunology And Infectious Diseases, Berlin, Germany, [17]Hannover Medical School, Rheumatology/immunology, Hannover, Germany, [18]ESID registry working party, Https://esid.org/working-parties/registry-working-party, Freiburg, Germany, [19]Institute for Immunodeficiency, Center for Chronic Immunodeficiency (CCI), Faculty of Medicine, Medical Center - University of Freiburg, Department of Rheumatology And Clinical Immunology, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany, [20]Medical Center - University of Freiburg, Institute for Immunodeficiency, Center for Chronic Immunodeficiency (CCI), Department of Rheumatology And Clinical Immunology, Freiburg im Breisgau, Germany

Background and Aims: Patient registries are one stronghold for investigating rare diseases, as most physicians only see a limited number of cases during their career. Rare inborn multi-organ autoimmunity is especially challenging, as this class of diseases is characterized by diverse clinical phenotypes and a highly variable expressivity.

Methods: The GAIN consortium (German multi-organ autoimmunity network) developed a dataset addressing these challenges. ICD-11, HPO, and ATC codes were incorporated to document various clinical manifestations and medications with a defined terminology. The GAIN dataset comprises detailed information on genetics, phenotypes, medication, and laboratory values.

Results: Since the start of the GAIN registry in November 2019, eleven centers for inborn errors of immunity (IEI) have registered 385 patients at risk for or with multi-organ autoimmunity. The median age at onset of symptoms related to IEI or autoimmunity? was 13 years (IQR 3 – 27) and the median time from onset to clinical diagnosis was 5 years (IQR 1 – 13). of 330 (85.7%) patients, which were genetically tested, 228 (59.2%) had a defined genetic cause. For 75 (19.5%) patients no mutation was found and for 82 (21.3 %) the result was pending. The most common gene affected was NFkB1 (45, 11.6%), the second common was CTLA4 (39, 10.1%), both fostered by specific research projects.

Conclusions: The GAIN registry can serve as a valuable resource for research in the IEI community by providing a platform for new etiological and diagnostic research projects, as well as observational trials on treatment options.

Disclosure: No.

Keywords: inborn error of immunity, Autoimmunity, primary immunodeficiency, epidemiology, rare diseases

PD423

PLATELET DYSFUCTION IN PATIENTS WITH SHWACHMAN-DIAMOND SYNDROME

POSTER DISPLAY 09: OTHER

Ivan Tesakov[1], Ekaterina Deordieva[2], Timofey Brontveyn[3], Eugenia Yushkova[1], Alexey Martyanov[1], Anastasia Ignatova[1], Julia-Jessica Korobkin[4], Elena Seregina[1], Nadezhda Podoplelova[1], Ekaterina Koltsova[1], Anna Shcherbina[2], Anastasia Sveshnikova[1]
[1]Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, High School of Molecular And Experimental Medicine, Moscow, Russian Federation, [2]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Department of Immunology, Moscow, Russian Federation, [3]Lomonosov Moscow State University, Faculty of Fundamental Medicine, Moscow, Russian Federation, [4]Center for Theoretical Problems of Physicochemical Pharmacology RAS, Laboratory of Intracellular Signalling And Systems Biology, Moscow, Russian Federation

Background and Aims: Neutropenia and thrombocytopenia are frequent features of Shwachman-Diamond syndrome (SDS). Defects of the F-actin polymerization and polarization in neutrophils have been described in SDS and thought to underly granulocytes' dysfunction. However, platelet production and function in SDS have not been studied in-depth.

Methods: We performed platelet functional studies in 10 patients with genetically confirmed SDS and moderate thrombocytopenia (median platelet count 104 000 per μL), which included: aggregometry (LTA for PRP), flow cytometry with platelet activation, and ex vivo thrombi formation assay in parallel-plate flow chambers. Coagulation status was assessed by thrombodynamics test. Bone marrow and blood smears were studied via immunofluorescent and light microscopy. Healthy age-matched volunteers were used as controls.

Results: Bone marrow investigation revealed marrow hypocellularity and decreased proplatelet formation by megakaryocytes. Microscopy of peripheral blood smears showed platelet cytoskeletal abnormalities: diffuse distribution of β1-tubulin, myosin IIa, actinin, and filamin. Platelet aggregation as well as intracellular calcium mobilization, platelet shape change, glycoprotein IIb/IIIa activation, fibrinogen binding, and dense granule secretion in response to PAR1-AP, adrenalin, ADP, and fucoidan, were significantly diminished in SDS as compared to control. However, collagen-induced platelet activation was unimpaired. Platelet ability to form thrombi ex vivo under a low shear rate was noticeably decreased in comparison with healthy controls. Surprisingly, we observed mild to moderate hypercoagulation in most of the patients.

Conclusions: This is the first demonstration of pronounced platelet functional abnormalities associated with cytoskeletal defects and impaired intracellular calcium signalling in SDS. The study was supported by Russian Science Foundation grant 21-74-20087.

Disclosure: No.

Keywords: Shwachman-Diamond syndrome, thrombocytopenia, platelet, hemostasis, cytoskeleton

PD424

ABNORMAL B CELL MATURATION AND INCREASED TRANSITIONAL B CELLS IN CBL SYNDROME

POSTER DISPLAY 09: OTHER

Fabiola Guerra[1], Tiziana Coliva[1], Francesca Vendemini[1], Marta Galbiati[2], Cristina Bugarin[2], Riccardo Masetti[3], Daniele Moratto[4], Marco Chiarini[4], Maria Iascone[5], Raffaele Badolato[6], Giovanni Cazzaniga[2], Charlotte Niemeyer[7], Christian Flotho[7], Andrea Biondi[1], Francesco Saettini[1]
[1]Fondazione MBBM, Pediatrics, Monza, Italy, [2]Tettamanti Research Center, Pediatrics, MONZA (MB), Italy, [3]Pediatric Hematology-Oncology Unit, Department of Medical and Surgical Sciences DIMEC, University of Bologna, Italy, Pediatrics, Bologna, Italy, [4]Flow Cytometry Laboratory, Diagnostic Department, Asst Spedali Civili, Brescia, Italy, brescia, Italy, [5]Laboratorio di Genetica Medica, ASST Papa Giovanni XXIII, Bergamo, Italy, Genetics, bergamo, Italy, [6]Pediatrics Clinic and "A. Nocivelli" Institute for Molecular Medicine, Department of Clinical And Experimental Sciences, University of Brescia, Asst- Spedali Civili of Brescia, Brescia, Italy, [7]7Department of Pediatrics and Adolescent Medicine, University Children's Hospital, University of Freiburg, Freiburg, Germany, Pediatrics, Freiburg, Italy

Background and Aims: CBL syndrome is a Noonan-like RASopathy whose immunological phenotype has not been extensively investigated.

Methods: We describe two patients with identical germline CBL variant c.1259G>A;pR420Q, whose B-cell phenotype overlaps with RALD and BENTA syndrome.

Results: Pt1 presented with splenomegaly, monocytosis, and thrombocytopenia and B-cell lymphocytosis. JMML was clinically diagnosed based on CBC and PB smear findings (myelocytes and metamyelocytes, anisocytosis in either erythrocytes or platelets). B-cell subsets showed a predominant immature/transitional phenotype. Bone marrow aspiration showed increased immature B cells ($CD10^{++}CD19^{+}CD20^{+}CD38^{+}$) without dysplastic features. Most of these immature B cells still expressed the CD34 antigen either in PB or BM. Pt2 exhibited splenomegaly, normal CBC and platelet anisocytosis with giant forms and partially hypergranulated granulocytes on PB smear. Lymphocyte subsets showed normal values. BM aspiration showed dysplastic features. Immunoglobulin levels were within normal range in Pt2 whereas Pt1 showed decreased IgA and increased IgE, with no sign of atopy.

Conclusions: Increased immature/transitional B cells can be depicted in CBL syndrome, ALPS, and BENTA. Our patients showed peculiar B-cell phenotype due to increased immature/transitional CD34+ B cells. This feature differentiates CBL syndrome from BENTA, pointing toward an abnormal proliferation of B cell early precursors. These cases expand the phenotypic spectrum of CBL syndrome, which overlaps with RALD and BENTA syndrome due to the increased immature/transitional B cells. Tejwani N et al, Somatic Hemizygous Y371H CBL Mutation with Loss of Heterozygosity Presenting with BENTA Type Lymphoid Proliferation. ISHBT. 2019;36(3):594-596 Calvo K et al. JMML and RALD: common genetic etiology yet clinically distinct entities. Blood. 2015;125(18):2753-2758

Disclosure: No.

Keywords: CARD11, CBL, RASopathies, RALD, BENTA, ALPS

PD425

RAG1/2 EXPRESSION DISCRIMINATES IPSC-DERIVED NK CELL DEVELOPMENT

POSTER DISPLAY 09: OTHER

Jasmin Sprissler[1], Hubert Schrezenmeier[2], Klaus Debatin[1], Klaus Schwarz[2], Kerstin Felgentreff[1]
[1]Univeristy Medical Center Ulm, Department of Pediatrics And Adolescent Medicine, Ulm, Germany, [2]Red Cross Blood Service Baden-Wuerttemberg-Hessen, Institute For Clinical Transfusion Medicine And Immunogenetics, Ulm, Germany

Background and Aims: The development of adaptive B and T lymphocytes coincides with the generation of diversified T (TCR) and immunoglobulin (Ig) receptors mediated by V(D)J recombination. Recombination of V, D, and J gene segments is initiated by recombination activation genes (RAG1/2) endonucleases targeting recombination signal sequences (RSS). NK cells lack such clonotypic receptors but stochastically express germline-encoded activating and inhibitory receptors. However, non-productive genetic rearrangements on TCR and Ig loci have also been observed in NK cells and aberrant NK-cell phenotypes and functions have been observed in RAG-deficient patients and mice.

Methods: We generated stable RAG1/2-fate mapping reporter human induced pluripotent stem cell (hiPSC) lines by introduction of RSS-invertedGFP constructs into the AAVS1 locus using CRISPR/Cas9. Reporter hiPSC were further differentiated into hematopoietic stem cells (HSCs) and NK cells on OP9-DL1 stroma cells in vitro.

Results: GFP expression could not be observed in HSCs, but activation of the reporter cassette occurred in 2-4% of NK cells indicating RAG1/2 expression. Interestingly, GFP^+ NK cells were predominantly $CD45^{dim}CD56^{dim}$ and demonstrated a memory-like and terminally differentiated phenotype compared to GFP^-CD45^{bright} NK cells. Furthermore, GFP^+CD45^{dim} NK cells were characterized by prominent degranulation, cytotoxic potential and a potent production of interferon gamma, but showed impaired DNA damage response (DDR) and survival in response to ionizing radiation (IR).

Conclusions: Our results suggest a role of RAG1/2 expression in NK-cell ontogeny that discriminates the development of memory-like $CD45^{dim}$ and $CD45^{bright}$ NK-cell subsets. However, the role of NK cells with RAG-expression-ontogeny in health and disease needs to be further elucidated.

Disclosure: No.

Keywords: ontogeny, recombination activating genes (RAGs), human induced pluripotent stem cells, natural killer cells, lymphocyte development plasticity, V(D)J recombination

PD426

MAGT1 DEFICIENCY CAUSES A PROMINENT PLATELETS DYSFUNCTION THROUGH IMPAIRMENT of MEMBRANE GLYCOPROTEINS N-GLYCOSYLATION

POSTER DISPLAY 09: OTHER

Alexandre Kauskot[1], Coralie Mallebranche[2,3], Jean Solarz[1], Miao Feng[1], Christelle Repérant[1], Jean-Claude Bordet[4], Arnaud Bruneel[5,6], Sven Kracker[7], Alban Ziegler[8], Dominique Lasne[1,9], Delphine Borgel[1,9], Cécile Denis[1], Marie Tuffigo[10], Benjamin Fournier[11,12], Charline Miot[2,3,13], Frédéric Adam[1]
[1]Paris-Saclay University, Inserm Umr S 1176, LE KREMLIN BICETRE, France, [2]CHU Angers, Pediatric Immuno-hemato-oncology Unit, Angers, France, [3]Univ Angers, Université de Nantes, Inserm, Cnrs, Crci2na, Sfr Icat, ANGERS, France, [4]Laboratoire d'Hémostase, Centre De Biologie Est, Hospices Civils De Lyon, Bron, France, [5]AP-HP, Hôpital Bichat-Claude Bernard, Biochimie Métabolique Et Cellulaire, Paris, France, [6]Université Paris-Saclay, Inserm Umr1193, Châtenay-Malabry, France, [7]Institut Imagine, U1163 Lymphohematopoiesis Lab, Paris, France, [8]CHU Angers, Department of Biochemistry And Genetics, angers, France, [9]AP-HP, Hôpital Necker-Enfants malades, Laboratory of Hematology, Paris, France, [10]CHU Angers, Laboratory of Hematology, ANGERS, France, [11]Necker Hospital for Sick Children, Pediatric Immunology, Hematology And Rheumatology Unit, Paris, France, [12]Laboratory of Lymphocyte Activation and Susceptibility to EBV Infection, Inserm, Umr 1163, Institut Imagine, Paris, France, [13]CHU Angers, Laboratory of Immunology And Allergology, Angers, France

Background and Aims: XMEN disease is a primary immunodeficiency due to loss-of-function mutations of the gene of the magnesium transporter 1 (MAGT1). MAGT1 is expressed in various cell types including lymphocytes and platelets and is involved in N-glycosylation of a large number of substrates. XMEN disease is therefore considered to be a congenital deficiency of glycosylation. Two patients presenting with severe hemorrhages during hematopoietic stem cell transplantation (HSCT) have been previously reported (Dimitrova, JCI 2019). Although XMEN-associated immunodeficiency is well described, platelet dysfunction has never been investigated.

Methods: Platelet morphology, glycoprotein expression and platelet functions were investigated in two unrelated children, including one before and after HSCT.

Results: Routine coagulation tests and platelet count were normal. Platelet analysis, by electron microscopy, highlighted abnormal elongated platelets and unusual barbell-proplatelets. Platelet aggregations induced by thrombin, PAR4-AP, collagen and ADP were impaired at low concentrations, and those induced by PAR1-AP were totally abrogated even at very high concentration (100 µM). These results were confirmed by flow cytometry using an antibody which recognizes the active conformation of integrin $\alpha_{IIb}\beta_3$. These defects were not due to an abnormal expression of the main receptors, but the analysis of the molecular weight of GPIbα, CD41 and GPVI by western-blot revealed a partial loss of their size, due to a defect of N-glycosylation. Interestingly, all these defects were corrected after HSCT.

Conclusions: Our results reveal a prominent platelet dysfunction related to MAGT1 deficiency and therefore a defective N-glycosylation of several platelet proteins. Overall, these results could explain the severe hemorrhages reported in XMEN patients.

Disclosure: No.

Keywords: MAGT1 deficiency, platelets dysfunction, XMEN syndrome, congenital deficiency of glycosylation, bleeding risk

PD427

EARLY DETECTION of NON-HODGKIN LYMPHOMA AND LEUKEMIA IN PATIENTS WITH CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY THROUGH IMMUNOGENETIC SEQUENCING

POSTER DISPLAY 09: OTHER

Pieter Martijn Kolijn[1], Roland Kuiper[2], Dilys Wijers[2], Agata Pastorczak[3], Jan Loeffen[2], Anton Langerak[4]
[1]Erasmus MC, Immunology, Laboratory of Medical Immunology, Utrecht, Netherlands, [2]Princess Máxima Center for Pediatric Oncology, Genetics, Utrecht, Netherlands, [3]Medical University of Lodz, Department of Pediatrics, Oncology And Hematology, Lodz, Poland, [4]Erasmus MC, Immunology, Laboratory of Medical Immunology, Rotterdam, Netherlands

Background and Aims: Patients with immune dysregulation are at increased risk of developing hematological malignancies. Previously, we have shown that chronic lymphocytic leukemia development can be detected up to 16 years prior to diagnosis through immunogenetic sequencing. Here, we aim to investigate if the immunoglobulin heavy chain (IGH) of the B-cell receptor and beta chain of the T-cell receptor (TRB) have value as a marker for detection of hematological malignancy in constitutional mismatch repair deficiency (CMMRD) patients.

Methods: We selected 6 CMMRD patients who developed hematological malignancies. Diagnostic bone marrow (BM) samples were available from all patients. A leader-based PCR was utilized to amplify the IGH and TRB of the BM samples before sequencing on a Illumina Miseq. For 5 out of 6 patients, whole exome sequencing (WES) data was available from diagnostic biopsy. Diagnostic clonotypes were extracted from the WES data using the WholeMark algorithm in the ARResT/Interrogate pipeline.

Results: In 5 out of 6 CMMRD patients skewed clonotypes were identified in the BM at diagnosis of hematological malignancy. For the four patients with WES data available, three out of four of the abnormal clonotypes matched the diagnostic clonotype extracted from WES data.

Conclusions: Immunogenetic skewing was detected in the BM compartment of CMMRD patients diagnosed with hematological malignancies. Our findings suggest hematological malignancies may be detectable in the circulating (lymphoid) compartment and thus pave the road for future studies into early detection of non-Hodgkin's lymphoma and leukemia in patients with DNA repair disorders.

Disclosure: No.

Keywords: Immunogenetics, CMMRD, Early detection, Leukemia and NHL

PD428

PROLONGED EXCRETION of POLIOVIRUS AMONG INDIVIDUALS WITH PRIMARY IMMUNODEFICIENCY DISORDERS

POSTER DISPLAY 09: OTHER

Ondrej Mach
World Health Organization, Polio Eradication, Geneva, Switzerland

Background and Aims: Persons with primary immune deficiency disorders (PID), especially those disorders affecting the B-cell system, are at substantially increased risk of paralytic poliomyelitis and chronic poliovirus excretion if exposed to live poliovirus (endemic poliovirus or from live oral poliovirus vaccine). These individuals will constitute the only remaining reservoir of poliovirus after eradication of wild and vaccine derived foci; and may delay certification of poliovirus eradication.

Methods: We analyzed the epidemiology of prolonged and chronic immunodeficiency-related vaccine-derived poliovirus cases in a registry maintained by the World Health Organization.

Results: Between 1962 and 2016, there were 101 cases of ling poliovirus excretion among immunodeficient individuals. We documented an increase in incidence in recent decades, with a shift toward middle-income countries, and a predominance of poliovirus type 2 in 73/101 (72%) cases. The median length of excretion was 1.3 years (95% confidence interval: 1.0, 1.4) and 90% of individuals stopped excreting after 3.7 years. Common variable immunodeficiency, SCID and other combined humoral deficiencies as well as antibody disorders were risk factors for long-term excretion.

Conclusions: Chronic poliovirus excretion remains a rare event even among individuals with PID. Nevertheless, because these individuals are often not paralyzed they are missed by current poliovirus surveillance; therefore, specific surveillance for polioviruses among PID patients presenting PIDs that had been associated with chronic poliovirus excretion must be established. Regional immunodeficiency societies, in collaboartion with WHO, could play an important role in creating awareness about chronic poliovirus excretion and the need to identify and treat chronic poliovirus excretors.

Disclosure: No.

Keywords: poliovirus eradication, B cell immunodeficiency, long-term viral excretion, oral poliovirus vaccine

PD429

RISKS of BCG INFECTION IN PRIMARY IMMUNODEFICIENCIES PATIENTS VACCINATED WITH THE RUSSIAN BCG STRAIN.

POSTER DISPLAY 09: OTHER

Alexandra Laberko[1], Daria Yukhacheva[1], Nelly Kan[1], Anna Roppelt[1], Yulia Rodina[1], Anna Mukhina[1], Dmitry Pershin[1], Olga Kadnikova[2], Galina Solopova[2], Alexander Mushkin[3], Galina Novichkova[4], Anna Shcherbina[1]
[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [2]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Infectious Disease Prevention And Control, Moscow, Russian Federation, [3]Saint-Petersburg Research Institute of Phthisiopulmonology, Pediatric Surgery And Orthopedic Clinic, St.Petersburg, Russian Federation, [4]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Medical Director, Moscow, Russian Federation

Background and Aims: The live attenuated Mycobacterium bovis BCG vaccine is widely used to prevent tuberculosis. Post-vaccination BCG-infection is common in primary immunodeficiencies (PID). Distinct BCG-vaccine strains are used worldwide, but the Russian BCG-strain vaccine complications in PID are poorly characterised.

Methods: 778 patients with PID who received the Russian BCG-strain were identified in our center.

Results: 15% of patients developed BCG-infection (36% local, 17% regional and 47% disseminated). BCG-infection was observed in 82% of the patients with chronic granulomatous disease (CGD), 57% with severe combined immunodeficiency (SCID), 50% with innate immune defects (IID), 5% with combined immune defects (CID); and 2% with other PID. The median age at presentation of BCG-infecion was 4-5 months in the patients with SCID, CGD, CID and other PID and 12 months in the patients with IID ($p<0,005$). Dihydrorhodamine test values in CGD, T- and NK- cell counts in SCID and specific affected gene in various PID groups did not influence BCG-infection risks. Anti-mycobacterial therapy was given to all vaccinated SCID at diagnosis, even when no active BCG-infection was evident. More anti-mycobacterial agents were needed in disseminated compared to local/regional disease ($p<0,0001$). Only 1 of 114 patients died of complications related to BCG-infection.

Conclusions: Particular PID are highly predisposed to BCG-infection. Early initiation of anti-mycobacterial therapy in combination with anti-cytokine agents for transplant-related inflammatory syndrome prophylaxis and treatment in SCID[1] and complete cure of BCG-infection before hematopoietic stem cell transplantation in non-SCID patients may dramatically reduce BCG-associated mortality.

Disclosure: No.

Keywords: primary immunodeficiency, Inborn errors of immunity, Bacillus Calmette-Guierin, BCG infection, BCG strain

PD430

VERY EALY ONSET IBD WITH MUTATION IN INTERFERON REGULATORY FACTOR-2 BINDING PROTEIN 2 (IRF2BP2)

POSTER DISPLAY 09: OTHER

Seyedehatefeh Hashemimoghaddam[1], Zahra Chavoshzadeh[2], Samin Sharafian[3]
[1]Shahid Beheshti University of Medical Sciences, Department of Immunology And Allergy, Mofid's Children Hospital,, Tehran, Iran, [2]Pediatric Infections Research Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3]shahid beheshti medical university, Allergy And Immunology, tehran, Iran

Background and Aims: Very early onset IBD is a specific group of immunodeficiency in which several genes are involved and their numbers are increasing dramatically around the world.
We are going to introduce a case with a mutation in Interferon Regulatory Factor-2 Binding Protein 2 (IRF2BP2) whose presentation was with very early onset IBD

Methods: We describe the case report of a 2 year old boy with mutation in IRF2BP2 gene that was presented with early onset IBD

Results: A 2 year-old boy from non-related parents initially presented with intermittent bloody diarrhea.He was suspicious to have food allergy and he was underwent dairy avoidance regimen, but no improvement was seen in his symptoms. At the age of 1 year he was admitted to hospital due to fever and exacerbated bloody diarrhea.
Colonoscopy was done and revealed multiple deep ulcer hemoraghic leasions and diffuse aphetuse and pathology results showed Focal active colitis and cryptitis that which all indicated the diagnosis of IBD. In immunological work up, immunoglobulins were upper limit normal.flowcytometery was abnormal(reverse ratio of CD4/CD8)
Whole exome sequencing was done and missense mutation in IRF2BP2 gene was detected. c.2659G> A | p.Arg48Gly is a missense variant in exon 1 of IRF2BP2 gene and that was confirmed with sanger sequencing.
the patient underwent full dose treatment of IBD and IVIG.

Conclusions: Due to the genetic diversity in early onset IBD, it seems that complete immunological screening and complementary genetic evaluation in these patients is necessary.

Disclosure: No.

Keywords: IBD, IRF2BP2

PD431

MALE-FEMALE DIFFERENCES IN IMMUNOGLOBULIN LEVELS IN PRIMARY ANTIBODY DEFICIENCY (PAD) PATIENTS IN THE UNPAD STUDY

POSTER DISPLAY 09: OTHER

Ineke Reijnen[1], Lisanne Janssen[2], Maria Garcia[3], Miriam Gonzalez Amores[3], Leif G Hanitsch[4], Renate Krueger[4], Maria Carrabba[5], Lucia Baselli[5], Efimia Papadopoulou-Alataki[6], Judith Potjewijd[7], Milos Jesenak[8,9,10,11,12,13,14], Abraham Rutgers[15], Stefanie Henriet[16], Jaap Ten Oever[17], Esther De Vries[2,18]
[1]Elisabeth-Tweesteden Hospital, Pediatrics, Tilburg, Netherlands, [2]Tilburg University, Tranzo, Tilburg, Netherlands, [3]Valld'Hebron University Hospital, Immunology, Barcelona, Spain, [4]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Institute of Medical Immunology, Berlin, Germany, [5]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, UOS Malattie Rare, Dipartimento Di Medicina Interna, Milano, Italy, [6]Papageorgiou General Hospital, 4th Department of Pediatrics, Thessaloniki, Greece, [7]Maastricht University Medical Center+, Department of Internal Medicine, Division of Immunology, Maastricht, Netherlands, [8]University Hospital in Martin, Department of Allergology And Clinical Immunology, Martin, Slovak Republic, [9]Jessenius Faculty of Medicine, Comenius University in Bratislava, Centre For Periodic Fever Syndromes, Department of Pulmonology And Phthisiology, Martin, Slovak Republic, [10]University Hospital Martin, Department of Allergology And Clinical Immunology, Martin, Slovak Republic, [11]Jessenius Faculty of Medicine, Comenius University in Bratislava, Centre For Primary Immunodeficiencies, Department of Pulmonology And Phthisiology, Martin, Slovak Republic, [12]Jessenius Faculty of Medicine, Comenius University in Bratislava, Centre For Primary Immunodeficiencies, Department of Pediatrics, Martin, Slovak Republic, [13]University Teaching Hospital in Martin, Centre For Primary Immunodeficiences - Esid Registry Site, Department of Children And Adolescents, Jessenius Faculty of Medicine, Comenius University In Bratislava, Martin, Slovak Republic, [14]Jessenius Faculty of Medicine, Comenius University in Bratislava, Department of Pediatrics, Martin, Slovak Republic, [15]UMC Groningen, Department of Rheumatology And Clinical Immunology, Groningen, Netherlands, [16]Radboud University Nijmegen Medical Centre, Pediatric Infectious Diseases And Immunology, Nijmegen, Netherlands, [17]Radboudumc, Internal Medicine, Infectious Diseases, Nijmegen, Netherlands, [18]Elisabeth-Tweesteden Hospital, Laboratory For Medical Microbiology And Immunology, Tilburg, Netherlands

Background and Aims: Primary antibody deficiencies (PADs) without an identified monogenetic origin form the largest and most heterogeneous group of inborn errors of immunity. These patients often remain undiagnosed for years. The (ongoing) unPAD study was started in the ESID online Registry to investigate these patients further. We started analyzing male-female differences in laboratory values.

Methods: Immunoglobulin levels at diagnosis of completely monitored patient data from nine participating centers, diagnosed with common variable immunodeficiency (CVID), selective IgA deficiency (sIgAdef) or unclassified antibody deficiency (unPAD) were analyzed.

Results: In total 1010 patients (279 <18yrs) comprised significantly more adult women (58%), but boys predominated in the pediatric cohort (55%). In CVID patients, there were no male-female differences in immunoglobulin levels. In adults with sIgAdef, men had lower IgG3 ($p=0.015$) and IgM ($p=0.014$) levels; in children, boys had lower IgG2 ($p=0.035$) levels (but all these within the normal range). In adults with unPAD, men had lower IgG ($p=0.029$) and IgM ($p<0.001$) levels. In children with unPAD, boys had significantly lower levels of IgG ($p=0.018$).

Conclusions: We did not find significant male-female differences in immunoglobulin levels in CVID patients. In sIgAdef and unPAD patients, however, we found lower levels in some immunoglobulins in men/boys than in women/girls. This could point to undiagnosed X-linked disease hidden within these groups. We also found a different male-female ratio in the number of registered children vs. adults, suggesting that pediatric and adult disease are (in part) different entities. These first findings in the unPAD study underscore the heterogeneity of the group.

Disclosure: No.

Keywords: immunoglobulin levels, Primary Antibody Deficiency, male-female difference, unPAD study, ESID online Registry

PD432

DEFINITION of THE ROLE of MIRNA IN THE CLINICAL VARIABILITY of 22Q11.2DS

POSTER DISPLAY 09: OTHER

Giuliana Giardino[1], Antonietta Tarallo[1,2], Elisabetta Toriello[1], Antonio De Rosa[1], Emilia Cirillo[1], Cosimo Abagnale[1], Francesca Cillo[1], Emma Coppola[1], Federico Habetswallner[1], Loredana Palamaro[1], Davide Cacchiarelli[1,2], Giancarlo Parenti[1,2], Claudio Pignata[1]
[1]University of Naples "Federico II", Translational Medical Sciences, Napoli, Italy, [2]Telethon Institute of Genetics and Medicine, Tigem, Pozzuoli, Italy

Background and Aims: Chromosome 22q11.2 deletion syndrome (22q11.2DS) is the most common microdeletion syndrome with a widely variable clinical spectrum, with >200 features reported. Genetic alone cannot explain the variability of the phenotype. DiGeorge Critical Region Gene 8 (DGCR8) encoded in the deleted region is crucial for miRNA biogenesis and therefore, for gene regulation. Aim of this study is to evaluate the role of miRNA in the clinical variability observed in 22q11.2DS.

Methods: We characterized miRNA expression profile in the peripheral leucocytes of 14 patients with a typical 3Mb deletion and 3 patients with a distal deletion not including TBX1 and DGCR8 compared to 10 age-matched healthy controls. Nine out of 17 patients had a familial form and came from 4 different families.

Results: The unbiased hierarchical cluster analysis revealed significant clustering of the 22q11.2DS samples compared to normal controls. Samples from patients with distal deletion, clustered with patients with typical deletion. Twenty-nine differentially expressed miRNAs (padj<0.05) were identified. As expected, the expression of miR185, encoded in the proximal part of the deleted region, was comparable to controls in 3 patients with distal deletion. High similarity of miRNA expression among patients coming from the same family was observed in 3 out of 4 families.

Conclusions: Patients with 22q11.2DS display a different miRNA expression profile compared to healthy controls. The correlation of different miRNA profiles with the clinical phenotype, especially in family members, will help define the role of specific miRNAs in the variability of the clinical phenotype.

Disclosure: No.

Keywords: 22Q11.2DS, microRNA, differential expression

PD433

LONG-TERM OUTCOME of MILD WAS/XLT PATIENTS: EXPERIENCE FROM THE FRENCH NATIONAL REFERENCE CENTER FOR PRIMARY IMMUNODEFICIENCIES (CEREDIH).

POSTER DISPLAY 09: OTHER

Coralie Mallebranche[1,2], Charline Miot[1,2,3], Alain Fischer[4,5,6], Virginie Courteille[7], Philippe Randrianomenjanahary[7], Mickaël Alligon[7], Nizar Mahlaoui[6,7], Isabelle Pellier[1,2]
[1]CHU Angers, Pediatric Immuno-hemato-oncology Unit, Angers, France, [2]Univ Angers, Université de Nantes, Inserm, Cnrs, Crci2na, Sfr Icat, ANGERS, France, [3]CHU Angers, Laboratory of Immunology And Allergology, Angers, France, [4]Collège de France, Collège De France, Paris, France, [5]Imagine Institute, Université De Paris, Paris, France, [6]Necker Hospital, Pediatric Hematology-immunology And Rheumatology Unit, Paris, France, [7]Necker Hospital, French National Reference Center For Primary Immunodeficiencies (ceredih), Paris, France

Background and Aims: Mutations of the gene encoding the Wiskott-Aldrich syndrome protein leads to Wiskott-Aldrich syndrome and X-linked thrombocytopenia-XLT (WAS/XLT). The disease severity can be assessed with the Ochs-Zhu score. Usually, patients aged 2 years and above and presenting with a score < or = 3 are considered as having a mild WAS/XLT disease. The management of these patients (including Bone Marrow Transplantation (BMT)) largely depends on this clinical scoring. However, there is no consensual management guidelines for mild WAS/XLT. Previous publications have shown that patients with a low score in the first two years of life may eventually present severe and life-threatening complications.

Methods: We extracted and analyzed WAS/XLT patients data included in the French national reference center for primary immunodeficiencies (CEREDIH) registry.

Results: Data from 284 patients were available. Median age at the time of last follow-up was 12.8 years (range 0.04-58.8). Ninety-eight patients were classified as severe and 156 as mild WAS/XLT. Overall survival was 58% among severe WAS vs 80% among mild WAS/XLT patients ($p<10^{-3}$). Out of the latter group, 46 patients (29.5%) reached an Ochs score = or > 4 after 2 years of age. Overall, in the entire cohort, 117 patients underwent BMT, 28 of whom died of transplant-related complications. Remarkably, no death occurred in patients transplanted after 2010.

Conclusions: In the French cohort, one third of mild WAS/XLT patients developed severe life-threatening complications. As BMT outcome has remarkably improved during the last decade, our findings support BMT indication for all WAS/XLT patients.

Disclosure: No.

Keywords: Wiskott-Aldrich Syndrome, Ochs-Zhu score, X-linked thrombocytopenia, Mild WAS/XLT, Bone Marrow Transplantation, French national reference center for primary immunodeficiencies

PD434

IMMUNE CELL PROFILING of FIVE GOOD SYNDROME PATIENTS

POSTER DISPLAY 09: OTHER

Martin Perez-Andres[1], Alba Torres Valle[1], Larraitz Aragon[2], Cristina Serrano[3], Miguel Marcos[4], Pedro Pablo Arenas Cabo[2], Carolien Bonroy[5], Jana Neirinck[6], Alvaro Prada[2], Jacques J.M. Van Dongen[1,7], Alberto Orfao[1]
[1]University of Salamanca (USAL), Cancer Research Centre (ibmcc, Usal-csic; Ciberonc Cb16/12/00400), Institute For Biomedical Research of Salamanca (ibsal), Department of Medicine And Cytometry Service (nucleus Research Support Platform), Salamanca, Spain, [2]Donostia University Hospital, Immunology Department, San Sebastian, Spain, [3]Fundacion Jimenez Diaz, Servicio De Inmunologia, Madrid, Spain, [4]Hospital Clin Univ Salamanca, Servicio De Medicina Interna, Salamanca, Spain, [5]Ghent University, Department of Diagnostic Sciences, Ghent, Belgium, [6]Ghent University, Diagnostic Sciences, Ghent, Belgium, [7]Leiden University Medical Cente, Department of Immunology, Leiden, Netherlands

Background and Aims: Good's syndrome (GS) was initially defined as a rare association of thymoma and hypogammaglobulinemia. Although it has been proposed that it is a subset of Common Variable Immunodeficiency with thymoma, the knowledge of the disease is hampered by the incomplete and inconsistent reports due to low prevalence of the disease (1.5 cases per million). A more detailed dissection of the immune cells in a significant set of patients would contribute to understand the pathophysiology of the disease.

Methods: Up to 350 immune subpopulations were analyzed in five GS patients (49-63 years) from 3 different hospitals and 45 age-matched controls using nex-generation flow.

Results: In line with the hypogammaglobulinemia, all patients consistently presented with lack of B-cells. In addition, significantly reduced count of total CD4+ cells, NK-cells, eosinophils, CD141+ and plasmacytoids dendritic cells, was observed as compared to age-matched controls. Decreased counts of total CD4+ T-cells was due to reduced numbers of naïve cells and, in addition, lower Treg, TFH, Th2, Th17, Th22, Th1/Th17 and Th1/Th2, meanwhile number of Th1 cells was not different from age-matched controls. Interestingly, counts of naïve CD8+ and TCRgd+ cells were normal, meanwhile total CD8+ and TCRgd+ were increased due to significantly expanded effector memory and terminally differentiated CD8+ and TCRgd+ cells. All the other immune subsets analyzed were within the normal range.

Conclusions: A complex profile of immunedeficiency was observed in GS patients including not only lack of B-cells, but a also large spectrum of defects in the adaptative (CD4+Tcells) and innate cells, but preserved cytotoxic response.

Disclosure: No.

Keywords: Good syndrome, Cytometry, Immune profiling, IEI phenocopies

PD435

EYE INVOLVEMENT IN ADENOSINE DEAMINASE (ADA) DEFICIENCY SCID PATIENTS

POSTER DISPLAY 09: OTHER

Kritika Chetty[1,2], Andrea González-Torbay[1], Jinhua Xu-Bayford[1], Timothy Ronan Leahy[3,4], Andrew Gennery[5,6], Claire Booth[1,2]
[1]Great Ormond Street Hospital, Department of Immunology & Gene Therapy, London, United Kingdom, [2]University College London, Division of Infection And Immunity, London, United Kingdom, [3]Children's Health Ireland at Crumlin, Department of Paediatric Immunology And Infectious Diseases, Dublin, Ireland, [4]University of Dublin, Trinity College, Pediatrics, Dublin, Ireland, [5]Newcastle University, Translational And Clinical Research Institute, Newcastle upon Tyne, United Kingdom, [6]Great North Children's Hospital, Children's Haematopoietic Stem Cell Transplant Unit, Newcastle upon Tyne, United Kingdom

Background and Aims: ADA-SCID is an inherited disorder of purine metabolism leading to profound defects in lymphocyte development and function. Affected patients have an increased susceptibility to life-threatening infections typical of SCID. Due to the ubiquitous expression of the ADA enzyme, a build-up of toxic metabolites in ADA-SCID not only affects lymphocytes, but also leads to various extra-immune complications previously described (1). Conversely, the prevalence and nature of ophthalmic manifestations associated with the condition is less well-known. We aim to describe the ophthalmic manifestations associated with ADA-SCID within a multi-centre cohort of ADA-SCID patients.

Methods: We conducted a retrospective analysis of treated ADA-SCID patients after HSCT or Gene Therapy between May 2002 – May 2022 within three tertiary Paediatric Immunology and HSCT centres.

Results: Preliminary analysis reveals 104 ADA-SCID patients were treated, of which 42 were treated with gene therapy, and 62 with HSCT. Initial evaluation demonstrates 15 of these patients had various ophthalmic manifestations ranging from astigmatism to amblyopia and hypermetropia. Further data are to follow upon comprehensive analysis.

Conclusions: Our case series demonstrates a possible association between ADA-SCID and ophthalmic manifestations that has not previously been described and warrants further investigation. Further understanding of this association may provide insight into the physiology of the ADA-enzyme within the ophthalmic system, and importantly, will assist in better screening and management of these patients at long-term follow-up. 1. Whitmore K v., Gaspar HB. Adenosine deaminase deficiency - more than just an immunodeficiency. Frontiers in Immunology. 2016 Aug 16;7(AUG):314.

Disclosure: No.

Keywords: gene therapy, HSCT, Case Series, Severe combined immunodeficiency, adenosine deaminase deficiency, Eye Manifestations

PD436

CHRONIC RHINOSINUSITIS IN PEDIATRIC PATIENTS WITH PRIMARY IMMUNODEFICIENCY

POSTER DISPLAY 09: OTHER

Ezgi Belhan[1], Chinara Aliyeva[2], Sezin Kisabacak[3], Hatice Betul Gemici Karaaslan[3], Ulviye Mustu[3], Mehmet Ada[2], Haluk Cezmi Cokugras[3], Ayca Kiykim[3]
[1]Istanbul University-Cerrahpasa, Pediatrics, Istanbul, Turkey, [2]Istanbul University-Cerrahpasa, Departments of Otolaryngology - Head And Neck Surgery, Istanbul, Turkey, [3]Istanbul University-Cerrahpasa, Pediatric Allergy And Immunology, Istanbul, Turkey

Background and Aims: Primary immunodeficiencies are a heterogeneous group of diseases associated with an increased incidence of infections, autoimmunity, autoinflammatory diseases, allergies, and cancer. Rhinosinusitis is one of the most common infections in these patients. In our study, we aimed to determine the frequency of chronic rhinosinusitis (CRS) in our patients with primary immunodeficiency and to investigate the etiology of CRS

Methods: Forty-four patients (age range:4-26) diagnosed with primary immunodeficiency were enrolled in our study. Patients were interviewed about the symptoms of chronic rhinosinusitis and nasal endoscopic examinations were performed. The results of laboratory tests, medications, skin allergy tests, and the patients' lung computed tomography were retrospectively recorded from patient files.

Results: The distribution of patients' diagnoses included 38.6% (n:17) primary antibody deficiencies, 6.6% (n:3) combined immunodeficiencies, 27.3% (n:12) combined immunodeficiencies with syndromic features , 6.8% (n:3) phagocytic disorders, and 20.5% (n:9) immune dysregulation disorders. There was no significant difference in the frequency of chronic rhinosinusitis among the different immunodeficiency groups. There were no significant differences between chronic rhinosinusitis and conditions such as atopy, hypogammaglobulinemia, and treatments with immunoglobulin and/or azithromycin. The incidence of chronic rhinosinusitis was 77.8% in patients with a history of acute sinusitis and 20% in patients without a history of sinusitis, with a statistically significant difference between them (p=0.002).

Conclusions: CRS is more common in patients with primary immunodeficiencies than in the normal population. For effective treatment, it is necessary to identify the factors that cause chronic rhinosinusitis. Further studies involving larger patient populations are needed to explain the mechanisms of CRS.

Disclosure: No.

Keywords: immunodeficiency, allergy, pediatrics, chronic rhinosinusitis

PD437

HYPOPARATHYROIDISM RETARDATION AND DYSMORPHISM SYNDROME DUE TO MUTATIONS IN TUBULIN-SPECIFIC CHAPERONE E GENE AS A CAUSE of COMBINED IMMUNE DEFICIENCY

POSTER DISPLAY 09: OTHER

Eyal Kristal[1,2], Odeya David[1,2], Arnon Broides[1,2,3], Galina Ling[1,2], Nurit Hadad[2,4], George Shubinsky[2,5], Amit Nahum[2,3,6]
[1]Soroka medical center, Pediatric Ambulatory Center, Beer sheva, Israel, [2]Ben Gurion University of the Negev, Faculty of Health Sciences, Beer sheva, Israel, [3]Soroka medical Center, Pediatric Immunology Clinic, Beer sheva, Israel, [4]Ben-Gurion University of the Negev, Infectious Disease Laboratory, Beer sheva, Israel, [5]Soroka medical Center, Flow Cytometry Unit, Beer sheva, Israel, [6]Ben Gurion University of the Negev, The Primary Immunodeficiency Research Laboratory, Beer sheva, Israel

Background and Aims: Background: Hypoparathyroidism, retardation, and dysmorphism (HRD) syndrome is a disease composed of hypoparathyroidism, growth retardation, developmental delay , and typical dysmorphic features, caused by Tubulin-specific chaperone E gene mutation. Many patients succumb in infancy due to overwhelming infections mainly caused by Pneumococcus spp. Knowledge related to the immune system in these patients in scarce. Aims: To define the immune phenotype of a cohort of HRD patients including cellular, humoral and neutrophil functions.

Methods: The study included HRD patients followed at Soroka University Medical Centerr during 2021-2022 . Clinical, and, immunological data were obtained, including immunoglobulin concentrations, specific antibodies titers, lLymphocytes subpopulations numbers , lymphocyte proliferation studies and neutrophil functions.

Results: Nine patients (5 females and 4 males) were enrolled, aged 6 months to 15 years. All received Amoxicillin prophylaxis as part of a routine established previously. Three patients had bacteremia with klebsiella, shigella spp. and Candida. Two patients hadout of the two patients who had confirmed Corona Virus associated Disease 19 (COVID19), both died from this infection. All patients had normal to high IgA level, low anti-Pneumococcal antibodies, and reduced frequency of naive B cell with increased frequency of $CD21^{low}/CD27^{-}$ B cell. All patients had abnormal T cell population's distribution, including reduced TEMRA CD8, and inverted CD4/CD8 ratio, and , poor lymphocytes mitogen induced proliferation. Superoxide production and chemotaxis were normal in all patients tested.

Conclusions: HRD is a combined immune deficiency (CID) with severe invasive bacterial and viral infections and extreme susceptibility to COVID19.

Disclosure: No.

Keywords: Corona Virus Associated Disease 19, Hypoparathyroidism Retardation and Dysmorphism, combined immune deficiency

PD438

A NOVEL ERCC2 MUTATION IS ASSOCIATED WITH IMPAIRED NUCLEOTIDE EXCISION REPAIR (NER), HYPOGAMMAGLOBULINEMIA AND ALTERED COMPOSITION of LYMPHOCYTE SUBPOPULATIONS IN A TRICHOTHIODYSTROPHY (TTD) PATIENT

POSTER DISPLAY 09: OTHER

Raphael Rossmanith[1,2], Alexander Leiss-Piller[2], Christoph Geier[2,3,4], Roman Stemberger[2], Svetlana Sharapova[5], Martha Eibl[2,6], Hermann Wolf[2,7]
[1]Institute of Molecular Biosciences, University of Graz, Graz, Austria, [2]Immunology Outpatient Clinic, Immunology Outpatient Clinic, Vienna, Austria, [3]University Medical Center Freiburg, Department of Rheumatology And Clinical Immunology, Freiburg, Germany, [4]University Medical Center Freiburg, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [5]Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Research Department, Minsk, Belarus, [6]Biomedizinische Forschung und Bioprodukte AG, Research Department, Vienna, Austria, [7]Sigmund Freud Private University, Medical School, Vienna, Austria

Background and Aims: Trichothiodystrophy (TTD) is an autosomal-recessive disease caused by mutations in genes involved in nucleotide-excision repair pathway (NER). Although it is known that TTD can present with immunodeficiency, the underlying molecular mechanism and immunological phenotype is not well understood.

Methods: We report a TTD patient presenting with short stature, ataxia, short-brittle hair, hypogammaglobulinemia and decreased antibody response following vaccination. DNA-repair efficiency was evaluated in UV-irradiation assays testing $CD4^+$ and $CD8^+$ T-cells, B-cells as well as a lymphoblastoid B-cell line (LCL). Furthermore, the response to chemically induced DNA double-strand breaks and proliferation capacity in response to different stimuli was tested. Cellular immune phenotype was investigated using multicolor flow cytometry.

Results: Whole-exome sequencing revealed a novel heterozygous 17-bp duplication in the intron-14 exon-15 boundary of one ERCC2 allele and a previously described pathogenic point-mutation in the second ERCC2 allele. Functional analysis of the patient's lymphocytes showed persisting γ-H2AX levels, decreased proliferation activity and reduced cell viability following UV-irradiation, whereas in contrast to AT- and NBS lymphocytes the response to chemically induced DSBs was normal. Analysis of B-cell subpopulations showed decreased numbers of naïve and transitional B-cells.

Conclusions: In summary, our analyses confirmed the pathogenicity of a novel ERCC2 mutation. Furthermore, our study shows that deficiency of functional ERCC2 results in altered B-cell differentiation and IgG antibody production. The altered composition of B-cell subsets and the reduced activation of lymphocytes indicate importance of functional ERCC2 during differentiation and activation of lymphocytes, in particular B-cells.

Disclosure: No.

Keywords: Nucleotide-excision repair (NER), Trichothiodystrophy (TTD), DNA-repair deficiency, Primary Immunodeficiency (PID), hypogammaglobulinemia

PD439

CLINICAL CHARACTERISTICS AND LONG-TERM FOLLOW UP of A COHORT of IRANIAN PATIENTS WITH COMBINED IMMUNODEFICIENCY (CID): A MULTI-CENTER SURVEY

POSTER DISPLAY 09: OTHER

Zahra Chavoshzadeh Natanzi[1], Arefeh Zahamtkesh[2], Mahnaz Jamee[3], Nima Rezaei[1,4], Mehrnaz Mesdaghi[5], Seyed Alireza Mahdaviani[6], Narges Bazgir[1], Amir Hossein Hajialigol[7], Farimah Fayaz[8], Samin Sharafian[9]
[1]Shahid Beheshti University of Medical sciences, Allergy Dept, Tehran, Iran, [2]Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, Immunology And Allergy Department, Tehran, Iran, [3]Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Pediatric Nephrology Research Center, Tehran, Iran, [4]Tehran University of Medical Sciences, Research Center For Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran, Iran, [5]Shahid Beheshti University of Medical Sciences, Department of Allergy And Clinical Immunology, Mofid Children's Hospital, Tehran, Iran, [6]National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Pediatric Respiratory Diseases Research Center, Tehran, Iran, [7]Alborz University of Medical sciences, Non Communicable Diseases Research Center, Tehran, Iran, [8]Iran University of Medical Scienses, Colorectal Research Center, Tehran, Iran, [9]shahid beheshti medical university, Allergy And Immunology, tehran, Iran

Background and Aims: Combined immunodeficiency is characterized by defects in both humoral and cellular limbs of the immune system. Herein, we investigated the characteristics of Iranian non-syndromic CID patients and followed up their current disease status and therapeutic outcomes.

Methods: Medical records of patients with definite diagnosis of non-syndromic CID referred to three referral hospitals between 2006 and 2021were investigated and contacted to determine the current status of patients

Results: A total number of 136 patients)48.5% female and 51.5% male) at a median (IQR)age of 60 (36-124)months participated in the study. 100 (73.6%) patients had consanguineous parents.Family history of immunodeficiency was documented in 40 (29.4%)patients. The median (IQR)age at disease onset and diagnosis were7(3.7-27) and 24 (7.5-50)months, respectively. The most common manifestations were infections (123,90.4%) [mainly pneumonia (76, 55.9%), chronic diarrhea (31,22.8%), (ENT) infections (26, 19.1%), candidiasis (24, 17.6%),abscess (19, 14%),bronchiectasis (14, 10.3%), and UTI(13, 9.6%)],followed by skin disorders (62, 45.6%), atopy (59,43.4%), failure to thrive (FTT) (56,41.2%), autoimmunity (50,36.8%), and enteropathy (45,33.1%). Among clinical manifestations, enteropathy(p=0.007), autoimmunity(p=0.004),and cardiovascular disorders (p=0.013) were meaningfully distributed among different follow-up groups, In addition, lymphocyte (p=0.037) and IgG(p=0.006)serum levels were reversely correlated with death outcome. Patients underwent treatment with IVIG(55.1%),antibiotics (52.2%),antivirals (19,14%) and antifungals (16.9%). 7out of 29 (24.1%)patients, candidate for HSCT, had received transplantation. The overall mortality rate was 33.8% (n=46).Sporadic patients had higher mortality rate compared to familial patients(HR: 2.043,p=0.069)

Conclusions: CID patients have heterogenous clinical features which predispose patients to variable outcomes.Precise follow-up of CID patients is an essential step for the improvement in their health condition.

Disclosure: No.

Keywords: clinical presentation, Followup, Inborn errors of immunity, combined immunodeficiency

PD440

POSITIVE INFLUENCE of CHEMOTHERAPY FOR A SECONDARY MALIGNANCY ON MYELOID ENGRAFTMENT IN A SCID-PATIENT AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

POSTER DISPLAY 09: OTHER

Felix Maier[1], Manfred Hönig[1], Ansgar Schulz[2], Ingrid Furlan[3], Kerstin Felgentreff[3], Eva Jacobsen[3], Klaus Debatin[4]
[1]Pediatric Immunology, Rheumatology and Stem Cell Transplantation, Ulm University Hospital, Department of Pediatrics And Adolescent Medicine, Pediatric Immunology, Ulm, Germany, [2]University Hospital of Ulm, Germany, Bone Marrow Transplant, Ulm, Germany, [3]University Medical Center Ulm, Germany, Department of Pediatrics And Adolescent Medicine, Ulm, Germany, [4]Univeristy Medical Center Ulm, Department of Pediatrics And Adolescent Medicine, Ulm, Germany

Background and Aims: Chemotherapy for Secondary malignancies in patients post HSCT can potentially challenge mixed donor chimerism.

Methods: We report on a boy with X-SCID, who received a MUD transplant without conditioning at the age of 11 months. Because of a stage 4 cutaneous aGvHD, which was refractory to extended therapy he needed a second transplant after conditioning with Alemtuzumab, Treosulfan and Fludarabine. This resulted in mixed chimerism with 100% donor T-cells, 75% donor non-T-cells and 40% donor granulocytes (which corresponds to stem cell level). At the age of 9 years he developed an Ewing-sarcoma of the proximal radial forearm and was treated with chemotherapy, surgery and radiotherapy according to the EWING 2008 protocol.

Results: Surprisingly the granulocyte and non-T-cell chimerism improved to a proportion of almost 100% after regular cessation of his chemotherapy. After 27 months of follow up the patient is in complete remission with normal immune function.

Conclusions: Chemotherapy for a post-transplant secondary malignancy in a patient with SCID does not necessarily jeopardize donor cell engraftment and can even improve mixed chimerism.

Disclosure: No.

Keywords: SCID, chemotherapy after HSCT, HSCT, mixed chimerism

PD441

PREVALENCE of COCCIDIOIDOMYCOSIS IN PRIMARY IMMUNODEFICIENCY: DATA FROM THE USIDNET REGISTRY

POSTER DISPLAY 09: OTHER

Ifat Krase[1,2], The Usidnet Consortium[3], Keith Sacco[2]
[1]Mayo Clinic Arizona, Allergy And Immunology, Scottsdale, United States of America, [2]Phoenix Children's Hospital, Allergy And Immunology, Phoenix, United States of America, [3]USIDNET, Consortium, Townson, United States of America

Background and Aims: Coccidiomycosisis is a fungal infection endemic to the Southwestern United States, caused by the dimorphic fungi species Coccidioides immitis and Coccidioides posadasii. Most commonly, coccidiomycosis causes a self-limited mild respiratory illness. However, in certain populations such as immunocompromised patients, it may cause disseminated disease, and may be fatal. We aimed to assess the prevalence of coccidioidomycosis in primary immunodeficiency (PID) using the USIDNET registry.

Methods: We queried the USIDNET database on 17 March 2022 requesting demographic data on PID patients with a diagnosis of coccidiomycosis.

Results: We identified ten patients. Four patients (40%) identified as male. Nine patients identified as Caucasian. The median age of diagnosis with PID was 31.2 years. The most frequently reported PID in the cohort was common variable immunodeficiency (CVID) in five patients followed by chronic granulomatous disease (CGD) in two patients. Six patients were diagnosed with coccidioidomycosis prior to their PID diagnosis. of the cohort, three developed disseminated disease. Two patients developed pulmonary complications and one developed hydrocephalus. Four patients received antifungal prophylaxis. No patients underwent gene therapy or stem cell transplantation. Two patients, one with a STAT1 gain-of-function mutation and another with an autosomal recessive NCF1 mutation, received interferon gamma therapy.

Conclusions: This is the first report on the prevalence of coccidioidomycosis from the USIDNET registry. The prevalence was much lower than expected and highlights the likelihood of underreporting of coccidiomycosis in the PID population. When evaluating a patient with disseminated coccidiomycosis, an immunodeficiency evaluation may be beneficial to uncover potential undiagnosed immune defects.

Disclosure: No.

Keywords: primary immunodeficiency, infectious disease, registry, immunology, Coccidioidomycosis

PD442

CLINICAL AND IMMUNOLOGICAL CHARACTERISTICS of FIVE PATIENTS WITH PROTEIN-LOSING ENTEROPATHIES AND IMMUNODEFICIENCIES

POSTER DISPLAY 09: OTHER

Reyhan Gumusburun[1], Ceyda Tunakan Dalgiç[1], Sinem Inan[1], Ozan Sarıkaya[2], Meryem Demir[1], Emine Mete Gokmen[1], Omur Ardeniz[1]
[1]Ege University Medical Faculty, Department of Internal Medicine, Division of Allergy And Immunology, Izmir, Turkey, [2]Ege University Medical Faculty, Department of Internal Medicine, Division of Gastroenterology, ızmır, Turkey

Background and Aims: Protein-losing enteropathies (PLEs) present with edema, ascites, malnutrition, hypogammaglobulinemia, and lymphopenia. The spectrum of immune defects and their correlation with the clinical findings are variable in PLEs. We aim to investigate the findings of patients with PLEs and immunodeficiencies (IDs).

Methods: We analyzed 5 cases (2 females and 3 males with a mean age of 41.6 years) that were followed by our outpatient immunology clinic retrospectively. The secondary causes of PLEs were excluded. The immunological, histological and radiological parametres were analysed in order to investigate the clinical overlap of PLEs and IDs.

Results: The main complatins were abdominal discomfort and diarrhea. Edema was present in all (Table 1). Low IgG, albumine, and vitamin-D levels were the common laboratory finding (Tables 2, 3). The immunological examination revealed decreased IgG1, IgG2 and lymphocytopenia with low CD3, CD4, CD8, CD19, and NK cells. A reduction in the percentages of naive CD4+ and CD8+, a predominance of effector memory CD4+ and CD8+ T cells, and increased percentages of CD21low B cells were present. CD55 expression levels were within the normal ranges on PBMCs. Primary intestinal lymphangiectasia(PIL) was diagnosed by endoscopic and/or histological evaluation in 3 of 5 patie nts (Table 4).

Table 1.The clinical findings of the 5 cases with PLEs

Patient	#1	#2	#3	#4	#5
Age/sex	59/F	21/M	20/M	54/M	54/F
Symtoms (age of onset)	Abdominal discomfort (58)	Abdominal discomfort (4), Diarrhea (4)	Chylous acid(3), Asymmetric edema	Diarrhea (2)	Abdominal discomfort (37), Diarrhea(37)
Peripheral edema (age of onset)	2+/ 2+pitting(6)	4+/4+(17)	2+/2+(1)	3+/3+ (5)	+1/+1(17)
Ascites (age of onset)	N	Y(17)	N	N	Y(17)
Chylous acid (age of onset)	N	N	Y (20)	N	Y(27)
Thrombosis	N	N	Y (Right vena saphena parva)	N	Y
Frequent infection	N	Y	N	N	N
Comorbidity	Nephrolithiasis, Cirrhosis,	Pituitary Hormone Deficiencies, Bipolar disorder	N	Hypertension, Dyslipidemia	Partial situs inversus Hypothyroidism, Hypertension, Celiac Disease Chronic kidney failure
Operation history	Appendicitis, Umbilical hernia	Resection of lymphangiectatic segment	Umbilical hernia Hydrocele Appendicitis	N	Surgery due to ring-like vesicle (band) and mesenteric LAP around the proximal jejunum

Y=present, N=not present

Table 2.The laboratory findings of the cases with PLEs and immunodeficiency

Patient	#1	#2	#3	#4	#5
Serum iron(µg/dl) (37-145)	81	**16**	89	94	80
Ferritin (µg/l) (13-150)	20	57	56.9	54	50
Vitamin B12(ng/l)(197-866)	416	274	257	216	311
Folate (µg/l) (3.89-26.8)	7.23	5.09	**3.3**	10.3	14.3
Vitamin D(ng/ml)(20-50)	12	**5**	**18**	**15**	**11**
Vitamin A (µg/l)(316-820)	635	**133**	678	**1261**	NA
Vitamin E(mg/l) (6.6-820)	7.8	**1.1**	12.8	13.9	NA
Calcium(mEq/l) (8.6-10.2)	8.74	8.7	9.4	8.8	8.7
Zinc(µg/dl) (70-120)	76	**43**	**68**	108	**57**
Magnesium(mg/l)(1.5-2.6)	2.07	1.87	2.06	2.1	2.1
Triglycerides(mg/dl) (<150)	65	68	36	**293**	96
HDL(mg/dl)(>50)	**42**	**29**	68	**49**	116
LDL(mg/dl)(<130)	109	93	93	118	109
VLDL(mg/dl)(2-30)	13	NA	7	**59**	NA
T.Cholesterol(mg/dl)(<200)	164	106	168	**226**	182
Apo A1(mg/dl)(108-225)	144	64	181	152	173
Apo B(mg/dl)(60-117)	104	70.3	81.6	143	100
Albumin(g/l)(35-52)	**27.4**	**25.5**	**25.2**	**26.3**	**23.9**
Globulin(g/l) (25-35)	**18.3**	**19.9**	**16**	**18.4**	**15.5**
C3(mg/dl) (90-180)	140	133	103	158	108
C4(mg/dl) (10-40)	21	31	15	28	20
Protein(urine)(mg/dL)	Negative	Negative	Negative	Negative	Protein (24 h. urine): Negative
Fecal alpha-1 antitrypsin (ug/g)	**>1800 (µg/g)(100-500)**	NA	**87.29(mg/dl) (<1mg/dl)**	**>1800 (µg/g)(100-500)**	**>1800 (µg/g)(100-500)**

NA=not available, (reference range), values outside reference range in bold

Table 4. The histologic and radiographic findings of the patients with PLEs and immunodeficiencies.

Patient	Histologic findings	Radiographic findings
#1	**Esophagogastroduodenoscopic biopsy:** Intestinal metaplasia, chronic atrophic gastritis, duodenal mucosa with minimally blunted villi, edematous small intestinal mucosa **Colonoscopic biopsy:** Creamy white, punctate ("snowflake") mucosal lesions on the ileum consistent with intestinal lymphangiectasia Subepithelial minimally enlarged lymphatic vessel structures were observed in some villus structures in D240 due. **Liver biopsy:** Chronic hepatitis + common bridge fibrosis	**Whole body CT:** A diffuse increase was observed in the wall thickness of the jejunal and ileal loops, intestinal lymphangiectasia is also included in the differential diagnosis. There is a loss of parenchyma with the decrease in right kidney size and parenchymal thickness. Dilatation was observed in the right kidney pelvicalyceal structures, irregularity in liver contours, moderate ascites at the level of segment 4, intraabdominal minimal fluid. **Portal system ultrasonography:** No portal hypertension was detected
#2	**Esophagogastroduodenoscopic biopsy:** In the samples taken from the duodenum, dilatation was observed in several superficial lymphatics. **In the surgical material of the 104 cm jejunum,** numerous enlarged lymphatic vessels were observed in the mucosa and submucosa. Macroscopically, on the cross-sectional surface of these areas, grayish-pearl cystic spaces with chylous material are observed. **Skin (flanks biopsy, over tester):** Vascular ectasia findings were observed.	**Thorax CT angiography:** Since the brachiocephalic vein is not developed, the subclavian vein opens directly into the second intercostal vein. In the second intercostal vein, the flow is towards the hemiazygos system and from here, the transition to the azygos system is observed. The return to the heart occurs from the left side through the azygos knob. **Abdominal MRI:** In the case of bilateral pleural effusion and intra-abdominal acid findings, nonspecific diffuse wall thickening and appearances that may support are hypertrophy were observed in the small intestines. Bilateral hydroceles were observed. The left testis is located in the inguinal canal. There is diffuse edema in the subcutaneous tissue. **Lymphoscintigraphy:** While the left common iliac, left internal iliac, and left lateral aortic lymph nodes are visualized in the pelvic images taken, lymphatic flow cannot be visualized in the symmetrical area. **Portal system ultrasonography:** Portal vein 15 mm, splenic vein 8 mm, superior mesenteric vein 13 mm. in diameter. Flow directions in these vessels are hepatopetal
#3	**Esophagogastroduodenoscopy:** Normal	**Abdominopelvic CT:** Asymmetrical thickening of the skin and subcutaneous fatty tissue, more prominent in the left half of the abdomen and the posterior part, increased vascularization together with fatty tissue heterogeneities brought to mind the possibilities of venous angioma and lymphangiectasia
#4	**Esophagogastroduodenoscopic biopsy:** Creamy white, punctate ("snowflake") mucosal lesions on duodenal mucosa consistent with intestinal lymphangiectasia **Colonoscopic biopsy:** Tubulovillous adenoma + focal high-grade dysplasia. Dilated lymphatic channels **Skin, shave biopsy:** Actinic keratosis **Skin, shave biopsy:** Squamous cell carcinoma in situ	**Whole body CT:** Hepatomegaly and mesenteric periaortic aortocaval millimetric multiple lymph nodes.
#5	**Esophagogastroduodenoscopic biopsy:** Antral foveolar hyperplasia + focal intestinal metaplasia. **Duodenal biopsy:** Flattening of the villous structure, blunting, sporadic mononuclear cell infiltration in the surface covering epithelium, which usually maintains regularity. **Jejunum biopsy:** Subtotal villous atrophy.	**Thorax CT:** Bilateral pleural fluid and pericardial fluid are present. Azygos continuous inferior vena cava variation and aberrant right subclavian artery variation in the aortic arch are observed. **Upper abdomen MR:** Situs inversus anomaly + congenital deformity in both kidneys. **Abdominal Ultrasonography:** Hepatosteatosis and pericardial effusion. Findings are compatible with chronic kidney failure.

ND=first done, A USG= abdominal usg

Table 3. The immunological evaluation of the patients with PLEs.

Patient	Normal Range	#1	#2	#3	#4	#5
IgG(mg/dl)	767-1590	**455**	**593**	**349**	**154**	**401**
IgM(mg/dl)	37-286	104	51	52	**18**	**640**
IgA(mg/dl)	61-356	109	87.7	107	**32**	192
IgE(kU/l)	<100	33.8	NA	46.6	23.8	NA
IgG1(mg/dl)	490-1140	**321**	**316**	**235**	**157**	**288**
IgG2(mg/dl)	150-640	163	**117**	**95**	**56.6**	**81**
IgG3(mg/dl)	11-85	35	21.7	**12.9**	**5.6**	20
IgG4(mg/dl)	3-200	<7.3	27.1	95.2	7.4	7
Lymphocytes absolute	650-2800	1380	**390**	**310**	**500**	750
CD3 (cells/µl)	700-2100	1228	**304**	**155**	**405**	**502**
CD4 (cells/µl)	300-1400	**441**	**85**	**37**	**40**	**277**
CD8 (cells/µl)	200-900	703	**168**	**77.5**	270	**135**
CD19 (cells/µl)	100-500	**82**	**27**	**77.5**	**20**	**52**
NK(cells/µl)	90-160	**82**	**46**	**71.3**	**75**	**172**
NKT		8.09	22	4	40	1.5
Naive B cells %	43.2-82.4	68.5	70.2	82.4	71.9	63.1
IgM memory cells %	7.2-30.8	**4.98**	9.09	**0.5**	11.8	9.9
Switched memory cells%	6.5-29.2	10.21	13.5	9.98	12.2	18.2
CD21 low cells %	0.8-7.7	**12.38**	**8**	2.1	**13.89**	**8.87**
Transitional cells %	0.6-3.5	1.92	1.51	1.4	**7.55**	**3.06**
Plasmoblast %	0.4-3.6	1.05	1.65	**6.4**	1.87	1.85
Naive CD4 %	14-67	NA	**4.52**	**3.87**	**11.46**	**2.3**
TCM CD4 %	26-64	NA	**23.09**	49.3	48.61	52.4
TEM CD4 %	5-30	NA	**71.08**	**44.5**	**38.45**	**44.5**
TEMRA CD4 %	0-4	NA	1.31	2.18	1.48	0.6
Naive CD8 %	25-73	**2.44**	**10.5**	**7.06**	**13.05**	**3.7**
TCM CD8 %	6-40	**3.58**	**4.16**	**4.84**	37.59	17.3
TEM CD8 %	6-34	**54.74**	33.9	**59.94**	28.90	**65.4**
TEMRA CD8 %	5-33	**39.23**	**52.08**	28.15	20.46	13.5
PPV23 antibody titers (µU/ml) (basal/after vaccination)		3010.2/NA	NA*	145.1/2041	NA*	270.1
Tetanus antibody titers (IU/ml) (basal/after vaccination)	<0.01	0.13/NA	NA*	0.61/>5	NA*	NA
Isohemagglutinin titers	≥1:10	1/128	1/16	1/32	1/32	1/16

NA=not available. PPV23= 23-valent pneumococcal capsular polysaccharide vaccines. *=could not be performed due to IVIG therapy

Conclusions: PIL should be considered in cases presented with hypoalbuminemia, hypogammaglobulinemia, lymphopenia and peripheral edema. Rarity of late-onset PIL might be linked to underestimation. Unlike the literature, our PIL cases presented low B and NK cells number.

Disclosure: No.

Keywords: Immunodeficiencies, Protein-Losing Enteropathies, Primary Intestinal Lymphangiectasia

PD443

CURRENT SEASONAL IGG MEDICINAL PRODUCTS ARE ACTIVE AGAINST EXPECTED FUTURE INFLUENZA VIRUS STRAINS

POSTER DISPLAY 09: OTHER

Jose Maria Diez, Daniel Casals, Carolina Romero, Rodrigo Gajardo
Grifols, Immunotherapies Unit, Bioscience R&d, Scientific Innovation Office, Barcelona, Spain

Background and Aims: Patients with primary immunodeficiency (PID) and secondary immunodeficiency (SID) experience frequent respiratory tract infections that are typically managed with antibiotics and immunoglobulin (IgG) replacement therapy. Influenza virus infectious is a serious concern for these patients and a global public health issue. Deaths due to influenza viruses are estimated between 290,000 and 650,000 annually. In this study, we have demonstrated that current IgG products (for intravenous, subcutaneous or intramuscular administration) have the capacity to neutralize and inhibit the hemagglutination not only with present virus strains, but also with future influenza virus strains.

Methods: Hemagglutination inhibition and or neutralization assays were performed with viruses from quadrivalent vaccine for use in the 2022-2023 influenza season in the northern hemisphere ─Influenza A: Victoria/2570/2019 (H1N1) and Darwin/9/2021 (H3N2)-like virus; Influenza B: Austria/1359417/2021 (B/Victoria lineage); and Phuket/3073/2013 (B/Yamagata lineage)─.

Results: All products tested showed the capacity to inhibit the hemagglutination and/or neutralize the virus, these results where compared with those previously obtained for present circulating virus strains which showed similar results.

Conclusions: Current IgG products have the potential to inhibit or neutralize influenza viruses expected for future influenza vaccines in addition to neutralize or inhibit current circulating strains, a relevant data for patients with immunodeficiencies since their response to vaccination is limited. Therefore, these products have potential for both preventing and treating influenza infections in immunocompromised patients. Further investigations are needed.

Disclosure: The authors of the study are full-time employees of Grifols, a manufacturer of intravenous immunoglobulins.

Keywords: SID, neutralization, hemagglutination inhibition, IgC, Influenza, PID

PD444

ACCREDITATION FOR IMMUNODEFICIENCY SERVICES – SUPPORTING QUALITY IMPROVEMENT

POSTER DISPLAY 09: OTHER

Claire Bethune[1], Katy Thistlethwaite[2], Dragana Smith[3]
[1]University Hospitals Plymouth NHS Trust, Immunology And Allergy Service, Plymouth, United Kingdom, [2]Royal College of Physicians, Accreditation Unit, London, United Kingdom, [3]Royal College of Physicians, Accreditation Unit, Plymouth, United Kingdom

Background and Aims: The Quality In Immunodeficiency Accreditation scheme (QPIDS) was established to support immunodeficiency centres to measure and improve the service provided for adults and children with immunodeficiencies. This review assesses the uptake and impact of the scheme.

Methods: Services that have registered were identified through the Royal College of Physicians (RCP) accreditation unit. Qualitative feedback was collected from services that have achieved accreditation as well as those registered services that have not yet completed the process.

Results: 39 services (over 90% of UK immunodeficiency services) have registered with the QPIDS scheme. Achieving accreditation requires submission of evidence demonstrating the achievement of specific standards in domains including leadership, clinical effectiveness, person centred care, workforce, patient safety and home therapy. Trained assessors review on-line evidence submitted by the service and then visit to interview the clinical team and inspect the facilities. Each year accredited services complete an annual report to demonstrate that they continue to achieve the standards. 21 services have been awarded accreditation through the QPIDS scheme. Services not yet accredited cite the time required to complete the submission as the main barrier. Feedback from accredited services report improvement in the service provision, team working and profile of the immunodeficiency service in the hospital.

Conclusions: The majority of UK immunodeficeincy services have registered with the QPIDs scheme and over half have achieved accreditation. Feedback from accredited services has been very positive. Further work needs to be done to identify the support needed that would help registered services achieve accreditation.

Disclosure: Claire Bethune is clinical lead for the RCP QPIDS accreditation scheme, Dragana Smith is Senior Project Manager and Katy Thistlethwaite is program coordinator both for the RCP QPIDS accreditation scheme

Keywords: Accreditation, Quality Improvement, immunodeficiency, Standards

PD445

WHAT HAS HAPPENED TO OUR IMMUNODEFICIENCY CLINICS?

POSTER DISPLAY 09: OTHER

Claire Bethune[1], Christine Symons[1], Katy Thistlethwaite[2]
[1]University Hospitals Plymouth NHS Trust, Immunology And Allergy Service, Plymouth, United Kingdom, [2]Royal College of Physicians, Accreditation Unit, London, United Kingdom

Background and Aims: The first COVID-19 lockdown in March 2020 led to a dramatic increase in remote consultations for patients with immunodeficiencies. The number of clinics held remotely was reviewed at different time points during the pandemic and a survey of attitudes of patients and clinicians to these clinics undertaken.

Methods: Information about outpatient clinic arrangements was collected in online surveys of immunodeficiency services (Quality in Immunodeficiency services census 2020/2021) and from patients (immunodeficiency UK patient survey 2021). The results were presented to an audience of immunodeficiency experts at the UKPIN conference and feedback from delegates was recorded using an online platform.

Results: Between February 2020 and April 2020 almost all face-to-face immunodeficiency clinic activity stopped in the UK, with the majority of appointments being replaced by remote consultations. The 2021 census revealed that despite the lifting of lock down restrictions only 27% of clinics for adult patients with immunodeficiencies were taking place in person by June 2021. The majority of remote consultations took place by telephone with only a minority using video consultations. Some advantages to remote consultations were described by patients and clinicians however significant disadvantages were also highlighted and some circumstances identified when a face to face appointment was felt to be essential.

Conclusions: Since the start of the pandemic more appointments for patients with immunodeficiencies have been held remotely however there is a consensus that some clinic appointments are better held in person. Work needs to be done to identify whether different outcomes result from the different types of consultation.

Disclosure: No.

Keywords: immunodeficiency, clinics, COVID-19

PD446

HEALTH-RELATED QUALITY of LIFE AMONG CHILDREN WITH INBORN ERRORS of IMMUNITY AT AIN SHAMS SPECIALIZED CHILDREN HOSPITAL, CAIRO, EGYPT : A CROSS SECTIONAL STUDY

POSTER DISPLAY 09: OTHER

Yehia El-Gamal[1], Azza Youssef[2], Abeer Sayed[3], Nesrine Radwan[1]
[1]Children's Hospital, Ain Shams University, Pediatric Allergy, Immunology & Rheumatology, Cairo, Egypt, [2]Children' Hospital, Ain Shams University, Developmental And Behavioral Paediatrics, Cairo, Egypt, [3]Ministry of Health, Pediatrics, Cairo, Egypt

Background and Aims: Background: Inborn Errors of Immunity (IEI) significantly influences patient life, limiting their physical and social activities. Health-related quality of life (HRQOL) can also be adversely impacted by delays in diagnosis and in treatment for infections.This study aimed at assessing the HRQOL of IEI patients at a major tertiary care hospital in Egypt, which is a country with moderate level health care facilities.

Methods: We used the Arabic version of pediatric quality of life inventory generic core scale (PedQl 4.0) questionnaire as reported by patients or one of their parents after approval.The Mapi Research Trust granted permissions for use (10-2-2020) .

Results: The study included 50 IEI patients, more than half of which were males (34=68%) and 16 (32%) females. Their mean ± SD of age 86.8 ± 36.9 months. The lowest score was reported for school functioning with a mean score of 33.23 (SD=14.06) and social functioning score were significantly lower among those older (P=0.034). Rate and Duration of hospitalization negatively affected the social functioning (p=0.035 and 0.002 respectively). The presence of pulmonary complications as bronchiectasis/interstitial lung disease caused a decline in quality of life (p=0.011). The intake of IVIG had no effect on the QOL in spite the burden of going to the hospital.

Conclusions: Conclusion: This study showed IEI patients suffer from a low quality of life score that influences both school and physical functioning. Healthcare providers managing IEI patients in Egypt should evaluate their quality of life to ensure optimal school and emotional wellbeing of the child.

Disclosure: No.

Keyword: Health Related Quality of life, In born Errors of Immunity, Intravenous Immunoglobulin

PD447

THE LIVED EXPERIENCE of HEREDITARY ANGIOEDEMA: THE RELATIONSHIP BETWEEN ILLNESS REPRESENTATIONS, WELLBEING, QUALITY of LIFE AND COPING IN PATIENTS WITH HEREDITARY ANGIOEDEMA

POSTER DISPLAY 09: OTHER

Jade Elliott[1], Isobel Lindsay-Wiles[1], Amy Burton[1], Daniel Herron[1], Alison Owen[1], Lavanya Diwakar[2], Hae Uk[3]
[1]Staffordshire University, Center For Psychological Research; Health, Science And Wellbeing, Stoke on Trent, United Kingdom, [2]University Hospitals of North Midlands NHS Trust, Immunology, Stoke on Trent, United Kingdom, [3]HAE UK, Charity Support Group, Bridgwater, United Kingdom

Background and Aims: Hereditary angioedema (HAE) is a rare inherited illness. Patients experience recurrent swellings commonly affecting the limbs, genitals, face, or abdomen. Attacks can be distressing and significantly impair quality of life. Illness representations are an individual's cognitive appraisal of a medical condition and its consequences and fall along five dimensions, timeline, control/curability, identity, causes and consequences. The self-regulation model of illness behaviour proposes that when an individual is faced with a health threat, they are motivated by their illness representations to reduce risk. This theoretical framework has been used to explore illness perceptions across a range of illnesses but has not yet been applied to HAE. This submission reports on the relationship between illness representations, quality of life and mental wellbeing as part of a wider mixed-methods study exploring the lived experience of HAE.

Methods: 65 participants from the United Kingdom were recruited via a specialist charity group and completed online questionnaires.

Results: HAE patient mental wellbeing was positively correlated with all aspects of quality of life. Patients with lower socioeconomic status, as measured by household income, experience HAE more negatively. Illness representations relating to impact on life, symptoms experienced, levels of concern with HAE and emotional affect were all negatively associated with mental wellbeing.

Conclusions: How patients with HAE think about their illness has significant implications for their mental wellbeing. Interventions to support the psychological needs of HAE patients are a priority, particularly for those of lower socioeconomic status for whom the negative impacts of HAE may be more acutely experienced.

Disclosure: No.

Keywords: Illness representations, coping, wellbeing, psychology, quality of life, Hereditary Angioedema

PD448

PEDIATRIC ARPC1B DEFICIENCY A CASE SERIES of FOUR CHILDREN IN MOROCCO

POSTER DISPLAY 09: OTHER

Ilham Fadil[1], Hind Ouair[2], Jouida Abla[3], Asmaa Drissi Bourhanbour[4], Jalila El Bakouri[5], Ibtihal Benhsaien[6], Ahmed Aziz Bousfiha[7], Fatima Ailal[6]
[1]Faculty of Medicine and Pharmacy, Hassan II University,, Laboratory of Clinical Immunology, Inflammation, And Allergy (licia), casablanca, Morocco, [2]Faculty of Medicine and Pharmacy, Hassan II University,, Laboratory of Clinical Immunology, Inflammation, And Allergy (licia),, casablanca, Morocco, [3]Faculty of Medicine and Pharmacy, Hassan II University,, Clinical Immunology Unit, Department of Infectious Diseases, casablanca, Morocco, [4]Clinical Immunology, Autoimmunity and Inflammation Laboratory (LICIA), Faculty of Medicine And Pharmacy of Casablanca, Hassan Ii University, CASABLANCA, Morocco, [5]Faculty of Medicine and pharmacy of Casablanca, Research Laboratory In Clinical Immunology And Inflammation (licia), Casablanca, Morocco, [6]Hassan II University, Faculty of Medicine And Pharmacy, Casablanca, Morocco, [7]Faculty of Medecine and Pharmacy, University Hassan II, Casablanca, Laboratory of Clinical Immunology, Inflammation And Allergy (licia), CASABLANCA, Morocco

Background and Aims: ARPC1B deficiency is an autosomal recessive syndrome, belonging to the group of combined immune deficiencies. Characterized by a wide range of heterogeneous clinical and immunological phenotypes, ranging from a picture of platelet abnormality, vasculitis, asthma, allergies, and predisposition to inflammatory diseases to an elevated IgA and IgE picture. We aimed to evaluate the spectrum of clinical and immunological features in pediatric patients with ARPC1B deficiency in Morocco

Methods: This case report concerns four pediatric patients with a diagnosis of IEI who were seen in the immunology department of the Abderahim Harouchi pediatric hospital in Casablanca. The clinical characteristics of the patients guided us to perform the following tests: complete blood count, serum immunoglobulin assay, lymphocyte subpopulation assay, and molecular study to confirm the diagnosis of ARPC1B deficiency.

Results: Common clinical features of patients were recurrent bacterial or viral respiratory and/or skin infections, allergic reactions, and growth retardation. In two of the four patients, there were bleeding disorders, eczema with achromic lesions pityriasis Versicolor in two patients Hypereosinophilia, normal platelet count and elevated total serum IgE were detected in all patients, while decreased mean platelet volume was recorded in one-two of the patients, with elevated IgA in only one. The genetic study revealed three new homozygous mutations that have never been reported before two mutations in exon 7 and one mutation in exon 4

Conclusions: We have identified three novel mutations of the ARPC1B gene, which lead to combined immune deficiency with recurrent skin and respiratory infections, allergic reactions, and bleeding disorders.

Disclosure: No.

PD449

MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE MASQUERADING AS HISTIOCYTOSIS

POSTER DISPLAY 09: OTHER

Archan Sil[1], Prabal Barman[2], Ankur Jindal[1], Amit Rawat[2], Deepti Suri[2], Surjit Singh[2]
[1]Postgraduate Institute of Medical Education and Research, Chandigarh, India, Allergy And Immunology Unit, Advanced Pediatrics Center, Chandigarh, India, [2]Post Graduate Institute of Medical Education and Research, Chandigarh, Allergy-immunology Unit, Dept of Paediatrics, Chandigarh, India

Background and Aims: Mendelian susceptibility to mycobacterial disease (MSMD) results in vulnerability to develop infections by weakly virulent mycobacteria.

Methods: We report a 2 year 11 month old girl who presented with abdominal distension for 1 year, and multiple neck swellings, intermittent fever and progressive pallor for 3 months.

Results: She had generalized lymphadenopathy, eczematous skin rashes, tachypnea and spleno-hepatomegaly. Laboratory investigations showed anemia and thrombocytopenia with elevated inflammatory markers. Infective work up including tuberculosis, kala-azar, cytomegalovirus and HIV came negative. Contrast enhanced computed tomography showed patchy consolidation with ground glass opacities in dependent region of both lungs. Fine needle aspiration from lymph node was suggestive of granulomatous inflammation. Lymph node biopsy and bone marrow biopsy showed infiltration of mixed histiocytic population. The child was started on oral prednisolone. Whole exome sequencing revealed a homozygous c.201-2A>G splice variant in intron 2 of IFN-γR1 gene. Therefore, immunological work up for MSMD were sent that showed reduced expression of phospho STAT-1 and phospho STAT-4 on gated monocytes and decreased IFN-γ receptor 1 expression on activated granulocytes and monocytes in the index child compared to control. Diagnosis of MSMD was considered. The child was started on anti-tubercular treatment with isoniazide, rifampicin, levofloxacin and ethambutol. There was recurrence of fever, rashes and organomegaly 4 months after initiation of treatment when Mycobacterium fortuitum was isolated from lymph node biopsy. Therefore, the child was started on injection amikacin, oral cefixime and oral levofloxacin in addition to isoniazide, rifampicin and ethambutol (HRE).

Conclusions: MSMD can rarely present as histiocytic disorders initially.

Disclosure: No.

Keywords: Mendelian susceptibility to mycobacterial disease, Histiocytosis, Mycobacteria

PD450

A RARE CAUSE of IMMUNODEFICIENCY : TWO SISTERS WITH DIAGNOSIS of ADENOSINE DEAMINASE (ADA) ENZYME DEFICIENCY

POSTER DISPLAY 09: OTHER

Ezgi Cay[1], Dilek Ozcan[2], Atıl Bisgin[3], Derya Ufuk Altıntaş[2]
[1]Cukurova University , Faculty of Medicine, Paediatrics, Adana, Turkey, [2]Cukurova University , Faculty of Medicine, Allergy And Immunology, Adana, Turkey, [3]Cukurova University , Faculty of Medicine, Medical Genetics, Adana, Turkey

Background and Aims: ADA enzyme deficiency is a rare cause of primary immunodeficiencies. We aimed to present the differentially progressing disease course of two sisters with ADA enzyme deficiency by comparing the clinical, laboratory and radiological examinations before and after treatment .

Methods: Case 1 applied with respiratory distress and recurrent lung infections when she was 3 months old. Case 2 applied with pneumonia when she was 1 month old. The clinical and laboratory findings of both were suggestive of immunodeficiency. Clinical exome analysis was sent for diagnostic purposes .Clinical exome was ADA gene; NM_000022.4 c.956_960delAAGAG (p.e319Gfs*3) (p.Glu319GlyfsTer3) (Homozygous) , in both cases .

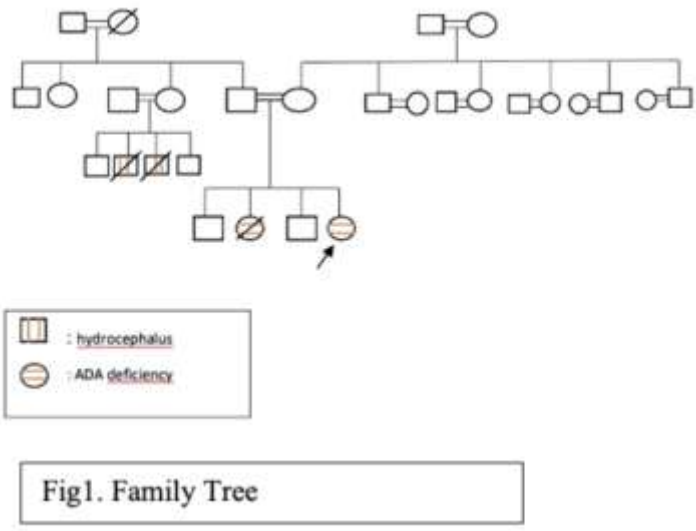


Fig1. Family Tree

Results: The first case was given IVIG treatment. Bone marrow transplantation (BMT) could not be performed because a suitable donor could not be found and the patient died due to sepsis when she was 8 months old. The second case was treated with IVIG treatment, ADA enzyme replacement therapy and unrelated allogeneic BMT. In both cases, lymphopenia was remarkable. While there was no improvement in lymphopenia after IVIG and enzyme replacement therapy in case 2, improvement in lymphopenia was noted after the BMT. The first case had unexplained hypertension , left ventricular hypertrophy .In both cases, scapular spurs were noticed at first admission. In the second case, the scapular spurs disappeared in the 6th month of treatment, but did not disappear in the first

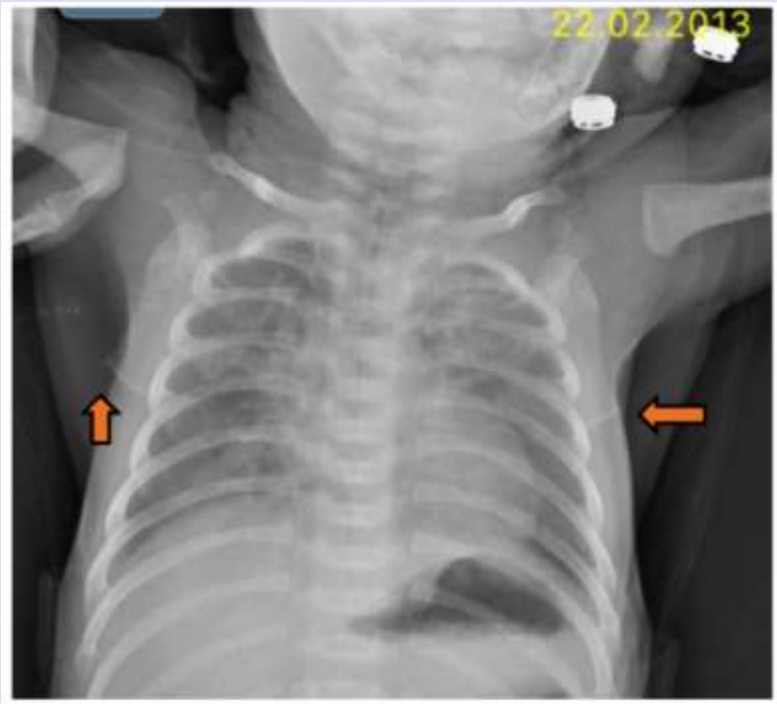
	06.02.2013	14.03.2013	03.05.2013	13.08.2013
WBC	5410	3790	6420	4100
Neutrophil	3690	2260	2380	2600
Lymphosit	100	100	50	100
Monocytes	790	500	400	1100
Eosinophil	750	300	20	400
Basophil	0	0	0	0
IG G	330 mg/dl	1160 mg/dl	1200 mg/dl	550 mg/dl
IG A	< 4 mg/dl	12 mg/dl	80 mg/dl	< 6 mg/dl
IG M	22 mg/dl	< 22 mg/dl	67 mg/dl	< 22 mg/dl
Total IG E	5 Iu / ml	7 Iu / ml	14.1 Iu /ml	5 Iu /ml

Case 1 Lab Table : Severe lymphopenia has been noted since the first diagnosis of the patient.

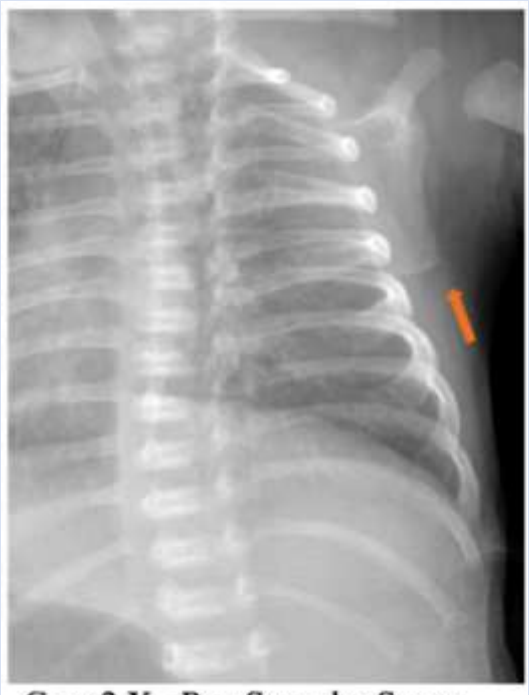
case.

	23.06.2019	05.07.2019	10.04.2020	13.07.2020	23.09.2021
WBC	8300	2500	6800	8200	6100
Neutrophil	6900	1700	4800	4200	2400
Lymphosit	100	100	400	1100	3300
Monocytes	800	700	1600	900	300
Eosinophil	1300	300	0	800	300
Basophil	0	0	0	0	0
IG G	320 mg/dl	1000	1000	1200	980
IG A	< 0.10 mg/dl	20 mg/dl	50 mg/dl	80 mg/dl	35 mg/dl
IG M	33 mg/dl	30 mg/dl	37 mg/dl	67 mg/dl	30 mg/dl
Total IG E	5.15 Iu / ml	5 Iu / ml	10 Iu /ml	14.1 Iu /ml	20 Iu / ml

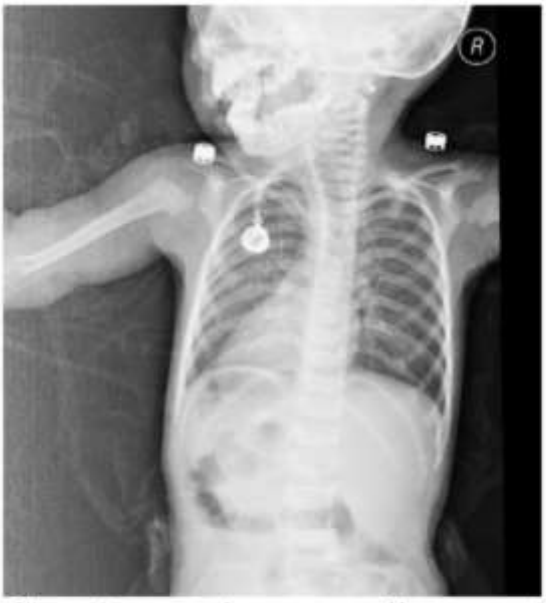
Case 2 Lab Table : The patient's severe lymphopenia at the time of admission was remarkable, enzyme replacement therapy and ivig therapy were started in July 2019, but 10 months after the treatment, lymphopenia continued even in April 2020. The improvement in lymphopenia after the first bone marrow transplant in May 2020 is remarkable .



Case 1 Chest X-ray at the time of application , scapular spurs



Case 2 X - Ray Scapular Spurs



Case 2 scapular spurs disappearing after treatment

Conclusions: Deficiency of ADA enzyme causes immunological and non-immunological symptoms. ADA enzyme deficiency can be suspected in the presence of non-immunological symptoms accompanying lymphopenia.

Disclosure: No.

Keywords: primary immunodeficiency, ADA enzyme deficiency, rare diseases, inherited disorders, lymphopenia

PD451

MALIGNANCY IN PATIENTS WITH INBORN ERRORS of IMMUNITY

POSTER DISPLAY 09: OTHER

Doo Ri Kim[1], Kyung-Ran Kim[2], Hwanhee Park[3], Joon-Sik Choi[4], Yoonsun Yoon[5], Keon Hee Yoo[1], Kangmo Ahn[1], Hee-Jin Kim[6], Eun Suk Kang[6], Junhun Cho[7], Su Eun Park[8], Kihyun Kim[9], Yae-Jean Kim[1]
[1]Samsung Medical Center, Pediatrics, Seoul, Korea, Republic of, [2]Gyeongsang National University Changwon hospital, Pediatrics, Changwon, Korea, Republic of, [3]Soonchunhyang University Bucheon Hospital, Pediatrics, Bucheon, Korea, Republic of, [4]Yongin Severance Hospital, Pediatrics, Yongin, Korea, Republic of, [5]Korea University Guro Hospital, Pediatrics, Seoul, Korea, Republic of, [6]Samsung Medical Center, Laboratory Medicine And Genetics, Seoul, Korea, Republic of, [7]Samsung Medical Center, Pathology, Seoul, Korea, Republic of, [8]Pusan National University Children's Hospital, Pediatrics, Yangsan, Korea, Republic of, [9]Samsung Medical Center, Medicine, Seoul, Korea, Republic of

Background and Aims: It is known that cancer incidence is higher in patients with Inborn Errors of Immunity (IEI) compared to the general population. We aimed to investigate the IEI patients who developed cancer in a single center.

Methods: Medical records of patients with IEI from November 1994 to August 2021 in Samsung Medical Center, Seoul, Korea, were reviewed. Patients with cancer were identified.

Results: Among 172 patients with IEI, six patients (3.5%) were diagnosed with cancer. Four cases were Epstein-Barr virus-associated lymphoma. The others were gastric cancer and multiple myeloma. The median age at cancer diagnosis was 16 years (range 1-59). In three patients, IEI was diagnosed after cancer confirmation. Among the patients with cancer in IEI, underlying IEIs were X-linked lymphoproliferative disease-1 (XLP-1, n=3), activated PI3 kinase disease (APDS, n=1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) haplo-insufficiency (n=2). One patient with APDS died during cancer treatment.

Conclusions: Cancer occurred in 3.5% of IEI patients at a single center in Korea. Physicians caring IEI patients should be aware of not only infectious complications and inflammation but also the potential risk of cancer.

Disclosure: Lee Kun-Hee Pediatric Cancer and Rare Disease Grant

Keywords: Inborn errors of immunity, X-linked lymphoproliferative disease-1, Malignancy, Lymphoma

PD452

EFFICACY AND IMPACT of CASCADE SCREENING AND EVALUATION of HAE (CASE-HAE)

POSTER DISPLAY 09: OTHER

Jane Wong, Philip Li
Queen Mary Hospital, Medicine, Hong Kong, Hong Kong PRC

Background and Aims: Hereditary angioedema (HAE) is an autosomal dominant disease with significant morbidity and mortality if left undiagnosed. Recommendations for family screening remain ambiguous and studies evaluating its implementation and efficacy are lacking. A novel screening programme, CAscade Screening and Evaluation of HAE (CaSE-HAE), was established to evaluate the clinical and psychological impact of cascade family screening (CFS).

Methods: Potential relatives were identified and screened for HAE through CFS. Prospective clinical data and questionnaire surveys completed at baseline and one year follow-up were analyzed.

Results: of 179 potential relatives, 94 were approached and 63 underwent screening. Twenty-nine (46%) patients were diagnosed with HAE; half (51.7%) were symptomatic. CFS resulted in a reduction in annual HAE attack frequency (2.5 vs. 1.0 episodes, p=0.011), annual hospital admissions (1 vs. 0, p=0.016) and length of stay (3 vs. 2 days, p=0.001). CFS reduced Hospital Anxiety and Depression Scale-anxiety scores (14.35±6.32 vs. 6.47±4.14, p=0.001) and improved Angioedema Quality-of-Life scores (55.4% vs. 34.7%, p<0.001). By extrapolation, CFS potentially led to a reduction of at least 1,200HKD (153USD) in HAE-related costs per person screened annually. Screening using a higher lower limit of normal C4 cut-off of 22.85mg/dL yielded 100% sensitivity and 77% specificity, which was superior to the manufacturers' suggested range.

Conclusions: CaSE-HAE was effective, feasible and should target relatives from all generations. CFS improved clinical and psychological outcomes. C4 is a good screening tool before C1inhA for type I, but higher than reference cut-off levels should be used.

Disclosure: No.

Keywords: Cascade family screening, Hospital Anxiety and Depression, Autosomal dominant, Hereditary Angioedema

PD453

BCG-RELATED COMPLICATIONS IN A LARGE COHORT of PATIETNS WITH PRIMARY IMMUNODEFICIENCIES AFFECTING CELLULAR AND HUMORAL IMMUNITY

POSTER DISPLAY 09: OTHER

Waleed Al-Herz[1], Mehdi Adeli[2], Tariq Al Farsi[3], Suleiman Al-Hammadi[4], Amna Amna Al Kuwaiti[4], Maryam Al-Nesf[5], Nashat Al Sukaiti[3], Salem Al-Tamemi[6], Hiba Shendi[4]
[1]Kuwait University-Faculty of Medicine, Pediatrics, Kuwait, Kuwait, [2]Sidra Medicine / Hamad Medical Corporation, Division of Pediatric Allergy And Immunology, Doha, Qatar, [3]The Royal Hospital, Pediatric Allergy And Clinical Immunology, Muscat, Oman, [4]Tawam Hospital, Pediatrics, Al-Ain, United Arab Emirates, [5]Hamad Medical Corporation, Division of Allergy And Immunology, Internal Medicine, Doha, Qatar, [6]Sultan Qaboos University Hospital, Departmentof Child Health, Muscat, Oman

Background and Aims: To present the details of BCG-related complications in patients with primary immunodeficiencies affecting cellular and humoral immunity (CID).

Methods: Five centers completed a data form which included general patients' information, clinical and laboratory data.

Results: Among 236 CID patients, 127 were BCG vaccinated. Having family history of CID and being diagnosed early in life by screening were inversely associated with administration of BCG vaccine. 41.9% of patients with family history of CID and 17.1% who were diagnosed by screening were BCG vaccinated. 23 patients (18.1%) developed BCG-related complications at a median age of 6 months (IQR:6) and the median time from vaccination to complications was 6 months (IQR: 6). Univariate analysis of T-lymphocyte subsets showed increased odds of BCG complications in patients with $CD3^+$, $CD4^+$ and $CD8^+$ counts of ≤250 cells/ul. Only $CD8^+$ count ≤250 cells/ul had increased such odds on multivariate analysis. Complications were disseminated in 13 patients and localized in 10 patients. Localized complication occurred earlier after vaccination (median: 4 months, IQR: 5) compared to disseminated ones (median: 7 months, IQR: 4.75). There were no significant associations between gender, administered vaccine strain, serum immunoglobulins levels, lymphocyte subsets counts and the chance of having either localized or disseminated BCG-related complications. There was 1 death related to BCG infection.

Conclusions: Despite having family history of CID and being diagnosed by screening some patients have been vaccinated with BCG. Low CD8+ count is a risk factor for BCG related complications and localized complications occurred earlier than disseminated ones.

Disclosure: No.

Keywords: BCG vaccine, epidemiology, infections, BCGosis, BCGitis, combined immunodeficiency

PD454

A SERIES of THREE ADULT PATIENTS WITH CHRONIC RHINOSINUSITIS AND PATHOGENIC MUTATIONS IN CYSTIC FIBROSIS OR PRIMARY CILIARY DYSKINESIA GENES

POSTER DISPLAY 09: OTHER

Mara Shapero, Tyrone Coyle, Blanka Kaplan
Zucker School of Medicine at Hofstra/Northwell Health, Allergy, Asthma, And Immunology, Great Neck, United States of America

Background and Aims: We present a series of three older patients who were evaluated in our immunology clinic for chronic rhinosinusitis and found to have abnormal genetic testing. Patient one, an 80-year-old female, presented with chronic rhinosinusitis (CRS) and recurrent pulmonary infections, including Pseudomonas aeruginosa (PA) pneumonia. Patient two is a 57-year-old female with aspirin-exacerbated respiratory disease, history of recurrent bacteremia, and PA mediport infection, as well as immune thrombocytopenia, and eosinophilic granulomatosis with polyangiitis. Our third patient, a 70-year-old woman, has chronic rhinosinusitis with nasal polyposis (CRSwNP) with a history of PA in sinus cultures, asthma, and chronic autoimmune urticaria.

Methods: The patients underwent immune evaluations, including humoral, cellular, and complement testing, and genetic sequencing analysis for cystic fibrosis (CF) and primary ciliary dyskinesia (PCD).

Results: Immune evaluation revealed mannan binding lectin deficiency in patient one and was unrevealing in patient three. Patient two has secondary immunodeficiency and is on immunoglobulin replacement therapy. Her sinus disease preceded immunodeficiency. All three patients were heterozygous for pathogenic genetic variants in CF or PCD genes. All had abnormal spirometry findings: patients one and two exhibited severe obstruction and patient three had mild restriction. Patient one was eligible for a genetic mutation-specific therapy to prevent CF exacerbations.

Conclusions: Heterozygous mutations in traditionally autosomal recessive conditions may confer clinically significant phenotypes. A diagnosis of CF or PCD should be considered in patients who present with CRS and PA infections, even if presenting as older adults. Timely diagnosis may improve outcomes with appropriate treatment, including mutation-specific therapies.

Disclosure: No.

Keywords: Genetic testing, chronic rhinosinusitis, Cystic fibrosis, Primary ciliary dyskinesia

PD455

PLASMA DONATIONS AND PLASMA-DERIVED PRODUCTS. SITUATION IN POLAND IN COMPARISON TO OTHER EU COUNTRIES

POSTER DISPLAY 09: OTHER

Bernadeta Prandzioch-Goretzki, Adrian Goretzki
Healthcare Education Institute, N/a, Katowice, Poland

Background and Aims: This poster aims to analyze and demonstrate current situation in Poland in the context of both using plasma derivatives and collection of plasma, in comparison with other EU countries. We want to analyze access to plasma-derived therapies in Poland, providing a review of current reimbursement policies and present key challenges that affect plasma market in Poland. We want to focus on patient safety, understood as the certainty of access to treatment.

Methods: We will analyze the available data from various institutions, incl. Ministry of Health, National Blood Center, Agency for Health Technology Assessment and Tariffs. We will perform a comparative analysis with data from other EU countries.

Results: The collected data are to show: how much plasma is collected in Poland in relation to the needs and consumption, how it looks compared to other countries, what is the consumption of PDMPs and what is the availability of products in Poland, whether patient safety is ensured - how high is the risk of medicine shortages on the market.

Conclusions: The collected data will help identify areas where patient advocacy efforts should be increased to ensure the safety of PID patients relying on plasma-derived medicines.

Disclosure: No.

Keywords: PDMPs, plasma-derived products, Poland, plasma, plasma donation

PD456

TREC BASED NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY DISEASE IN KUMAMOTO: RESULTS of THE FIRST THREE YEARS

POSTER DISPLAY 09: OTHER

Madoka Nishimura[1], Tomoyuki Mizukami[2], Shinichiro Yoshida[3], Takaaki Sawada[4], Kimitoshi Nakamura[4]
[1]Kumamoto City Hospital, Department of Pediatrics, Kumamoto, Japan, [2]National Hospital Organization Kumamoto Medical Center, Department of Pediatrics, Kumamoto, Japan, [3]KM Biologics CO., Ltd, Newborn Screening Center, Kumamoto, Japan, [4]Kumamoto University Hospital, Department of Pediatrics, Kumamoto, Japan

Background and Aims: T cell receptor excision circles (TREC) quantification from dried blood spots (DBS) is a reliable screening method to detect newborns with severe combined immunodeficiency (SCID). Kumamoto prefecture, located in southwest Japan, started TREC-based newborn screening in February 2019, and here we report the results of the first three years.

Methods: TREC level from DBS was initially measured by in-house direct RT-PCR. With TREC below the cutoff level (20 copies/μL), samples underwent RT-PCR using DNA extracted from DBS. If the TREC value remained low, a second DBS was requested. Newborns with low TREC levels in the second DBS were referred for flow cytometry analysis.

Results: Between February 2019 and January 2022, 41,533 newborns were evaluated. of these, 62 (1 in 670 newborns) were requested a second DBS, and six newborns were recalled for immunological evaluation. Three cases (1 in 13,844 newborns) were finally diagnosed with T cell lymphopenia (TCL). One newborn with complete DiGeorge/CHARGE syndrome received hematopoietic stem cell transplantation (HSCT). The other two newborns were diagnosed with combined immunodeficiency and with secondary immunodeficiency following surgery for congenital heart disease, respectively, and both of them were treated appropriately. No newborns with SCID were detected.

Conclusions: The TREC-based screening program in Kumamoto prefecture has identified three newborns with TCL, including a case who underwent HSCT. Though SCID patients have not been detected yet, our results indicated an effectiveness of this screening to find newborns with clinically important TCL. It is needed to accumulate the number of screening tests and to consider test methods.

Disclosure: No.

Keywords: T-cell receptor excision circles, Severe combined immunodeficiency, T-cell lymphopenia, newborn screening

PD457

WHAT WE CAN LEARN FROM TRG AND IGH REPERTOIRE ANALYSES IN PATIENTS WITH WISKOTT-ALDRICH SYNDROME (WAS)

POSTER DISPLAY 09: OTHER

Yu Nee Lee, Dahlia Palevski, Amos Simon, Atar Lev, Raz Somech
Sheba Medical Center, Pediatric Department A, Ramat Gan, Israel

Background and Aims: Patients with Wiskott-Aldrich Syndrome (WAS) suffer from immunodeficiency, microthrombocytopenia, eczema, and harbor mutations in the WAS gene. Since WAS patients often present with eczema, and γdT-cells are known to play an important role in skin homeostasis and immune response, we wanted to examine whether the T-cell Receptor Gamma (TRG) repertoire of the γdT-cells is affected in these patients. In addition, the Immunoglobulin Heavy chain (IGH) repertoire from genomic DNA of WAS patients was not yet studied. One of the advantages of studying the immune repertoire from genomic DNA is availability of the sample. In most centers diagnosing Inborn Errors of Immunity (IEI), such as our laboratory, have repositories of genomic DNA readily available. Thus, we sought to determine the effects that specific WAS mutations from our patients have in shaping the TRG and IGH immune repertoires.

Methods: We studied a total of four unrelated patients each harboring a different mutation in the WAS gene. Using Next Generation Sequencing (NGS), we sequenced and analyzed their TRG and IGH repertoires using genomic DNA isolated from their peripheral blood.

Results: The TRG repertoire of the WAS patients showed altered dynamics of clonal expansion, unique to each patient in addition to significantly lower number of total sequences compared to healthy controls. The IGH repertoire showed significantly different parameters of the IGH repertoire in the WAS patients compared to healthy controls.

Conclusions: Thus, immune repertoire determined using genomic DNA of the peripheral blood showed that WAS have significant effects in shaping the TRG and IGH adaptive immune repertoires.

Disclosure: No.

Keywords: IMMUNE REPERTOIRE, TRG REPERTOIRE, WAS, IGH REPERTOIRE, ECZEMA

PD458

IMAGING CHEST FEATURES IN INBORN ERRORS of IMMUNITY

POSTER DISPLAY 09: OTHER

Cristina Tomacinschii[1], Rodica Selevestru[1], Eugenia Crivceanschi[2], Eva Gudumac[3], Svetlana Sciuca[1]
[1]Nicolae Testemitanu State University of Medicine and Pharmacy, Pediatrics, Chisinau, Moldova, [2]Institute of Mother and Child, Radiology, Chisinau, Moldova, [3]Nicolae Testemitanu State University of Medicine and Pharmacy, Pediatric Surgery, Chisinau, Moldova

Background and Aims: Inherited errors of immunity (IEI) are a group of rare disorders characterized by a broad spectrum of manifestations as infections (severe and recurrent), autoimmune disorders, allergies, and increased risk of malignancy. Thoracic imaging has an important role in the diagnosis of IEI due to the high rates of repeated respiratory infections and congenital disorders frequently associated. Aim: To evaluate the thoracic imaging features of IEI in children.

Methods: were performed a retrospective study by analyzing medical records of fifteen children with IEI. Patients underwent chest X-ray and high-resolution computed tomography (HRCT).

Results: In our series of patients, 7 (46,6%) were with antibody deficiency and 8 (53,3%) were with combined types of immunodeficiency. All of them were investigated by imaging during respiratory infections, being identified opacity in all patients, pulmonary destruction in 14,2%, 95%CI[0,3;57,8] in antibody deficiency group, and 12,5%, 95%CI[0,3;52,6] in combined immunodeficiency group, empyema in 20% (n=3). HRCT showed mucoid impactions in 42,8%, 95%CI[9,9;81,5] in antibody deficiency group and 12,5% 95%CI[0,3;52,6] in combined immunodeficiency group, bronchiectasis in 33,3% (n=5), lung fibrosis in 33,3% (n=5), hilar and mediastinal adenopathies (n=2).

Conclusions: Chest imaging has a crucial role for IEI patients allowing initial identification of thoracic manifestations and monitoring the response to treatment.

Disclosure: No.

Keyword: primary immunodeficiency, children, chest imaging, HRCT, respiratory infections

PD459

KABUKI SYNDROME

POSTER DISPLAY 09: OTHER

Anna Bobcakova[1], Robert Vysehradsky[1], Milos Jesenak[1,2,3]
[1]Jessenius Faculty of Medicine, Comenius University in Bratislava, Centre For Primary Immunodeficiencies, Department of Pulmonology And Phthisiology, Martin, Slovak Republic, [2]University Hospital Martin, Department of Allergology And Clinical Immunology, Martin, Slovak Republic, [3]Jessenius Faculty of Medicine, Comenius University in Bratislava, Centre For Primary Immunodeficiencies, Department of Pediatrics, Martin, Slovak Republic

Background and Aims: Kabuki syndrome is a rare genetic disorder associated with several immunological and non-immunological manifestations. Facial dysmorphism, short stature, cutaneous and visceral abnormalities, intellectual disability, susceptibility to infections, immune deficiency and autoimmune manifestations are common.

Methods: We present a case of 28-year-old male patient with growth and mental retardation, hypogonadism, recurrent pneumonia, pyogenic infections of the skin, oral/oesophageal candidiasis, persisting immune thrombocytopenia and leukopenia, hospitalized due to bilateral spiculated nodular condensations of the lungs, thickening of interstitium and focal bronchioloectasis. Based on positivity of candida mannan from BALF, Candida pneumonia was suspected and the patient was treated with itraconazole with minimal regression of lung infiltrates. Laboratory examinations revealed specific cellular deficiency, dysgammaglobulinemia (increased IgM, decreased IgG and IgA), and impaired response to pneumococcal vaccine. Secondarily impetiginized facial and digital lesions, several dysmorphic facial features including abnormal dentition with conical teeth were also noted.

Results: Combined immune deficiency with syndromic features was suspected. Substitution of facilitated subcutaneous immunoglobulins lead to normalization of serum IgG and IgM concentrations with decrease of respiratory infections rate and regression of lung infiltrates. Whole-exome sequencing later confirmed pathogenic mutation in the gene KMT2D consistent with the diagnosis of Kabuki syndrome, pathogenic variant/VUS in the gene KLHL10 associated with spermatogenic failure and pathogenic variant/VUS in the gene KRT12 related to Meesmann corneal dystrophy.

Conclusions: In patients with recurrent unusual infections, autoimmune features, facial, skeletal or cutaneous abnormalities, immune deficiency should be suspected. WES can be useful in refining the diagnosis when the diagnostic criteria of several nosological units are met.

Disclosure: No.

Keywords: facial dysmorphism, WES, Kabuki syndrome, dysgammaglobulinemia, persisting immune thrombocytopenia

PD460

XLA LIFE: AN ADVOCACY GROUP FOR X-LINKED AGAMMAGLOBULINEMIA

POSTER DISPLAY 09: OTHER

Austin Stack[1], Keith Sacco[2]
[1]XLA Life Corp., President, Rye, United States of America, [2]Phoenix Children's Hospital, Allergy And Immunology, Phoenix, United States of America

Background and Aims: X-linked agammaglobulinemia (XLA) is a monogenic X-linked primary immune deficiency (PI) caused by mutations in the BTK gene, resulting in an inability to produce B cells and antibodies. XLA patient survival has improved with the advent of earlier diagnosis, prophylactic antimicrobials and immunoglobulin replacement. However, a proportion of older patient may have significant infectious and non-infectious disease morbidity, including the severe and underestimated complication nodular regenerative hyperplasia. This has led to re-examination of XLA immunopathology including the role of T cells in XLA morbidity. Despite its discovery as the first PI in 1952, XLA has lacked a specific patient advocacy group (PAG). XLA Life is a non-profit organization founded by an XLA patient in 2022. Our mission is to foster the unification and empowerment of the global X-linked agammaglobulinemia (XLA) community through education, advocacy, and initiatives that aim to improve the overall quality of life for those affected by XLA.

Methods: N/A [no methods applicable]

Results: XLA Life aims to promote discovery in three main areas: Investigating hematopoetic stem cell transplantation and gene therapy as definitive treatment Identification and management of non-infectious comorbidities Characterize the phenotype of X-linked carriers

Conclusions: PAGs are a vital supplement to exisiting PI advocacy groups, and have made significant improvements in their respective diseases. With functional cures feasibly just several years away, PAGs are needed more than ever before. XLA Life will unite the community to create a positive impact on the management of XLA.

Disclosure: No.

Keywords: gene therapy, XLA, x-linked agammaglobulinemia, Patient Advocacy, Non-Profit, x-linked carriers

PD461

A PATIENT WITH STAT3 LOSS-OF-FUNCTION PRESENTS PERSISTENT HUMAN PAPILLOMAVIRUS SKIN INFECTION

POSTER DISPLAY 09: OTHER

Kyung-Ran Kim[1,2], Hwanhee Park[1,3], Doo Ri Kim[1], Areum Shin[1], Sohee Son[1], Hee-Jin Kim[4], Lee Dongyoun[5], Kangmo Ahn[1], Yae-Jean Kim[1]
[1]Samsung Medical Center, Pediatrics, Seoul, Korea, Republic of, [2]Gyeongsang National University Changwon hospital, Pediatrics, Changwon, Korea, Republic of, [3]Soonchunhyang University Bucheon Hospital, Pediatrics, Bucheon, Korea, Republic of, [4]Samsung Medical Center, Laboratory Medicine And Genetics, Seoul, Korea, Republic of, [5]Samsung Medical Center, Dermatology, Seoul, Korea, Republic of

Background and Aims: Signal transducer and activator of transcription 3 (STAT3) gene loss-of-function (LOF) variant are responsible for autosomal dominant Hyper-IgE syndrome (AD-HIES) and result in Th17 cells differentiation failure, increasing susceptibility to bacterial and fungal infection. Impaired cytotoxic T cell and natural killer cell cytotoxicity are related to recurrent human papillomavirus (HPV) Infection. Recurrent HPV infection has been reported in patients with autosomal recessive HIES (AR-HIES), epidermodysplasia verruciformis, and Warts, Hypogammaglobulinemia, Infections, and Myelokathexis syndrome. We report a patient with STAT3 LOF variant with refractory HPV infection.

Methods: Flow cytometry and Sanger sequencing analysis of the STAT3 were used. HPV was confirmed by immunochemistry.

Results: A male patient was diagnosed with STAT3 LOF based on genetic study that revealed de novo heterozygous missense mutation in the linker domain of STAT3, c.1591A>G (p.Lys531Glu) at the age of 5 years. When he was 17 years old, he developed brownish plaque-like skin lesions on the anterior chin, neck, and chest, which extended to both extremities. The skin biopsy showed hyperkeratotic epidermal tissue without atypia, and HPV was positive in wart immunochemistry. He was treated with cryotherapy, a topical steroid, and a calcineurin inhibitor. However, cutaneous HPV did not respond to the therapy. Patients with AR-HIES caused by DOCK8 and TYK2 variant, are known to be susceptible to HPV infection. However, HPV infection in AD-HIES is unknown and rarely reported. Additional studies on relations between STAT3 LOF variant and HPV infection are needed.

Conclusions: We reported a refractory HPV infection in a patient with STAT3 LOF variant during adolescence.

Disclosure: No.

Keyword: HPV infection, STAT3 LOF variant, Primary immunodeficiency, AD-HIES, AR-HIES

PD462

A NOVEL WASP SPLICE-SITE MUTATION IN A PATIENT WITH WISKOTT-ALDRICH SYNDROME

POSTER DISPLAY 09: OTHER

Elisabetta Toriello[1], Rosa Maritato[1], Antonio De Rosa[1], Carla Damiano[1,2], Emilia Cirillo[1], Cosimo Abagnale[1], Francesca Cillo[1], Emma Coppola[1], Federico Habetswallner[1], Enrico Maria Surace[1], Claudio Pignata[1], Giuliana Giardino[1]
[1]University of Naples "Federico II", Translational Medical Science, Naples, Italy, [2]Telethon Institute of Genetics and Medicine, Tigem, Pozzuoli, Italy

Background and Aims: Wiskott-Aldrich syndrome (WAS) (MIM #301000) is a rare X-linked primary immunodeficiency due to mutations in Wiskott-Aldrich syndrome protein (WASP) gene, characterized by thrombocytopenia with small platelets, eczema, recurrent infections and an increased incidence of autoimmunity and malignancies. Aim of this report is to describe the functional characterization of a novel WASP mutation.

Methods: Here we report on the case of a 2-month-old boy presenting with petechiae, thrombocytopenia (23000/mm^3, MPV 6.9 fL), slightly increased eosinophil count (620 cells/mm^3) and reduced CD8+ (6%; 267 cells/mm^3) and IgM levels (20.9 mg/dL). Targeted NGS revealed a novel 4 nucleotides deletion from position +3 to +6 of intron 8 (c.777+3_777+6delGACT) of WASP. To characterize the pathogenetic role of this deletion we performed a Polymerase Chain Reaction (PCR) analysis on cDNA obtained from white blood cells using primers annealing on exon 8 (Fw) and 9 (Rev). Western Blot was used to evaluate protein expression.

Results: In the mature transcript we observed the complete retention of intron 8, suggesting a splicing defect, due to the loss of a splice donor site at the 5'-end of intron 8. By sequencing the PCR product, we identified a premature stop at codon 269. No WAS protein was detectable in peripheral blood mononuclear cells (PBMC) from the patient.

Conclusions: We identified and characterized a novel splice site mutation in a patient presenting with petechiae and thrombocytopenia. The young age of the patient did not allow to define the phenotype (classical WAS vs X-linked thrombocytopenia) associated with the mutation.

Disclosure: No.

Keywords: Mutation, splicing, Wiskott- Aldrich syndrome

PD463

THE LIVED EXPERIENCE of HEREDITARY ANGIOEDEMA: EXPERIENCES of MEDICATION USE AND EMERGENCY CARE

POSTER DISPLAY 09: OTHER

Amy Burton[1], Isobel Lindsay-Wiles[1], Daniel Herron[1], Alison Owen[1], Jade Elliott[1], Lavanya Diwakar[2], Hae Uk[3]
[1]Staffordshire University, Center For Psychological Research; Health, Science And Wellbeing, Stoke on Trent, United Kingdom, [2]University Hospitals of North Midlands NHS Trust, Immunology, Stoke on Trent, United Kingdom, [3]HAE UK, Charity Support Group, Bridgwater, United Kingdom

Background and Aims: Hereditary angioedema (HAE) is a rare inherited illness characterised by recurrent swellings affecting almost any part of the body. 2% of attacks occur in the throat and are life threatening. Historically, misdiagnosis or inappropriate treatments were common. New self-administered agents for the prevention and management of acute attacks have potential to improve patient quality of life. This paper reports on patient use and perceptions of treatment as part of a wider study exploring the lived experience of HAE.

Methods: 65 participants recruited via a specialist charity group completed online surveys comprised of open and closed-ended questions. Eleven participants also volunteered to share images with the research team to be discussed as part of in-depth semi structured photo-prompted life-story interviews. Themes were developed from open-ended responses and interview transcripts using reflexive thematic analysis.

Results: Self-administered treatments were life changing, but some delayed treatment administration due to not attributing symptoms to HAE, concerns about treatment cost, and ‘gaps’ in healthcare provision. Delays to emergency care resulted from a lack of HCP knowledge about HAE and mistrust of patients' knowledge and self-advocacy. Negative experiences at Emergency departments could exacerbate fears regarding treatment efficacy for future life-threatening throat-attacks.

Conclusions: HAE patients need psychological support to process fears and negative experiences. In addition, education for emergency practitioners is needed to improve provision of emergency treatment. Improvements in treatment provision would reduce psychological burden of delayed emergency care. Psychological barriers to treatment administration must also be addressed to ensure treatment is used effectively.

Disclosure: No.

Keywords: emergency care, Hereditary Angioedema, medication use, Qualitative, interviews

PD464

INTERSTITIAL LUNG DISEASE IN CVID (GLILD): CLINICAL PRESENTATION AND COMPARISON TO CVID WITHOUT ILD

POSTER DISPLAY 09: OTHER

Vivien Somogyi[1], Monika Eichinger[2], Felix Lasitschka[3], Jutta Kappes[1], Michael Kreuter[1]
[1]Thoraxklinik, University Hospital Heidelberg, German Center for Lung Research, Center For Interstitial And Rare Lung Diseases, Heidelberg, Germany, [2]Thoraxklinik, University Hospital Heidelberg, Translational Lung Research Center Heidelberg, Member of the German Center for Lung Research, Department of Diagnostic And Interventional Radiology, Heidelberg, Germany, [3]University Hospital Heidelberg, Translational Lung Research Center Heidelberg, Member of the German Center for Lung Research, Department of Pathology, Heidelberg, Germany

Background and Aims: Common variable immunodeficiency (CVID) patients are susceptible to respiratory diseases including bronchiectasis and granulomatous lymphocytic interstitial lung disease (GLILD). As data on evaluating CVID with and without GLILD are sparse, we aimed to compare these groups.

Methods: 21 CVID patients were analyzed retrospectively for characteristics and outcomes and grouped into CVID with (ILD,n=9) and without GLILD (noILD,n=12). CT scoring (CTS) assessed 11 patterns (ground glass opacities, reticulations, traction bronchiectasis, honeycombing, consolidations, air-trapping, nodules, bronchial wall thickening, bronchiectasis, mucus plugging, effusion). Histology scoring (HS) evaluated changes of the bronchial wall and of the interstitium (fibrosis, inflammation, anthracosis, granuloma, tumor, infection, metaplasia, mucoid impactation, microhoneycombing, eosinophilia).

Results: Baseline characteristics were similar between groups. Most CVID patients received immunoglobulins (Ig) and all ILD patients were treated immunosuppressive (IS). Under Ig and IS lung function remained stable in ILD. CTS were worse for ILD than noILD (ILD:16.5±8.7 vs. noILD:9.4±4.9, p=0.02) while HS (ILD:5.8±2.7, noILD 6.0±2.6) were similar. CTS deteriorated in ILD but not in noILD with pattern changes in ILD, from initial mainly GGO to fibrosis (p<0.01), while noILD, mainly bronchial wall thickening, remained stable. HS mainly showed fibrosis and chronic inflammation in both groups. After a median of 3.8 years, there were no deaths.

Conclusions: CVID with and without GLILD has similar clinical characteristics but differs mainly in CT scoring. Future work has to assess clinical predictors of GLILD.

Disclosure: No.

Keywords: immunosuppression, Orphan diseases, Idiopathic pulmonary fibrosis

PD465

A RIPK1-DEFICIENT PATIENT PRESENTED WITH COMBINED IMMUNODEFICIENCY AND VERY EARLY-ONSET INFLAMMATORY BOWEL DISEASE.

POSTER DISPLAY 09: OTHER

Hasret Erkmen[1], Sule Haskologlu[1], Avniye Baskin[1], Nazli Deveci Demirbas[1], Ufuk Ates[2], Serdar Ceylaner[3], Tanil Kendirli[4], Figen Dogu[1], Aydan Ikinciogullari[1]
[1]Ankara University School of Medicine, Department of Pediatric Immunology And Allergy, ANKARA, Turkey, [2]Ankara University School of Medicine, Department of Pediatric Surgery, ANKARA, Turkey, [3]Intergen Genetics and Rare Diseases Diagnosis Research & Application Center, Department of Genetics, ANKARA, Turkey, [4]Ankara University School of Medicine, Department of Pediatric Intensive Care Medicine, ANKARA, Turkey

Background and Aims: RIPK1 (receptor-interacting serine/threonine-protein kinase 1) is a key molecule controlling inflammation and cell death in intestinal epithelial cells. Mutations in the RIPK1 gene result in decreased NF-B activity, defective T and B cell differentiation, increased inflammasome activity, and impaired response to TNFR1-mediated cell death.

Methods: We present a 4-month-old boy with RIPK1 deficiency who was born through consanguineous marriage and had recurrent infection and chronic diarrhea.

Results: The patient was born 27 weeks premature and weighed 1100g, was monitored in the neonatal intensive care unit for two months. He had sepsis due to K.pneumonia when he was 16 days old. RSV pneumonia, CMV viremia, severe diaper dermatitis, and moniliasis developed during his follow-up. He was referred to our department after learning that his cousin had similar complaints and died at the age of three while being investigated for primary immunodeficiency. Immunological tests revealed CD3+CD4+ T cell lymphopenia and increased TCR ɣ/δ. NGS analysis discovered a homozygous deletion in the RIPK1 gene. There was no HLA-matched donor in the family. During the follow-up period, hypoalbuminemia, ascites, gastrointestinal bleeding, and sepsis developed. The patient underwent surgery for intestinal perforation. Pathological examination revealed multifocal ulceration, regeneration, and serositis. Six days after surgery, the patient died of septic shock.

Conclusions: In patients with severe infections and early-onset inflammatory bowel disease, RIPK1 deficiency should be considered. There is no consensus on the curative treatment of the disease. HSCT improves immunological findings in RIPK1 deficiency, however, it has no effect on the intrinsic defect in the intestinal epithelium.

Disclosure: No.

Keyword: RIPK1 deficiency, immunodeficiency, inflammatory bowel disease

PD466

CASE REPORT: C3 DEFICIENCY IN A FAMILY

POSTER DISPLAY 09: OTHER

Agustin Bernacchia, Alejandra Ginaca, Daniela Di Giovanni, Maximiliano Dominguez, Sabrina Rotondo, Patricia Carabajal
Hospital de Niños Ricardo Gutiérrez, Immunology Unit, Ciudad Autonoma de Buenos Aires, Argentina

Background and Aims: C3 has a crucial role in Complement System (CS) activation, clearing of pathogens, cellular debri, immunocomplexes and in modulating adaptive response through B-cell coestimulation. CS protein deficiencies increase susceptibility to infections abnormal inflammation and autoimmunity.
Our aim is to describe clinical and immunological findings in a family with C3 deficiency

Methods: Retrospective chart review. Investigation of CH50, AH50, C1q, C2, C3, C4,Properdin, FI, FH, FB, sC5b9, C3nef, C3 activation products (CAPs),anti-FH, anti-C1q, Immunoglobulins, antibody response to protein and polysaccharide antigens, lymphocyte subsets and molecular testing of complement proteins.

Results: P1 is a 12 yo female born to non-consanguineous healthy parents and P2 her 10 yo sister. Both sisters showed persistent undetectable C3 levels, CH50 and AH50, without C3NEF activity, CAPs and decreased unswitched memory B cells. P1 suffered multiple hospitalizations from 6 mo because of Pneumonia, sinusitis, osteomyelitis and HUS at 5 yo. She developed 4 episodes of acute otitis media (AOM) per year. She showed a-C1q, a-FH, abnormal response to polysaccharide antigens. P2 had 8 hospitalizations (2 mo up 4 yo) due to respiratory tract infections, pneumonia and AOM, low IgG levels and increased transitional B cells. Molecular testing revealed two variants in C3: c.305dup and c.1269+5G>A in both. They received vaccine immunization and antibiotic prophylaxis. Due to persistents infections they started IVIG with good clinical response

Conclusions: We report two cases of total C3 deficiency presenting with severe recurrent infections, altered B cell compartment and autoantibodies. Prompt recognition of complement deficiencies allows early treatment instauration and prevents more severe infections.

Disclosure: No.

Keywords: Complement, severe infections, B cells, autoantibodies

PD467

CLINICAL, IMMUNOLOGICAL AND MOLECULAR FEATURES of 132 CHRONIC GRANULOMATOUS DISEASE PATIENTS

POSTER DISPLAY 09: OTHER

Najla Mekki[1,2], Sondes Beji[3], Afef Rais[1], Amel Ben Chehida[4], Monia Ben-Khaled[5], Hager Barakizou[6], Fatma Khalsi[7], Monatassar Ben-Dhia[8], Meriem Ben Ali[2], Elhem Ben Fradj[9], Samia Rekaya[9], Beya Largueche[3], Amal Elleuch[10], Fethi Mellouli[9], Slah-Eddine Chouchene[11], Imen Chabchoub[10], Asma Bouaziz[12], Monia Ouedrni[9], Imen Ben-Mustapha[2], Mohamed-Ridha Barbouche[2]
[1]Institut Pasteur de Tunis, Laboratory of Transmission, Control And Immunobiology of Infections (lr11ipt02), Tunis, Tunisia, [2]Institut Pasteur de Tunis, Immunology, Tunis-belvédère, Tunisia, [3]Institut Pasteur de Tunis, Immunology, Tunis, Tunisia, [4]La Rabta Hospital, Department of Pediatrics, Tunis, Tunisia, [5]Bone Marrow Transplantation Center Tunis, Pediatric Immuno-hematology Unit, Tunis, Tunisia, [6]Military Hospital of Tunis, Department of Pediatrics, Tunis, Tunisia, [7]Bechir Hamza Children's Hospital of Tunis, Pediatrics B, Tunis, Tunisia, [8]Hospital of Nabeul, Pediatrics, Nabeul, Tunisia, [9]Bone MarrowTransplant Center, Tunis, Department of Pediatrics: Immunology, Hematology And Stem Cell Transplantation, Tunis, Tunisia, [10]Hédi Chaker Hospital of SFAX, Pediatrics, SFAX, Tunisia, [11]Fattouma Bourguiba Hospital of Monastir, Pediatrics, Monastir, Tunisia, [12]Ben Arous Hospital of Tunis, Pediatrics, Tunis, Tunisia

Background and Aims: Chronic granulomatous disease (CGD) is an inborn error of immunity due to genetic defects in the NADPHoxidase complex of phagocytes. Patients suffer from recurrent and severe life-threatening bacterial and fungal infections as well as inflammatory and autoimmune symptoms.

Methods: Herein, we describe clinical and immunogenetic features of 132 patients diagnosed at Pasteur Institute of Tunis.

Results: They are belonging to 120 families among which 62 were consanguineous. Mean onset age was 1.5years. Infections are the most frequent symptom, mainly represented by abscesses, mycobacterial and aspergillosis infections. Twelve patients developed granulomas. Behcet's disease (1patient), systemic lupus erythematosus (1patient), autoimmune hepatitis (1patient) and coeliac disease (2patients) were also observed. NBT-test was negative in 121 cases and reduced in the remaining one. DHR-test, performed in 31 patients, showed a defect of oxidation in all cases. Genetic analysis (20patients) found one CYBB mutation (c.1359G>A), one NCF1 deletion (c.75_76delGT), two CYBA mutations (c.70G>A and 295-301delGTGCCCG) and two NCF2 mutations. These latters include a substitution (c.78A>T) found in one patient and a founder mutation (c.257+2T>C) occurring in 11 cases.

Conclusions: In the present study, we reported a large series of Tunisian and Maghrebian CGD patients. The high frequency of mycobacterial infections could be in part due to the universal BCG vaccination at birth and/or the high prevalence of tuberculosis in Tunisia. Moreover, autosomal-recessive inheritance is by far the most frequent one. This highlights the specific nature of highly consanguineous populations. Moreover, the identification of founder mutation will facilitate the implementation of preventive approaches through genetic counseling in affected families.

Disclosure: No.

Keyword: Chronic granulomatous disease, NADPH oxidase, Consanguinity, founder mutation

PD468

CLINICAL, LABORATORY FEATURES, TREATMENT AND OUTCOME IN CHRONIC GRANULOMATOUS DISEASE (CGD)

POSTER DISPLAY 09: OTHER

Sule Haskologlu[1], Dilara Besli Celik[2], Avniye Baskin[1], Candan Islamoglu[1], Sevgi Bal[1], Deniz Bayrakoğlu[1], Dogan Kaymaz[1], Nazli Deveci Demirbas[1], Hasret Erkmen[1], Caner Aytekin[3], Baran Erman[4], Serdar Ceylaner[5], Figen Dogu[1], Aydan Ikinciogullari[1]
[1]Ankara University School of Medicine, Department of Pediatrics, Division of Immunology And Allergy, Ankara, Turkey, [2]Ankara University School of Medicine, Department of Pediatrics, Ankara, Turkey, [3]Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Pediatric Immunology, Ankara, Turkey, [4]Hacettepe University, Can Sucak Research Lab For Translational Immunology, Center For Genomics And Rare Diseases, Ankara, Turkey, [5]Intergen Genetics and Rare Diseases Diagnosis Research & Application Center, Department of Genetics, ANKARA, Turkey

Background and Aims: Chronic granulomatous disease (CGD) is an inborn error of immunity (IEI) characterized by recurrent and life-threatening infections as well as excessive and troublesome inflammatory responses occasionally. In the mean time Dihydrodamine-123 oxidation (DHR-123) assay via flow cytometry is the most rapid diagnostic tool whereas HSCT is the only curative treatment approach for CGD. Here, we present the clinical, laboratory features, treatment and outcome who were diagnosed and/or treated during the last 10 years at our department

Methods: The data related to 16 patients that was obtained from hospital/department based records were analyzed retrospectively.

Results: Among 16 patients, there were 4 girls (25%) and 12 (75%) boys. The median age at onset of symptoms was 11 months (6 days-72 months). Parental consanguinity detected in 50% with a positive family history of 37.5%. Major presenting symptoms related to lower respiratory tract infections (87%) and septicemia (50%); mycobacterium (56%), aspergillus (50%), gram negative bacteria (50%) were identified as the most common agents. Lymphoproliferation and colitis described in 68% and 44% among all cases retrospectively. Genetic defect detected in nine (five in CYBA, three in CYBB, one in NCF2). All patients received antimicrobial prophylaxis and interferon gamma treatment. Hematopoietic stem cell transplantation (HSCT) performed via various donor cells in 8 (50%) patients. All 8 transplanted among 14 alive CGD cases were cured, but two died of severe septicemia before HSCT.

Conclusions: It is possible to achieve favorable outcome and cure by early and correct diagnosis and successful HSCT in CGD.

Disclosure: No.

PD469

IMMUNODEFICIENCY-CENTROMERIC INSTABILITY-FACIAL ANOMALIES SYNDROME 4 PRESENTING IN THE NEONATAL PERIOD WITH SEVERE IUGR, RESPIRATORY DISTRESS, AND CONGENITAL HEART DISEASE

POSTER DISPLAY 09: OTHER

Paul Torpiano[1], Sarah Prentice[1], Ratha Sritharan[2], Anay Kulkarni[3], Sahar Mansour[2], Katja Doerholt[1]
[1]St George's Hospital, Paediatric Infectious Diseases And Immunology, London, United Kingdom, [2]St George's Hospital, Genetics, London, United Kingdom, [3]St George's Hospital, Neonatal Intensive Care Unit, London, United Kingdom

Background and Aims: Immunodeficiency-Centromeric instability-Facial anomalies syndrome 4 (ICF4) is a rare syndrome characterised by recurrent infections in the context of hypo/agammaglobulinemia. We present a case of ICF4 syndrome in a neonate with severe intrauterine growth restriction (IUGR) and critical congenital heart defect, not previously described in this condition.

Methods: A female infant was born to consanguineous parents by emergency caesarean section at 30+2 weeks gestation with birth weight of 630 grams. Antenatal scans demonstrated severe IUGR with abnormal uterine dopplers, aortic coarctation and ventricular septal defect. The couple had a previous stillbirth with IUGR at 28 weeks' gestation and another daughter who was born at term with a normal birthweight. The couple had lost a daughter at 9 months of age following a severe Pneumocystis jirovecii pneumonitis, who was subsequently diagnosed with ICF4 syndrome.

Results: The patient was confirmed to be homozygous for the pathogenic HELLS frameshift variant, NM_018063.5:c.462_466del p.(Asn154Lysfs*4), the same mutation previously identified in her sister, confirming ICF4 syndrome. Initial immunophenotyping was largely unremarkable, though she has been commenced on antimicrobial and antifungal prophylaxis in view of her sister's history of fatal opportunistic infection. A full clinical exome with a gene agnostic approach failed to identify a genetic cause for the congenital heart disease.

Conclusions: ICF4 syndrome may present in the neonatal period with IUGR and may lead to fatal opportunistic infections in infancy such as Pneumocystis jirovecii pneumonia. It is not clear whether the congenital heart disease is a previously unreported associated finding or has a separate aetiology.

Disclosure: No.

Keywords: Immunodeficiency-centromeric instability-facial anomalies syndrome 4, Intrauterine growth restriction, Congenital heart disease

PD470

MYELODYSPLASTIC SYNDROME AND HEBO DEFICIENCY

POSTER DISPLAY 09: OTHER

Alla Volokha
Shupyk National Healthcare University of Ukraine, Pediatric Infectious Diseases And Pediatric Immunology, Kyiv, Ukraine

Background and Aims: Bone marrow failure caused by ERCC6L2 mutations is considered to be a genome instability syndrome. New data show that the patients with ERCC6L2 mutations are defective in the repair of transcription-associated DNA damage. ERCC6L2 gene mutations have been associated with bone marrow failure that includes developmental delay and microcephaly.

Methods: We report a case of bone marrow failure without other syndromic features.

Results: A 11-yr-old boy was admitted for bruising and several episodes of epistaxis during last months. He had pneumonia two months before hospitalization. Thrombocytopenia (50x109/liter) associated with moderate neutropenia (0.6x109/ liter). Bone marrow smears and biopsies showed reduced cellularity (<10%-20%) with myelodysplastic features of refractory cytopenia of childhood.. The erythrocytic lineage was mostly preserved. No cytogenetic abnormalities were found. Genetic panel sequencing revealed a homozygous nonsense mutation in Hebo, a new DNA repair factor encoded by the ERCC6L2 gene: c.1687C>T (p.Arg563*) and c.3603_3607dup(p.Pro1203Hisfs*10). The patient also has heterozygous mutation c.169-5C>G (Intronic) in gene PRL26.
The boy was from a healthy non-consanguineous couple. He has had persistent mild thrombocytopenia since 7th year of age. He has short stature but does not have any learning difficulties and developmental delay. Microcephaly was absent. He is transfusion-independent. He receives regular follow-ups due to his disease, but at the moment, allogeneic hematopoietic stem cell transplantation is not planned.

Conclusions: We report the atypical variant of HEBO deficiency in a patient with isolated bone marrow failure without developmental delay and microcephaly caused by homozygous mutation in ERCC6L2. Pediatric myelodysplastic syndrome may be associated with primary immunodeficiency

Disclosure: No.

Keyword: Myelodysplastic syndrome, primary immunodeficiency, children

PD471

LATE ONSET COMBINED IMMUNODEFICIENCY: ABOUT 4 CASES

POSTER DISPLAY 09: OTHER

Islam Mansouri[1], Ibtihal Benhsaien[1,2], Hind Ouair[1], Jalila El Bakouri[3,4], Asmaa Drissi Bourhanbour[5,6], Fatima Ailal[2,7], Ahmed Aziz Bousfiha[1,8]
[1]Faculty of Medecine and Pharmacy, University Hassan II, Casablanca, Laboratory of Clinical Immunology, Inflammation And Allergy (licia), CASABLANCA, Morocco, [2]Abderrahim El Harouchi Children Hospital, University Hospital Center Ibn Rochd, Casablanca, Morocco., Clinical Immunology Unit, Department of Infectious Diseases, Casablanca, Morocco, [3]Faculty of Medicine and pharmacy of Casablanca, Research Laboratory In Clinical Immunology And Inflammation (licia), Casablanca, Morocco, [4]IBN Rochd University Hospital,, Immunology Laboratory, Casablanca, Morocco, [5]Clinical Immunology, Autoimmunity and Inflammation Laboratory (LICIA), Faculty of Medicine And Pharmacy of Casablanca, Hassan Ii University, CASABLANCA, Morocco, [6]IBN Rochd University Hospital, 1. immunology Laboratory, CASABLANCA, Morocco, [7]Faculty of Medicine and pharmacy of Casablanca, 1) research Laboratory In Clinical Immunology And Inflammation (licia), Casablanca, Morocco, [8]Clinical Immunology Unit, Department of Infectious Diseases, Abderrahim El Harouchi Children Hospital, University Hospital Center Ibn Rochd, Casablanca, Morocco

Background and Aims: Locid is a common variable immunodeficiency (CVID) subphenotype. It is characterized by repeated opportunistic infections and a profound cellular immune deficiency (TCD4 lymphocyte count < 200/mm3). The prognosis is poor compared to DICV.

Methods: Here we present clinical cases of patients with a clinical phenotype of LOCID (late onset combined immunodeficiency) reffered to our clinical unit.

Results: The first two cases are two unrelated girls who suffered from respiratory tract infections, récurrent ear-nose-throat infections and bacterial skin infections with extremely low immune parameters. The third case is a 14 YO inbred girl with abnormal Warts on her trunk and limbs. Skin biopsy revealed an HPV infection. The fourth case was a boy from consanguineous mariage suffering from repeated respiratory and skin infections. His skin biopsy showed a verruciform dysplasia. Unfortunately, we lost one patient who died at age of 15, following severe respiratory distress.

Conclusions: LOCID differs from classical CVID by its clinical and immunological characteristics. Identification of this phenotype should lead to a more appropriate diagnostic and therapeutic approach and should provide information for genetic diagnosis.

Disclosure: No.

Keywords: clinical phenotype, CVID, LOCID

PD472

FOCAL NODULAR HYPERPLASIA IN A PEDIATRIC PATIENT WITH ATAXIA-TELANGIECTASIA

POSTER DISPLAY 09: OTHER

Catarina Granjo Morais[1], Lucia Baselli[2], Martina Cucchetti[2], Claudia Ballerini[2], Rita Stracquadaino[2], Marco Salvi[2], Federica Nuti[2], Rosa Dellepiane[2]
[1]Centro Hospitalar e Universitário de São João, Department of Pediatrics, Porto, Portugal, [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlnico, Pediatric Department, Milano, Italy

Background and Aims: Ataxia-telangiectasia (A-T) is a neurodegenerative disease with cancer predisposition. Hepatic involvement in A-T is limited to metabolic associated fatty liver disease (MAFLD). Focal nodular hyperplasia (FNH) is a benign hepatic mass caused by arterial malformations and changes in perfusion. To our knowledge, there are no reports of FNH in pediatric patients with A-T.

Methods: We report the case of histologically confirmed FNH in an adolescent with A-T.

Results: A female patient was diagnosed with A-T at two years-old in the context of cerebellar ataxia, abnormal eye movements and elevated alpha-fetoprotein, confirmed by a homozygous deletion mutation in ATM gene. Later she displayed other characteristic features, namely immunodeficiency (reduction of naive CD4+ T cells, poor proliferation to mitogens) and ocular telangiectasias. MAFLD was also observed, so periodical abdominal ultrasounds were performed to monitor steatosis and exclude secondary lesions. At 14 years-old, an ultrasound showed a 1.5 cm lesion in hepatic segment VIII, confirmed by MRI (T1-hypointense, T2-hyperintense). Etiological investigation for tumoral and infectious causes was inconclusive. Repeated MRI showed the same lesion, without “washout” sign but with restricted diffusion. Histopathological characterization by liver biopsy confirmed aberrant arteries in the stroma of the portal canal and cholangiolar proliferation, suggestive of FNH.

Conclusions: Causal correlation between FNH and A-T is unclear, however it could be explained by dysfunctional control of DNA damage repair and reactive oxygen species. No risk factors associated with FNH were identified (e.g., estrogen therapy). Although FNH is a benign neoplasm, periodical follow-up remains essential due to cancer predisposition in A-T.

Disclosure: No.

Keywords: Focal Nodular Hyperplasia, Ataxia Telangiectasia, Metabolic Associated Fatty Liver Disease

PD473

GENOTYPE-PHENOTYPE CORRELATION IN A CHILD WITH WISKOTT ALDRICH SYNDROME

POSTER DISPLAY 09: OTHER

Cristina Tomacinschii[1], Mihaela Bataneant[2], Victoria Secara[3], Ina Palii[1], Rodica Selevestru[1], Svetlana Sciuca[1]
[1]Nicolae Testemitanu State University of Medicine and Pharmacy, Pediatrics, Chisinau, Moldova, [2]Louis Turcanu Children Hospital, Iiird Pediatric Clinic, Timisoara, Romania, [3]Institute of Mother and Child, Genetics, Chisinau, Moldova

Background and Aims: Wiskott-Aldrich syndrome due to WAS gene mutation is manifested by 3 different clinical phenotypes:classic WAS, XLT and X-linked neutropenia. Lack of WASP protein expression leads to classical WAS(microthrombocytopenia, eczema, susceptibility to infections, increased risk of autoimmune disease and malignancy) and missense mutations lead to XLT. There are several genetic variants of the WAS gene mutation described in the literature, c.172 C>A not being fully defined. Aim: To evaluate the clinical manifestations of a child with the pathogenic variant of the WAS gene mutation (c.172C>A).

Methods: We analyzed the medical record of a 5-year-old boy diagnosed with WAS by sequence analysis(Invitae Primary Immunodeficiency Panel)

Results: The child born in a nonconsanguineous family was admitted with hemocolitis at the age of 2weeks. From the age of 1 month, he has had frequent respiratory infections and eczema on the face. Following a blood test, thrombocytopenia with a normal MPV(7,6fL) is detected, which is maintained in the following tests. Serum immunoglobulins were within normal limits except for IgE(103-500UI⁄Ml). An absolute increased number of CD16+CD56+ were identified in lymphocyte immunophenotyping test(0.88; normal values 0,2–0,6x10^{3}⁄L). Despite the normal volume of platelets, the sequencing causes the mutation c.172C>A(p.Pro58Thr) in the WAS gene, revised in November 2019 as a pathogen. After the age of 3, eczema subsided, the infectious episodes became rarer with the persistence of bruising and petechiae and bleeding from minor accidents.

Conclusions: WAS is a disorder with a broad spectrum of disease severity. Mild forms are less described in relation to the variant of the genetic mutation, but they require a comprehensive evaluation and monitoring.

Disclosure: No.

Keyword: Wiskott Aldrich, pediatric, eczema, c.172C>A, infections, GENOTYPE

PD474

THROMBOCYTOPENIA AS INITIAL PRESENTATION IN PATIENTS WITH INBORN ERRORS of IMMUNITY

POSTER DISPLAY 09: OTHER

Sofia Tantou[1], Athina Dettoraki[2], Marianna Tzanoudaki[1], Aikaterini Michalopoulou[2], Nefeli Papageorgiou[2], Theodora Papastamatiou[1], Helen Pergantou[2], Manolis Liatsis[1]
[1]'Aghia Sophia' Children's Hospital, Department of Immunology-histocompatibility, Specialized & Referral Center For Primary Immunodeficiency-paediatric Immunology, Athens, Greece, [2]'Aghia Sophia' Children's Hospital, Haemostasis And Thrombosis Unit, Haemophilia Centre, Athens, Greece

Background and Aims: Cytopenia including refractory to treatment thrombocytopenia may be the initial symptom in patients with inborn errors of immunity (IEI), which present either with minimal signs of bleeding or with severe episodes of bleeding. Various pathogenic mechanisms of thrombocytopenia are described in these diseases.

Methods: Medical history and laboratory results, including immunological work-up, of 13 patients presented with thrombocytopenia and diagnosed with an inborn error of immunity were reviewed.

Results: The patients' age ranged from 26 days to 22 years at diagnosis. Platelet count ranged from 5.000-95.000. Immunoglobulins levels were below <2 percentile for age in 8/13 patients. Peripheral immunophenotyping revealed B lymphocytes <2% in 1/13 patients, low CD3+CD8+ T-cells in 4 patients and low memory-switched B cells in 8/13 patients. Btk and Wasp expression were undetectable leading to XLA and WAS diagnosis in one patient and four patients respectively. Seven patients were eventually diagnosed with CVID and one with undefined hypogammaglobulinemia. WAS patients were treated with HSCT while the other patients commenced on g- globulin replacement therapy.

Conclusions: Many patients with IEI experience thrombocytopenia among variable symptoms. Multidisciplinary approach can lead to early diagnosis resulting in targeted therapy with positive impact in prognosis and patients' quality of life.

Disclosure: No.

Keywords: thrombocytopenia, Inborn errors of immunity, multidisciplinary approach

PD475

TRANSFERRING PATIENTS TO SUBCUTANEOUS HOME THERAPY DUE TO IMMUNOGLOBULIN SHORTAGE FOLLOWING A GLOBAL PANDEMIC.

POSTER DISPLAY 09: OTHER

Natalie Leslie[1], Claire Bethune[2], Christine Symons[2]
[1]University Hospital Plymouth, England, Department of Immunology And Allergy, Plymouth, United Kingdom, [2]University Hospitals Plymouth NHS Trust, Immunology And Allergy Service, Plymouth, United Kingdom

Background and Aims: The Covid-19 pandemic resulted in a global shortage of immunoglobulin. In the UK the supply of Intravenous immunoglobulin (IVIg) was impacted more than that of subcutaneous immunoglobulin (scIg). Patients who had previously been treated with IVIg needed to be converted to scIg in order to maintain their treatment with replacement immunoglobulin. To follow up patients started on scIg between July 2021 and February 2022 and to assess patient satisfaction with the training and continuing self-administration of scIg.

Methods: All patients who were set up to receive sc replacement immunoglobulin between July 2021 and February 2022 were identified. This involved patient referrals from other hospitals across the Southwest of England to Peninsula Immunology Service. This included 24 patients stable on replacement IVIG and 8 never previously treated with IG replacement. Patients were trained to use either rapid push or pumped infusions with 2-3 training sessions. A survey was sent to all 32 patients via post.

Results: All of the patients were trained by an Immunology Nurse and all 15 were satisfied with their training programme reporting that they were given support during their transition to home therapy.

Conclusions: The results showed that despite the transition to scIg replacement being triggered by supply issues rather than patient choice, all patients were happy with the training and felt supported in the transition to the new delivery mode.

Disclosure: No.

Keywords: Shortage, Pandemic, Transferring, Subcutaneous, Immunoglobulin, Home

PD476

LYMPHOMATOID GRANULOMATOSIS IN A PATIENT WITH DOCK8 DEFICIENCY

POSTER DISPLAY 09: OTHER

Eduardo Liquidano-Perez[1], Sara Solorzano-Morales[1], Rodolfo Rodríguez-Jurado[1], Gilberto Ramirez Ristori[2], Tania Barragan Arévalo[3], Marco Yamazaki-Nakashimada[4], Selma Scheffler-Mendoza[4], Maria Edith González Serrano[1]
[1]National Institute of Pediatrics, Primary Immunodeficiency Research Unit, Mexico City, Mexico, [2]National Institute of Pediatrics, Pathology, Mexico City, Mexico, [3]Institute of Ophthalmology “Conde de Valenciana”, Genetics, Mexico City, Mexico, [4]National Institute of Pediatrics, Immunology, Mexico City, Mexico

Background and Aims: DOCK8-deficiency (DOC8-Def) is an inborn immunity error (IEI) characterized by allergy, autoimmunity, neoplasms, and recurrent infections. Lymphomatoid granulomatosis (LYG) is an EBV-associated lymphoproliferative disorder. Immunity defects impair EBV response, resulting in LYG rather than viral clearance.

Methods: We present a 16-year-old female patient with DOCK8-Def due to homozygous deletion of exons 4-26.

Results: She presented with increased oxygen requirements, pleuritic chest pain, and fever. On pulmonary examination, she showed expiratory wheezing and crackles. Imaging studies revealed a 333-cc image with irregular walls and internal lobulation in the right lung. A lung biopsy was performed, exhibiting an EBER-positive neoplastic lymphoid proliferation of atypical, large cells, with abundant, vacuolated cytoplasm, hyperchromatic nuclei, compatible with stage 3 LYG. Curative treatment was impossible; thus, we treated her with rituximab 375 mg/m2sc/week as palliative care. Unfortunately, after two doses, she died.

Conclusions: DOCK8 protein is necessary for the survival, migration, and formation of the immunological synapse by the lymphocyte. LYG results from impaired immune surveillance. In DOCK8-Def patients, both conditions converge, explaining the increased risk of viral-associated neoplasms. Patients with DOCK8-Def rarely experience severe EBV infection, though an increased virus burden may contribute to EBV+ lymphomas and lymphoproliferative disease. Regardless of staging, LYG treatment includes immunomodulation to control EBV-enhance the response against EBV. These findings suggest that lymphoproliferative diseases require immunological surveillance defects for their development. We consider that in every patient with an IEI affecting the lymphocyte's migration and survival, we must be alert for infectious complications and malignancy, regardless of age.

Disclosure: No.

Keywords: DOCK8, combined immunodeficiency, Lymphomatoid Granulomatosis, Lymphoproliferative disorder, EBV-infection

PD477

THE PREVALENCE of HYPOALBUMINEMIA AMONG PATIENTS WITH COMBINED IMMUNODEFICIENCY: A MULTI-CENTER SURVEY FROM IRAN

POSTER DISPLAY 09: OTHER

Fatemeh Nazarpack[1], Mahnaz Jamee[2], Seyed Alireza Mahdaviani[3], Nima Rezaei[4], Samaneh Delavari[4], Nasrin Esfandiar[2], Samin Sharafian[1], Narges Eslami[1], Zahra Chavoshzadeh[5]
[1]Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Immunology And Allergy Department, Tehran, Iran, [2]Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Pediatric Nephrology Research Center, Tehran, Iran, [3]National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Pediatric Respiratory Diseases Research Center, Tehran, Iran, [4]Tehran University of Medical Sciences, Research Center For Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran, Iran, [5]Pediatric Infections Research Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Background and Aims: Combined immune deficiencies (CIDs) include are a group of inherited monogenic disorders characterized by cellular and humoral defects of the immune system. By conducting this study, we tend to evaluate CID patients in terms of demographic and clinical characteristics, prevalence, and impact of hypoalbuminemia on the outcome.

Methods: In this retrospective cross-sectional study, medical records of all CID patients admitted in three referral hospitals in Tehran from 2010 to 2021 were searched; if the serum level of albumin was available, they were included in the study. A comprehensive data sheet was designed to gather information. Data analysis was performed using SPSS statistical software version 26 (v. 26.0, Chicago, IL). The significance level was set at P-value<0.05.

Results: 46 out of 82 (56.09%) patients were identified to have hypoalbuminemia, of which 27 (58.75%) were male and 19 (41.3%) female. 34(73.9%) patients of CID with hypoalbuminemia had parental consanguinity. Failure to thrive, malabsorption, gastrointestinal ulcer, rheumatologic disorder, and hematologic disorder had a statistically significant correlation with hypoalbuminemia (P=0.05). The most common first clinical manifestations in CID patients were respiratory manifestation (29.33%) and diarrhea (9.1%). The median (IQR) age of death was 21.0 (12.2-84.0) months. The mortality rate was higher in CID patients with hypoalbuminemia (37%) compared to patients without hypoalbuminemia (29.3%). CID patients without hypoalbuminemia had a longer survival time than the group with hypoalbuminemia.

Conclusions: Hypoalbuminemia is an important and often neglected complication among CID patients. Detection of hypoalbuminemia can contribute to reducing morbidity and mortality in CID patients.

Disclosure: No.

Keyword: Combined immunodeficiency, Inborn errors of immunity, Hypoalbuminemia

PD478

CHRONIC GRANULOMATOUS DISEASE IN THE MAYAN ETHNIC GROUP

POSTER DISPLAY 09: OTHER

Ana Karen Peñafiel Vicuña[1], Lizbeth Blancas Galicia[1], Rogelio Guzman Cotaya[1], Sara Espinosa Padilla[1], Jacinta Bustamante[2,3,4,5,6,7,8,9,10]
[1]National Institute of Pediatrics, Research Unit For Immunodeficiencies, Mexico City, Mexico, [2]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Paris, France, [3]Paris Hospital, Study Center For Primary Immunodeficiencies, Paris, France, [4]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, New York, United States of America, [5]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, New York, United States of America, [6]Imagine Institute, Paris Cité University, Paris, France, [7]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1163, Paris, France, [8]AP-HP, Study Center For Primary Immunodeficiencies, Necker Hospital For Sick Children, Paris, France, [9]Paris Cité University, Imagine Institute, Paris, France, [10]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1136, Paris, France

Background and Aims: Chronic granulomatous disease (CGD) is an inborn error of immunity characterized by phagocyte dysfunction with an impaired ability to produce oxygen intermediate species (1). Describe the first reported cases of CGD in the Mayan ethnic group.

Methods: Dihydrorhodamine assay, detected $p67^{phox}$ production, amplified and sequenced NCF2 gene

Results: Patient I, manifested at 10 months with gastroenteritis due to Salmonella spp.; furthermore presented BCGitis with right axillary adenopathy, and pneumonia due to Serratia marcescens. Patient II, had a family history of a deceased brother and presented at 10 months with BCGosis, which manifested as delay in healing at the site of application of the BCG vaccine and multiple adenomegalies. GeneXpert assay showed M. tuberculosis complex. In both patients, the test for detecting hydrogen peroxide in neutrophils resulted null, the protein affected was $p67^{phox}$, compound heterozygous mutations nonsense were found in the NCF2 gene, for the patient I exon 4 c.304C>T and exon 11 c.979G>T, for patient II in exon 11 c.979G>T and exon 15 c.1369A>T.

Conclusions: CGD increases susceptibility to bacterial infections, including mycobacterial. The BCG vaccine is mandatory at birth causing clinical manifestations. In autosomal recessive forms of CGD in the Mexican population, mutations in NCF2 gene are more frequent versus NCF1 gene, as evidenced in the cases described. Both Mayan patients share the same pathogenic variant in exon 11, being from communities without miscegenation and with little access to health services. 1. Blancas-Galicia L, et al. Genetic,Immunological, and Clinical Features of the First Mexican Cohort of Patients with Chronic Granulomatous Disease. J Clin Immunol.

Disclosure: No.

Keyword: Inborn error of immunity ; Chronic granulomatous disease; Dihydrorhodamine, NCF2 gene, Mayan

PD479

IGG2 DEFICIENCY OR SOMETHING ELSE? A MISLEADING PHENOTYPE of ACTIVATED PI3-KINASE DELTA SYNDROME TYPE 1

POSTER DISPLAY 09: OTHER

Lucia Baselli[1], Martina Cucchetti[2], Rita Stracquadaino[2], Rozan Abdallah[2], Marco Salvi[2], Maria Carrabba[3], Rosa Dellepiane[1]
[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlnico, Pediatric Department, Milano, Italy, [2]Università degli Studi di Milano, Pediatric Department, Milano, Italy, [3]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, UOS Malattie Rare, Dipartimento Di Medicina Interna, Milano, Italy

Background and Aims: Activated PI3-kinase syndrome 1 (APDS1) is a primary immunodeficiency caused by gain-of-function mutations in PIK3CD gene. Clinical presentation and severity are widely variable, thus making diagnosis challenging.

Methods: We describe the case of an 8-year-old patient diagnosed with APDS1, mimicking IgG2 subclass deficiency.

Results: The patient came to our attention at the age of 7 for IgG2 deficiency and recurrent respiratory tract infections (RTI). He had recurrent upper and lower RTI since the first year of life, and monthly episodes of perforated acute otitis media since the age of 3. At 6 years old thorax CT scan showed bronchiectasis. Cystic fibrosis and ciliary dyskinesia were excluded. First line immunological work-up showed reduced levels of IgG2, with normal total IgG and increased IgM. Leucocytes count and specific response to vaccinations, including anti-pneumococcal vaccine, were normal. Lymphocyte subpopulation were normal, except for a reduced CD4/CD8 ratio (0.67). Extensive B and T cells phenotype was performed showing reduced switched memory B cells (2.4%) and increased transitional B cells (61.4%), while naïve helper T cells were low but within the normal range. Abdominal ultrasound showed mild hepatosplenomegaly with few abdominal lymphadenopathies. NGS gene panel identified a heterozygous mutation in PI3KCD gene (c.G3061A;p.E1021K), previously described as causative for APDS1. Subcutaneously immunoglobulin replacement therapy was started with a decrease of RTI frequency and global clinical improvement.

Conclusions: Our case suggested the pivotal importance of extending immunological investigations when clinical phenotype is not fully explained by initial laboratory assessment. Flow cytometry is useful to address genetic diagnosis.

Disclosure: No.

Keywords: APDS1, IgG subclasses deficiency, IgG2 deficiency, recurrent respiratory infection

PD480

HYPOGAMMAGLOBULINEMIA WHICH HELPS TO EXPLAIN A DIFFICULT INTERPRETATION of A MICROCYTIC ANEMIA

POSTER DISPLAY 09: OTHER

Antonino Trizzino[1], Maria Catania[2], Clara Mosa[1], Angela Trizzino[1], Irene Regina[2], Giorgio Bellina[2], Simona Ferrari[3], Paolo D'Angelo[1]
[1]Civico Hospital, Paediatric Haematology Oncology Unit, Palermo, Italy, [2]University of Palermo, Postgraduate School of Paediatrics, Palermo, Italy, [3]Policlinico S. Orsola Malpighi, Medical Genetic Unit, Bologna, Italy

Background and Aims: Sideroblastic Anemia, Immunodeficiency, Fevers, Development Delay (SIFD) Syndrome and Microcytic Anemia and Retinitis Pigmentosa (RPEM) are the two most common phenotypes of tRNA Nucleotidyltransferase (TRNT1) deficiency. However, this condition determines pleiotropic phenotypes with variable clinical severity depending on the enzyme deficiency degree. Most common clinical signs include congenital sideroblastic anemia, hypogammaglobulinemia, periodic fevers, delayed neuropsychomotor development, epilepsy, retinitis pigmentosa; less frequent signs are hearing loss, skin manifestations, nephrocalcinosis and hypertrophic cardiomyopathy. The aim of this case report is to emphasize the importance of early diagnosis of complex diseases to promptly recognize and prevent further complications.

Methods: A 3-month-old child was thoroughly tested for a microcytic anemia, but pathogenic mutations were not detected. When he was 9 months old, he was hospitalized for severe encephalitis. During hospitalization, lymphocyte typing and serum immunoglobulin dosage were done; other genetic tests were performed later.

Results: Blood tests showed reduction in CD19+ lymphocytes (<2%) and agammaglobulinemia. The Bruton tyrosine-kinase (BTK) gene was studied, without any evidence of gene variants. Subsequently, a more extensive genetic study using Next Generation Sequencing (NGS) highlighted two mutations in compound heterozygosity in the TRNT1 gene, which can cause both microcytic anemia and agammaglobulinemia.

Conclusions: The child is being treated with subcutaneous immunoglobulin infusions. His follow-up includes eye examination, auditory evoked potentials, audiometry, echocardiography, abdominal ultrasound scan, electroencephalogram, which are currently negative. After the diagnosis, it is mandatory to detect the presence of any clinical manifestations and to intervene promptly, thus reducing the impact on quality of life.

Disclosure: No.

Keywords: TRNT1, Agammaglobulinemia, microcytic anemia

PD481

A RARE CAUSE of COMBINED IMMUNODEFICIENCY: ORAI-1 DEFECT

POSTER DISPLAY 09: OTHER

Hasret Erkmen[1], Sule Haskologlu[1], Avniye Baskin[1], Nazli Deveci Demirbas[2], Tanil Kendirli[3], Figen Dogu[1], Aydan Ikinciogullari[1]
[1]Ankara University School of Medicine, Department of Pediatric Immunology And Allergy, ANKARA, Turkey, [2]Ankara University School of Medicine, Department of Pediatric Immunology And Allergy, Ankara, Turkey, [3]Ankara University School of Medicine, Department of Pediatric Intensive Care Medicine, ANKARA, Turkey

Background and Aims: Loss of function (LOF) mutations in ORAI1 cause severe combined immunodeficiency (SCID)-like disease, autoimmunity, muscular hypotonia, and ectodermal dysplasia, as well as dental enamel defects.

Methods: Here, we report a patient with a homozygous mutation in the ORAI-1 gene presenting with severe recurrent pneumonias, CMV infection, hypotonicity and anhidrosis.

Results: The patient was admitted with hypotonicity to the hospital for the first time when she was 2.5 months old. She was admitted to the pediatric intensive care unit at the age of three months with pneumonia. CMV PCR was positive, and ganciclovir treatment was given. The patient was examined for metabolic and neurological diseases, as well as facial dysmorphism, umbilical hernia, anhidrosis, and swallowing dysfunction. The parents are from the same village. After whole-exome sequencing analysis revealed homozygous mutations in the ORAI1 gene, she was referred to our department for HSCT. CMV PCR positivity persisted when she applied. She also had parainfluenza type 3 pneumonia, norovirus-related diarrhea, generalized lymphadenopathy, and moniliasis. During the immunological examinations, no pathology was discovered except for a low RTE (CD45RA+CD31+) level. In the family and unrelated donor screening, no HLA-matched donors were discovered. For the patient, who had no other curative treatment options other than HSCT, haploidentical HSCT from her father was performed using a RIC regimen and TCRαß and CD19 depletion. On the $+9^{th}$ day after transplantation, she died from K.pneumoniae sepsis.

Conclusions: ORAI and other channelopathy disorders cause a multisystemic disease. Delayed diagnosis of these diseases leads to severe infections, organ damage, and reduces the success of HSCT.

Disclosure: No.

Keyword: ORAI-1 gene, LOF mutation, HSCT

PD482

PROGNOSTIC ROLE of PRESEPSIN, NEOPTERIN, AND PROCALCITONIN IN SEPSIS IN INBORN ERRORS of IMMUNITY

POSTER DISPLAY 09: OTHER

Neslihan Karaca[1], Ilke Bas[1], Guzide Aksu[1], Necil Kutukculer[1], Elif Azarsiz[2]
[1]Ege University Faculty of Medicine, Department of Pediatrics, Izmir, Turkey, [2]Ege University Faculty of Medicine, Department of Biochemistry, Izmir, Turkey

Background and Aims: Early diagnosis of invasive infections is important for the early initiation of life-saving treatments in patients with inborn errors of immunity. Presepsin and neopterin are new biomarkers that are used in the diagnosis and follow-up of diseases. These parameters are elevated in infectious and non-infectious inflammatory conditions (such as autoimmune diseases and chronic inflammatory conditions). Early diagnosis of infections is important in terms of reducing complications due to recurrent infections and preventing morbidity and mortality with appropriate treatment. The aim of the study is to investigate the role of presepsin and neopterin, in the diagnosis of infections in IEI, and investigate their superiority and/or safety compared to other well-known acute phase reactants such as CRP and procalcitonin.

Methods: Patients aged 0-18 years,who presented with fever,circulatory collaps and respiratory distress and were hospitalized with the preliminary diagnosis of bacteremia,sepsis, and septic shock were included. Plasma presepsin, neopterin, procalcitonin levels were analyzed by ELISA in patients(n=39) and controls(n=37).

Results: The most common type of infection was lower respiratory tract infection. The most sensitive and specific biomarkers were presepsin and neopterin,respectively. There was no significant difference between the laboratory findings (complete blood count,CRP,presepsin procalcitonin, neopterin) in the patient group according to the presence of the causative microorganism at the time of infection, localized/invasive nature of the infection, or the type of isolated microorganism.

Conclusions: Presepsin and neopterin will be used more frequently as they are more specific and sensitive compared to CRP,PCT,and hemogram parameters. More clinical studies are needed for the reliability of new biomarkers.

Disclosure: No.

Keyword: presepsin, neopterin, sepsis, immunodeficiency

PD483

PRIMARY IMMUNODEFICIENCY DISORDERS IN UGANDA: EVALUATION of KNOWLEDGE ON CLINICAL AND LABORATORY DIAGNOSIS

POSTER DISPLAY 09: OTHER

Obondo Sande[1], Brian Matovu[1], Alice Bayiyana[1], Ezekiel Mupere[2], Joseph Olobo[1]
[1]Makerere University, College of Health Sciences, Immunology And Molecular Biology, Kampala, Uganda, [2]Makerere University, College of Health Sciences, Paediatrics, Kampala, Uganda

Background and Aims: Primary Immunodeficiency Disorders (PIDDS) is a neglected issue in Uganda, where infectious diseases are common and the main focus of healthcare, thus the diagnosis of PIDDs is often missed. Limited clinician awareness about PIDDs maybe a major barrier to early detection and diagnosis. However, the extent of knowledge about PIDDs is under-studied in Uganda. The aim of the study was to evaluate clinical and laboratory diagnostic knowledge about PIDDs.

Methods: A questionnaire of 21 questions was used to compare responses of 71 graduate doctors pursuing Masters of medicine in pediatrics, Internal Medicine, Obstetrics and gynecology. The questionnaire was divided into four sections: Warning signs in both children and adults (6 questions); general signs of PIDDs (5 questions); specific signs about PIDDs (4 questions); laboratory screening of suspected PIDDs (6 questions). The questions were of “true, “false, “don’t know” type, with two possible answers. The questionnaires were distributed on-site during class hours. Ethical approval was obtained from MHREC-2021-38.

Results: The majority of the respondents were female: 43 (60.6%) versus male, 28 (39.4%). A significantly higher percentage of doctors knew that failure of a child to gain weight normally could be a sign of PIDD (76% versus 24%, $p<0.0001$). The majority of respondents didn’t know specific signs of XLA (77% versus 23%, $p<0.0001$). The majority of respondents didn’t know laboratory tests to screen for B, T, NK, phaogocytic cells, complement or TLR signaling defects (91% versus 9%, $p<0.0001$).

Conclusions: There is limited knowledge on specific signs and laboratory screening tests for PIDD in Uganda.

Disclosure: No.

Keywords: Evaluation, Clinical, Laboratory, Knowledge, immunodeficiency, detection

PD484

SPECTRUM of DISEASE MANIFESTATIONS IN PEDIATRIC PATIENTS WITH WISKOTT-ALDRICH SYNDROME

POSTER DISPLAY 09: OTHER

Cristina Tomacinschii[1], Mihaela Bataneant[2,3], Rodica Selevestru[1], Valentin Turea[1], Eugen Popovici[4], Victoria Secara[5], Svetlana Sciuca[1]
[1]Nicolae Testemitanu State University of Medicine and Pharmacy, Pediatrics, Chisinau, Moldova, [2]Louis Turcanu Children Hospital, Iiird Pediatric Clinic, Timisoara, Romania, [3]"Victor Babeș" University of Medicine and Pharmacy, Iiird Pediatric Clinic, Timisoara, Romania, [4]Institute of Mother and Child, Hematology, Chisinau, Moldova, [5]Institute of Mother and Child, Genetics, Chisinau, Moldova

Background and Aims: Wiskott Aldrich syndrome (WAS) is a rare inherited error of immunity described by bacterial and viral infections, eczema, thrombocytopenia, autoimmunity, and malignancy. Due to WAS gene mutations spectrum of disease severity is ranging from a severe to a milder phenotype. Aim: We proposed to evaluate the spectrum of disease manifestations in pediatric patients with WAS.

Methods: A retrospective study of the data obtained from medical records of 4 children with WAS. WAS diagnosis was established using Sanger sequencing.

Results: Infections were recorded in all patients of which respiratory were the most frequent. Recurrent upper respiratory infections and bronchitis were recorded in all patients (n=4), and pneumonia was recorded in 3 (75%) patients. Two of the patients suffered intestinal infections with bloody diarrhea that was a key moment in the diagnosis establishment. Another highly prevalent manifestation was eczematous dermatitis (n=3, 75%) and petechiae (n=4). One (25%) patient suffered autoimmune clinical manifestations like arthritis. Unfortunately one of the patients developed hematological malignancy (non-Hodgkin lymphomas, 25%).

Conclusions: The clinical manifestations of WAS encompass a large spectrum of infectious, non-infectious diseases, and malignancy. These should be diagnosed, monitored, and treated early as possible.

Disclosure: No.

Keyword: Wiskott Aldrich, pediatric, malignancy, infections, lymphoma, eczema

PD485

CLINICAL, IMMUNOLOGICAL AND MOLECULAR CHARACTERISTICS of DOCK8 DEFICIENCY: FIRST SERIES FROM INDIA

POSTER DISPLAY 09: OTHER

Archan Sil[1], Ridhima Aggarwal[2], Ankur Jindal[3], Amit Rawat[4], Biman Saikia[5], Sanjib Mondal[4], . Sanchi[4], Pandiarajan Vignesh[4], Surjit Singh[4]
[1]Postgraduate Institute of Medical Education and Research, Chandigarh, India, Allergy And Immunology Unit, Advanced Pediatrics Center, Chandigarh, India, [2]Postgraduate Institute of Medical Education and Research, Department of Pediatrics, Advanced Pediatrics Cente, Chandigarh, India, [3]Postgraduate Institute of Medical Education and Research, Pediatrics, Chandigarh, India, [4]Post Graduate Institute of Medical Education and Research, Chandigarh, Allergy-immunology Unit, Dept of Paediatrics, Chandigarh, India, [5]Postgradute Institute of Medical Education & Research (PGIMER), Immunopathology, Chandigarh, India

Background and Aims: Dedicator of Cytokinesis 8 (DOCK8) deficiency, caused by loss of function mutations in DOCK8 gene, is characterised by eczema, recurrent cutaneous warts, molluscum, repeated ear discharge and increased susceptibility to malignancy and autoimmunity. There is paucity of reports on DOCK8 deficiency from India.

Methods: We reviewed records of patients diagnosed to have primary immunodeficiency in our unit. of these, 6 patients from 5 families were diagnosed to have DOCK8 deficiency. Clinical, immunological and molecular characteristics of these patients were studied in detail.

Results: Median age at diagnosis was 7.5 years (range: 2-13 years) with male: female ratio of 5:1. Predominant manifestations at presentation were recurrent eczema, cutaneous warts, skin pustules, ear discharge and pneumonia. Two patients presented with cutaneous warts and eczema only. One developed non-Hodgkin lymphoma at the age of 5. One patient succumbed to an intra-cranial mass lesion. Laboratory investigations showed lymphopenia with reduced T and B cells in 3/6 patients and eosinophilia in 5/6 patients. IgE was elevated in all (range 664 - 13,100 IU/ml). Th17 cells and pSTAT-3 expression were normal in all except one who had reduced Th17 cells. In 5 patients, a pathogenic variant in DOCK-8 gene was identified. Deletion mutations were seen in 2, missense mutation in 1 and 2 patients had non-sense mutations.

Conclusions: We report the first series on DOCK-8 deficiency from India. DOCK-8 deficiency should be suspected in patients with hyper-IgE phenotype with viral infections.

Disclosure: No.

Keywords: genetic, DOCK 8, Clinical, Immunological

PD486

OUTCOMES IN PATIENTS WITH SCHIMKE'S IMMUNO-OSSEOUS DYSPLASIA – A REGISTRY-BASED INTERNATIONAL SURVEY

POSTER DISPLAY 09: OTHER

Paul Torpiano[1], Aoife Waters[2], Antonia Bouts[3], Stephen Marks[2], Olivia Gillion-Boyer[4], Beata Lipska[5], Matthew Buckland[1], Austen Worth[6]
[1]Great Ormond Street Hospital, Immunology, London, United Kingdom, [2]Great Ormond Street Hospital, Nephrology, London, United Kingdom, [3]Amsterdam UMC, Nephrology, Amsterdam, Netherlands, [4]Necker Children's Hospital, Nephrology, Paris, France, [5]Medical University of Gdansk, Genetics, Gdansk, Poland, [6]Great Ormond Street Hospital, Department of Immunology And Gene Therapy, London, United Kingdom

Background and Aims: Schimke's Immuno-osseous Dysplasia (SIOD) is an autosomal recessive multi-system disorder caused by homozygous mutations in the SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1 (SMARCAL1) gene leading to spondyloepiphyseal dysplasia and short stature, progressive nephropathy, T-cell deficiency, and an increased risk of vascular abnormalities and haemorrhagic stroke. There is little research to inform management decisions, particularly those around haematopoietic stem cell (HSCT) and renal transplant. We propose a collaborative international survey assessing outcomes in SIOD and relating them to the timing of haematopoietic stem cell transplant and renal transplantation.

Methods: Questionnaires will be targeted at clinicians leading the care for children and adults with SIOD, who will be contacted via international renal, bone marrow transplant and immunodeficiency networks and associations. The questionnaire will explore 7 key areas: diagnosis of SIOD, clinical course (infection, neuro-vascular complications, renal disease, immunedysregulation/autoimmunity, malignancy, lymphoproliferation, other end-organ damage), therapeutic and prophylactic options (immunoglobulin replacement, antibiotic/antifungal/antiviral prophylaxis, antiplatelet/anticoagulant therapy, G-CSF, orthopaedic intervention, immunomodulation, renal replacement therapy and renoprotection, dialysis) transplantation (HSCT and renal), immunophenotyping, and death.

Results: Statistical analysis will focus on analysing all areas examined in the questionnaire at 8 important time points in the course of SIOD: symptom onset, genetic diagnosis, pre/post-HSCT, pre/post-renal transplant, time of questionnaire, and death (if applicable).

Conclusions: The results of this proposed international collaboration aims to inform discussions around therapeutic options and prognosis of SIOD patients in the coming years, and provide a clearer picture of the recommended timing of HSCT and renal transplantation.

Disclosure: No.

Keywords: Schimke immuno-osseous dysplasia, Haematopoietic stem cell transplant, Renal transplantation, Outcomes

PD487

INFLUENCE of SEX DIFFERENCES ON THE DISTRIBUTION of DIFFERENT LEUKOCYTE POPULATIONS

POSTER DISPLAY 09: OTHER

Ivon Rodriguez, Carlos Parra López
Universidad Nacional de Colombia, Movimiento Corporal Humano, Bogotá, Colombia

Background and Aims: Women and men differ in several physiological aspects, including the immune response. These differences may be related to sex steroid hormones, genetics, and environmental factors. Epidemiological evidence shows that while older men are more susceptible to complicated infectious diseases and death from cancer, older women tend to generate a more vigorous immune response that favors a higher incidence of autoimmunity. Aim: Identify changes in the distribution of different leukocytes' subsets

Methods: We set out peripheral blood samples from women and men healthy donors (n: 10 each). We have done an ex vivo characterization of monocytes' subsets, NK cells, and T cells by multi-parametric Flow cytometry. The protocol was approved by the ethics committee of the Faculty of Medicine.

Results: Men have a significantly higher percentage of intermediate monocytes than women, an increase in the CD56dim subpopulation, both young and older, and a significant decrease in the CD56bright subset, mainly in young men. While women had a significantly higher percentage of naïve T cells of CD4+ and CD8+ T cells, men had a significant increase in central memory CD4 + T cells and effector CD8 + T cells.

Conclusions: Our findings indicate that sex plays a crucial role in differential aging of the immune system. More studies are needed to identify correlation factors between aging, sex, and chronic diseases.

Disclosure: No.

Keywords: T cell, Monocytes, Immunosenescence, Natural killer cell

PD488

DESCRIPTION of PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE AND TOOTH LOSS

POSTER DISPLAY 09: OTHER

Jorge Beltrán[1], Lizbeth Blancas Galicia[2], Sara Espinosa Padilla[3], Jacinta Bustamante[4,5,6,7], Coyatzin Vazquez Armenta[8]
[1]National Institute of Pediatrics, Inmunology, Mexico city, Mexico, [2]National Institute of Pediatrics, Research Unit For Immunodeficiencies, Mexico city, Mexico, [3]National Institute of Pediatrics, Research Unit For Immunodeficiencies, Mexico City, Mexico, [4]Paris Hospital, Study Center For Primary Immunodeficiencies, Paris, France, [5]The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, New York, United States of America, [6]Necker Hospital for Sick Children, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1163, Paris, France, [7]Paris Cité University, Imagine Institute, Paris, France, [8]National Institute of Pediatrics, Stomatology, Mexico city, Mexico

Background and Aims: Chronic granulomatous disease (CGD) is an inborn error of immunity with impaired production of reactive oxygen species in phagocytes. Hyperinflammation in these patients poses a risk for gingivitis, chronic periodontitis, and subsequent tooth loss. [1–8] Aim: Describe cases with CGD with accelerated and early tooth loss.

Methods: Collected cases and telephone interview

Results: Case 1: 42-year-old female, carrier of X-linked defect, preferential X-chromosome inactivation. Poor dental hygiene. At 20 years old, loss of 4 teeth (35, 36, 45, 46), and later 4 teeth without carious lesions (14,15, 24, 25). At 30 years of age, chronic periodontitis was diagnosed, with grade 2 tooth mobility in teeth 22 and 32. Case 2: A 30-year-old female with an autosomal recessive defect in p47phox. Good dental hygiene. At 29 years old, she presented gingivitis and chronic periodontitis with loss of teeth 17, 27, 45, 46, 47 in 1 year. Currently with dental mobility grade 3, of teeth 11, 12, 13, 21, 22, 23, 31, 32, 33, 41, 42, 43 Case 3: 57-year-old male with X-linked defect, good dental hygiene, with chronic periodontitis since 28 years old with almost total progressive tooth loss, with an impact on quality of life.

Conclusions: Hyperinflammation in EGC leads to gingivitis and chronic periodontitis, causing accelerated tooth loss, more than in carious lesions. This loss occurs 2 to 3 decades earlier than the general population. References: 1. Cohen MS, cols. Phagocytic Cells in Periodontal Defense: Periodontal Status of Patients with Chronic Granulomatous Disease of Childhood. J Periodontol. 1985;56(10):611-7.

Disclosure: No.

Keyword: chronic granulomatous disease, hyperinflammation, periodontitis, tooth loss

PD489

AUTOIMMUNE MANIFESTATIONS IN A LARGE MULTI-CENTRE COHORT of PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY IN INDIA.

POSTER DISPLAY 09: OTHER

. Sanchi[1], Ankur Jindal[1], Himanshi Chaudhary[2], Rahul Tyagi[1], Deepti Suri[1], Amit Rawat[1], Kavadichanda Chengappa[3], Sagar Bhattad[4], Latika Gupta[5], Puja Srivastava[6], Inderpaul Singh[7], Pratap Patra[8], Silky Jain[9], Vignesh Pandiarajan[1], Rajni Sharma[2], Ruchi Saka[2], Surjit Singh[1]
[1]Postgraduate Institute of Medical Education and Research, Department of Pediatrics, Advanced Pediatrics Centre, Chandigarh, India, [2]Post graduate Institute of Medical Education and Research, Department of Pediatrics, Advanced Pediatrics Centre, Chandigarh, India, [3]Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India, Clinical Immunology, Puducherry, India, [4]Aster CMI Hospital, Pediatric Immunology And Rheumatology, Department of Pediatrics,, Bengaluru, India, [5]Sanjay Gandhi Postgraduate Institute of Medical Sciences (SPGIMS), Department of Clinical Immunology And Rheumatology,, Lucknow, India, [6]STAR Rheumatology Clinic, Ahmedabad, India, Star Rheumatology Clinic, Ahmedabad, India, [7]Postgraduate Institute of Medical Education and research, Department of Pulmonary Medicine,, Chandigarh, India, [8]All India Institute of Medical Sciences, Patna, India., Department of Paediatrics, Patna, India, [9]Jaypee Hospital, Department of Pediatric Hemato-oncology, Noida, India

Background and Aims: Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency (PID). In this study we aim to report autoimmune manifestations of patients with CVID from India.

Methods: A predesigned Microsoft Excel sheet was circulated via email to all centres across the country. Diagnosis of CVID was based on the European Society for Immunodeficiency (ESID) 2014 classification criteria.

Results: This study included 126 patients diagnosed with CVID. Median age at onset of symptoms and diagnosis was 7 and 15 years respectively. Autoimmune manifestations were seen in 43 patients (34.12%). Autoimmune hemolytic anemia and autimmune hepatitis were the most common manifestions(5.55% each) followed by autoimmune thrombocytopenia, inflammatory arthritisand systemic lupus erythematosus (3.96% each), autoimmune thyroiditis(3.17%), celiac disease and alopecia areata(2.6% patients each) and autoimmune neutropenia, pure red cell aplasia,chronic inflammatory demyelinating polyneuropathy (1.58% each). Vasculitis, psoriasis, antiphospholipid antibody positivity, inflmmatory Bowel Disease (IBD) were seen in one patient each We compared the clinical and immunological profile of CVID patients with autoimmunity (CVID+AI) or without autoimmunity (CVID-AI). CVID+AI group had a significantly higher recurrent infections (76.74% vs 69.87%, p value 0.02)and fungal infections (9.30% vs 7.22, p value 0.02)compared to CVID-AI group. CVID+AI group had significantly low IgG (300.29±248.52 vs 338.29±367.54, p value 0.021) and highIgM levels (76.25±119.98 vs 52.25±78.14, p value 0.010)compared to CVID-AI group. 50% of CVID+ AI group had monogenic defect compared to 66% of CVID-AI group.

Conclusions: This is the first large multicentre cohort of patients with CVID from India. Autoimmune manifestations are seen in 1/3rd of all patients with CVID

Disclosure: No.

Keywords: Common variable immunodeficiency, Autoimmunity, Primary Immunodeficiecny

PD490

GUT IMMUNOPATHOLOGICAL SIGNATURES IN HUMANS AND MICE CARRYING RAG1 HYPOMORPHIC MUTATIONS

POSTER DISPLAY 09: OTHER

Riccardo Castagnoli[1,2,3], Francesca Pala[1], Ai Ing Lim[4], Marita Bosticardo[1], Elena Fontana[5], Cihan Oguz[6], Ottavia Delmonte[1], Ivan Vujkovic-Cvijin[4], Poorani Subramanian[7], Grace Smith[8], Andrew Burns[9], Sean Conlan[10], Clay Deming[10], Danielle Fink[11], Vasileios Oikonomou[1], Cristina Corsino[1], Lisa Ott De Bruin[12], John Manis[13], Angelina Angelova[7], Yu Han[1], Emilia Falcone[14,15], Douglas Kuhns[11], Miriam Quinones[7], Gian Luigi Marseglia[2,3], Heidi Kong[16], Michail Lionakis[1], Stefania Pittaluga[8], Anna Villa[17,18], Julie Segre[10], Yasmine Belkaid[4], Luigi Notarangelo[1]
[1]National Institutes of Health, Laboratory of Clinical Immunology And Microbiology, Bethesda, United States of America, [2]Fondazione IRCCS Policlinico San Matteo, Pediatric Clinic, Pavia, Italy, [3]University of Pavia, Department of Clinical, Surgical, Diagnostic And Pediatric Sciences, Pavia, Italy, [4]National Institutes of Health, Laboratory of Host Immunity And Microbiome, Bethesda, United States of America, [5]IRCCS Humanitas Research Hospital, Human Genome And Biomedical Technologies Unit, Milan, Italy, [6]National Institutes of Health, Niaid Collaborative Bioinformatics Resource (ncbr), Bethesda, United States of America, [7]National Institutes of Health, Bioinformatics And Computational Biosciences Branch, Bethesda, United States of America, [8]NIH, Center For Cancer Research, Bethesda, United States of America, [9]National Institutes of Health, Niaid Microbiome Program, Bethesda, United States of America, [10]National Institutes of Health, National Human Genome Research Institute, Bethesda, United States of America, [11]National Institutes of Helath, Neutrophil Monitoring Lab, Bethesda, United States of America, [12]Leiden University Medical Center, Willem-alexander Children's Hospital, Department of Pediatrics, Laboratory For Pediatric Immunology, Leiden, Netherlands, [13]Boston Children's Hospital, Division of Immunology, Boston, United States of America, [14]Montreal Clinical Research Institute, Department of Medicine, Montreal (Quebec), Canada, [15]McGill University Health Centre, Research Institute, Montreal, Canada, [16]NIH, Niams, Bethesda, United States of America, [17]San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), Ircss San Raffaele Scientific Institute, Milan, Italy, [18]Milan Unit, Istituto di Ricerca Genetica e Biomedica (IRGB), Consiglio Nazionale Delle Ricerche (cnr), Milan, Italy

Background and Aims: Hypomorphic *RAG1* mutations have been found in patients presenting with delayed-onset combined immunodeficiency with granulomas and/or autoimmunity (CID-G/AI) and atypical SCID.

Methods: To investigate the role of these mutations in intestinal disease, we studied the interplay of gut immunity and microbiota in a hypomorphic *Rag1* mouse model carrying a mutation described in patients with atypical SCID (R972W, $Rag1^{w/w}$ mice).

Results: Analysis of gut tissue in $Rag1^{w/w}$ mice revealed severe spontaneous colitis with lymphocytic infiltrates, which become histologically evident after 3 weeks of age. To assess the relative contribution of genetic and environmental factors on the pathogenesis of gut inflammation, we combined flow cytometry, single-cell RNA-seq and microbiome studies. Phenotypical and gene expression analysis of T cells infiltrating the colon lamina propria showed skewing towards a Th1/Th17 phenotype in $Rag1^{w/w}$ mice. Analysis of the fecal microbiota composition revealed a severe restriction of microbial diversity in mutant mice.

Conclusions: To evaluate the role of the microbiota in inducing gut inflammation, we administered broad-spectrum antibiotics to $Rag1^{w/w}$ mice. Although the lymphocytic infiltrate was quantitatively normalized, the colonic lamina propria T cells maintained the skewing towards the Th1/Th17 phenotype, indicating a preponderant effect of the genotype on colitis induction. Hematopoietic stem cell transplantation resulted in an almost complete donor chimerism with donor-derived T cells in the colon lamina propria showing a wild-type phenotype, without Th1/Th17 skewing. Similarly, histology and RNAscope on colonic tissue from RAG patients with CID-G/AI and enteropathy confirmed the lymphocytic infiltrate with Th1/Th17 skewing, and fecal microbiota analysis showed reduced microbial diversity.

Disclosure: No.

Keywords: RAG, IEI, microbiota, Inflammatory bowel disease, CID, GUT

PD491

POOR HEALTH-RELATED QUALITY of LIFE IN PATIENTS WITH STAT3-DN HYPER-IGE SYNDROME: PRELIMINARY RESULTS of AN INTERNATIONAL MULTICENTRIC STUDY

POSTER DISPLAY 09: OTHER

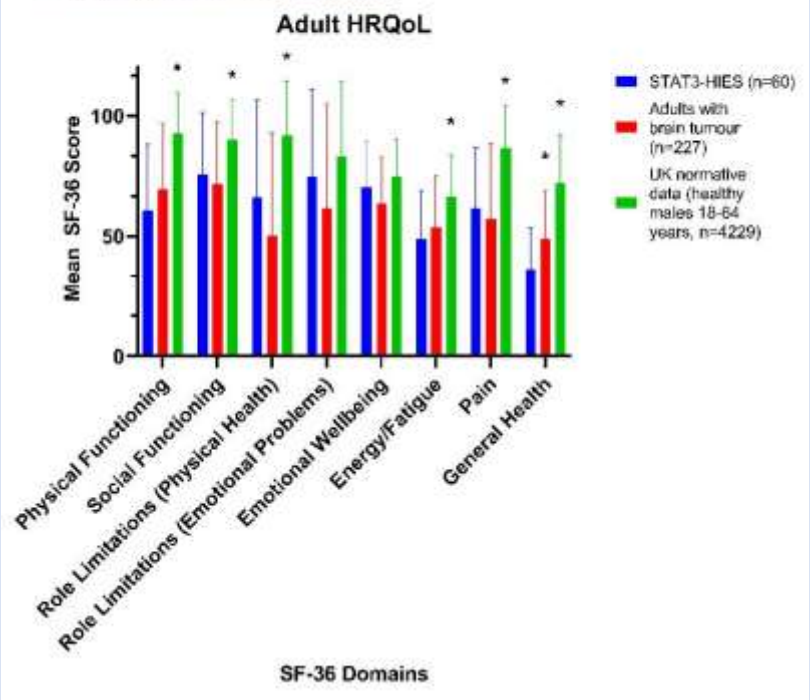
Christo Tsilifis[1,2], Christine Lafeer[3], Jean Ulrick[3], Paul Gray[4], Corina Gonzalez[5], Dimana Dimitrova[6], Jennifer Kanakry[6], Suzanne Elcombe[7], Austen Worth[8], Alexandra Freeman[3], Andrew Gennery[1,2]
[1]Newcastle University, Translational And Clinical Research Institute, Newcastle upon Tyne, United Kingdom, [2]Great North Children's Hospital, Children's Haematopoietic Stem Cell Transplant Unit, Newcastle upon Tyne, United Kingdom, [3]National Institute of Allergy and Infectious Diseases, Laboratory of Clinical Immunology And Microbiology, Bethesda, United States of America, [4]Sydney Children's Hospital, Immunology And Infectious Diseases, Randwick, Australia, [5]National Institutes of Health, Immune Deficiency Cellular Therapy Branch, National Cancer Institute, Bethesda, United States of America, [6]Center for Cancer Research, National Cancer Institute, National Institutes of Health, Center For Immuno-oncology, Bethesda, MD, United States of America, [7]Newcastle Hospitals NHS Foundation Trust, Department of Clinical Immunology, Newcastle, United Kingdom, [8]Great Ormond Street Hospital, Department of Immunology And Gene Therapy, London, United Kingdom

Background and Aims: Patients with primary immunodeficiency report poor health-related quality-of-life (HRQoL), as do caregivers of chronically unwell children. There are no published data for the impact of STAT3-DN hyper IgE syndrome (HIES) on patient or parental HRQoL. To evaluate patient and parental HRQoL across an international cohort with STAT3-DN-HIES to better understand the impact of the disease and treatment on patient lives.

Methods: Multicentric international prospective study using validated questionnaires (adults: SF-36, children: PedsQL™4.0 SF15, parents/caregivers: PedsQL™2.0 Family Impact Module). Data presented as mean±standard deviation or median [range]; comparisons made by independent-sample t-test. Questionnaires are scored 0-100 with higher scores indicating better HRQoL.

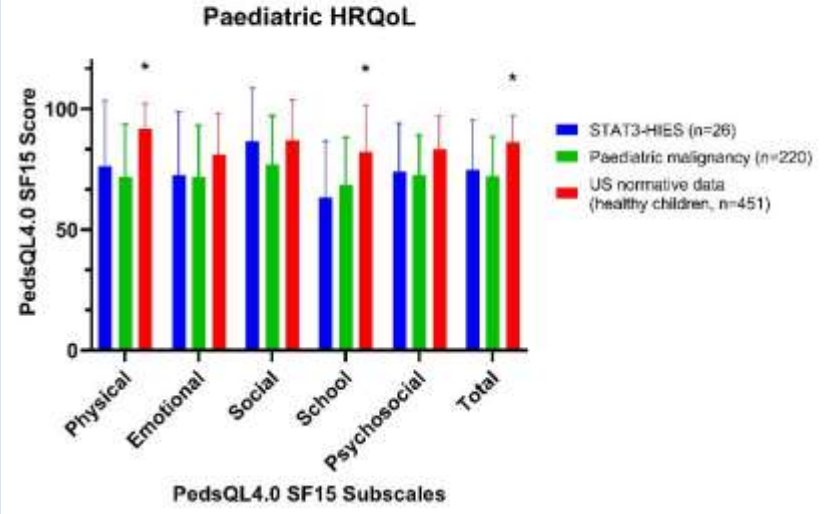
Results: Preliminary data were collected from 87 patients. Sixty adult patients (median age: 35.5 [18.0-70.0] years) had significantly lower mean scores for physical function (60.44±27.58), social function (75.63±25.67), energy (48.67±20.25), pain (61.31±25.36), and general health (36.17±17.21) versus healthy adult norms, comparable to patients with brain tumours, except general health which was poorer (mean difference: 12.77±2.59, $p<0.001$, **Figure 1**).

Figure 1 – SF-36 subscale scores in adults with STAT3-HIES compared to adults with brain tumours (Bunevicius et al, Health Qual Life Outcomes 2017;15(1):92), and normative data from healthy UK adults (Jenkinson et al, BMJ 1993;306:1440). Higher scores indicate better HRQoL for each domain. Data expressed as mean with standard deviation. Asterisks (*) indicate significant difference in mean score compared to STAT3-HIES patients, by independent sample t-test.



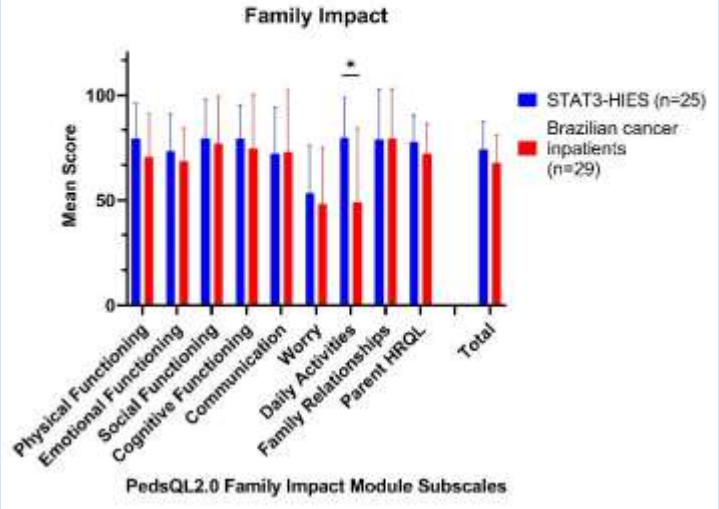
Twenty-seven children (13.0 [3.0-17.0] years) had significantly poorer mean scores in physical function (76.41±27.07), school function (63.14±23.47) and overall QOL (74.74±20.72), versus healthy children ($p<0.001$), comparable to children with malignancy (**Figure 2**).

Figure 2 – PedsQL4.0 SF15 subscale scores for children and young people with STAT3-HIES compared to children with malignancy (Varni et al, Cancer 2002;94(7):2090-106) and normative data from healthy US children (Chan et al, Med Care 2005;43(3):265). Higher scores indicate better HRQoL for each domain. Data expressed as mean with standard deviation. Asterisks (*) indicate significant difference in mean score compared to STAT3-HIES patients, by independent sample t-test.



For parents, HRQoL was not significantly different to those of children with malignancy (**Figure 3**) except for daily activities, which was better (mean difference: 30.82±7.63, $p=0.002$).

Figure 3 – PedsQL 2.0 Family Impact Module subscale scores in parents and caregivers of children and young people with STAT3-HIES compared to caregivers of children receiving inpatient care for malignancy (Soanes et al, Health Qual Life Outcomes 2008;6:35). Data expressed as mean with standard deviation. Higher scores indicate better HRQoL for each domain. Data expressed as mean with standard deviation. Asterisks (*) indicate significant difference in mean score compared to STAT3-HIES patients, by independent sample t-test.



Conclusions: STAT3-DN-HIES patients have poor HRQoL, comparable to patients with malignancy. We will expand this dataset to explore impact of clinical phenotype, treatment, and allogeneic haematopoietic stem cell transplantation, to better inform future care.

Disclosure: No.

Keywords: health-related quality of life, QOL, SF-36, PedsQL, parents, hyper IgE

PD492

RESPIRATORY AND DERMATOLOGICAL SYMPTOMS AND QUALITY of LIFE IN PATIENTS WITH STAT3-DN HYPER-IGE SYNDROME: PRELIMINARY RESULTS of AN INTERNATIONAL MULTICENTRIC STUDY

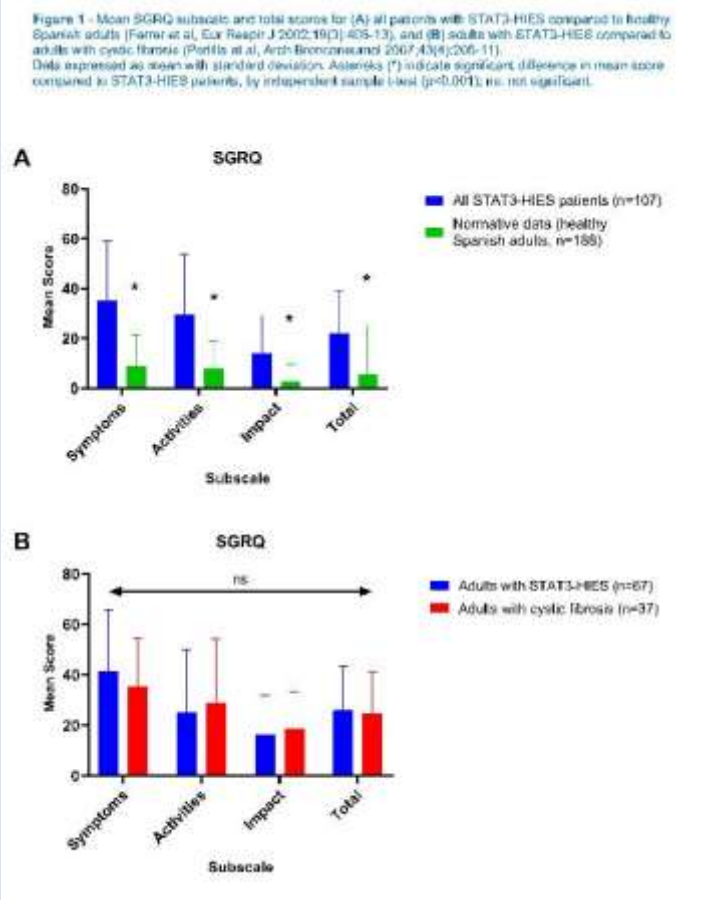
POSTER DISPLAY 09: OTHER

Christo Tsilifis[1,2], Christine Lafeer[3], Jean Ulrick[3], Maria Fasshauer[4], Michael Borte[4], Petra Kaiser-Labusch[5], Catharina Schuetz[6], Leonora Pietzsch[6], Begoña Carazo Gallego[7], Elena Seoane-Reula[8], Hector Balastegui[8], Ana Méndez Echevarría[9], Huawei Mao[10], Seyed Alireza Mahdaviani[11], Mohammad Gharagozlou[12], Mahnaz Jamee[13], Zahra Chavoshzadeh[13], Satoshi Okada[14], Yoko Mizoguchi[14], Woei Kang Liew[15], Yae-Jean Kim[16], Paul Gray[17], Juan Aldave Becerra[18], Nima Rezaei[19], Hassan Abolhassani[19], Intan Abd Hamid[20], Zarina Thasneem Zainudeen[20], Ilie Fadzillah Hashim[20], Corina Gonzalez[21], Dimana Dimitrova[22], Jennifer Kanakry[22], Suzanne Elcombe[23], Peter Olbrich[24], Olaf Neth[24], Raffaele Badolato[25], Austen Worth[26], Alexandra Freeman[3], Andrew Gennery[1,2]
[1]Newcastle University, Translational And Clinical Research Institute, Newcastle upon Tyne, United Kingdom, [2]Great North Children's Hospital, Children's Haematopoietic Stem Cell Transplant Unit, Newcastle upon Tyne, United Kingdom, [3]National Institute of Allergy and Infectious Diseases, Laboratory of Clinical Immunology And Microbiology, Bethesda, United States of America, [4]Hospital for Children & Adolescents, St. Georg Hospital, Leipzig, Academic Teaching Hospital of The University of Leipzig, Immunodeficiency Center Leipzig (idcl),leipzig, Leipzig, Germany, [5]Klinikum Bremen-Mitte, Eltern-kind Zentrum Prof. Hess, Bremen, Germany, [6]University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Pediatric Immunology, Dresden, Germany, [7]Hospital Universitario Regional de Málaga, Infecciosos Pediátricos, Málaga, Spain, [8]Hospital General Universitario Gregorio Marañon, Immunology, Madrid, Spain, [9]La Paz University Hospital, Department of Pediatric Infectious Diseases, Madrid, Spain, [10]Beijing Children's Hospital, Capital Medical University, Department of Immunology, Beijing, China, [11]National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Pediatric Respiratory Diseases Research Center, Tehran, Iran, [12]Children's Medical Center, Tehran University of Medical Sciences, Department of Allergy And Clinical Immunology, Tehran, Iran, [13]Pediatric Infections Research Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [14]Hiroshima University Graduate Schools of Biomedical and Health Sciences, Pediatrics, Hiroshima, Japan, [15]Mount Elizabeth Novena Hospital, Paediatric Allergy Immunology Rheumatology Centre, Singapore, Singapore, [16]Samsung Medical Center, Sungkyunkwan University School of Medicine, Pediatrics, Seoul, Korea, Republic of, [17]Sydney Children's Hospital, Immunology And Infectious Diseases, Randwick, Australia, [18]18. Hospital Nacional Edgardo Rebagliati Martins, Pediatrics, Lima, Peru, [19]Tehran University of Medical Sciences, Research Center For Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran, Iran, [20]Institut Perubatan & Pergigian Termaju, Universiti Sains Malaysia, Primary Immunodeficiency Diseases Group, Department of Clinical Medicine, Pulau Pinang, Malaysia, [21]National Institutes of Health, Immune Deficiency Cellular Therapy Branch, National Cancer Institute, Bethesda, United States of America, [22]Center for Cancer Research, National Cancer Institute, National Institutes of Health, Center For Immuno-oncology, Bethesda, MD, United States of America, [23]Newcastle Hospitals NHS Foundation Trust, Department of Clinical Immunology, Newcastle, United Kingdom, [24]Pediatric Infectious Diseases, Rheumatology and Immunology Unit, Hospital Universitario Virgen Del Rocío, Instituto De Biomedicina De Sevilla, Ibis/ Universidad De Sevilla/csic, Red De Investigación Traslacional En Infectología Pediátrica Ritip, Seville, Spain, [25]Specialty School of Paediatrics, University of Brescia, Spedali Civili di Brescia, Paediatrics Clinic, Brescia, Italy, [26]Great Ormond Street Hospital, Department of Immunology And Gene Therapy, London, United Kingdom

Background and Aims: STAT3-DN hyper-IgE syndrome (HIES) causes recurrent skin and pulmonary infections leading to bronchiectasis. Patient-reported data on quality of life (QOL) in STAT3-DN-HIES is limited. To evaluate respiratory and dermatology-specific QOL in STAT3-DN-HIES across an international cohort to inform understanding and future treatment.

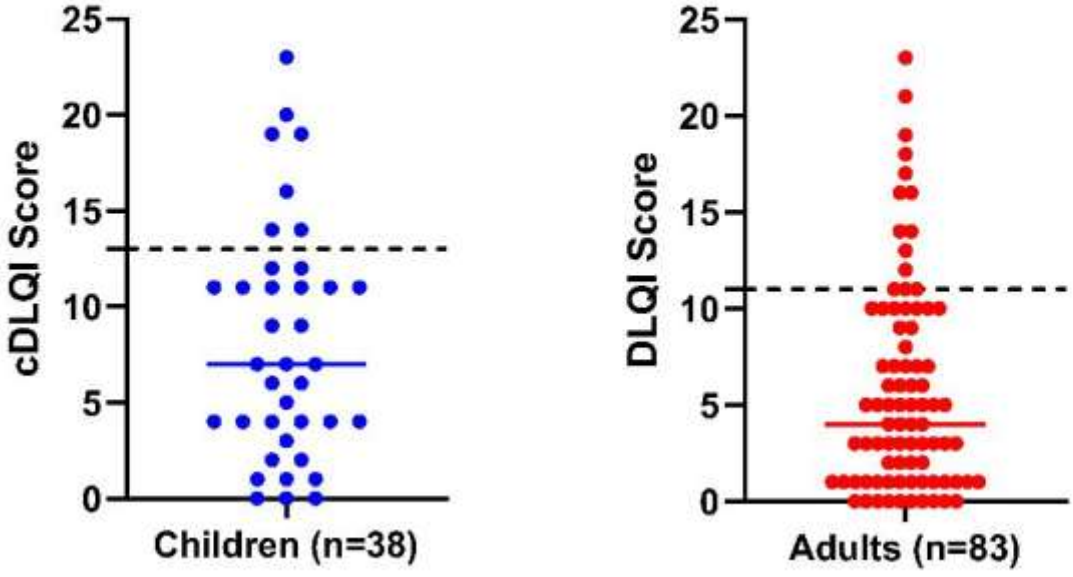
Methods: Preliminary data from a multicentric international prospective study using validated translated questionnaires (St George's Respiratory Questionnaire, SGRQ, scored 0-100; Dermatology Life Quality Index, DLQI/children's DLQI, cDLQI, scored 0-30). Higher scores indicate poorer patient-reported QOL. Data presented as median [range]. Mean scores compared using independent sample t-test, correlation calculated using Pearson's R.

Results: Data were collected from 147 patients from 11 countries, with median age 23.0 years [3.0–70.0]. In 67 adults, median total SGRQ score was 23.8[0.00-71.6] and subscale scores were: symptoms, 35.3[0.00-85.8]; activities, 11.7[0.00-62.4]; and impact, 24.2[0.00-71.6]. In 40 children, median total SGRQ score was 10.1[0.00-50.8], with subscale scores: symptoms, 12.2[0.00-66.2]; activities, 4.0[0.00-43.3]; and impact, 10.0[0.00-50.8]. Both groups had poorer QOL than healthy adults ($p<0.001$), and adults scored similarly to patients with cystic fibrosis (**Figure 1**). SGRQ scores worsened with increasing age ($r=0.434\pm0.175$, $p<0.0001$).



Median DLQI score in 83 adults was 4 [0-23], and in 38 children median cDLQI was 7 [0-23] (**Figure 2**). Scores indicating 'severe impact' were seen in 14 adults (16.8%, DLQI score ≥11) and 7 children (18.4%, cDLQI score ≥13).

Figure 2 - Dermatology Life Quality Index scores for individual children (left) and adults (right). Coloured line represents median, and black dashed line represents score indicating "severe impact to quality of life" (≥13 for children and ≥11 for adults).



Conclusions: Our preliminary findings demonstrate heterogeneous but significant negative respiratory and dermatological QOL. We will gather additional data to explore how clinical phenotype, treatments such as immunoglobulin replacement and allogeneic haematopoietic stem cell transplantation modify QOL indices.

Disclosure: No.

Keywords: St George's Respiratory Questionnaire, dermatology, hyper IgE, quality of life, respiratory health

PD493

SEROLOGICAL RESPONSE of ADULT AND PEDIATRIC PATIENTS WITH PRIMARY AND SECONDARY IMMUNODEFICIENCY TO SARS-COV2 BNT16B2 AND MRNA-1273 VACCINES, AND BREAKTHROUGH INFECTIONS IN CANADA

POSTER DISPLAY 09: OTHER

Dana Unninayar[1], Donald Vinh[2], Emilia Falcone[2], Hugo Chapdelaine[2], Karina Top[3], Beata Derfalvi[3], Alejandro Palma[4], Thomas Issekutz[4], Lisa Barrett[3], Sharon Oldford[3], Gina Lacuesta[3], Helene Decaluwe[5], Marc-Andre Langlois[6], Anne Pham-Huy[7], Julia Upton[8], Stephen Betschel[9], Tamar Rubin[10], Chrystyna Kalicinsky[10], Sneha Suresh[11], Luis Murguia-Favela[12], Nicola Wright[12], Juthaporn Cowan[13]
[1]The Ottawa Hospital, Medicine, Ottawa, Canada, [2]McGill University Health Centre, Research Institute, Montreal, Canada, [3]Dalhousie University, Medicine, Halifax, Canada, [4]IWK Health Centre/Dalhousie University, Pediatrics; Division of Immunology, Halifax, Canada, [5]CHU Ste Justine, Centre De Recherche, Montreal, Canada, [6]University of Ottawa, Faculty of Medicine, Ottawa, Canada, [7]Children's Hospital of Eastern Ontario, Infectious Diseases, Ottawa, Canada, [8]The Hospital for Sick Children, University of Toronto, Department of Pediatrics, Division of Immunology And Allergy, Toronto, Canada, [9]Unity Health Toronto, Clinical Immunology And Allergy, Toronto, Canada, [10]University of Manitoba, Medicine, Winnipeg, Canada, [11]University of Alberta, Medicine, Edmonton, Canada, [12]University of Calgary, Medicine, Calgary, Canada, [13]Ottawa Hospital Research Institute, Infectious Diseases, Ottawa, Canada

Background and Aims: Adults and children with inborn or acquired immunodeficiency (ID) are at increased risk of severe SARS-CoV-2 infection. Data on vaccine immunogenicity and effectiveness in ID is limited. Vaccine Immunogenicity and Safety in ImmunoDeficient patients (VISID) study is a nationwide multicenter prospective study to assess ID SARS-CoV-2 mRNA vaccine responses.

Methods: Recruitment of eligible ID and healthy controls began July 2021 and remains open. Blood for immunogenicity analysis was collected pre- and post-vaccination. Anti-Spike IgG was measured by ELISA. Rates of post-vaccination SARS-CoV-2 infection were estimated.

Results: 150 adult and 69 pediatric ID patients as well as 19 adult and 18 pediatric controls were recruited. Seroconversion rates in ID were 12/16(75%), 46/53(87%), 54/58(93%) after dose 1, 2, 3 respectively compared to 12/12(100%) and 6/6(100%) after dose 1 and 2 respectively in controls. In adult ID, the magnitude of vaccine response at 4-weeks post-dose 3 (3216.33BAU/mL(669.18)) was comparable to that at 4-weeks post-dose 2 in controls (3436.69BAU/mL(1711.13)). Pediatric ID had higher anti-Spike titres compared to ID adults post-dose 2 ($p<0.01$) and 3 ($p=0.04$). SARS-CoV-2 infection rates were similar between ID(15%) and controls(11%), and between adult ID(15%) and pediatric ID(15%). The majority of infections in ID occurred post-dose 3 and after January 2022. None was hospitalized.

Conclusions: Although the seroconversion rate is lower in ID, the magnitude of antibody response after 3 doses is comparable to after 2 doses in controls. Breakthrough infections occurred in vaccinated ID and controls although none was severe. Thus, this data supports the recommendation of a 3-dose primary series for ID.

Disclosure: No.

Keywords: COVID-19, Vaccination, primary immunodeficiency, pediatric, SARS-CoV-2

PD494

MOLECULAR FINDINGS AND CLINICAL MANIFESTATIONS IN NINE IRANIAN CHILDREN WITH GRISCELLI SYNDROME TYPE 2

POSTER DISPLAY 09: OTHER

Shaghayegh Tajik[1], Mohsen Badalzadeh[1], Massoud Houshmand[2], Zahra Alizadeh[1], Leila Moradi[1], Amir Ali Hamidieh[3], Alireza Shafiei[4], Javad Ahmadiani Heris[5], Anahita Razaghian[1], Mostafa Moin[1], Mohammad-Reza Fazlollahi[1], Zahra Pourpak[1]
[1]Immunology, Asthma and Allergy Research Institute, 4th Floor, Building No. 3, Children's Hospital Medical Center, Qarib Street, Keshavarz Blvd., Tehran, Iran, Immunology, Asthma And Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran, -, Iran, [2]Department of Medical Genetics, National Institute of Genetic Engineering and Biotechnology (NIGEB), Tehran, Iran, Department of Medical Genetics, National Institute of Genetic Engineering And Biotechnology (nigeb), Tehran, Iran, Tehran, Iran, [3]Department of Pediatric Hematology and Oncology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran, Department of Pediatric Hematology And Oncology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran, Tehran, Iran, [4]Department of Immunology, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, Iran, Tehran, Iran, [5]Department of Allergy and Clinical Immunology, Pediatric Hospital, Tabriz University of Medical Sciences, Tabriz, Iran, Department of Allergy And Clinical Immunology, Pediatric Hospital, Tabriz University of Medical Sciences, Tabriz, Iran, Tehran, Iran

Background and Aims: Griscelli syndrome type 2 (GS2) is an autosomal recessive immunodeficiency, clinically characterized by partial albinism (hypopigmentation of the hair), episodes of acute fever, hepatosplenomegally, pancytopenia and haemophagocytic lymphohistocytosis (HLH). This study aims to find genetic changes and clinical features in nine children with GS2 caused by *RAB27A* gene defect.

Methods: Nine Iranian children with autosomal recessive Griscelli syndrome type 2 who were presented with silver gray hair and frequent pyogenic infection, referred to Immunology, Asthma and Allergy Research Institute (IAARI) and included in this study. After recording demographic and clinical data, PCR amplification of was performed by direct DNA sequencing for all exons.

Results: Light microscopy study of hair was showed large irregular clumps of pigment. Mutation analysis of *RAB27A* gene identified five different mutations including c.514_518delCAAGC, c.150_151delAGinsC, c.400_401delAA, c.340delA, c.428T>C. The mutation c.514_518delCAAGC was the most frequent and found in the patients; this mutation may be considered as a hotspot in Iran.

Conclusions: Identification of *RAB27A* mutations can facilitate prompt diagnosis and treatment, and aid genetic counselling and prenatal diagnosis, which will help in the improvement of the disease outcome. These genetic results could be urgent to make a timely decision for hematopoietic stem cell transplantation and prenatal diagnosis of the next generation in the affected families.

Disclosure: No.

Keywords: Hypopigmentation, Partial albinism, Griscelli Syndrome, RAB27A gene

PD495

A CASE DIAGNOSED WITH COCKAYNE SYNDROME WHILE INVESTIGATING PRIMARY IMMUNODEFICIENCY

POSTER DISPLAY 09: OTHER

Candan Islamoglu[1], Ali Can Demirel[1], Ahmet Cevdet Ceylan[2], Ayse Metin[1]
[1]Ankara City Hospital, Peidatric Immunology And Allergy, Ankara, Turkey, [2]Ankara City Hospital, Genetics, Ankara, Turkey

Background and Aims: Cockayne Syndrome is a rare autosomal recessive heterogeneous multisystem disease characterized by syndromic features such as microcephaly, failure to thrive, sensorineural hearing loss, cataract, retinal dystrophy. These patients die due to life-threatening liver failure after using metronidazole.

Methods: Here, we present a case who was consulted to our pediatric immunology clinic in terms of primary immunodeficiency due to recurrent lung infections and consanguinity.

Results: Case: A 2.5-year-old girl, born from consanguineous marriage was consulted to our pediatric immunology clinic due to recurrent lung infections. According to her history, she was hospitalized 3 times due to severe pneumonia, at 14, 21 and 30 months old. It was learned that 4 of her siblings died in the early period of life due to jaundice and liver dysfunction. Physical examination revealed microcephaly, failure to thrive, developmental delay and atypical facial appearance. Complete blood count was normal in laboratory tests, and biochemistry tests were normal except for mild ALT elevation (42 U/L). Ig G,A,M levels were within normal range. In the lymphocyte subgroup analysis, a slight decrease was found in CD3+ T lymphocytes. In the B lymphocyte subgroup analysis, low memory B cells were detected. Swallowing dysfunction was found in the swallowing evaluation performed due to recurrent lung infections. Genetic analysis revealed homozygous c.2551 T>A mutation in the ERCC6 gene.

Conclusions: Primary immunodeficiencies may not be the only cause of frequent infections. Diseases that cause systemic involvement such as Cockayne Syndrome in children with unexplained failure to thrive, microcephaly, hearing loss, and cataract should be considered.

Disclosure: No.

Keywords: Failure to thrive, hepatic failure with metronidazole, microcephaly

PD496

MYCOBACTERIAL INFECTIONS IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE: AN EXPERIENCE FROM NORTH INDIA

POSTER DISPLAY 09: OTHER

Archan Sil, Ridhima Aggarwal, Sanjib Mondal, Vignesh Pandiarajan, Amit Rawat, Surjit Singh
Postgraduate Institute of Medical Education and Research, Chandigarh, India, Allergy And Immunology Unit, Advanced Pediatrics Center, Chandigarh, India

Background and Aims: Chronic granulomatous disease (CGD) is a phagocytic defect characterized by recurrent bacterial and fungal infections. Mycobacterial infections have been reported in children with CGD from countries where BCG is given as a part of routine immunization or tuberculosis is prevalent. We report clinical, laboratory and genetic profile of CGD patients with mycobacterial disease in a cohort from North India.

Methods: A review of clinical and laboratory records was carried out for patients with CGD and mycobacterial disease registered at Pediatric Immunodeficiency Clinic, Postgraduate Institute of Medical Education and Research, Chandigarh, India between January,1990 and December, 2021.

Results: of the 99 patients with CGD, 22 had mycobacterial infections. Infections due to Mycobacterium tuberculosis and M. bovis were noted in 11 patients each. Six patients had localised from and 5 had disseminated BCG disease. Median age at onset of symptoms and diagnosis of BCG disease was 5 months and 15 months respectively. of 11 patients with tuberculosis, pulmonary, pleuro-pulmonary, abdominal and disseminated forms were present in 6, 1, 2 and 2 patients respectively. Median age at onset of symptoms and diagnosis of tuberculosis was 129 months and 130 months respectively. While disseminated forms of BCG occurred only in patients with mutation in CYBB gene, BCG disease was not noted in NCF1 group. However, NCF1 group had increased prevalence of M. tuberculosis infection. Mortality was seen in 6 patients.

Conclusions: Evaluation for CGD is warranted in any patient with severe and unusual forms of mycobacterial disease.

Disclosure: No.

Keywords: BCG disease, Chronic Granulomatous Disease, Mycobacterial infections, Tuberculosis

PD497

HYPER IGE SYNDROME (HIES) CAUSED BY BI-ALLELIC HYPOMORPHIC MUTATIONS IN THE STAT3 GENE.

POSTER DISPLAY 09: OTHER

Viktoriya Bludova[1], Tiphanie Phillips Vogel[2], Dmitry Pershin[3], Mariia Fadeeva[4], Amina Kieva[5], Herda Ona[2], Ekaterina Deordieva[6], David Hagin[7], Elena Raykina[5], Yulia Rodina[1], Anna Shcherbina[1]
[1]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Immunology, Moscow, Russian Federation, [2]Baylor College of Medicine and Texas Children's Hospital, Division of Rheumatology, Department of Pediatrics, Houston, TX, United States of America, [3]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Laboratory of Transplantation Immunology And Immunotherapy of Hemoblastoses, Moscow, Russian Federation, [4]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Laboratory of Hematopoietic Stem Cell Transplantation And Immunotherapy, Moscow, Russian Federation, [5]Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Laboratory of Molecular Biology, Moscow, Russian Federation, [6]Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation, Department of Immunology, Moscow, Russian Federation, [7]Tel-Aviv Sourasky Medical Center, Allergy And Clinical Immunology Unit, Tel-Aviv, Israel

Background and Aims: HIES is a well-described primary immunodeficiency classically caused by heterozygous dominant-negative mutations in the *STAT3* gene. Complete *STAT3* knockout is embryonic lethal in mice, and to our knowledge, no patients with pathogenic, bi-allelic *STAT3* mutations have been described to date.

Methods: Genetic evaluation was performed using a custom NGS panel. Th17 cells were enumerated using flow cytometry. *STAT3* variants were functionally validated using a luciferase reporter assay.

Results: We evaluated a 2-year-old male patient with typical HIES features and infections (HIES score 37) and found 2 novel *STAT3* variants: c.1781_1786dup, p.Glu594_Arg595dup and c.2177T>C, p.Met726Thr. The mildly symptomatic father (Score 17) and older sister (Score 13) are each heterozygous for the c.2177T>C variant. The healthy mother is a mosaic carrier of the c.1781_1786dup variant in 20% of her hematopoietic and non-hematopoietic cells. The patient, but not the other family members, had decreased Th17 lymphocytes. Both *STAT3* variants were confirmed to have reduced transcriptional activity compared to wild-type using luciferase assay. The patient has been treated with immunoglobulin replacement therapy and prophylactic azithtomycin, itraconazole with drastic decrease of infections.

Conclusions: This is the first report of HIES caused by bi-allelic hypomorphic *STAT3* mutations. The germline status of the c.2177T>C variant might explain presence of the mild phenotype in the father and sister, compared to the unaffected mother carrying the c.1781_1786dup in only a fraction of cells.

Disclosure: No.

PD498

CLINICAL CASE of SUCCESSFUL VACCINATION of A CHILD WITH INCOMPLETE DI GIORGI SYNDROME

POSTER DISPLAY 09: OTHER

Tatiana Kaliuzhnaia, Marina Fedoseenko, Firuza Shakhtakhtinskaya, Svetlana Tolstova, Arevaluis Selvyan
Pediatrics and Child Health Research Institute of Petrovsky National Research Centre of Surgery, Vaccines And Disease Prevention, Moscow, Russian Federation

Background and Aims: Di Giorgi syndrome is a rare genetic disease that occurs as a result of so–called micro-breaks on chromosome 22 at the 8-th week of intrauterine development. Patients with this syndrome do not receive prophylaxis vaccines , because due to the presence of an immunodeficiency, pediatricians are afraid to vaccinate them. However, they are the most vulnerable in terms of joining various infections. The aim is to evaluate the effectiveness and safety of vaccination of a patient with Di Giorgi syndrome and develop a personalized approach to immunization for children with this syndrome.

Methods: 13-year-old girl with Di Giorgi syndrome receives preventive vaccinations from the age of 7 years old. The patient vaccinated with combined pediatric vaccines and against additional infections (against meningococcal infection and hepatitis A). Once vaccinated against measles, rubella, mumps. The girl is regularly monitored for the level of immunological protection against measles, rubella, mumps, hepatitis B virus, whooping cough, diphtheria, tetanus with the help of ELISA.

Results: All vaccines were well tolerated. After completing the course of vaccination, there was a low immunogenic activity to the mumps and diphtheria. Taking into account the results obtained, revaccination against whooping cough, diphtheria, tetanus is recommended. When planning vaccination against mumps, it is recommended to suspend replacement therapy with intravenous immunoglobulin for 3 months. An additional immunization with a 23-valent PPV is also recommended.

Conclusions: Patients with Di Giorgi syndrome need regular monitoring of antibodies to resolve the issue of further immunization and individual correction. Cocoon vaccination of close contacts is also indicated.

Disclosure: No.

PD499

THE SPECTRUM of INBORN ERRORS of IMMUNITY IN SUDAN: AN 8-YEAR EXPERIENCE FROM 2 TERTIARY CENTERS

POSTER DISPLAY 09: OTHER

Lamis Beshir[1], Salwa Musa[2], Mohamed Abdullah[3], Nahla Erwa[4]
[1]Sudan Medical Specialization Board, Department of Clinical Immunology, Khartoum, Sudan, [2]Gaafar Ibnouf Pediatric Hospital, Paediatric Endocrinology Unit, Khartoum, Sudan, [3]Gaafar Ibnouf Pediatric Hospital, Paediatric Endocrinology, Khartoum, Sudan, [4]University of Khartoum, Faculty of Medicine - Department of Medical Microbiology, Khartoum, Sudan

Background and Aims: Inborn Errors of Immunity (IEI) are heterogeneous disorders of immunity with recurrent infections, autoimmunity and lymphoproliferation. Despite advances in the diagnosis of IEI, their identification remains difficult, especially in sub-Saharan Africa, where many infections are endemic. We aim to describe the demographics, clinical characteristics, categories, and treatment modalities of patients with IEI in a resource-limited setting.

Methods: This is a retrospective study conducted on patients who attended Soba University Hospital and Gaafar Inbouf Specialized Children Hospital from 2014-2022.

Results: We identified 172 patients with IEI, of whom 162 were children. The age of onset of symptoms ranged from birth to 68 years. Patients were classified as; immunodeficiencies affecting cellular and humoral immunity n=19 (11%), combined immunodeficiencies with associated or syndromic features n=25 (14.5%), predominantly antibody deficiencies n=34 (19.7%), immune dysregulation n=23 (13.3%), congenital defects of phagocytes number or function n=30 (17.4%), defects in intrinsic and innate n=4 immunity (2.3%), complement deficiency n=3 (1.74%), bone marrow failure n=10 (5.8%). 24 had an unresolved diagnosis. Genetic testing was performed in 14 patients with a diagnostic yield of 100%.
Complications included bronchiectasis, tuberculosis, necrotising fasciitis and infections. Treatment modalities included Immunoglobulin therapy, antimicrobial prophylaxis and immunosuppressive medications. One patient only underwent hematopoietic stem cell transplantation (HSCT) abroad. The overall mortality rate could not be determined since many patients were lost to follow-up.

Conclusions: This report highlights the burden and categories of prevalent IEI in Sudan. Ongoing education of physicians, the establishment of a national registry, improvement of diagnostic tests and screening are recommended to improve outcomes.

Disclosure: No.

PD500

AN X-LINKED AGAMMAGLOBULINAEMIA (XLA) PATIENT HAMPERED BY MULTIPLE IATROGENIC COMPLICATIONS

POSTER DISPLAY 09: OTHER

Soha Khaled Amar, Zoe Adhya, Rohit R Ghurye, Dorothea Grosse-Kreul, Mohammad A A Ibrahim
King's College London, King's Health Partners, King's College Hospital NHS Foundation Trust, Immunology & Allergy, London, United Kingdom

Background and Aims: Iatrogenic complications can have knock-on effects that can threaten survival in primary immune deficiency. There is a surprising lack of systematic reviews concerning this topic. We highlight this through a case summary.

Methods: Our patient was diagnosed with X-linked agammaglobulinaemia (XLA) aged 8 years, having presented with recurrent chest infections and poliomyelitis following the live polio vaccine. He started intramuscular immunoglobulin but contracted Hepatitis C when 33 years old (thought to be from infected blood products). Failed interferon therapy led to a liver transplant aged 44 years necessitating tacrolimus immunosuppression. He developed a tongue lesion, considered to be post-transplant lymphoproliferative disease but later diagnosed as diffuse B cell lymphoma requiring rituximab. Aged 64 years, he underwent a nephrectomy for renal cell carcinoma but developed *Escherica coli* septicaemia leading to multi-organ failure and subsequent death.

Results: Our case illustrates multiple iatrogenic complications culminating in the death of our XLA patient. The complications included viral transmission from infected blood products and immunosuppression further compounding the immunodeficiency and inducing malignancies.

Conclusions: There is a need to evaluate iatrogenic morbidity and mortality in primary immunodeficiency. Determining the exact prevalence and nature of such complications would raise clinicians' awareness to limit their effects where possible. References: Adverse Effects of Immunoglobulin Therapy. Guo Yi, Tian Xin, Wang X, Xiao Z. Front Immunol 2018; 9: 1299 Iatrogenesis: a review on nature, extent and distribution of healthcare hazards. Peer RF, Shabir N. J Family Med Prim Care. 2018; 7(2): 309-314

Disclosure: No.

Keywords: complications, Iatrogenic, morbidity, mortality, Primary Immune deficiency, X-linked agammaglobulinaemia

PD501

RUPTURED CEREBRAL MYCOTIC ANEURISMS AS A PRESENTING SIGN of PRIMARY IMMUNODEFICIENCY IN A 17Y OLD GIRL WITH HISTORY of CONGENITAL HEART DISEASE

POSTER DISPLAY 09: OTHER

Velma Selmanovic[1], Adisa Cengic[1], Aida Omercahic-Dizdarevic[1], Zina Lazovic[1], Faeriha Hadzagic-Catibusic[1], Almira Kadic[1], Mirza Halimic[1], Zijo Begic[1], Selma Dizdar[1], Semra Cepic-Kapic[1], Amina Kozaric[1], Alma Sejtareija-Memisevic[2], Ibrahim Omerhodzic[3]
[1]Children's Hospital University Clinical Center Sarajevo, Department For Allergology, Rheumatology And Clinical Immunology, Sarajevo, Bosnia and Herzegovina, [2]Children's Hospital University Clinical Center Sarajevo, Infective Disease Specialist, Sarajevo, Bosnia and Herzegovina, [3]Children's Hospital University Clinical Center Sarajevo, Clinic For Neurosurgery, Sarajevo, Bosnia and Herzegovina

Background and Aims: Intracerebral mycotic aneurism(IMA) develop as a complication of infective endocarditis(IE) in up to 5% of IE patients. Congenital heart disease is know risk factor for development of IE. Aim was to present case with IE, complicated with ruptured IMA, leading to final diagnosis of primary immunodeficiency

Methods: medical records evaluation

Results: 17y girl presented with a 2mo of unexplained fever, followed by malaise, arthralgia, and polymorphous complaints. Her past history included :1) sucessfull urgent neurosurgical treatement abroad for ruptured left middle cerebral branch 4mo ago; noticed other multiple intracerebral aneurisms; 2) operative treatment of transposition of great arteries in neonatal period. Thereafter, she was lost for follow up. Broad diagnostic multidisciplinary investigation was undertaken as well as detailed analysis of past medical records. Interesting family anamnesis Figure1. On clinical examination: chronically sick, pale, mild facial dysmorphia in sence of Sy DiGeorge, intermitent Janeway lesions, livedo reticularis were seen. Cardiac echo:endocarditis. Labs: mildly raised inflamatory markers; anemia of chronic disease, T-lymphopenia (T-cells <200/mm3), normal immunoglobulin levels, negative FISH for Sy DiGorge; in hemocultures Staphylococcus epidermidis were isolated. Antimicrobial treatment resulted in significant improvement of general condition. Nine months later, patient had rapid deterioration of general condition, with two new aneurisms seen on brain MRI/MRA and sudden unfavourable outcome.

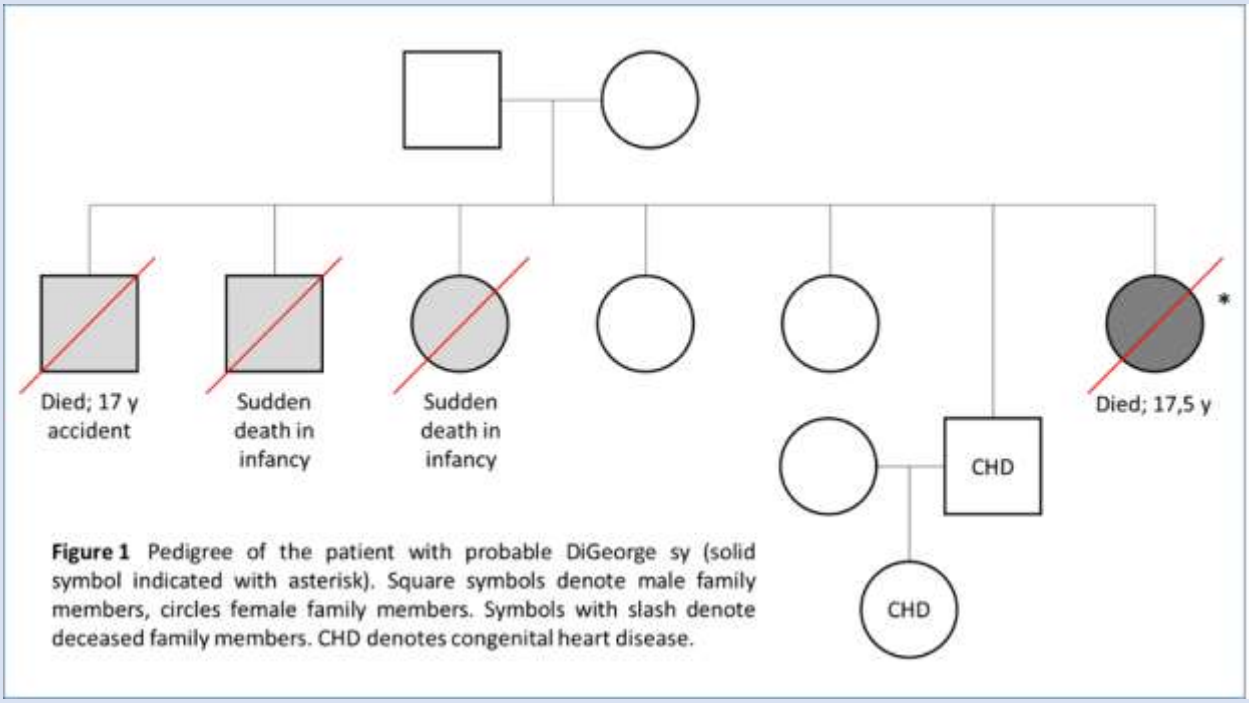


Figure 1 Pedigree of the patient with probable DiGeorge sy (solid symbol indicated with asterisk). Square symbols denote male family members, circles female family members. Symbols with slash denote deceased family members. CHD denotes congenital heart disease.

Conclusions: congenital heart disease with facial dysmophia should raise suspicion to Sy DiGeorge, and negative FISH analysis does not exclude it. Close follow up immunodeficient patient as well as IE prophilaxis should be widelly aplied.

Disclosure: No.

Keyword: mycotic aneurism, bacterial endocarditis, congenital heart disease

PD502

PREDICTIVE FACTORS of PRIMARY HEMOPHAGOCYTOSIS LYMPHOHISTIOCYTOSIS

POSTER DISPLAY 09: OTHER

Monia Ben Khaled, Malek Naffatti, Samya Rekaya, Ilhem Benfraj, Takwa Lamouchi, Ridha Kouki, Mohamed Bejaoui, Fethi Mellouli, Monia Ouederni
University Tunis el Manar Faculty of Medicine of Tunis, Pediatrics: Immunology, Hematology And Stem Cell Transplantation, Rue jebel lakhdhar bab Saadoun Tunis, Tunisia

Background and Aims: Hemophagocytosis lymphohistiocytosis (HLH) is a cytokine storm due to excessive activation of lymphocytes and macrophages. An exhaustive etiological assessment is required in order to differentiate between primary or secondary causes and offer appropriate therapy. The aim of our study was to identify the predictive factors of a primary HLH.

Methods: It was a retrospective and analytical study carried out in immune-hematology pediatric service of Tunisia over 16 years (2005-2020) including all patients with HLH. The diagnosis of HLH was established according to the Histiocyte Society 2004 criteria. Predictors of primary HLH were established using cox regression by comparing the two groups of primary and secondary HLH.

Results: Thirty-two patients were included , 23(72%) with primary and 9(28%) with secondary HLH. The mean age at symptom onset was 22.3 months (range 0.4 - 144 months). The main causes of primary HLH were Familial HLH (n=7), Chediak-Higashi and Griscelli syndromes (n=85) and Griscelli syndrome (n=3). Secondary HLH was caused bydue to: a severe infection (n=3), acute leukemia (n=2) or combined immunodeficiency (n=3). In univariate analysis, primary HLH was significantly correlated with history of early death (p=0.02), jaundice (p=0.009), abdominal distension (p=0.003), persistence of splenomegaly after 15 days of treatment (p=0.04) as well as recurrence of HLH (p=0.01). Multivariate analysis showed that recurrence of HLH was predictive of primary HLH (p=0.02, HR=13.4, CI 95%= [1.3; 137.9]).

Conclusions: Primary HLH should be evoked if the HLH picture is early, severe, persistent or recurrent, especially in cases of consanguinity or a family history of HLH or early death.

Disclosure: No.

Keywords: Lymphohistiocytosis, Hemophagocytic, pediatrics, Deficiency Syndromes, Immunologic

PD503

RESPIRATORY DISORDERS IN COMMON VARIABLE IMMUNODEFICIENCY

POSTER DISPLAY 09: OTHER

Monia Ben Khaled, Ikram Zaiter, Yousra Mesbahi, Ilhem Benfraj, Samya Rekaya, Malek Naffatti, Takwa Lamouchi, Ridha Kouki, Mohamed Bejaoui, Fethi Mellouli, Monia Ouederni
University Tunis el Manar Faculty of Medicine of Tunis, Pediatrics: Immunology, Hematology And Stem Cell Transplantation, Rue jebel lakhdhar bab Saadoun Tunis, Tunisia

Background and Aims: Common Variable Immunodeficiency (CVID) is likely to be complicated by infectious or non-infectious respiratory involvement. This study was aimed to describe the clinical, radiological and therapeutic aspects of lung diseases in CVID patients and to identify the factors associated.

Methods: This was a retrospective descriptive study conducted over 23 years in the pediatric Immunohematology department of the National Bone Marrow Transplantation Centre of Tunisia. It had included CVID patients with respiratory manifestations at pediatric age (<18 years).

Results: Nineteen patients were included. The median age at diagnosis of CVID was 17 years [EIQ= 14-24]. The median age at onset of respiratory symptoms was five years [EIQ=3-10]. Fourteen patients had respiratory infections at diagnosis: bronchitis (n=8), pneumonia (n=3) and pleuropneumopathy (n=3). Clinical signs of bronchiectasis had started at a median age of 14 years [EIQ=8.5-14.5]. It was isolated in 13/17 cases, cylindrical (11 cases), bilateral (11 cases), localized in the middle lobe (n=7), left lower lobe (n=8), right lower lobe (n=6), lingula (n=8). Lymphadenopathy (p=0.04), interstitial lung disease (p=0.05) and systemic corticosteroid therapy (p=0.01) were correlated with bronchiectasis extension (n=6). Five patients had interstitial lung disease at diagnosis: PO (n=1), GLILD (n=4). Interstitial lung disease was correlated with lymphadenopathy (p=0.02), Evans syndrome (p=0.007), and thrombocytopenia (p=0.012). Factors associated with recurrent pneumonia were Evans syndrome (p=0.02), interstitial lung disease (p=0.007) and resistant Haemophilus influenzae (p=0.03).

Conclusions: This study highlighted the importance early diagnosis of CVID in order to avoid the insidious progression to chronic lung disease and respiratory function decline.

Disclosure: No.

Keywords: Common Variable Immunodeficiencies, Bronchiectasis, pediatrics, Lung diseases, interstitial

PD504

SARS-COV-2 SYMPTOMATIC REINFECTION AMONG PATIENTS WITH PRIMARY ANTIBODY DEFICIENCY

POSTER DISPLAY 10: COVID-19

Nufar Marcus Mandelblit[1], Liat Ashkenazi-Hoffnung[2], Adi Ovadia[3], Ilan Dalal[3], Siril Yoffe[1], Nesia Kropach[4], Neta Zuckerman[5], Oded Scheuerman[6]
[1]Schneider Children's medical center of Israel, Immunology, Petach Tikva, Israel, [2]SCMCI, Department of Day Hospitalization, Petach Tikva, Israel, [3]Edith Wolfson medical center, Pediatric Allergy Unit, Holon, Israel, [4]SCMCI, Genetics, Petach Tikva, Israel, [5]Israel Ministry of Health Chaim Sheba Medical Center, Central Virology Laboratory, Ramat Gan, Israel, [6]SCMCI, Pediatric B, Petach Tikva, Israel

Background and Aims: Background and Aims: Reports on the Impact of SARS-CoV-2 infection on patients with Primary Antibody Deficiency (PAD) have revealed conflicting results. While initial reports described a moderate and non-fatal course in many of these patients, others have highlighted the susceptibility of patients with B cell abnormalities to infection with this virus. Among immunocompetent hosts, reinfection with SARS-CoV-2 is considered rare. However, the rate of reinfection of SARS-CoV-2 in among PAD patients has not been described Aims: To evaluate the rate of SARS-CoV-2 reinfection among PAD patients.

Methods: A retrospective review of all patients with PAD followed in 2 immunology centers in Israel who presented with SARS-CoV-2 infection from March 2020-October 2021.

Results: Our cohort included 65 patients with PAD of them 11 patients presented with SARS-CoV-2 infection. Months after their first infection, five of these patients, presented with a symptomatic reinfection during the new delta variant wave. In one of the patients, reinfection was associated with a complicated clinical course that included pneumonia and respiratory distress necessitating treatment with systemic steroids, convalescent plasma and Remdesivir. Another patient suffered from prolonged isolation due to failure of viral clearance.

Conclusions: Conclusion: SARS-CoV-2 reinfection in PAD patients is common and might be severe. Although all five PAD patients were treated with optimal immunoglobulin replacement therapy, infection and reinfection occurred. Our finding highlights the susceptibility of PAD patients to SARS-CoV-2 infection and the need for further investigation of prophylactic treatment such as monoclonal antibodies hyper immune IVIG, vaccination or antiviral medications.

Disclosure: No.

Keyword: SARS-CoV-2, COVID 19, Primary antibody deficiency, Immunodeficiency, Inborn errors of immunity, XLA

PD505

RESPONSE TO ANTI-SARS-COV-2 VACCINE IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY: 4 VACCINE DOSES AND 4TH WAVE IN ITALY

POSTER DISPLAY 10: COVID-19

Maria Carrabba[1], Lucia Baselli[2], Rosa Dellepiane[2], Dario Consonni[3], Ferruccio Ceriotti[4], Massimo Oggioni[4], Marina Zarantonello[5], Giovanna Fabio[1]
[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Dipartimento Di Medicina Interna, Milano, Italy, [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Pediatric Department, Milano, Italy, [3]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Epidemiologia Clinica, MILANO, Italy, [4]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlnico, Clinical Laboratory, MILANO, Italy, [5]Università degli Studi, Dipartimento Di Scienze Cliniche E Di Comunità, MILANO, Italy

Background and Aims: Common Variable Immunodeficiency (CVID) and CVID-like disorders have a spectrum of B and T cell defects that cause a defective antibody response. Humoral and cellular responses to the currently used COVID-19 mRNA vaccines remain to be elucidated. This study evaluates the immune response along time after COVID-19 mRNA vaccines in CVID patients

Methods: CVID patients have been diagnosed according to ESID criteria. They have been vaccinated with anti-SARS-CoV-2 mRNA vaccines. Humoral and cellular responses have been measured.

Results: We analysed 60 CVID patients, 46 were responders. 4-weeks after the primary cycle the median Ig anti-S level was 609 U/mL. It was higher in the 11 previously infected patients than in the uninfected (4302 vs 297.5 U/mL). Six months after, the median Ig anti-S titre dropped to 313 U/mL. After the third vaccine dose, the median Ig anti-S level raised to 3442 U/mL and the differences between the previously infected and uninfected patients reduced (3680 vs 2867.5, respectively). The SARS-CoV-2-T-cell responses analysis showed that 78.3% patients maintained a positive cellular response before the booster, almost unchanged after it. Six subjects remained not-responders. 3-4 months after the booster dose, 21/60 patients got SARS-CoV-2 infection. The evaluation of the response to the 2nd boster vaccine dose is ongoing

Conclusions: Six month after the primary cycle of vaccination, the humoral response dropped significantly. The booster dose produced an antibody response in several. This strengthens the indication for the 2nd booster, while monoclonal prophylaxis is recommended for not-responders. The T cell response to vaccine maintains over time

Disclosure: No.

Keywords: Common Variable Immunodeficiency (CVID), COVID vaccine, mRNA vaccine, T-cell response, humoral response, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

PD506

T-CELL DEFECTS ASSOCIATED TO LACK of SPIKE-SPECIFIC ANTIBODIES AFTER BNT162B2 FULL IMMUNIZATION FOLLOWED BY A BOOSTER DOSE IN PATIENTS WITH COMMON VARIABLE IMMUNE DEFICIENCIES

POSTER DISPLAY 10: COVID-19

Federica Pulvirenti[1], Stefano Di Cecca[2], Eva Piano Mortari[3], Sara Terreri[3], Cristian Albano[3], Eleonora Sculco[4], Bianca Laura Cinicola[5], Cinzia Milito[6], Simona Ferrari[7], Franco Locatelli[2], Rita Carsetti[3,8], Isabella Quinti[4,9,10], Concetta Quintarelli[2]
[1]AOU Policlinico Umberto I, Reference Centre For Primary Immune Deficiencies, Dpt of Internal Medicine And Infectious Diseases, ROMA, Italy, [2]Bambino Gesù Children Hospital, IRCCS,, Department Onco-haematology, And Cell And Gene Therapy, Rome, Italy, [3]Bambino Gesù Children's Hospital, IRCCS,, B Cell Unit, Immunology Research Area,, Rome, Italy, [4]Sapienza University of Rome, Molecular Medicine, Rome, Italy, [5]Sapienza University of Rome, Pediatric Immunology And Allergology, Rome, Italy, [6]Sapienza University of Rome, Department of Molecular Medicine, Rome, Italy, [7]Policlinico S. Orsola Malpighi, Medical Genetic Unit, Bologna, Italy, [8]Diagnostic Immunology Research Unit, Multimodal Medicine Research Area, Bambino Gesù Children's Hospital, IRCCS; Viale di San Paolo,15, Rome, Italy, Diagnostic Immunology Research Unit, Multimodal Medicine Research Area, Bambino Gesù Children's Hospital, Irccs; Viale Di San Paolo,15, Rome, Italy, Roma, Italy, [9]Regional Reference Centre for Primary Immune Deficiencies, Azienda Ospedaliera Universitaria Policlinico Umberto I, Rome, Italy, Regional Reference Centre For Primary Immune Deficiencies, Azienda Ospedaliera Universitaria Policlinico Umberto I, Rome, Italy, Roma, Italy, [10]Sapienza University of Rome, Regional Reference Centre For Primary Immune Deficiencies, Azienda Ospedaliera Universitaria Policlinico Umberto I, Roma, Italy

Background and Aims: Following the third booster dose of the mRNA vaccine, Common Variable Immunodeficiencies (CVID) patients may not produce specific antibodies against the virus spike protein. The T-cell abnormalities associated with the absence of antibodies are still a matter of investigation.

Methods: Spike-specific IgG and IgA, peripheral T cell subsets, CD40L and cytokine expression, and Spike-specific specific T-cells responses were evaluated in 47 CVID and 26 healthy donors after three doses of BNT162b2 vaccine. Testing was performed two weeks after the third vaccine dose.

Results: Thirty-six percent of the patients did not produce anti-SARS-CoV-2 IgG or IgA antibodies. Non responders patients had lower peripheral blood lymphocyte counts, circulating naïve and central memory T-cells and low CD40L expression on the CD4+CD45+RO+ T-cells, indicating a more severe impairment of T cell activation. NR also showed highest numbers of cells expressing IFNγ and TNFα revealing a more pronounced inflammatory signature and defective release of IFNγ and TNFα following stimulation with Spike peptides. Non responders had a more complex disease phenotype, with higher prevalence of chronic lung disease, bronchiectasis and autoimmune cytopenia. Thirty-five percent of them developed a SARS-CoV-2 infection after immunization in comparison to twenty percent of CVID who responded to immunization with antibodies production.

Conclusions: CVID-associated T cell abnormalities contributed to the absence of SARS-CoV-2 specific antibodies after full immunization.

Disclosure: No.

Keywords: Common Variable Immunodeficiencies, COVID-19, T-cells, vaccine, IgA, BNT162b2

PD507

ANTIBODY RESPONSE FOLLOWING THE THIRD AND FOURTH SARS-COV-2 VACCINE DOSE IN INDIVIDUALS WITH COMMON VARIABLE IMMUNODEFICIENCY

POSTER DISPLAY 10: COVID-19

Bibi Nielsen[1], Camilla Heldbjerg Drabe[1], Mike Barnkob[2], Isik Johansen[3], Anne Hansen[3], Anne Nilsson[2], Line Rasmussen[3]
[1]Rigshospitalet, Infectious Diseases, Copenhagen, Denmark, [2]Odense University Hospital, Clinical Immunology, Odense, Denmark, [3]Odense University Hospital, Infectious Diseases, Odense, Denmark

Background and Aims: Background: The antibody response after vaccination is impaired in Common Variable Immunodeficiency (CVID). Objective: We aimed to study the spike receptor-binding domain IgG antibody (anti-S-RBD) levels during a four-dose SARS-CoV-2 vaccination strategy and after monoclonal antibody (mAB) treatment in CVID. Moreover, we assessed the anti-S-RBD levels in immunoglobulin replacement therapy (IgRT) products.

Methods: In an observational study, we examined anti-S-RBD levels after the second, third and fourth dose of mRNA SARS-CoV-2 vaccines. Moreover, we measured anti-S-RBD after treatment with mAB. Finally, anti-S-RBD were assessed in common IgRT products. Antibody non-responders (anti-S-RBD <7.1) were compared by McNemar's test and anti-S-RBD levels were compared with paired and non-paired Wilcoxon signed rank tests as well as Kruskal-Wallis tests.

Results: Among 33 individuals with CVID, anti-S levels increased after the third vaccine dose (165 BAU/mL [95% confidence interval: 85; 2280 BAU/mL], p=0.006) and tended to increase after the fourth dose (193 BAU/mL, [-22; 569 BAU/mL], p=0.080) compared to the previous dose. With increasing number of vaccinations, the proportion of patients who seroconverted (anti-S > 7.1) increased non-significantly. mAB treatment resulted in a large increase in anti-S-RBD and a higher median level than gained after the fourth dose of vaccine (p=0.011). IgRT products had varying concentrations of anti-S (p<0.001), but none of the products seemed to affect the overall antibody levels (p=0.460).

Conclusions: Conclusion: Multiple SARS-CoV-2 vaccine doses in CVID, seem to provide additional protection, as antibody levels increased after the third and fourth vaccine dose. However, anti-S-RBD levels from mAB outperform the levels mounted after vaccination.

Disclosure: No.

Keywords: CVID, humeral response, SARS-CoV-2, booster vaccine, COVID-19, Vaccination

PD508

LIFE-THREATENING COVID-19 PNEUMONIA IN AN 11-YEAR-OLD CHILD WITH AUTOANTIBODIES AGAINST TYPE I IFNS

POSTER DISPLAY 10: COVID-19

Erika Cantarelli[1], Michele Zagariello[1], Daniela Di Luca[2], Arianna Dondi[3], Alessandro Borghesi[4], Paul Bastard[5,6,7], Emmanuelle Jouanguy[5,6,7], Christian Thorball[8], Claire Redin[8], Jacques Fellay[8,9], Marcello Lanari[3], Jean-Laurent Casanova[5,6,7,10], Andrea Pession[11], Francesca Conti[11]
[1]Specialty School of Paediatrics, Alma Mater Studiorum - University of Bologna, Bologna, Italy, [2]Department of Anesthesiology, Sant'orsola-malpighi Hospital, University of Bologna, Bologna, Italy, [3]Pediatric Emergency Unit, Irccs Azienda Ospedaliero-universitaria Di Bologna, Sant'orsola University Hospital, Bologna, Italy, [4]Neonatal Intensive Care Unit, Fondazione Irccs Policlinico San Matteo, Pavia, Italy, [5]Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital For Sick Children, Paris, France, [6]St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, United States of America, [7]University of Paris, Imagine Institute, Paris, France, [8]Precision Medicine Unit, Biomedical Data Science Center, Lausanne University Hospital And University of Lausanne, Lausanne, Switzerland, [9]School of Life Sciences, Ecole Polytechnique Fédérale De Lausanne, Lausanne, Switzerland, [10]Howard Hughes Medical Institute, , Washington, United States of America, [11]Pediatric Unit, Irccs Azienda Ospedaliero-universitaria Di Bologna, Bologna, Italy

Background and Aims: Coronavirus disease 2019 (COVID-19) spread worldwide since December 2019. Despite children exhibit lower susceptibility and milder illness than adults, small proportion of them have been critically unwell, especially if comorbidities occur. Recently, inborn errors of type I interferons (IFN-I) immunity and neutralizing immunoglobulin G autoantibodies against IFN-I were shown to underlie life-threatening COVID-19. Inborn errors prevail before 60 years of age, autoantibodies at all ages, but especially over the age of 70. Anti-IFN-I antibodies were described in patients with autoimmune polyendocrinopathy syndrome type I (APS-I) and preceding any infectious manifestation.

Methods: We report the case of an 11-year-old previously healthy girl, except for autoimmune thyroiditis, who presented with near-fatal COVID-19 pneumonia needing extracorporeal membrane oxygenation. After 40 days of hospitalization, the patient fully recovered.

Results: Extensive immunological workup excluded the main primary immunodeficiencies. Neutralizing autoantibodies against IFN-I were found. Genetic susceptibility to critical COVID-19 infection is currently under examination by whole-exome sequencing. To investigate APS-I, an autoantibodies panel was tested with detection of anti-glutamate decarboxylase and anti-parietal cells antibodies. AIRE gene sequencing did not identify pathogenetic variants.

Conclusions: Our report highlights the role of autoimmunity against type I IFNs in severe COVID-19 disease of apparently healthy subjects, even in younger ages. Autoantibodies neutralize the ability of IFN-I in fighting COVID-19, resulting in B cell autoimmune phenocopy of inborn errors of IFN-I immunity. This finding may hold first clue for underlying autoimmune disorder, bringing forward disease onset. Other genetic causes of immune system dysregulation should be explored.

Disclosure: No.

Keywords: COVID-19, immune system dysregulation, type 1 IFNs, inborn error of immunity, autoantibodies, life-threatening pneumonia

PD509

EMERGENCE of SARS-COV-2 ANTIBODIES IN AN INTRAVENOUS IMMUNOGLOBULIN PREPARATION

POSTER DISPLAY 10: COVID-19

Christopher Hein[1], Viola Marschall[2], Veit Braun[1], Matthias Germer[3], Jörg Schüttrumpf[4]
[1]Biotest AG, Bioanalysis, Dreieich, Germany, [2]Biotest AG, Analytical Development And Validationi, Dreieich, Germany, [3]Biotest AG, Preclinical Research, Dreieich, Germany, [4]Biotest AG, Cso, Dreieich, Germany

Background and Aims: Human intravenous immunoglobulin (IVIG) preparations are produced from large pools of plasma from healthy donors and contain a uniform level of antibodies against a multitude of pathogens. Thus, they are in use to protect patients with immunodeficiencies from severe infections. We have investigated the antibodies against the emergent pathogen SARS-CoV-2 in an IVIG preparation

Methods: IgG preparations from convalescent, vaccinated donors and successive batches of an approved IVIG (Intratect™) were analysed. Modified commercial and proprietary ELISA systems were used to determine the binding of various bacteria, viruses and fungi. Antibodies against SARS-CoV-2 were quantified using an in-house ELISA based on the spike protein. Antibody kit systems from Meso-Scale-Diagnostic were used for the determination of antibodies against SARS-CoV-2 variants or other respiratory pathogens.

Results: Titres against common and clinically relevant bacteria, viruses and fungi were consistent. While batches from pre-pandemic plasma had no detectable anti-SARS-CoV-2 activity, it increased in recent batches, reaching similar activity to hyperimmunoglobulin preparations from convalescent or vaccinated plasma. In parallel, reactivity increased against MERS and SARS-CoV-1, but not othr respiratory viruses. The antibodies recognised all SARS-CoV-2 variants tested including omicron.

Conclusions: Whithin two years of the onset of the pandemic outbreak SARS-CoV-2 specific titers could reach comparable irrespective of the production with plasma from convalescent, vaccinated or normal donors. As antibody titres and virus neutralisation correlate, these antibodies could be beneficial for immunocompromised patients. Clinical studies have shown successful prophylaxis and therapy of mild diseases with individual hyperimmune plasma. Likewise an IVIG preparation could be beneficial for certain patient populations.

Disclosure: All authors are employees of Biotest AG, Dreieich, Germany.

Keywords: Immunoglobulin, Coronavirus, PID, SID, COVID-19, IVIG

PD510

COVID-19 SEVERITY AND POSTVACCINATION OUTCOMES AFTER BNT162B2 VACCINE ADMINISTRATION IN PATIENTS WITH INBORN ERRORS of IMMUNITY

POSTER DISPLAY 10: COVID-19

Tomas Milota[1], Jitka Smetanova[1], Aneta Skotnicova[2], Michal Rataj[1], Anna Sediva[1], Tomas Kalina[2]
[1]Motol University Hospital, Department of Immunology, Prague, Czech Republic, [2]Second Faculty of Medicine Charles University, Childhood Leukemia Investigation Prague, Prague, Czech Republic

Background and Aims: Inborn errors of immunity (IEI) are characterized by higher susceptibility to infections and a broad spectrum of non-infectious complications. Therefore, IEI patients may be regarded as a high-risk group for severe COVID-19, and response to anti-SARS-CoV-2 is questionable, particularly in patients with antibody deficiency. Thus, we initiated two-part study focused on severity of COVID-19 disease and postvaccination response.

Methods: In the first part, a multicenter retrospective survey-based study, the demographic, clinical, and laboratory data were collected by investigating physicians from 8 national referral centers. The second part, a prospective observational study, focused on vaccination outcomes, safety, and dynamics of postvaccination response to the BNT162b2 vaccine in Common variable immunodeficiency (CVID) patients.

Results: In the first part, 81 IEI patients were found to have 2.3-times higher risk for hospital admission and higher mortality ratio (2.4% vs. 1.7% in the general population). COVID-19 severity was associated with clinically relevant comorbidities, lymphopenia, and hypogammaglobulinemia. In the second part, 21 CVID patients were included in the prospective study. At the end of follow-up (month 6), the humoral response was observed in 33.3% and T-cell immune response was measurable in 50% of CVID patients. RT-PCR confirmed infection in 3 patients (14.3%), and all of them had a mild course. We also demonstrated a favorable safety profile.

Conclusions: IEI are associated with higher risk for a severe course of COVID-19 disease and mortality ratio. BNT162b2 vaccine may elicit a measurable humoral and T-cell immune response in CVID patients. Vaccination also showed a favorable safety profile and good clinical postvaccination outcomes.

Disclosure: No.

Keywords: Inborn errors of immunity, COVID-19, Postvaccination response, Common variable immunodeficiency

PD511

IMMUNOGENICITY of THE MRNA-1273 COVID-19 VACCINE IN ADULT PATIENTS WITH INBORN ERRORS of IMMUNITY : SIGNIFICANT DECLINE IN BINDING ANTIBODY LEVELS SIX MONTHS AFTER VACCINATION

POSTER DISPLAY 10: COVID-19

Leane Van Leeuwen[1], Corine Geurtsvankessel[1], Pauline Ellerbroek[2], Godelieve De Bree[3], Abraham Rutgers[4], Hetty Jolink[5], Frank Van De Veerdonk[6], Marit Van Gils[7], Rory De Vries[1], Judith Potjewijd[8], Virgil Dalm[9]
[1]Erasmus University Medical Center, Viroscience, Rotterdam, Netherlands, [2]UMC Utrecht, Department of Internal Medicine, Utrecht, Netherlands, [3]Amsterdam University Medical Center, Internal Medicine, Amsterdam, Netherlands, [4]UMC Groningen, Department of Rheumatology And Clinical Immunology, Groningen, Netherlands, [5]Department of Infectious Diseases, Leiden University Medical Center, Leiden, Netherlands, [6]Radboud University Medical Center, Internal Medicine, Nijmegen, Netherlands, [7]Amsterdam UMC, Department of Medical Microbiology And Infection Prevention, Amsterdam Institute For Infection And Immunity, Amsterdam, Netherlands, [8]Maastricht University Medical Center, Nephrology And Clinical Immunology, Maastricht, Netherlands, [9]Erasmus MC University Medical Center, Department of Internal Medicine, Division of Allergy & Clinical Immunology And Department of Immunology, Rotterdam, Netherlands

Background and Aims: Effective protection against COVID-19 is of great importance in patients with inborn errors of immunity (IEI). However, little is known about the immunogenicity of COVID-19 vaccines in IEI patients, and the longevity of the responses.

Methods: In a prospective, national, multicenter study we assessed the immunogenicity of two doses of the mRNA-1273 vaccine in 361 patients with IEI (van Leeuwen, et al. PMID:35421449), including common variable immunodeficiency (CVID, n=173), X-linked agammaglobulinemia (XLA, n=18), combined immunodeficiency (CID, n=19), isolated antibody deficiencies (n=151), and controls (n=152). Full-spike(S) protein-specific binding IgG-antibodies were assessed 28 days and six months after complete vaccination.

Results: Vaccination with mRNA-1273 vaccine resulted in seroconversion in 84% of IEI patients 28 days after second vaccination (100% in controls). Antibody levels were significantly lower in all patient cohorts, compared to controls. Six months after second vaccination, antibody levels had significantly declined in all cohorts. The geometric mean titer declined from 3489 (28 days after second vaccination) to 693 BAU/ml in controls, from 410 to 151 BAU/ml in CVID, from 1608 to 286 BAU/ml in CID, and from 2264 to 375 BAU/ml isolated antibody deficiencies.

Conclusions: SARS-CoV-2-specific binding antibody levels significantly declined in IEI patients as well as controls 6 months after complete vaccination. Antibody titers at 28 days and 6 months after vaccination were significantly lower in IEI patients compared to controls. Although clinical consequences and correlate of protection remain to be determined, booster vaccination may be considered in IEI patients.

Disclosure: No.

Keywords: IgG antibodies, CVID, CID, COVID-19 vaccination, inborn errors of immunity (IEI)

PD512

COVID-19 VACCINATION AND NATURAL INFECTION'S RESPONSES IN A COHORT of PATIENTS WITH INBORN ERROR of IMMUNITY FROM ARGENTINA

POSTER DISPLAY 10: COVID-19

Lorenzo Erra[1], Ignacio Uriarte[2], Ana Colado[3], Virginia Paolini[4], Analia Seminario[5], Julieta Fernández[1], Lorena Tau[6], Juliana Bernatowiez[3], Ileana Moreira[5], Sebastian Vishnopolska[1], Martín Rumbo[6], Chiara Cassarino[3], Gustavo Vijoditz[7], Ana López[4], Renata Curciarello[6], Diego Rodríguez[2], Gastón Rizzo[6], Malena Ferreyra[6], Leila Ferreyra Mufarregue[7], Leila Romina[7], María Pérez Millán[1], Patricia Baré[3], Itatí Ibañez[8], Roberto Pozner[3], Mercedes Borge[3], Guillermo Docena[6], Liliana Bezrodnik[5], María Almejun[1]
[1]Departamento de Fisiología, Biología Molecular y Celular, Instituto de Biociencias, Biotecnología y Biología Traslacional (IB3) e IQUIBICEN, FCEN, UBA, CONICET, Caba Argentina, CABA, Argentina, [2]Hospital Vitorio Tetamanti, Mar Del Plata, Buenos Aires, Argentina, Buenos Aires, Argentina, Argentina, [3]Instituto de Medicina Experimental, Academia Nacional de Medicina, CONICET, Caba Argentina, CABA, Argentina, [4]Hospital General de Agudos C. G. Durand, CABA, Argentina, Caba, Argentina, CABA, Argentina, [5]Children's Hospital Ricardo Gutierrez, Center For Clinical Immunology, Immunology Group, Buenos Aires, Argentina, [6]Instituto de Estudios Inmunológicos y Fisiopatológicos (IIFP), UNLP, CONICET, asociado a CIC PBA, Facultad de Ciencias Exactas, Departamento de Ciencias Biológicas, La Plata, Argentina y Laboratorio de Salud Pública de la Facultad de Ciencias Exactas, UNL, La Plata, Argentina, La Plata, Argentina, Argentina, [7]Hospital Nacional Profesor Alejandro Posadas, Buenos Aires, Argentina, Buenos Aires, Argentina, Buenos Aires, Argentina, Argentina, [8]Instituto de Química Física de los Materiales, Medio Ambiente y Energía (INQUIMAE), CONICET, FCEN, UBA, CABA, Argentina, Caba, Argentina, CABA, Argentina, Argentina

Background and Aims: Patients with Inborn Errors of Immunity (IEI) in Argentina were encouraged to receive the authorized Sputnik, AstraZeneca, Sinopharm, Moderna and Pfizer vaccines. Most data on available vaccines derive from trials conducted on healthy individuals. Our aim was to evaluate the safety and immunogenicity of the different vaccines in IEI patients in Argentina.
Methods: The study cohort included adults and pediatric IEI patients (n=118) and age-matched healthy-controls (HC) (n=37). Samples were collected before, 28+/-3 days after the first and the second doses (T2) of the vaccine. B-cell response was evaluated by measuring IgG anti-Spike(S)/RBD and anti-nucleocapsid(N) antibodies by ELISA. Neutralization antibodies were also assessed at T2 with an alpha-S protein-expressing pseudo-virus assay. The T-cell response was analyzed by IFN-γ secretion on S or N-stimulated PBMC by ELISPOT and the frequency of S-specific circulating T follicular-helper cells (TFH) by flow cytometry.
Results: No moderate/severe vaccine-associated adverse events were observed. Regarding the antibody response, anti-S/RBD titers showed significant differences between IEI patients pediatric and adults with the age-matched HC cohort ($p<0,05$). Neutralizing antibodies were detected in 71/99 patients and were also significantly lower than age-matched HC ($p<0.01$). Positive S-specific IFN-γ response was observed in 86.2% of IEI patients and 83.9% presented S-specific TFH cells.
Conclusions: In conclusion, COVID-19 vaccines showed safety in IEI patients, and although immunogenicity was lower than in healthy controls, they showed specific anti-S/RBD IgG, neutralizing antibody titers and T-cell-dependent cellular immunity with IFN-γ secreting T-cells. These findings may guide the recommendation of vaccination in IEI patients to prevent COVID-19 disease.
Disclosure: This work was supported by grants from Agencia Nacional de Promoción Científica y Tecnológica obtained by AMB and a grant from TAKEDA obtained by AMB and UI. The remaining authors declare no competing financial interests.

Keywords: COVID-19, vaccines, B-cell, T-cell, THF-cells

PD513

IMPACT of VACCINATION ON HOSPITALISATION AND MORTALITY FROM COVID-19 IN PATIENTS WITH PRIMARY AND SECONDARY IMMUNODEFICIENCY: THE UNITED KINGDOM EXPERIENCE.

POSTER DISPLAY 10: COVID-19

Adrian Shields[1], Susan Tadros[2], Adam Al-Hakim[3], Sarah Goddard[4], John Dempster[5], Magdalena Dziadzio[5], Smita Patel[6], Shuayb Elkalifa[7], Sujoy Khan[8], Archana Herwadkar[9], David Lowe[10], Sinisa Savic[11], Siobhan Burns[12], Alex Richter[1]
[1]University of Birmingham, Clinical Immunology Service,, Birmingham, United Kingdom, [2]Royal Free Hospital, Department of Immunology, London, United Kingdom, [3]Leeds Teaching Hospital NHS Trust, Department of Clinical Immunology, Leeds, United Kingdom, [4]University Hospitals of North Midlands NHS Trust, Immunology And Allergy, Stoke-on-Trent, United Kingdom, [5]University College Hospital NHS Foundation Trust, Department of Clinical Immunology, London, United Kingdom, [6]University of Oxford, Nihr Brc Oxford Biomedical Research Centre, Oxford, United Kingdom, [7]Salford Royal Foundation Trust, Immunology, Manchester, United Kingdom, [8]Castle Hill Hospital, Immunology & Allergy, Cottingham, United Kingdom, [9]Northern Care Alliance, Clinical Immunology, Salford, United Kingdom, [10]Royal Free, Immunology, London, United Kingdom, [11]St James's University Hospital, Clinical Immunology And Allergy, Leeds, United Kingdom, [12]University College London, Institute of Immunity And Transplantation, London, United Kingdom

Background and Aims: The UK reported amongst the higher infection fatality rate (IFR) in patients with primary immunodeficiency (PID) and secondary immunodeficiency (SID) compared to the general population during the early COVID-19 pandemic. Vaccination has uncoupled SARS-CoV-2 infection from severe COVID-19 in the general population. It's impact upon outcomes in patients with PID and SID is unknown.

Methods: Hospitalisation, treatment and outcome data following SARS-CoV-2 infection after January 2021 were collected from participants enrolled in the COV-AD study, plus additional individuals with PID or SID at three UK immunology centres. These data were compared to a pre-vaccination cohort, collated between March and July 2020 (Shields AM – JACI 2021 Mar;147(3):870-875.e1.).

Results: The prevalence of SARS-CoV-2 infection in COV-AD is 19.1% (n=105/549), significantly lower than the general population (~70%). The majority of infections I after July 2021, following the relaxation of most UK legal restrictions on social interaction. Comprehensive outcome data was available for 140 individuals (65 COV-AD participants, 75 non-COV-AD participants). Compared to 2020 (pre-vaccine), significantly improved IFR and 668ypogammaglobul rates were observed for patients with PID and SID infected after January 2021: PID: 668ypogammaglobul 16.8% vs 53.3% ($p<0.00001$), IFR 2.8% vs 20.0% ($p=0.0001$); SID: 668ypogammaglobul 18.2% vs 75.8% ($p<0.00001$), IFR 9.1% vs 33.3% ($p=0.02$). Subgroup analysis of double-vaccinated, infection-naïve individuals who had received no COVID-19 specific treatments also demonstrated statistically significant improvements in 668ypogammaglobul and mortality.

Conclusions: COVID-19 morbidity and mortality in patients with PID and SID have significantly improved. Despite suboptimal responses to vaccination, SARS-CoV-2 vaccines demonstrate a protective effect against 668ypogammaglobul and mortality in this cohort.

Disclosure: No.

Keywords: primary immunodeficiency, SARS-CoV-2, Vaccination, Secondary Immunodeficiency, COVID-19, Inborn errors of immunity

PD514

IMMUNOGENICITY of A THIRD PRIMARY SARS-COV-2 VACCINATION IN PATIENTS WITH ANTIBODY DEFICIENCY: A COV-AD STUDY UPDATE

POSTER DISPLAY 10: COVID-19

Adrian Shields[1], Sian Faustini[1], Harriet Hill[2], Saly Al-Taei[1], Chloe Tanner[1], Fiona Ashford[1], Sarita Workman[3], Fernando Moreira[3], Nisha Verma[4], Hollie Wagg[5], Gail Heritage[5], Naomi Campton[5], Zania Stamataki[2], Mark Drayson[1], Paul Klenerman[6], James Thaventhiran[7], Shuayb Elkalifa[8], Sarah Goddard[9], Sarah Johnston[10], Aarn Huissoon[11], Claire Bethune[12], Suzanne Elcombe[13], David Lowe[14], Smita Patel[15], Sinisa Savic[16], Alex Richter[1], Siobhan Burns[14]
[1]University of Birmingham, Clinical Immunology Service,, Birmingham, United Kingdom, [2]University of Birmingham, Institute of Immunology And Immunotherapy, Birmingham, United Kingdom, [3]Royal Free Hospital, Clinical Immunology, London, United Kingdom, [4]Royal Free London NHS Foundation Trust, Department of Immunology, London, United Kingdom, [5]University of Birmingham, Institute For Translational Medicine, Birmingham, United Kingdom, [6]University of Oxford, Nuffield Department of Medicine, Oxford, United Kingdom, [7]University of Cambridge, Mrc Toxicology Unit, QR, United Kingdom, [8]Salford Royal Foundation Trust, Immunology, Manchester, United Kingdom, [9]University Hospitals of North Midlands NHS Trust, Immunology And Allergy, Stoke-on-Trent, United Kingdom, [10]North Bristol NHS Trust, Department of Immunology, Bristol, United Kingdom, [11]University Hospitals Birmingham NHS Foundation Trust, Department of Clinical Immunology, Birmingham, United Kingdom, [12]University Hospitals Plymouth NHS Trust, Immunology And Allergy Service, Plymouth, United Kingdom, [13]Newcastle Hospitals NHS Foundation Trust, Department of Clinical Immunology, Newcastle, United Kingdom, [14]UCL, Institute of Immunity And Transplantation, London, United Kingdom, [15]University of Oxford, Nihr Brc Oxford Biomedical Research Centre, Oxford, United Kingdom, [16]St James's University Hospital, Clinical Immunology And Allergy, Leeds, United Kingdom

Background and Aims: Compared to healthy controls, individuals with antibody deficiency demonstrate diminished humoral responses to a two-dose SARS-CoV-2 vaccination schedule. Third primary immunisations have been recommended to improve immunity in patients with clinically significant immunodeficiency, but the effectiveness of this strategy is unknown.
Methods: Participants enrolled in the UK multi-site, COVID-19 in patients with antibody deficiency (COV-AD) study were sampled before (n=111) and after (n=161) their third vaccination. Serological and cellular responses were determined using ELISA, live-virus 669ypogammaglobu and ELISPOT assays.
Results: 100% of controls vs. 61.4% of patients with antibody deficiency mounted a humoral response following two SARS-CoV-2 vaccine doses. Amongst patients with antibody deficiency, a third primary 669ypogammaglo significantly increased seroprevalence to 76.0% and was accompanied by significant increases in the magnitude of the antibody responses, its 669ypogammaglo capacity and cross-reactivity with the Omicron variant-of-concern. However, antibody levels remained significantly lower than healthy controls (IgGAM ratio: 7.61 vs. 4.54, $p<0.0001$). No difference in humoral responses were observed between recipients of homologous and heterologous vaccines schedules, however significantly more participants had detectable T cell responses after receiving two doses of ChAdOx1 nCoV-19 followed by an mRNA booster, compared to recipients of three doses of Pfizer BioNTech 162b2 (61.5% vs 11.1%, $p=0.009$). 10.6% of participants failed to mount either a T cell or a humoral immune response: these individuals shared no obvious common clinicodemographic characteristics.
Conclusions: Third primary immunisations significantly improve humoral immunity in patients with antibody deficiency. The potential of heterologous vaccine regimens to improve cellular immunity in these patients with antibody deficiency should be explored further.
Disclosure: No.
Keywords: COVID-19, CVID, primary immunodeficiency, Secondary Immunodeficiency, SARS-CoV-2, Vaccination

PD515

ANTIBODY AND CELLULAR IMMUNE RESPONSE TO COVID-19 INFECTION AND/OR IMMUNIZATION IN CVID PATIENTS

POSTER DISPLAY 10: COVID-19

Cristina Kokron[1], Loisi Pereira[1], Jhosiene Magawa[1], Andreia Takara[1], Greyci Sasahara[1], Giuliana Medeiros[1], Myrthes Maragna Toledo Barros[1], Jorge Kalil[2], Ana Karolina Marinho[1], Edécio Cunha-Neto[2], Keity Santos[1], Octávio Grecco[1], Fabiana Lima[1]
[1]Faculdade de Medicina, Universidade de São Paulo, Clinical Immunology And Allergy Division, Hospital Das Clínicas, São Paulo, Brazil, [2]Heart Institute, School of Medicine, University of Sao Paulo, Laboratory of Immunology, Sao Paulo, Brazil

Background and Aims: Introduction: In general, Common Variable Immunodeficiency (CVID) patients have mainly impaired antibody but also cellular immune responses. Objectives: To evaluate immune responses of CVID patients to immunization against COVID-19, with or without previous infection.

Methods: Thirty CVID patients were included, 23 of which had no previous COVID-19. Nine of these were vaccinated with Astrazeneca (AZ), 11 with Sinovac and 3 with Pfizer. Seven contracted COVID-19 prior to vaccination with Sinovac. Levels of IgG against RBD and Spike proteins of SARS-CoV-2 by ELISA and IFN-γ and IL-2 production after virus peptides stimulation in a whole blood assay were determined.

Results: In general, after 2 vaccine doses, 60% produced humoral and/or cellular response. Specifically, after AZ vaccination, 89% produced IgG anti-RBD and anti-Spike, after Pfizer, 67% had IgG anti-RBD and anti-Spike, and after Sinovac none produced antibodies. For cellular response, AZ induced production at 33% of IFN-γ and of IL-2. After Sinovac only 25% produced IFN-γ. With Pfizer, 33% produced IL-2. With a booster of Pfizer after Sinovac 50% produced IgG anti-RBD and 70% IgG anti-Spike, 50% IFN-γ and IL-2. Among the group with previous COVID-19, 57% produced IgG anti-RBD and anti-Spike IgG, 71% IFN-γ and 29% IL-2.

Conclusions: CVID patients showed heterogeneous immune response after vaccination and these responses were higher in convalescents. AZ showed the highest rate of immune responses. In those vaccinated with Sinovac, responses were only improved after Pfizer booster dose, suggesting that the vaccine booster is essential as well as the change of vaccine platform used.

Disclosure: No.

Keywords: antibody deficiency, SARS-CoV-2, Immunization, immune response, COVID-19, CVID

PD516

IMMUNE RESPONSE AFTER FULL IMMUNIZATION FOLLOWED BY A BOOSTER DOSE of BNT162B2 MRNA COVID-19 VACCINE IN PATIENTS WITH 22Q11.2 DELETION SYNDROME

POSTER DISPLAY 10: COVID-19

Federica Pulvirenti[1], Ane Fernandez Salinas[2], Sara Terreri[2], Eva Piano Mortari[2], Carolina Putotto[3], Bianca Laura Cinicola[4,5], Bruno Marino[3], Rita Carsetti[6], Isabella Quinti[4]
[1]AOU Policlinico Umberto I, Reference Centre For Primary Immune Deficiencies, Dpt of Internal Medicine And Infectious Diseases, ROMA, Italy, [2]Bambino Gesù Children's Hospital, IRCCS,, B Cell Unit, Immunology Research Area,, ROMA, Italy, [3]Sapienza University of Rome, Materno Infantile E Scienze Uroginecologiche, rome, Italy, [4]Sapienza University of Rome, Molecular Medicine, Rome, Italy, [5]Sapienza University of Rome, Pediatric Immunology And Allergology, Rome, Italy, [6]Diagnostic Immunology Research Unit, Multimodal Medicine Research Area, Bambino Gesù Children's Hospital, IRCCS; Viale di San Paolo,15, Rome, Italy, Diagnostic Immunology Research Unit, Multimodal Medicine Research Area, Bambino Gesù Children's Hospital, Irccs; Viale Di San Paolo,15, Rome, Italy, Roma, Italy

Background and Aims: In patients with 22q11.2 deletion syndrome (22q11.2DS) immunological defects may be widely variable, ranging from a SCID-like phenotype to less severe manifestations, with T lymphocytopenia and recurrent sinopulmonary infections and autoimmunity. Due to the immune defect, 22q11.2DS individuals represent a potential at-risk group in the current COVID-19 pandemic. Data on immune responses to immunization for SARS-CoV-2 in 22q11.2DS are lacking, posing questions about the efficacy of actual immunization actual strategies.

Methods: Sixteen patients with 22q11.2DS and 28 healthy age-matched controls (HD) were analyzed to evaluate the differences in terms of anti-Spike, generation of Spike-specific memory B-cells (MBC) with low (S+) or high affinity (S++), and Spike-specific T-cells two week after the second BNT162b2 vaccine dose, and two weeks after the third one.

Results: After two doses the BNT162b2 vaccine induced Spike-specific IgG and IgA antibody responses in all HD and in 15/16 22q11.2DS patients, with levels rising significantly after the booster dose. Similar levels of anti S1IgG and IgA were recorded in the study groups. In HD, S+MBC were generated after the second dose, being increased after the third dose. Differently, 22q11.2DS patients developed S+MBC only after the third dose. Moreover, after completing third doses, 22q11.2DS raised lower levels of S++ MBC in comparison to the HD. Specific T-cell responses were evident in all HD and heterogeneous in 22q11.2DS patients.

Conclusions: In patients with 22q11.2DS early immune responses after BNT162b2 immunization occurred, being boosted by the additional dose of vaccine. Our data highlights the need for supplemental vaccine doses for patients not previously infected.

Disclosure: No.

Keywords: 22q11.2 Deletion Syndrome, COVID-19, vaccine, BNT162b2, Memory B cells, Spike Protein

PD517

ANTIBODY RESPONSES FOLLOWING COVID-19 VACCINATION IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY (CVID)

POSTER DISPLAY 10: COVID-19

Theodora Papastamatiou[1,2], Sofia Tantou[2], Evaggelia Zaimaki[2], Stavroula Mpatsikoura[2], Marianna Tzanoudaki[2], Manolis Liatsis[2]
[1]Aglaia Kiriakou Hospital, 2nd Department of Pediatrics of The National And Kapodistrian University of Athens, ATHENS, Greece, [2]'Aghia Sophia' Children's Hospital, Department of Immunology-histocompatibility, Specialized & Referral Center For Primary Immunodeficiency-paediatric Immunology, Athens, Greece

Background and Aims: Patients with primary antibody deficiencies are at risk in the current COVID-19 pandemic due to their impaired response to infection and vaccination. Given the lack of information on effectiveness of anti-SARS-CoV-2 vaccines in common variable immunodeficiency (CVID) patients, we seek to describe the immunogenicity of the COVID-19 vaccines in CVID patients.

Methods: Ten patients (15-60 years) with CVID were enrolled in this study according to ESID criteria. Seven patients were naïve to SARS-CoV-2 infections and received mRNA COVID-19 vaccine, with a schedule of two doses with 21 days apart. Blood samples were collected at least 7 days after the second dose. Three CVID patients, unvaccinated and non-infected with SARS-CoV-2 were also tested. Ten healthy donors similarly vaccinated and non-infected with SARS-CoV-2 were used as controls(HC). The EliA SARS-CoV-2-Sp1 IgG (Thermo Fisher S1 IgG) assay was used for the measurement of SARS-CoV-2 (Covid-19) IgG antibodies.

Results: Overall, both HC and CVID patients showed a detectable SARS-CoV-2 specific humoral after COVID-19 vaccination, with only the three unvaccinated CVID patients lacking anti- SARS-CoV-2 Abs. of note, CVID patients showed a lower anti- SARS-CoV-2 titers compared to HC.

Conclusions: These results suggest that CVID patients can still benefit from vaccination. Thus, they should be encouraged to get vaccinated. Additional studies will be needed to further define the variability of humoral and cellular protective immune response after COVID-19 vaccination in immunocompromised patients.

Disclosure: No.

Keywords: COVID-19 vaccination, SARS-CoV-2, with common variable immunodeficiency, CVID

PD518

THE "BREAKTHROUGH" COVID-19 IN 3-DOSES VACCINATED PATIENTS WITH INBORN ERRORS of IMMUNITY AND THE EARLY TREATMENT WITH MONOCLONAL ANTIBODIES AND ANTIVIRALS

POSTER DISPLAY 10: COVID-19

Maria Carrabba[1], Lucia Baselli[2], Alessandra Bandera[3], Serena Serafino[1], Rosa Dellepiane[2], Giovanna Fabio[1]
[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Dipartimento Di Medicina Interna, Milano, Italy, [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Pediatric Department, Milano, Italy, [3]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlnico, Infectious Diseases, MILANO, Italy

Background and Aims: Inborn errors of the immunity (IEI) patients may have a reduced or absent humoral and cellular response to vaccination due their underlying immune defects. Early treatment with monoclonal antibodies (mAbs) and/or antivirals is a valuable tool in this population. We aim to assess safety and clinical outcomes of early treatments for COVID-19 among IEI patients.

Methods: We retrospectively reviewed all IEI patients who received an early treatment with mAbs or antivirals (673ypogammag or 673ypogamm) for COVID-19, according to IEI centre at a tertiary hospital. Outcomes are evaluated, in particular frequency of adverse drug reaction (ADR), duration of molecular swab positivity, duration of symptoms, reinfections.

Results: Early treatments were administered to 37 IEI patients (25 CVID, 2 XLA, 3 AD-HIES, 1 CGD, 1 complement deficiency, 1 Good Syndrome, 3 UnPAD, 1 sDIgA with bronchiectasis). Antivirals plus mAbs were administrated to 10 patients, 8 patients received only antivirals (because mAbs were not available) and 19 patients received only mAbs. All the patients were vaccinated with 3-doses mRNA vaccines. One subject reported ADR that needed stopping antiviral treatment. Median time from the treatment to molecular swab negativity ranged from 1 to 8 weeks, symptoms solved in 2-4 days. During the observation period of 6 months after treatment administration, nobody was hospitalized for causes related to COVID-19 nor died. One patients had new SARS-CoV-2 infection 15 weeks after the administration of mAbs for the first SARS-CoV-2 infection and was treated with antiviral.

Conclusions: Treatments in the early stages of COVID-19 have favourable outcomes in IEI patients.

Disclosure: No.

Keywords: inborn errors of immunity (IEI), primary immunodeficiencies (PIDD), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19), monoclonal antibody

PD519

RELATIONSHIP BETWEEN SWITCHED MEMORY B-CELL LEVELS AND THE CLINICAL COURSE of COVID-19 IN CVID PATIENTS

POSTER DISPLAY 10: COVID-19

Tuğba Önalan, Fatih Çölkesen, Filiz 674ypo Aykan, Şevket Arslan
Necmettin Erbakan University Meram Medical Faculty, Clinical Immunology And Allergy, Konya, Turkey

Background and Aims: The clinical course of COVID-19 varies considerably among patients. Our study aims to investigate the relationship of switched memory B cells (SMBCs) (CD19+ CD27+ IgM- IgD-) with the clinical course of COVID-19 in CVID patients.

Methods: CVID patients followed in Necmettin Erbakan University Meram Medical Faculty Clinical Immunology and Allergy clinic were included in the study. of these patients, clinical course data and basal SMBCs levels of those who had COVID-19 between March 2020 and June 2021 (SARS-CoV-2 PCR positive) were obtained from patient files.

Results: of the 62 CVID patients, 24 who had COVID-19 were included in the study. SMBCs counts in CVID patients were significantly lower in the severe COVID-19 group. (p=0.018). In the patients whose SMBCs levels were lower than the normal range, the duration of hospitalization, duration of disease symptoms, and SARS-CoV-2 PCR positivity duration were higher (p=0.021, 0.034, and 0.012, respectively). In addition, a significant negative correlation was found between SMBCs levels and SARS-CoV-2 PCR positivity duration in CVID patients who had had COVID-19 (r= -0.397, p=0.038).

Conclusions: T cells and B cells have essential roles in the clearance of viral infections. SMBCs that develop during acute infection induces the development of plasma cells in the event of reinfection, who mediate the antibody response. It has been shown that low levels of SMBCs in CVID patients may be associated with severe COVID-19. In this group of CVID patients, the administration of aggressive treatment modalities in the early stages of COVID-19 may allow morbidity and mortality rates to decrease.

Disclosure: No.

Keywords: COVID-19, CVID, switched memory B

PD520

IMPACT of HYPOGAMMAGLOBULINEMIA ON THE COURSE of COVID-19 IN A NON-INTENSIVE CARE SETTING: A SINGLE-CENTER RETROSPECTIVE COHORT STUDY.

POSTER DISPLAY 10: COVID-19

Riccardo Scarpa[1], Alessandro Dell'Edera[1], Francesco Muscianisi[1], Renato Finco Gambier[1], Nicholas Landini[2], Carlo Agostini[1], Marcello Rattazzi[1], Francesco Cinetto[1]
[1]University of Padua, Department of Medicine, Treviso, Italy, [2]Ca' Fondello Hospital, Radiology Unit, Treviso, Italy

Background and Aims: Severity and mortality of COVID-19 largely depends on virus clearance by host immunity. Among various comorbidities potentially impacting on this process, the weight and the consequences of an antibody deficiency have not yet been clarified.

Methods: Serum protein electrophoresis (SPE) was evaluated in a cohort of consecutive patients with COVID-19, hospitalized in non-intensive care setting. Disease severity, measured by a validated score and by the need for semi-intensive (sICU) or intensive-care-unit (ICU) admission, and mortality were compared between patients with (HYPO) and without (no-HYPO) hypogammaglobulinemia. Anamnestic data and clnical records were also evaluated.

Results: We enrolled 374 patients, of which 39 representing the HYPO cohort (10.4%). In 10/39 the condition was previously neglected, while in the other 29/39 hematologic malignancies were common (61,5%); 2/39 were on regular immunoglobulin replacement therapy (IgRT). Patients belonging to the HYPO group more frequently developed a severe COVID-19 and more often required sICU/ICU admission than no-HYPO patients. IgRT were administered in 8/39 during hospitalization; none of them died or needed sICU/ICU. Among HYPO cohort, we observed a significantly higher prevalence of neoplastic affections, of active oncologic treatment and bronchiectasis, together with higher prevalence of superinfections, mechanical ventilation, and longer disease duration. The analysis of the mortality rate in the whole cohort showed no significant difference between HYPO and no-HYPO.

Conclusions: Hypogammaglobulinemia was associated to a more severe COVID-19 and more frequent admission to s-ICU/ICU, particularly in absence of IgRT. Our findings emphasize the add-value of routine SPE evaluation in patients admitted with COVID-19 and to consider IgRT initiation during hospitalization.

Disclosure: No.

Keywords: hypogammaglobulinemia, immunoglobulins replacement therapy, internal medicine, COVID-19, intensive care unit, antibody deficiency

PD521

IFNAR2 HAPLOINSUFFICIENCY IN A CASE of SEVERE COVID-19

POSTER DISPLAY 10: COVID-19

Lisa Roels[1,2], Leslie Naesens[1,2], Levi Hoste[1,2], Karlien Claes[1,2], Veronique Debacker[1,2], Stephanie Dobbelaere[3], Emmanuelle Jouanguy[4,5,6], Qian Zhang[6], Jean-Laurent Casanova[4,5,6,7,8], Simon Tavernier[2,9,10,11], Filomeen Haerynck[1,2]
[1]Ghent University Hospital, Department of Internal Medicine And Pediatrics, Division of Pediatric Pulmonology, Infectious Diseases And Inborn Errors of Immunity, Ghent, Belgium, [2]Ghent University, Primary Immune Deficiency Research Laboratory, Department of Internal Diseases And Pediatrics, Centre For Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis And Research Centre, Ghent, Belgium, [3]AZ Delta, Pneumology, Roeselare, Belgium, [4]Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital For Sick Children, Paris, France, [5]University of Paris, Imagine Institute, Paris, France, [6]St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, United States of America, [7]Howard Hughes Medical Institute, -, New York, United States of America, [8]Necker Hospital for Sick Children, Pediatric Hematology-immunology And Rheumatology Unit, Paris, France, [9]VIB, Vib-ughent Center For Inflammation Research, Laboratory of Molecular Signal Transduction In Inflammation, Ghent, Belgium, [10]Ghent University, Department of Biomedical Molecular Biology, Ghent, Belgium, [11]Ghent University Hospital, Center For Medical Genetics, Ghent, Belgium

Background and Aims: Inborn errors of type I interferon (IFN) immunity and auto-antibodies against type I IFN account for at least 3.5% and 10.2% of life-threatening coronavirus disease 2019 (COVID-19) cases, highlighting the importance of type I IFN in critical COVID-19. We identified a heterozygous frameshift variant in the extracellular domain of IFNAR2 (p.Glu140fs) in an otherwise healthy female who suffered from severe COVID-19. IFNAR2 is a subunit of the interferon-α/β receptor (IFNAR) complex composed of IFNAR1 and IFNAR2 which induces IFN-stimulated gene (ISG) expression through JAK/STAT phosphorylation. We hypothesized that this frameshift results in loss of IFNAR2 expression and impaired type I IFN signaling.

Methods: To study this, we performed staining of the IFNAR2 receptor, phosphoflow signaling assays and ISG expression analysis on fibroblasts, peripheral blood mononuclear cells and phytohemagglutinin stimulated T cells.

Results: Compared to healthy control samples, our data demonstrated reduced IFNAR2 expression as well as impaired STAT1, STAT2 and STAT3 phosphorylation and a variable effect on ISG expression (reduced to normal) upon type I IFN stimulation (IFNα2, IFNβ and IFNω). SARS-CoV-2 infection experiments of patient fibroblasts are ongoing.

Conclusions: These results are in line with the hypothesis that IFNAR2 haploinsufficiency underlies severe COVID-19 due to defective type I IFN signaling (Q. Zhang et al., Science 2020).

Disclosure: No.

Keywords: Type I IFN signaling, COVID-19, Innate Immunity

PD522

VARIANTS IN SSRP1, MRPS25 AND EXOSC8 MAY INCREASE SUSCEPTIBILITY TO CRITICAL COVID-19

POSTER DISPLAY 10: COVID-19

Sofie Jørgensen[1,2], Anne Hollensen[1,2], Michelle Thomsen[1,2], Jacob Bodilsen[3], Andreas Ronit[4], Merete Storgaard[2], Trine Mogensen[1,2]
[1]Aarhus University, Department of Biomedicine, Aarhus C, Denmark, [2]Aarhus University Hospital, Department of Infectious Diseases, Aarhus N, Denmark, [3]Aalborg University Hospital, Department of Infectious Diseases, Aalborg, Denmark, [4]Hvidovre Hospital, Department of Infectious Diseases, Hvidovre, Denmark

Background and Aims: Several factors predispose to critical COVID-19, including old age, various co-morbidities and host genetics. Particularly, genetic variants impairing type I interferon (IFN) responses increase susceptibility to COVID-19. Additionally, autoantibodies against type I IFN also increase susceptibility significantly. However, not all patients who develop critical COVID-19 fall into one of these known susceptibility groups. Thus, we hypothesize that variants in genes involved in non-IFN antiviral mechanisms can significantly impact on host susceptibility to critical COVID-19.

Methods: We included patients with critical COVID-19 in Denmark and performed whole exome sequencing (WES). To identify novel susceptibility genes, the WES data were filtered based on CRISPR screen data available in the literature. By this approach we identified variants in several different genes, which in the CRISPR screens had shown antiviral activity against SARS-CoV-2.

Results: These variants included two missense variants in SSRP1, p.R316W and p.S651L, a nonsense variant in MRPS25, p.R132* and a frameshift variant in EXOSC8 N21Lfs*4. By siRNA knockdown in A549 hACE2 cells SSRP1, MRPS25 and EXOSC8 were confirmed to have strong antiviral activity against SARS-CoV-2. Expression of the patient variants in HEK293T cells demonstrated equal expression of wild type (WT), p.R316W and p.S651L SSRP1. MRPS25 p.R132* gave rise to a truncated protein expressed at decreased levels compared to WT MRPS25, whereas the EXOSC8 frameshift variant completely abolished expression of EXOSC8 protein.

Conclusions: We are currently investigating the mechanisms by which SSRP1, MRPS25 and EXOSC8 inhibit SARS-CoV-2 replication, as well as the functional impact of the identified gene variants in patients.

Disclosure: No.

Keywords: SSRP1, MRPS25, EXOSC8, COVID-19, WES, Antiviral

PD523

ELEVATED LEVELS of CXCL16 IN SEVERE COVID-19 PATIENTS: EFFECTS ON MORTALITY

POSTER DISPLAY 10: COVID-19

Sandra Smieszek
Vanda Pharmaceuticals Inc., Genetics, Bethesda, United States of America

Background and Aims: Genome-wide association studies have recently identified 3p21.31, with lead variant pointing to the CXCR6 gene, as the strongest thus far reported susceptibility locus for severe COVID-19. CXCL16 is synthesized as a transmembrane molecule that is expressed as a cell surface-bound molecule, and as a soluble chemokine. The CXCR6/CXCL16 axis mediates homing of T cells to the lungs in disease and hyper-expression is associated with 678ypogamma cellular injury. The aim was to characterize the CXCR6/CXCL16 axis in the pathogenesis of severe COVID-19.

Methods: Plasma concentrations of CXCL16 collected at baseline from 115 hospitalized COVID-19 patients participating in ODYSSEY COVID-19 clinical trial (and controls) were assessed. Another cohort of samples (n 79) was used to see if the effect replicates. CXCL16 levels in plasma were determined with ELISA assay. Furthermore, whole-genome sequencing was conducted on all samples.

Results: We report elevated levels of CXCL16 in a cohort of COVID-19 hospitalized patients. We previously reported elevated levels of CXCL16 in a cohort of COVID-19 severe hospitalized patients (P-value<0.02). Importantly we report a significant effect of elevated CXCL16 on mortality (P-value<0.03) effect that is now replicated (mortality (P-value<0.0004)). Clinically, at 700pg/mL, the OR is 20.6, (p-value 0.04) essentially suggesting one has a ~25% mortality when CXCL16 levels are above ~700pg/ml. We also further characterize the role of the CXCR6 expression on CD8 T cells.

Conclusions: These latest findings further support the significant role of the CXCR6/CXCL16 axis in the immunopathogenesis of severe COVID-19 and warrant further studies to understand which patients would benefit most from targeted treatments.

Disclosure: SPS is an employee of Vanda Pharmaceuticals Inc.

Keyword: COVID-19 immune responses, genetics, chemokines, CXCL16, genetic markers, CD8 T cells

PD524

ANTIVIRAL ROLE of AUTOPHAGY IN PATIENTS WITH CRITICAL COVID-19

POSTER DISPLAY 10: COVID-19

Lili Hu[1], Alice Pedersen[1], Anne Hollensen[1], Sofie Jørgensen[2], Johanna Heinz[2], Michelle Thomsen[1], Aurélie Cobat[3], Jean-Laurent Casanova[4], Christian Holm[2], Trine Mogensen[1]
[1]Aarhus University, Department of Biomedicine, Aarhus C, Denmark, [2]Aarhus University (AU), Department of Biomedicine, Aarhus, Denmark, [3]Université Paris Descartes, Génétique Humaine Des Maladies Infectieuses, Paris, France, [4]Necker Hospital, Pediatric Hematology-immunology And Rheumatology Unit, Paris, France

Background and Aims: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the global pandemic with high morbidity and mortality. There is an incomplete understanding of the genetic and immunological factors conferring diverse host immune response.

Methods: We use whole gene sequence to identify gene variant in patients with critical COVID-19. Also we applied Western Blot, qPCR, and CRISPR Cas9 to explore the role of autophagy in antiviral defenses against SARS-CoV-2.

Results: Here, we identify a patient with severe COVID-19 who carries a rare monoallelic variant in the autophagy gene RB1CC1. SARS-CoV-2 induces autophagy in ACE2 A549 cells and primary pulmonary epithelial cells, however the induction of autophagy in patient monocyte-derived macrophages (MDMs) is reduced. Knock down (KD) of RB1CC1 by nucleofection in ACE2 A549 cells results in defective autophagy, increased SARS-CoV-2 replication with preserved interferon (IFN) and IFN-stimulated gene responses.

Conclusions: This study gives us a greater understanding of how defective autophagy may represent an inborn error of immunity that can lead to increased susceptibility to SARS-CoV-2 infection, suggesting an important role for autophagy in antiviral immunity.

Disclosure: No.

Keywords: RB1CC1, Autophagy, SARS-CoV-2, COVID-19, FIP200

PD525

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN ASSOCIATED WITH COVID-19 INFECTION (EXPERIENCE of ONE CENTRE)

POSTER DISPLAY 10: COVID-19

Otilia Petrovicova[1], Martin Kostkova[2], Lenka Kapustova[1], Peter Banovcin[1], Milos Jesenak[1]
[1]University Teaching Hospital in Martin, Centre For Primary Immunodeficiences – Esid Registry Site, Department of Children And Adolescents, Jessenius Faculty of Medicine, Comenius University In Bratislava, Martin, Slovak Republic, [2]University Teaching Hospital in Martin, Department of Children And Adolescents, Rheumatology Outpatient Department, Jessenius Faculty of Medicine, Comenius University In Bratislava, Martin, Slovak Republic

Background and Aims: Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 is a complication, that may occur within 2 to 6 weeks after the primary infection. The pathogenesis is not fully understood, but there could be some genetic susceptibility including defects in genes, that regulate cytokine signalling.

Methods: This is observational prospective clinical study with case series. We present a group of 22 patients (15 boys, 7 girls) with MIS-C hospitalized from November 2020 to May 2022. The mean age of the patients was 8.9±4.3 years.

Results: The mean time interval from the onset of COVID-19 infection to clinical manifestation of MIS-C was 26.7±9.8 days. Initial clinical picture was variable – fever (n=22) with mean duration of 4.9±2.1 days, cardiovascular (n=20), gastrointestinal (n=15) and respiratory (n=10) symptoms, palmoplantar erythema (n=7), skin rash (n=14), conjunctivitis (n=12), skin peeling (n=4), polyserositis (n=16). We detected a typical elevation of inflammatory markers, coagulopathy and elevated cardiac markers (patients with cardiovascular disease). In the immune profile, we detected lymphopenia and moderate to critical cellular deficiency (n=20) with evidence of immune paralysis (n=11), monocyte anergy syndrome (n=1), NK cell depletion (n=12). All patients were treated according to the protocol for MIS-C, 1 patient was given anakinra – IL-1 receptor antagonist.

Conclusions: Children with MIS-C need multidisciplinary approach (paediatric intensivist, immunologist, cardiologist, rheumatologist, pulmonologist, haematologist). Early protocolar treatment can prevent complications. More case reports or series and cohort studies are needed to better understand the underlying process and risk for development of this condition after COVID-19 infection.

Disclosure: No.

Keywords: COVID-19, MIS-C, Children, Immune profile, multidisciplinary approach

PD526

A RARE CASE of IMMUNODEFICIENCY-ICF 1 SYNDROME DIAGNOSED FOLLOWING COVID-19 INFECTION

POSTER DISPLAY 10: COVID-19

Hilal Karabağ Çıtlak[1], Ayberk Turkyilmaz[2], Nergiz Kendirci[3], Hakan Kot[3], Fatih Koç[3], Zeynep Gayretli Aydın[4], Fazıl Orhan[3]
[1]Karadeniz Technical University, Pediatric Allergy And Immunology, Trabzon, Turkey, [2]Karadeniz Technical University, Department of Medical Genetics, Trabzon, Turkey, [3]Karadeniz Technical University, Department of Pediatric Allergy And Immunology, Trabzon, Turkey, [4]Karadeniz Technical University, Department of Pediatric İnfectious Diseases, Trabzon, Turkey

Background and Aims: ICF syndrome is a rare autosomal recessive heterogeneous disease characterized by immunodeficiency, centromeric instability and facial anomalies. Here, we present a case of ICF1 syndrome diagnosed following Covid 19 infection.

Methods: An 8-year-old girl referred for immunologic evaluation after a two-week period of intravenous 681ypogammag treatment with no significant improvement due to lung infection and diarrhea following Covid 19 infection. Her history revealed repetitive hospitalization due to lung infections and diarrhea since the neonatal period. Her parents were cousins and she had a history of two siblings death. Her body weight was 20 kg (3-10p) and height was 119 cm (3-10p). She had a narrow, elongated face, flat nasal bridge, low-set ears, micrognathia and mild mental retardation.(Fig.1).Computed tomography of the thorax showed bronchiectasis in both lungs and a ground-glass appearance. Laboratory examinations revealed normal range of B, T, NK cell counts and percentages in lymphocyte subgroups in addition to 681ypogammaglobulinemia. Specific antibody responses were low. Whole exome sequencing detected a predefined mutation in the DNMT3B gene (c.1721G>A p.R574Q)and the patient was diagnosed with ICF. The genetic findings were then confirmed by karyotype analysis on peripheral blood. In the cytogenetic analysis; instability was observed in the 1st and 16th chromosomes(Fig. 2).

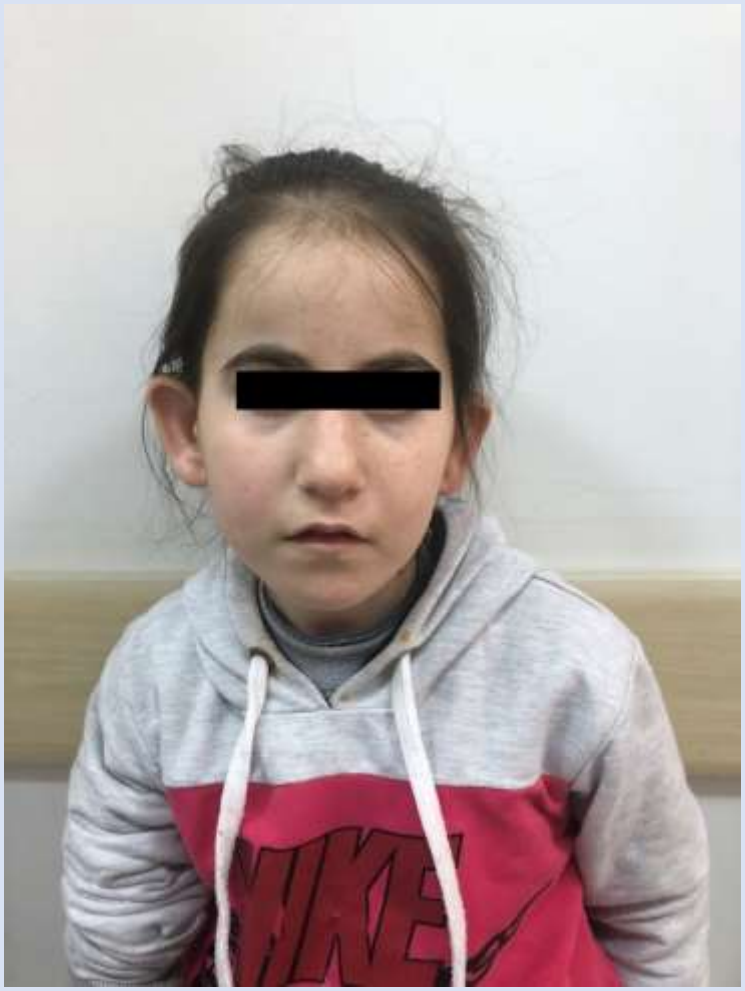


Figure 1 : Facial appearance of patient

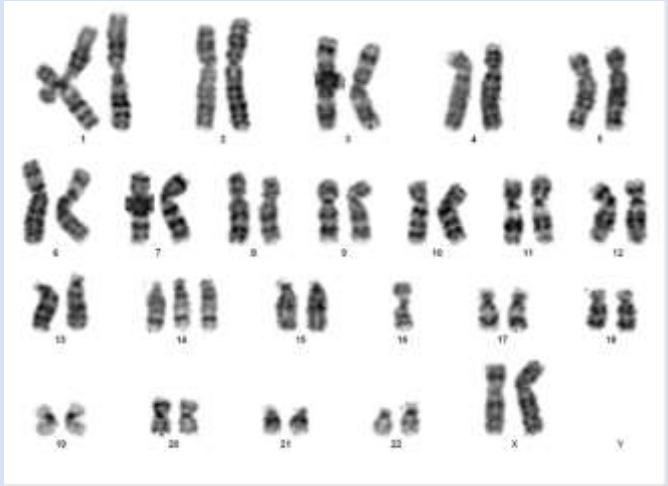


Figure 2: Centromeric instability of chromosomes 1 and 16

Results: Our case is the first ICF1 patient diagnosed following Covid 19 infection.

Conclusions: Combined immun deficiencies should be considered in syndromic paitiens with frequent and sustained enfections.

Disclosure: No.

Keywords: covid-19 infection, syndromic combined immunodeficiency, child

PD527

UNDERLYING GENETIC CAUSES IN YOUNG PATIENTS TREATED WITH INTENSIVE CARE FOR SEVERE COVID-19

POSTER DISPLAY 10: COVID-19

Laura Covill[1], Anton Sendel[2], Tessa Campbell[3], Sara Lind Enoksson[4], Emilie Wahren Borgström[5], Susanne Hansen[5], Per Marits[2], Anna Carin Norlin[6], Jessica Kåhlin[7], Lars Eriksson[7], Carl Inge Edvard Smith[8], Peter Bergman[5], Yenan Bryceson[3]
[1]Karolinska Institute, Center For Hematology And Regenerative Medicine, Stockholm, Sweden, [2]Karolinska University Hospital, Clinical Immunology And Transfusion Medicine, Stockholm, Sweden, [3]Karolinska Institutet, Medh (herm), Stockholm, Sweden, [4]Karolinska Institutet, Department of Clinical Immunology And Transfusion Medicine, Stockholm, Sweden, [5]Karolinska Institutet, Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden., Huddinge, Sweden, [6]Karolinska Institutet, Department of Clinical Immunology, Huddinge, Sweden, [7]Karolinska University Hospital, Perioperative Medicine And Intensive Care, Stockholm, Sweden, [8]Karolinska Institutet, Department of Laboratory Medicine, Biomolecular And Cellular Medicine,, Stockholm, Sweden

Background and Aims: Since the inception of the COVID-19 pandemic, investigation has been ongoing into factors impacting infection severity, which can range from asymptomatic to ARDS and death. Previous COVID-19 patient cohorts have been highly heterogenous in clinical presentation, age, and other parameters. We collected and clinically characterized a cohort of young (n=38, <50 years), previously healthy individuals who were hospitalized in intensive care units during the first COVID-19 pandemic wave. We set out to identify immunological and genetic factors underlying the severity of their disease.

Methods: Blood samples were collected after convalescence. DNA was isolated and subjected to genome sequencing and analyses for inborn errors of immunity (IEI). Leukocytes were cryopreserved and analyzed functionally for viral sensing and type I interferon (IFN) signaling. We also analyzed serum for type I IFN autoantibodies.

Results: Most patients were previously unaffected by infectious disease and clinical examination did not suggest IEI. In two patients, anti-IFNα-autoantibodies were identified. Genome sequencing analysis revealed rare variants in the type I IFN pathway as well as a few other immune genes in some patients. Nonetheless, functional analyses of plasmacytoid dendritic cell sensing of TLR7 and TLR9 agonists or lymphocyte phosphorylation of STAT1 upon type I IFN stimulation was not defective in any of the patients.

Conclusions: We conclude that deficiency in type I IFN, as observed in a significant proportion of young patients with life-threatening COVID-19, does not explain the majority of non-familial cases, Investigation into a wider range of causes may be beneficial in young and fit patients with severe COVID-19.

Disclosure: No.

Keywords: COVID-19, Inborn errors of immunity, interferon, Genetics

PD528

COURSE of COVID-19 IN PATIENTS WITH PREDOMINANTLY ANTIBODY DEFICIENCIES

POSTER DISPLAY 10: COVID-19

Öner Özdemir, Ümmügülsüm Dikici
Sakarya University Medical Faculty, Pediatric Allergy And Immunology, Sakarya, Turkey

Background and Aims: Knowledge in the literature regarding PIDs or inborn error of immunity (IEI) as a risk factor for severe COVID-19 is scarce. Our aim is here to elaborate the course of COVID-19 in patients with PIDs, especially in predominantly antibody deficiencies.

Methods: We retrospectively included 18 cases (13 male, 5 female), aged 30 months to 32 years old, with predominantly antibody deficiencies of our IEI group of 120 patients in this cross-sectional study. Their mean age was 12.2 (3-32) years. This study retrospectively evaluated the patients from February 2020 to February 2022 to determine the prevalence of COVID-19; including IEI patients with COVID-19. Assays used: polymerase chain reaction (PCR) tests for SARS-CoV-2 were detected by nasopharyngeal swab as positive.

Results: Bronchiectasis in 1 patient, there was no other comorbidity. A total of 18/120 PID patients, aged 30 months to 32 years, were tested positive for SARS-CoV-2. All of the patients were on routine monthly IVIG replacement therapy at the time of virus detection. Also, 9/18 patients received intermediate dose IVIG treatment. Moreover, 2/18 patients were completely asymptomatic, but 16 out of 10 patients were symptomatic. Consequently, none of the patients displayed severe illness and even none required supplemental oxygen and/or intensive care unit admission. Other than intermediate dose IVIG treatment in 9/18 patients, one utilized hydroxychloroquine, one used favipiravir and 4 patients used antibiotics.

Conclusions: The all of our patients presented a benign course and better outcome than general population, suggesting a possible protective factor related with younger age despite IEI.

Disclosure: No.

Keyword: COVID-19, antibody deficiency, primary immunodeficiency, SARS-CoV-2

PD529

COVID-19 INFECTION TREATED WITH MONOCLONAL ANTIBODIES IN 5 PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA

POSTER DISPLAY 10: COVID-19

Marc-Antoine Nadeau[1], Marie-Lee Simard[1], Amélie Gauthier[1], Guilhem Cros[2], Hugo Chapdelaine[2], Aubert Lavoie[1]
[1]CHU de Québec, Immunology, Québec, Canada, [2]Centre Hospitalier de l'Université de Montréal, Immunology, Montréal, Canada

Background and Aims: Patients with X-linked agammaglobulinemia (XLA) are predisposed to recurrent infections due to failure in B cell development. COVID-19 infection in XLA patients was initially reported as mild. This case series includes 5 XLA patients with a heterogenous symptomatology following COVID-19 infection and a favorable outcome while treated with monoclonal antibodies. So far, only convalescent plasma and antiviral medications have been reported as treatments in this setting.

Methods: Medical records were reviewed to extract data regarding the diagnosis of XLA, past medical history, vaccination status, COVID-19 disease presentation, treatments and evolution. This case series includes adult patients with XLA diagnosed with COVID-19 between march 1st 2020 and march 31st 2022.

Results: Among the 7 XLA patients followed at the immunodeficiency clinic of CHU de Québec, 5 of them tested positive for COVID-19. Three had mild symptoms, two were hospitalized and only one of them was admitted to the intensive care unit. All 5 patients were treated with monoclonal antibodies. Sotrovimab was used in three cases and the combination of Casirivimab and Imdevimab in two. The more severe cases were observed with the Delta variant. Only one patient presented a cytokine storm syndrome and was treated with steroids and Tocilizumab.

Conclusions: Clinical presentation of COVID-19 is heterogenous among these patients with the same immunodeficiency. All patients had a favorable outcome after receiving monoclonal antibodies. The low rate of cytokine storm syndrome observed amongst XLA patients may be related to the deficiency of Bruton‘s tyrosine kinase by preventing the activation of macrophage and Interleukin-6 production.

Disclosure: No.

Keywords: COVID-19, x-linked agammaglobulinemia, bruton's tyrosine kinase, monoclonal antibody, sotrovimab, SARS-CoV-2

PD530

COVID-19 IN PATIENTS WITH INBORN ERRORS of IMMUNITY; THE EGYPTIAN EXPERIENCE

POSTER DISPLAY 10: COVID-19

Ali Sobh[1], Zeinab El-Sayed[2], Elham Hossny[2], Shereen Reda[2], Dalia El-Ghoneimy[2], Rasha El-Owaidy[2], Ghada Shousha[2], Naglaa Osman[3], Walaa Shoman[4], Nesrine Radwan[2]
[1]Mansoura University Children's Hospital, Mansoura University Faculty of Medicine, Department of Pediatricspediatrics, Mansoura, Egypt, [2]Ain Shams University, Department of Pediatrics, Cairo, Egypt, [3]Assiut University, Department of Pediatrics, Assiut, Egypt, [4]Alexandria University, Department of Pediatrics, Alexandria, Egypt

Background and Aims: Some studies have evaluated the clinical course of COVID-19 in patients with PID and the genetic predisposition or underlying inborn errors of immunity and reported a variable course from asymptomatic to severe and complicated course of COVID-19 in this patient population. In this study, we report the clinical course, follow-up, and outcome of COVID-19 in patients with PID followed at tertiary PID centers in Egypt with the aim of contributing information regarding the course of the disease.

Methods: Data were collected from May 2021 to April 2022. Demographical and clinical data including age, PID type, and underlying genetic cause if known, COVID-19 presentation and diagnosis, treatment, and outcomes were collected from all patients who tested positive for COVID-19 during the study period.

Results: We reported 35 PID patients who tested positive for COVID-19 (23 male patients and 12 female patients). Their age ranged from 8 months to 16 years. Eight patients had predominant antibody deficiency and 14 patients with combined immunodeficiency. Thirty-four patients were admitted to the hospital, and 11 of them were admitted to ICU and required mechanical ventilation. Three patients developed MIS-C and one of them died. Seven patients died due to respiratory failure.

Conclusions: Although it is clear that mortality in patients with PID is higher than in the general population, it is difficult to suggest a group among primary immunodeficiencies as riskier for severe COVID-19 infection, according to the data published so far. A relatively small cohort of only 35 patients is an important limiting factor for this study.

Disclosure: No.

Keywords: Inborn errors of immunity, COVID-19, primary immunodeficiency, Egypt

PD531

COVID-19 IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY - SINGLE CENTER EXPERIENCE

POSTER DISPLAY 10: COVID-19

Maja Stojanovic[1,2], Rada Miskovic[1,2], Radovan Mijanovic[1,2], Aleksandra Peric-Popadic[1,2], Jovan Ranin[3,4], Branka Bonaci-Nikolic[1,2]
[1]University of Belgrade, Faculty of Medicine, Department of Internal Medicine, Belgrade, Serbia, [2]University Clinical Center of Serbia, Clinic of Allergy And Immunology, Belgrade, Serbia, [3]University of Belgrade, Faculty of Medicine, Department of Infectious Diseases, Belgrade, Serbia, [4]University Clinical Center of Serbia, Clinic of Infectious Diseases, Belgrade, Serbia

Background and Aims: Patients with primary immunodeficiency (PID) have been considered particularly vulnerable to SARS-CoV-2 infection.

Methods: Clinical and laboratory data from the medical' records of 57 patients with different types of PID, between March 2020 and February 2022, have been retrospectively analyzed (median follow up 10, IQR 3.5-12.5months).

Results: Among our PID patients, 22/57 (38.6%) had COVID-19 (PID/COVID), so the cohort of PID/COVID encompassed 15/22 (68.1%) patients with Common Variable Immunodeficiency (CVID), 4/22 (18.1%) with Agammaglobulinemia (AGA), 1/22 (4.6%) with Chronic granulomatous disease (CGD), 1/22 (4.6%) with CTLA-4 deficiency syndrome (CTLA-4DS), and 1/22 (4.6%) with 21q deletion syndrome (21qDS). Mild/moderate form of COVID-19 had 68.1%, severe 27.3%, and critical 4.6% patients; 41.5% required hospitalization and 4.6% had the lethal outcome. Patients from different PID categories (AGA, CVID, CGD, and CTLA-4DS) suffered from severe, while patient with combined immunodeficiency (21qDS) developed critical illness. In comparison, healthy people usually present with mild/moderate in 80%, severe disease in 15%, while 5% progress to critical illness. Prolonged SARS-CoV-2 positivity and inflammatory relapses had 3/22 (13.6%), two patients with AGA and the patient with CGD. Most of our PID/COVID patients were treated with antibiotics (77.3%), while 63.6% received antivirals (favipiravir, remdesivir, molnupiravir), 36.4% corticosteroids, 13.5% convalescent plasma, 9.1% tocilizumab, and 9.1% monoclonal antibodies (casirivimab/imdevimab).

Conclusions: Bronchiectasis, malignancies, enteropathy, IgG concentrations below normal values, and combined immunodeficiency have been associated with severe/critical illness. Prolonged positivity and post COVID-19 inflammatory relapses were associated with agammaglobulinemia, bronchiectasis and regular antibiotic prophylaxis due to presence of severe chronic lung disease.

Disclosure: No.

Keywords: primary immunodeficiency, COVID-19, CVID, agammaglobulinaemia

PD532

INCIDENCE AND CLINICAL CHARACTERISTICS of SARS-COV-2 INFECTION IN PATIENTS WITH INBORN ERRORS of IMMUNITY AFTER COVID-19 IMMUNIZATION IN A BRAZILIAN REFERENCE CENTER

POSTER DISPLAY 10: COVID-19

Vitor Gabriel Lopes Da Silva[1], Ana Marli Sartori[2], Alexander Roberto Precioso[3], Kathleen E Sullivan[4], Carolina Sanchez Aranda[1], Maria Isabel De Moraes-Pinto[1]
[1]Universidade Federal de São Paulo, Pediatrics, São Paulo, Brazil, [2]Universidade de São Paulo, Infectious And Parasitic Diseases, São Paulo, Brazil, [3]Instituto Butantan, Divisão De Ensaios Clínicos, São Paulo, Brazil, [4]The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Pediatrics, Division of Allergy And Immunology, Philadelphia, United States of America

Background and Aims: SARS-CoV-2 infection can be more severe in Inborn Errors of Immunity (IEI) patients with a high mortality rate. We assessed the frequency and clinical features of SARS-CoV-2 infection in individuals with IEI after Covid-19 vaccine.

Methods: Prospective longitudinal study involving 25 volunteers aged 18-52y with IEI: 15 Common Variable Immunodeficiency; 3 HyperIgM Syndrome; 2 X-linked Agammaglobulinemia; 2 Specific antibody deficiency; 1 Hypogammaglobulinemia; 2 Combined immunodeficiency. The 25 volunteers received three doses of Covid-19 vaccines between June and November 2021 and 23 patients received the fourth dose between January and March 2022. Two inactivated SARS-CoV-2 vaccine doses (CoronaVac) followed by two BNT162b2 doses were administered. Individuals with suspected Covid-19 symptoms collected a nasopharyngeal swab for RT-PCR and viral genome sequencing.

Results: of the 25 patients, 2 (8%) had mild Covid-19 before study enrollment. Over 11 months, 28 Covid-19 RT-PCR tests were performed for suspected cases, with 9 positive results (32.1%). There was one severe case, requiring ICU and mechanical ventilation 11 days after the first vaccine dose, with a mild reinfection 132 days after the third dose. Remaining 7 cases were mild (77.7%) during the circulation of Omicron variant. Viral genome sequencing revealed 5 cases of the Omicron BA.1 lineage, 3 inconclusive cases and 1 case still under investigation.

Conclusions: Vaccination of patients with IEI was associated with low severity of Covid-19 cases, suggesting that, besides humoral immune response, specific cellular immunity may be involved in the protection of individuals with IEI against severe disease, hospitalization and death.

Disclosure: No.

Keywords: Inborn errors of immunity, COVID-19, Immunization, Covid-19 Vaccines, Primary Immunodeficiency disorders, SARS-CoV-2

PD533

IMMUNOLOGICAL EVALUATION of PEDIATRIC COVID-19 CASE

POSTER DISPLAY 10: COVID-19

Ezgi Topyildiz[1], Ayşe Aygün[1], Raziye Burcu Guven[2], Neslihan Karaca[3], Necil Kutukculer[1], Guzide Aksu[1]
[1]Ege University, Faculty of Medicine, Depatment of Pediatric Allergy And Immunology, IZMIR, Turkey, [2]Ege University, Faculty of Medicine Depatment of Pediatric Rheumatology, İzmir, Turkey, [3]Ege University, Faculty of Medicine, Department of Pediatrics, Izmir, Turkey

Background and Aims: SARS-CoV-2 infection has a milder variable course in children than adults.There are not enough studies on the effect of basic immunological mechanisms on the course of the disease.In our study, we planned to perform the clinical and basic immunological evaluation of patients with different clinical presentations followed up and to determine their effect on the prognosis of COVID-19.

Methods: Sixty-eight patients who were diagnosed with Covid-19 in Ege University Pediatrics Clinic between May/2020 and February/2021 were included in the study.Demographic characteristics,clinical findings,treatments,follow-ups and laboratory (routins,Ig-levels,lymphocyte-subgroups,T-lymphocyte-panel and B-cell-differentiation-test) results of these patients were recorded.

Results: of the 68 patients,47.1%-female(n:32),52.9%-male(n:36), mean age was 68-months.Concomitant chronic disease was detected in 21 patients;5 of them were diagnosed with primary immunodeficiency (Di-George-Syndrome, APECED mutation, 3 cases unidentified-hypogammaglobulinemia).58.8%-of the patients received inpatient treatment, and 10.3%-of them needed intensive care.Clinically,75%-of them were asymptomatic-mild,25%-of them had moderate-severe course,MIS-C developed in six patients and one patient died.Considering the relationship between disease severity and laboratory findings;significant correlation between disease severity and percentages of leukocytes,neutrophils, $CD19^{+}$lymphocytes,$CD19^{+}CD38^{+}IgM^{low}$lymphocytes, $CD19^{+}CD38^{+}CD27^{high}IgM^{high}$lymphocytes(p values;0.016, 0.000, 0.000, 0.024 and 0.029,respectively) and significant inverse correlation between disease severity and percentage of lymphocytes, $CD3^{-}CD16^{+}CD56^{+}$lymphocytes(p values 0.04,0.038,respectively) was found.In addition, the rates of inpatient treatment and need for intensive care unit were significantly higher in patients with low CD3 levels.

Conclusions: As the severity of the disease increased,neutrophil,leukocyte count and $CD19^{+}$,$CD19^{+}CD38^{+}IgMl^{ow}$ and $CD19^{+}CD38^{+}CD27^{high}IgM^{high}$lymphocyte percentages increased,on the contrary,lymphocyte and NK cell percentage decreased.Except for the patient with the APECED mutation,our patients with underlying primary immune deficiency did not have a severe disease course during COVID 19 infection.

Disclosure: No.

Keywords: immun deficiency, B cell, COVID-19, pediatri, immunology

PD534

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN DURING COVID-19 PANDEMIC IN EGYPT: A SINGLE-CENTRE EXPERIENCE

POSTER DISPLAY 10: COVID-19

Ali Sobh[1,2], Mai Korkor[1], Doaa Mosa[3], Nada Khaled[4], Marwa Elnagdy[5], Mohammed El-Bayoumi[6]
[1]Mansoura University Faculty of Medicine, Pediatrics, Mansoura, Egypt, [2]Mansoura University Children's Hospital, Mansoura University Faculty of Medicine, Department of Pediatricspediatrics, Mansoura, Egypt, [3]Mansoura University Faculty of Medicine, Rheumatology And Rehabilitation, Mansoura, Egypt, [4]Manssoura University Faculty of Medicine, Clinical Pathology, Mansoura, Egypt, [5]Mansoura University Faculty of Medicine, Medical Biochemistry, Mansoura, Egypt, [6]Mansoura University Faculty of Medicine, Department of Pediatrics, Mansoura, Egypt

Background and Aims: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection may result in a life-threatening hyperinflammatory condition named multisystem inflammatory syndrome in children (MIS-C). We aimed to assess the demographics, clinical presentations, laboratory characteristics, treatment, and outcomes of patients with MIS-C at Mansoura University Children's Hospital; a tertial Children's hospital in Egypt.

Methods: We performed a retrospective study of patients with MIS-C admitted to Mansoura University children's Hospital in Egypt between August 2020 and August 2021. We studied and analyzed their demographic data, clinical manifestations, laboratory tests, treatment, and outcomes.

Results: A total of 29 children were studied with ages ranging from 2 to 9 years. Eighteen of them are male patients and 11 female patients. Recent SARS-COV-2 infection was identified in all of them (100%). Eight patients required Pediatrics Intensive Care Unit (PICU) admission, and 7 of them required mechanical ventilation. Lab investigations revealed high ESR, ferritin, and D-Dimer in all. Low hemoglobin (Hb), and thrombocytosis in 88% and 75% of them, respectively. Treatment with intravenous immunoglobulin was used in all patients in addition to steroids, acetylsalicylic acid, and/or Anti-IL6 in a selected group of patients. 5 patients died due to shock or severe multiorgan failure. Fifteen patients recovered completely and 9 patients recovered with sequelae like dilated coronaries, tachycardia, or myocardial dysfunction.

Conclusions: Children with MIS-C have variable clinical presentations. The long-term outcome is generally favorable. Cardiovascular manifestations resolved in the majority of the children during follow-up. It is essential to make patient-based decisions and a stepwise approach to the treatment of this life-threatening disease.

Disclosure: No.

Keywords: multisystem inflammatory syndrome in children, MIS-C, COVID-19, Egypt

PD535

SARS-COV-2 VACCINATION IN CVID ELICITS A ROBUST T CELL RESPONSE BUT FORMATION of B CELL MEMORY IS IMPAIRED DESPITE THE PRESENCE of CIRCULATING ANTIBODIES

POSTER DISPLAY 10: COVID-19

Sophie Steiner[1], Tatjana Schwarz[2,3], Victor Corman[2,3], Sandra Bauer[1], Carmen Scheibenbogen[1,4], Leif G Hanitsch[1]
[1]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Institute of Medical Immunology, Berlin, Germany, [2]Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, and German Centre for Infection Research (DZIF), associated partner, Institute of Virology, Charité, Berlin, Germany, [3]Universitätsmedizin Berlin, Berlin Institute of Health At Charité, Berlin, Germany, [4]Berlin Institute of Health at Charité, Universitätsmedizin Berlin, Bih Center For Regenerative Therapies (bcrt), Berlin, Germany

Background and Aims: Generation of SARS-CoV-2-specific T-cellular and humoral immunity was observed after COVID-19 vaccination in CVID patients. It is unknown, whether seroconversion in CVID patients could also result in the development of a functional B-cell memory. We therefore aimed to investigate T-cellular and humoral immune responses in CVID and HC as well as functional B-cell memory formation after COVID-19 vaccination in CVID patients with specific antibody response.

Methods: All 16 CVID patients had a documented impaired pneumococcal vaccine response and reduced switched memory B cells (MBC). CVID patients with (n=10) and without (n=6) SARS-CoV-2-specific IgG/IgA antibodies and 8 HC were examined for SARS-CoV-2-specific T cell immunity using flow cytometry. Formation of a functional B cell memory was assessed by SARS-CoV-2-ELISpot

Results: After vaccination, analyses of antigen specific T cells in CVID and HC revealed a significant and similar increase of activated CD4+CD154+CD137+ T cells as well as the generation of polyfunctional (IFNγ+TNFα+IL-2+) cytokine responses in response to stimulation with SARS-CoV-2 spike peptide pools. SARS-CoV-2 MBC ELISpot revealed that seroresponsive CVID patients were not able to generate a SARS-CoV-2 MBC recall response. Differentiation into antibody secreting cells after SAC stimulation was detectable in 7/10 CVID patients, but at lower levels than in HC.

Conclusions: CVID patients mounted a robust, memory-like T cellular immune response after SARS-CoV-2 vaccination irrespective of antibody response. Despite seroconversion in some CVID patients, formation of a functional B cell memory was impaired. Atypical antibody response might indicate short lived humoral immunity. Reasons for different antibody formation in CVID remain to be determined.

Disclosure: Dr. Victor M Corman is named together with Euroimmun on a patent application filed recently regarding detection of antibodies against SARS-CoV-2. The other authors have declared that no competing interests exist.

Keywords: Primary Immunodeficiency (PID), SARS-CoV-2 vaccination, B cell memory, T cell response, SARS-CoV-2 antibodies, Common Variable Immunodeficiency Disorder (CVID)

PD536

X-LINKED AGAMMAGLOBULINEMIA AND SARS-COV-2

POSTER DISPLAY 10: COVID-19

Maria Carrabba[1], Lucia Baselli[2], Giorgia Moschetti[3], Francesca Clemente[3], Alessandra Cattaneo[4], Laura Porretti[4], Claudia Ballerini[5], Rosa Dellepiane[2], Jens Geginat[3,6], Giovanna Fabio[1]
[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Dipartimento Di Medicina Interna, Milano, Italy, [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlnico, Pediatric Department, Milano, Italy, [3]Istituto Nazionale di Genetica Molecolare "Romeo ed Enrica Invernizzi, Lab, MILANO, Italy, [4]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Flow Cytometry Laboratory, Clinical Laboratory, MILANO, Italy, [5]Università degli Studi di Milano, Paediatric Department, Milano, Italy, [6]Università degli Studi di Milano, Dipartimento Di Scienze Mediche E Di Comunità, MILANO, Italy

Background and Aims: This study aims to report a monocentric experience on SARS-CoV-2 infection in X-linked agammaglobulinemia (XLA) due to genetic defects in Bruton's tyrosine kinase (BTK).

Methods: The 12 XLA patients enrolled are carriers of pathogenic mutations on BTK gene, atypical phenotype was confirmed with functional tests. Evaluation of humoral and T-cell response after infection and/or after administration of COVID-19 mRNA vaccine have been analysed.

Results: During the 2nd-wave infection, two paediatric patients were mild symptomatic and negativized in 2 weeks. Specific T-CD4+ response was absent. Two months after their primary cycle vaccination, they got again mild/asymptomatic infection during the fourth wave and recovered in 2 weeks without therapy. Two adults were hospitalised for COVID-19 during the 2nd-wave: the younger recovered 10 weeks later only after monoclonal Abs, he had poor T-CD4+ response; the older was admitted to ICU for 6 weeks and negativized after 10 weeks. This patient, who has an atypical phenotype, presented both humoral and good SARS-CoV-2-specific T-CD4+ response. During the 4th-wave infection (after two-doses anti-COVID vaccine), one 12-years-old and one 38-years-old got COVID-19. The child recovered one week after monoclonal Abs. The adult received monoclonal Abs+antivirals and four weeks later, another antiviral-course because he remained positive. The 6 XLA previously uninfected patients received three doses of COVID-19 mRNA-vaccine. All the patients had detectable IFN-gamma production confirming T-cell response. Three patients, with atypical phenotype, developed also humoral response.

Conclusions: Among adult XLA patients, persistent infection could be common and SARS-CoV-2 specific T-cell responses, when present, appear insufficient to achieve viral clearance.

Disclosure: No.

Keywords: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Bruton's tyrosine kinase (BTK), x-linked agammaglobulinemia (XLA), mRNA vaccine response, T-cell response, COVID-19

PD537

MEASUREMENT of SARS-COV-2 ABS IN PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA (XLA) RECEIVING IMMUNOGLOBULIN PRODUCTS

POSTER DISPLAY 10: COVID-19

Theodora Papastamatiou[1,2], Sofia Tantou[1], Evaggelia Zaimaki[1], Stavroula Mpatsikoura[1], Marianna Tzanoudaki[1], Manolis Liatsis[1]
[1]"Aghia Sophia" Children's Hospital, Dept. of Immunology & Histocompatibility, Athens, Greece, [2]Aglaia Kiriakou Hospital, 2nd Department of Pediatrics of The National And Kapodistrian University of Athens, ATHENS, Greece

Background and Aims: The possible protective effect against COVID-19, of circulating antibodies to other coronaviruses in immunoglobulin products remains unclear. This is an important consideration for people with X-linked agammaglobulinemia (XLA) as their health depends on treatment with immunoglobulin preparations that need to contain neutralizing antibodies against pathogens in the environment.

Methods: 10 unvaccinated for SARS-CoV-2 patients (aged 0-21y) with XLA who received immunoglobulin replacement therapy and with no history of Covid-19 infection were enrolled in this study. 10 healthy adults that received the BNT162b2 mRNA COVID-19 vaccine were also used as positive controls. The EliA SARS-CoV-2-Sp1 IgG (Thermo Fisher S1 IgG) assay was used for the measurement of SARS-CoV-2 (Covid-19) IgG antibodies.

Results: All patients (100%) with XLA receiving immunoglobulin replacement therapy showed no levels of anti-Covid-19 antibodies in their sera compared to the healthy vaccinated controls who showed high levels of CoV-2-Sp1 IgG antibodies.

Conclusions: The absence of CoV-2-Sp1 IgG antibodies are highly unlikely to offer any protection against Covid-19 in XLA patients receiving immunoglobulin products. Further research and clinical experience are necessary to fully elucidate these observations.

Disclosure: No.

Keywords: SARS-CoV-2 Abs, immunoglobulin products, IVIG, SCIG, x-linked agammaglobulinemia (XLA), XLA

PD538

DELAYED PRESENTATIONS of SEVERE COMBINED IMMUNODEFICIENCY DURING THE SARS-COV-2 PANDEMIC

POSTER DISPLAY 10: COVID-19

Levi Hoste[1,2], Giorgia Bucciol[3], Anniek Corveleyn[4], Stijn Cornelis[5], Victoria Bordon[6], Annick De Jaeger[7], Heidi Schaballie[8], Ellen Deolet[9], Jo Van Dorpe[9], Gregory Strubbe[10], Elizaveta Padalko[10], Inge Roukaerts[11], Lars Desmet[12], Leen Moens[3], Xavier Bossuyt[13], Filomeen Haerynck[1,2], Isabelle Meyts[14,15]
[1]Ghent University Hospital, Department of Internal Medicine And Pediatrics, Division of Pediatric Pulmonology, Infectious Diseases And Inborn Errors of Immunity, Ghent, Belgium, [2]Ghent University, Primary Immune Deficiency Research Laboratory, Department of Internal Diseases And Pediatrics, Centre For Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis And Research Centre, Gent, Belgium, [3]KU Leuven, Laboratory Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [4]University Hospitals Leuven, Center For Human Genetics, Leuven, Belgium, [5]KU Leuven, Faculty of Medicine, Leuven, Belgium, [6]Ghent University Hospital, Pediatric Hemato-oncology, Gent, Belgium, [7]Ghent University Hospital, Pediatric Intensive Care, Gent, Belgium, [8]Ghent University Hospital, Department of Internal Medicine And Pediatrics, Division of Pediatric Pulmonology, Infectious Diseases And Inborn Errors of Immunity, Gent, Belgium, [9]Ghent University Hospital, Department of Pathology, Gent, Belgium, [10]Ghent University Hospital, Laboratory of Medical Microbiology, Gent, Belgium, [11]Sciensano, Viral Diseases, Brussels, Belgium, [12]UZ Leuven, Pediatric Intensive Care, Leuven, Belgium, [13]KU Leuven, Clinical And Diagnostic Immunology, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium, [14]KU Leuven, Department of Immunology, Microbiology And Transplantation, Laboratory of Inborn Errors of Immunity, Leuven, Belgium, [15]KU Leuven, Laboratory of Inborn Errors of Immunity, Department of Microbiology, Immunology And Transplantation, Leuven, Belgium

Background and Aims: Severe combined immunodeficiency (SCID) is characterized by severe T lymphocyte dysfunction and variable B/NK cell abnormalities. With extreme susceptibility for infection, SCID usually evolves fatal in the first months in the absence of treatment.. For multiple infectious diseases, epidemiological dynamics were altered during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.
Methods: We describe two SCID patients with delayed onset of symptoms during the SARS-CoV-2 pandemic.
Results: P1, a boy, presents with first symptoms of respiratory tract infection at age of 14 months. P2, another boy, presented lower respiratory tract infection and gastroenteritis at 8 months. Previously, both patients had remained free from severe infections, failure-to-thrive or developmental delay. Daycare attendance was postponed because of lockdown measures. Absent thymic shadows prompted further investigations in both instances. Lymphopenia with a T-B+NK+ (P1) and T-B-NK+ (P2) phenotype was found. Pulmonary infection with vaccine-strain measles and parainfluenza (P1) and disseminated adenovirus infection (P2) was documented. Despite broad antimicrobial treatment (including ribavirin (P1) and cidofovir (P2)) respiratory disease progressed. Cardiogenic shock (P1) and hemophagocytic syndrome (P2) developed. Ultimately, multiple organ failure resulted in fatal outcome in both. Genetic testing revealed a homozygous c150_153del in IL7R (P1) and compound heterozygous c.442dupG and c.241C>T in DCLRE1C (P2).
Conclusions: We describe two patients with SCID, yet late presentation. Their exposure to infection could have been diminished because of reduced microbial transmission during the pandemic. Clinicians should be aware of delayed presentations of severe immune disorders during a global sanitary crisis. *the first and last two authors contributed equally.

Disclosure: No.

Keywords: SCID, COVID-19, SARS-CoV-2, Pandemic

PD539

IMMUNE RESPONSE AGAINST SARS-COV-2 INFECTION AND VACCINATION IN A CD8 ALPHA CHAIN-DEFICIENT WOMAN

POSTER DISPLAY 10: COVID-19

Daniel Arroyo Sánchez[1], Oscar Cabrera-Marante[2], Patricia Almendro-Vázquez[2], Edgar Rodríguez-Frías[2], Estela Paz-Artal[2], Daniel E. Pleguezuelo[2]
[1]Hospital 12 De Octubre, Immunology, Madrid, Spain, [2]University Hospital 12 de Octubre, Immunology, Madrid, Spain

Background and Aims: We report the clinical characteristics of COVID-19 together with the SARS-CoV-2-specific humoral and cellular response in a patient with lack of CD8+ T cells due to the rare Gly111Ser mutation in the CD8α chain.

Methods: Measurement of humoral response was done by detection of S1- and neutralizing antibodies. The cellular response was measured by S1-specific IFN-γ T-cell response by Fluorospot.

Results: In 2020 the patient received the two-doses mRNA-1273 vaccine. In December 2021, before receiving the third dose, she experienced myalgias, arthralgias, odynophagia, dysphonia, fever, cough and dyspnea, and the PCR resulted positive. She experienced thorax pain without radiological lung lesions and a mild infection course no supplementary oxygen nor hospitalization required). After treatment with corticoids, AINEs and amoxicillin-clavulanic acid, she fully recovered. A blood sample was collected 15 days after the disease resolution and before the 3rd vaccination dose. The patient was positive for anti-S, anti-N and neutralizing antibodies, and for the cellular response (IFNγ+ T cells specific for S1, N and M). The reactivity against N and M demonstrated immune response to natural infection. Due to the lack of pre-infection sample, we ignore if the vaccination or the natural infection was the origin of the anti-S response.

Conclusions: The lack of CD8 co-receptor did not seem to impair the recognition of SARS-CoV-2 antigens and the mounting of an optimal immune response. These results together with the mild COVID-19 suggest that CD8-defective lymphocytes largely maintain their cytotoxic capacity and are capable of coping with COVID-19

Disclosure: No.

Keyword: CD8+ T-Lymphocytes, CD8 Deficiency, Immunity Cellular, COVID-19; Immunity, Cellular; Vaccination

PD540

RECURRENT SARS-COV-2 INFECTION IN A CHILD WITH PREDOMINANTLY ANTIBODY DEFICIENCY; CASE REPORT

POSTER DISPLAY 10: COVID-19

Öner Özdemir, Ümmügülsüm Dikici
Sakarya University Medical Faculty, Pediatric Allergy And Immunology, Sakarya, Turkey

Background and Aims: In many studies, it has been reported that the SARS-CoV-2 PCR test became positive again in recovered covid-19 patients. The reasons for recurrent positivity are controversial. We present our immunodeficient patient who was found to be SARS-CoV-2 PCR positivity twice, 10 months apart.

Methods: Case presentation: A 4-year-old girl, who had been receiving intravenous immunoglobulin (IVIG) therapy since 19 months of age due to severe transient hypogammaglobulinemia in an infant, had 2 SARS-CoV-2 infections with an interval of 10 months. She had no fever at her first infection. She was describing a runny nose, cough, and headache.

Results: There was no lymphopenia or neutropenia. The C-reactive protein (CRP) value was 10 (upper limit: 5). An intermediate dose of 1 gr/kg IVIG was given to the patient whose computed thorax tomography was reported as normal. The patient recovered after 5 days. In her second/recurrent infection, she had a fever. Cough and runny nose did not describe. She had neutropenia (1.560/mm3) and lymphopenia (780/mm3). CRP value was <3.3. Intermediate IVIG at the dose of 400 mg /kg was given to the patient. Her fever did not recur after 48 hours. The patient recovered in 3 days.

Conclusions: Several possibilities recovered COVID-19 patients will retest positive for SARS-CoV-2. First, the positive signal of viral RNA may be from "dead" viruses / viral gene fragments without active replications. Secondly, in an immunodeficient patient, viral clearance may vary from patient to patient. Comorbidities also delay virus clearance.Viral clearance could not be achieved in our patient due to immunodeficiency.

Disclosure: No.

Keyword: SARS-CoV-2, child, antibody deficiency, immunodeficiency

PD541

SEVERE COURSE of SARS-COV-2 PNEUMONIA IN A PATIENT WITH PATHOLOGICAL HETEROZYGOUS VARIANT IN RAG1 GENE

POSTER DISPLAY 10: COVID-19

Milica Zecevic[1], Aleksandra Minic[1], Gordana Petrovic[2], Stefan Kotlajic[2], Predrag Minic[3,4], Srdjan Pasic[1,4]
[1]Institute for mother and child health care of Serbia "dr Vukan Cupic", Clinical Immunology And Allergy Department, Belgrade, Serbia and Montenegro, [2]Institute for mother and child health care of Serbia "dr Vukan Cupic", Clinical Immunology And Allergy Department, Belgrade, Serbia, [3]Institute for mother and child health care of Serbia "dr Vukan Cupic", Pulmology Department, Belgrade, Serbia and Montenegro, [4]University of Belgrade, Medical Faculty, Belgrade, Serbia

Background and Aims: RAG 1 mutations have recently been detected in patients with delayed-onset disease exibiting granulomas and/or autoimmune manifestations. In this group, early-onset severe infections are infrequent, but late-onset immune dysregulation and infections cause significant morbidity. We aim to present a 17 year old boy with compound heterozygous variant c.256_257delAA (NM_000448.2) in RAG1 gene with autoimmune thyroiditis, vitiligo, splenomegalia with cytopenias, IgG_4 subclass deficiency, chronic supurative lung disease and severe SARS-CoV-2 pneumonia.

Methods: We retrospectively analysed medical documentation of our patient.

Results: A 17 year old boy was diagnosed with chronic supurative lung disease and IgG_4 subclass deficiency. He was previously treated from the age of 9 beacause of his vitiligo and autoimmune hypothyreosis. He had severe splenomegalia with autoimune cytopenias, so he underwent splenectomy. Clinical exzome sequencing revealed that he has pathogenic heterozygous variant c.256_257delAA (NM_000448.2) in RAG 1 gene. After splenectomy his blood counts normalised, but for a short period of time. He developed CMV reactivation with oligoclonal expansion of TCRγδ and autoimmune neutropenia which has been treated with steroids. He also developed severe SARS-CoV-2 pneumonia and he has been succesfuly treted with tocilizumab and steroids.

Conclusions: Pateints in inborn errors of immunity were usualy reported to have mild COVID 19 course, but over all higher fatality rate than general population. The severity of SARS-CoV-2 infection seems to be related to type of comorbidities especially bronchiectasies. We also report a distinct form of RAG1 deficiency with autoimmune neutropenia upon CMV reactivaion and oligoclonal expansion of TCRγδ+ T cells.

Disclosure: No.

Keywords: RAG 1 deficiency, SARS CoV-2 pneumonia, Autoimmunity, tocilizumab

PD542

CELLULAR AND HUMORAL IMMUNOGENICITY of S1 NEOANTIGEN of SARS-COV-2 VACCINES IN PATIENTS WITH SYSTEMIC AUTOIMMUNE RHEUMATIC DISEASES

POSTER DISPLAY 10: COVID-19

Kauzar Mohamed Mohamed[1], Inés Pérez San Cristobal[2], Cristina Martínez Prada[2], Dalifer Freites[2], Maria Paula Álvarez[2], Teresa Mulero[2], Maria Rodero[2], Cecilia Bravo[2], Silvia Sánchez-Ramón[3], Gloria Candelas[2]
[1]Hospital Clinico San Carlos, Department of Immunology, Iml And Idissc, Madrid, Spain, [2]Hospital Clinico San Carlos, Ugc of Rheumatology, Hospital Clínico San Carlos, Idissc, Madrid, Spain, [3]San Carlos Clinical Hospital, Clinical Immunology Department, Madrid, Spain

Background and Aims: Data on cellular and humoral immunogenicity triggered by SARS-CoV-2 vaccines in patients with systemic autoimmune rheumatic diseases (SAIRD) are limited. In this study, we evaluated specific cellular and humoral responses in patients treated with different biological therapies after the third dose of SARS-CoV-2 vaccine.

Methods: We studied 79 patients with SAIRD for specific anti-SARS-CoV-2 interferon-gamma (IFN-γ) production between 8-12 weeks after the third dose of the SARS-CoV-2 vaccine. In addition, anti-Spike IgG antibody titers were measured.

Results: Seventy-nine SAIRD patients (51 women, 28men; mean age 57±11.3), were studied. Post-vaccine results displayed positive T cellular immune responses in 68 out of 79 (86.1%) SAIRD patients with a median anti-SARS-CoV-2 IFN-γ titre of 1,606.85 mUI/ml. Seven (8.9%) SAIRD patients showed negative SARS-CoV-2 IFN-γ levels, whereas 4 (5%) present borderline titres. Anti-Spike antibodies were detectable in all SAIRD patients.

Conclusions: Our preliminary data show that the majority of SAIRD patients were able to mount an adequate specific cellular response after SARS-CoV-2 vaccination, emphasizing the relevance of vaccination in this group. Detectable specific antibody responses anti-SARS-CoV-2 vaccination was attained in all SAIRD patients. Our data might support the relevance of these immunological studies to personalize preventive and treatment decisions.

Disclosure: No.

Keywords: SARS-CoV-2 cellular response, SARS-CoV-2 humoral response, SARS-CoV-2 vaccines, SAIRD patients

PD543

STRONG ANTIBODY AND T-CELL RESPONSES AGAINST SARS-COV-2 IN A PATIENT WITH CYTOTOXIC T-LYMPHOCYTE ANTIGEN-4 (CTLA-4) INSUFFICIENCY DUE TO THE NOVEL MUTATION P.GLY142ASP IN CTLA-4.

POSTER DISPLAY 10: COVID-19

Mercedes Díaz-Luna[1], Trinidad Alba[1,2], Luis Allende[3], Carmen Rodriguez Sainz[1], Hector Balastegui[1], Francisco Javier Díaz[4], Santiago Osorio[5], Ignacio Marín[6], Javier Menárguez[4], Eduardo Fernandez Cruz[1], Juana Gil Herrera[1]
[1]Hospital General Universitario Gregorio Marañón, Immunology Department, Madrid, Spain, [2]Hospital General Universitario Gregorio Marañón, Immunology, Madrid, Spain, [3]Hospital Universitario 12 de Octubre, Immunology Department, Madrid, Spain, [4]Hospital General Universitario Gregorio Marañón, Pathological Anatomy Department, Madrid, Spain, [5]Hospital General Universitario Gregorio Marañón, Hematology Department, Madrid, Spain, [6]Hospital General Universitario Gregorio Marañón, Digestive Department, Madrid, Spain

Background and Aims: Autosomal dominant mutations in CTLA-4 lead to lymphoproliferation, autoimmunity and immunodeficiency. We aim to describe a patient with an inborn error of immunity (IEI) and the immune responses to SARS-CoV-2 during her follow-up.

Methods: A whole exome sequencing was carried out. CD25/CD134 coexpression was analysed on memory $CD4^+$T-cells by 6-colour-flow cytometry (BD Biosciences).

Results: A 16-year-old female was first admitted with severe thrombopenia. Next admission was due to thrombocytopenic purpura and polyadenopathy. During her third admission (fever, polyadenopathy, thrombopenia, lymphopenia, splenomegaly, leishmaniasis and EBV reactivation), CT disclosed pulmonary infiltrates and biopsy showed granulomatous-lymphocytic interstitial lung disease (GLILD). As for immunosuppression, she had just received intermitent steroid therapy. Weakly positive ASMA and anti-tiroglobulin autoantibodies were detected. Immunoglobulins, lymphocyte percentages, memory and thymic output and functional HLH-oriented studies were normal. A new, “de novo” heterozygous missense mutation c.425G>A (p.Gly142Asp) in CTLA-4 was identified, affecting a conserved Ig-V domain of the protein and probably pathogenic according to our in silico results (PolyPhen). She suffered a mild form of COVID-19 in 2020, showing IgG anti-SARS-CoV-2-Spike (694.0 UA/mL) 6 months later. Following two SARS-CoV-2 BNT162b2 vaccinations, specific IgG >40.000 UA/mL and anti-SARS-CoV-2-Spike T-CD4+ memory cells responses were detected.

Conclusions: We report a young patient with a new heterozygous mutation in CTLA-4 associating GLILD. The close mutation p.Gly146Arg has been recently described in IEI patients with immune dysregulation. Our patient was able to generate robust specific T-cell and IgG responses against SARS-CoV-2, while other insufficient CTLA-4 patients showed suboptimal antibody responses to SARS-CoV-2, probably due to stronger immunosuppressor therapies.

Disclosure: No.

Keywords: CTLA-4, SARS-CoV-2, GLILD, CD4 T-cell memory, Antibody response

PD544

IMPACT of DNA REPAIR DEFECTS ON SARS-COV-2 INFECTION IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY

POSTER DISPLAY 10: COVID-19

Yating Wang, Hassan Abolhassani, Qiang Pan-Hammarström, Lennart Hammarström
Karolinska Institutet, Bionut, HUDDINGE, Sweden

Background and Aims: Clinical information on SARS-CoV-2 infection in patients with inborn error of immunity (IEI) during the current COVID-19 pandemic is still limited. Proper DNA repair machinery is required for the development of adaptive immunity, which provides specific and long-term protection against SARS-CoV-2.

Methods: Although IEIs show a 1.23-higher incidence of SARS-CoV-2-infection, the infection incidence rate can be extremely higher than normal populations if they expose to the same condition as the normal population. We evaluate the impact of SARS-CoV-2-infections on IEI patients with DNA repair disorders and summarize susceptibility risk factors, pathogenic mechanisms, clinical manifestations and therapeutic strategies of COVID-19 in this special patient population.

Results: Among the 54 SARS-CoV-2 infected patients with a DNA-repair disorder(48%female) reported thus far, 91% of patients had syndromic CIDs, and 9% of patients had non-syndromic CIDs. The median age at the time of SARS-CoV-2 infection was 9.3/years. To date, 44 patients had Ataxia telangiectasia(81%); 3-patients had RAG deficiency(5%); 1-patient had DCLRE1C/deficiency(2%); 1 patient had DNA-PKcs deficiency (2%); 1 patient had NBS(1%); 3-patients had ICF syndrome(6%) and 1-patient had T-B- severe CID without a genetic diagnose (2%). The overall mortality rate was 9.2%(5/54) among these patients which is similar to the mortality rate in the previous 2 IEIs cohorts 8.1% (49/604) and 9.5% (9/94). of note, a huge difference in the mortality rate exists between DNA damage subtypes, being 2.27%, 33.33%, and 66.7% in the ATM, RAG and DNMT3B patient groups.

Conclusions: DNA repair disorders have a positive association with intensified innate immune response and a negative association with adaptive immunity underlying SARS-CoV-2 infection.

Disclosure: No.

Keywords: Primary Immunodeficiency (PID), COVID-19, DNA repair mechanism, inborn errors of immunity (IEI)

PD545

NEUTRALIZING SARS-COV-2 ANTIBODIES IN COMMERCIAL IMMUNOGLOBULIN PRODUCTS GIVE PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA LIMITED PASSIVE IMMUNITY TO THE OMICRON VARIANT

POSTER DISPLAY 10: COVID-19

Hannes Lindahl[1], Jonas Klingström[2], Rui Da Silva Rodrigues[1], Wanda Christ[2], Puran Chen[2], Hans-Gustaf Ljunggren[2], Marcus Buggert[2], Soo Aleman[2], Carl Inge Edvard Smith[3], Peter Bergman[4]
[1]Karolinska University Hospital, Clinical Immunology, Huddinge, Sweden, [2]Karolinska Institutet, Medicine Huddinge, Huddinge, Sweden, [3]Karolinska Institutet, Department of Laboratory Medicine, Biomolecular And Cellular Medicine,, Stockholm, Sweden, [4]Karolinska Institutet, Department of Clinical Microbiology, Huddinge, Stockholm, Sweden

Background and Aims: Immunodeficient individuals often rely on donor-derived immunoglobulin (Ig) replacement therapy (IGRT) to prevent infections. The passive immunity obtained by IGRT is limited and reflects the state of immunity in the plasma donor population at the time of donation. The objective of the current study was to describe how the potential of passive immunity to SARS-CoV-2 in commercial off-the-shelf Ig products used for IGRT has evolved during the pandemic.

Methods: Samples were collected from consecutive Ig batches (n=60) from three Ig producers from the start of the SARS-CoV-2 pandemic until January 2022. SARS-CoV-2 antibody concentrations and neutralizing capacity were assessed in all samples.

Results: In vivo relevance was assessed by sampling patients with XLA (n=4), lacking endogenous immunoglobulin synthesis and on continuous IGRT, for plasma SARS-CoV-2 antibody concentration. SARS-CoV-2 antibody concentrations in commercial Ig products increased over time but remained inconsistently present. Moreover, Ig batches with high neutralizing capacity towards the Wuhan-strain of SARS-CoV-2 had 32-fold lower activity against the Omicron variant. Despite increasing SARS-CoV-2 antibody concentrations in commercial Ig products, four XLA patients on IGRT had relatively low plasma concentrations of SARS-CoV-2 antibodies with no potential to neutralize the Omicron variant in vitro. Notably, three out the four XLA-patients had symptomatic COVID-19 during the Omicron wave.

Conclusions: Two years into the pandemic the amounts of antibodies to SARS-CoV-2 varies considerably among commercial Ig batches obtained from three commercial producers. Importantly, in batches with high concentrations of antibodies directed against the original virus strain, protective passive immunity to the Omicron variant appears to be insufficient.

Disclosure: No.

Keywords: primary immunodeficiency, immunoglobulin replacement therapy, SARS-CoV-2, Omicon

PD546

ANTI-SARS-COV-2 S ANTIBODIES IN HEALTHY DONOR PLASMA POOLS AND IGG MEDICINAL PRODUCTS: FOLLOW-UP SINCE MARCH 2020

POSTER DISPLAY 10: COVID-19

Carolina Romero, Jose Maria Diez, Rodrigo Gajardo
Grifols, Immunotherapies Unit, Bioscience R&d, Scientific Innovation Office, Barcelona, Spain

Background and Aims: SARS-CoV-2 vaccines have demonstrated reduced immunogenicity in patients with antibody deficiencies. It is therefore important to investigate the levels of anti-SARS-CoV-2 antibodies in the IgG products they are prophylactically treated with. . Here, we show more than 2 years-evolution of anti-S (Spike) antibodies against SARS-CoV-2 virus in plasma pools collected among Europe and U.S. and IgG medicinal products, and their neutralization capacity to wild virus and variants of concern (VOC).

Methods: Antibodies to SARS-CoV-2 S protein were determined by ELISA in plasma pools from Europe and U.S. and final products (IgG). Neutralization assays were performed to determine the capacity to neutralize VOC using pseudovirus expressing S protein.

Results: • Anti-SARS-CoV-2 S antibodies showed elevated titers since July‘20 in plasma from Europe and U.S. with dramatically high titers regardless of geographic origin, corresponding to the evolution of the pandemic and the vaccines campaigns worldwide. • Titers of anti-S antibodies in IgG medicinal products showed similar evolution over time as those seen in pooled plasma from March‘20 until now. IgG products showed high SARS-CoV-2 neutralizing capacity including latest VOC.

Conclusions: Anti-SARS-CoV-2 S antibodies titers in pooled plasma and IgG medicinal products reflect the exposure to SARS-CoV-2 virus and the immunological status of the general population including vaccination campaigns worldwide. Current IgG medicinal products contain high anti-SARS-CoV-2 S antibodies with high neutralization capacity against previous and latest VOC including Omicron. Since these IgG are indicated for immunodeficient patients, a continued monitoring of the evolution of these antibodies deserves great interest.

Disclosure: The authors of the study are full-time employees of Grifols, a manufacturer of intravenous immunoglobulins.

Keywords: Ig, SARS-CoV-2, PID, SID, anti-Spike antibodies, neutralization

PD547

SAFETY AND EFFICACY of THE MRNA BNT162B2 VACCINE AGAINST SARS-COV-2 IN FIVE GROUPS of IMMUNOCOMPROMISED PATIENTS AND HEALTHY CONTROLS IN A PROSPECTIVE OPEN-LABEL CLINICAL TRIAL

POSTER DISPLAY 10: COVID-19

Peter Bergman[1], Ola Blennow[2], Lotta Hansson[3], Stephan Mielke[4], Piotr Nowak[2], Puran Chen[5], Gunnar Söderdahl[6], Anders Österborg[3], Carl Inge Edvard Smith[7], David Wullimann[5], Jan Vesterbacka[2], Gustaf Lindgren[3], Lisa Blixt[3], Gustav Friman[6], Emilie Wahren Borgström[8], Anna Nordlander[2], Angelica Gomez[5], Mira Akber[5], Davide Valentini[3], Anna Carin Norlin[9], Anders Thalme[2], Gordana Bogdanovic[10], Sandra Muschiol[10], Peter Nilsson[11], Sophia Hober[11], Karin Loré[12], Margaret Chen[13], Marcus Buggert[5], Hans-Gustaf Ljunggren[5], Per Ljungman[3], Soo Aleman[2]
[1]Karolinska Institutet, Department of Clinical Microbiology, Huddinge, Stockholm, Sweden, [2]Karolinska University Hospital, Infectious Diseases, Huddinge, Sweden, [3]Karolinska University Hospital, Haematology, Stockholm, Sweden, [4]Karolinska University Hospital, Laboratory Medicine, Huddinge, Sweden, [5]Karolinska Institutet, Medicine Huddinge, Huddinge, Sweden, [6]Karolinska University Hospital, Transplantation Surgery, Huddinge, Sweden, [7]Karolinska Institutet, Department of Laboratory Medicine, Biomolecular And Cellular Medicine,, Stockholm, Sweden, [8]Karolinska Institutet, Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden., Huddinge, Sweden, [9]Karolinska Institutet, Department of Clinical Immunology, Huddinge, Sweden, [10]Karolinska University Hospital, Clinical Microbiology, Stockholm, Sweden, [11]Royal Institute of Technology, Protein Science, Stockholm, Sweden, [12]Karolinska Institutet, Medicine Solna, Stockholm, Sweden, [13]Karolinska Institutet, Dental Medicine, Huddinge, Sweden

Background and Aims: Patients with immunocompromised disorders have mainly been excluded from clinical trials of vaccination against COVID-19. Thus, the aim of this prospective clinical trial was to investigate safety and efficacy of BNT162b2 mRNA vaccination in five selected groups of immunocompromised patients and healthy controls.

Methods: 539 study subjects (449 patients and 90 controls) were included. The patients had either primary (n=90), or secondary immunodeficiency disorders due to human immunodeficiency virus infection (n=90), allogeneic hematopoietic stem cell transplantation/CAR T cell therapy (n=90), solid organ transplantation (SOT) (n=89), or chronic lymphocytic leukemia (CLL) (n=90). The primary endpoint was seroconversion rate two weeks after the second dose. The secondary endpoints were safety and documented SARS-CoV-2 infection.

Results: Adverse events were generally mild, but one case of fatal suspected unexpected serious adverse reaction occurred. 72.2% of the immunocompromised patients seroconverted compared to 100% of the controls (p=0.004). Lowest seroconversion rates were found in the SOT (43.4%) and CLL (63.3%) patient groups with observed negative impact of treatment with mycophenolate mofetil and ibrutinib, respectively.

Conclusions: The results showed that the mRNA BNT162b2 vaccine was safe in immunocompromised patients. Rate of seroconversion was substantially lower than in healthy controls, with a wide range of rates and antibody titres among predefined patient groups and subgroups. This clinical trial highlights the need for additional vaccine doses in certain immunocompromised patient groups to improve immunity.

Disclosure: No.

Keywords: HIV, Covid-19 mRNA vaccination, primary immunodeficiency, Chronic lymphocytic leukemia, Solid organ transplantation, human stem cell transplantation

PD548

SARS-COV-2 BOOSTER VACCINATION IN PATIENTS WITH COMMON VARIABLE IMMUNE DEFICIENCY: USEFULL OR USELESS?

POSTER DISPLAY 10: COVID-19

Leane Van Leeuwen[1], Corine Geurtsvankessel[1], Pauline Ellerbroek[2], Godelieve De Bree[3], Judith Potjewijd[4], Abraham Rutgers[5], Hetty Jolink[6], Frank Van De Veerdonk[7], Marit Van Gils[8], Rory De Vries[1], Virgil Dalm[9]
[1]Erasmus University Medical Center, Viroscience, Rotterdam, Netherlands, [2]UMC Utrecht, Department of Internal Medicine, Utrecht, Netherlands, [3]Amsterdam University Medical Center, Internal Medicine, Amsterdam, Netherlands, [4]Maastricht University Medical Center, Nephrology And Clinical Immunology, Maastricht, Netherlands, [5]UMC Groningen, Department of Rheumatology And Clinical Immunology, Groningen, Netherlands, [6]Department of Infectious Diseases, Leiden University Medical Center, Leiden, Netherlands, [7]Radboud University Medical Center, Internal Medicine, Radboud Center For Infectious Diseases (rci), Nijmegen, Netherlands, [8]Amsterdam UMC, Department of Medical Microbiology And Infection Prevention, Amsterdam Institute For Infection And Immunity, Amsterdam, Netherlands, [9]Erasmus MC University Medical Center, Department of Internal Medicine, Division of Allergy & Clinical Immunology And Department of Immunology, Rotterdam, Netherlands

Background and Aims: Effective protection against COVID-19 is of great importance in patients with common variable immunodeficiency (CVID). In a Dutch multicenter study 81% of CVID patients showed seroconversion after two mRNA-1273 COVID-19 vaccines. Anti-Spike(S) binding-antibody (IgG) titers were however significantly lower than in controls (van Leeuwen, et al. PMID: 35421449). Additional vaccination may be beneficial in CVID patients.

Methods: According to Dutch COVID-19 vaccination guidelines, CVID patients on immunosuppressive drugs were eligible for a third (mRNA) vaccination. We assessed immunogenicity of a third dose of an mRNA COVID-19 vaccine in 24 CVID patients. Full S-protein-specific binding IgG-antibody levels were assessed 28 days and 6 months after second vaccination and 28 days after third vaccination (which was given 1-4 weeks after the measurement at 6 months).

Results: Twenty-four patients with CVID were included. In 12 patients anti-S antibodies were detectable 28 days after two vaccinations with a mean geometric mean titer (GMT) of 424.0 BAU/ml (controls 3489 BAU/ml). Six months after vaccination GMT had declined to 77.1 BAU/ml (controls 693 BAU/ml). Eighteen days after third vaccination, the GMT increased to 212.2 BAU/ml. Twelve patients did not show seroconversion upon 2 vaccinations. None of these patients showed seroconversions after third vaccination.

Conclusions: Third vaccination may be useful in CVID patients to boost the already acquired immunity. However, in CVID patients that did not respond to two mRNA-1273 COVID-19 vaccines, a third vaccination also did not mount an antibody response. Further in-depth analysis may further explain the differences in CVID patients, and may warrant personalized vaccination regimens.

Disclosure: No.

Keywords: CVID, immunosuppressive drugs, COVID-19 vaccination, IgG antibodies

PD549

DYNAMICS of ANTI-SARS-COV-2 NUCLEOPROTEIN ANTIBODIES IN IGG MEDICINAL PRODUCTS AS A DIRECT REFLECTION of VIRUS EXPOSURE of THE DONOR POPULATION: FOLLOW-UP SINCE MARCH 2020

POSTER DISPLAY 10: COVID-19

Carolina Romero, Jose Maria Diez, Rodrigo Gajardo
Grifols, Immunotherapies Unit, Bioscience R&d, Scientific Innovation Office, Barcelona, Spain

Background and Aims: Patients with primary (PID) or secondary immunodeficiencies (SID) receive Immunoglobulin (Ig) as replacement therapy to prevent infections, since PID/SID patients have limited vaccine response capacity they could experience a high risk of severe COVID-19 disease. Here, we show more than 2 years-evolution of anti-N (Nucleocapsid) antibodies against SARS-CoV-2 virus in IgG medicinal products from plasma collected among Europe and USA.

Methods: Batches of IVIG medicinal products from pooled plasma collected among Europe (Spain, Italy, Germany, Czech Republic, Slovakia, Hungary) and USA have been analyzed by ELISA for anti N and S IgG.

Results: Anti-SARS-CoV-2 N antibodies showed elevated titers in IgG final products which fluctuate in a wavy state depending on the evolution of the pandemic, as a reflection of direct virus exposure and not to SARS-CoV-2 vaccines. These N antibodies were also evidenced in pre-pandemic IgG products at low level, presumably due to cross-reactions with other coronaviruses. N antibody titers in IgG products increase as a reflection of the amount and time/phase of COVID-19 infection. The current S/N anti SARS-CoV-2 protein ratio clearly reflects the vaccine effects within the population in each country in front of its COVID-19 state.

Conclusions: Anti-SARS-CoV-2 N titers in IgG medicinal products reflect wild virus exposure and the humoral immunological status of the population. Current IgG medicinal products contain anti-SARS-CoV-2 N antibodies which titers vary depending on the viral exposure and the state/phase of the pandemic worldwide. Continuous monitoring of anti-N antibodies would be beneficial for PID/SID patients and their future treatments.

Disclosure: The authors of the study are full-time employees of Grifols, a manufacturer of intravenous immunoglobulins

Keywords: SID, Anti-Nucleoprotein antibodies, anti-Spike antibodies, IgG, SARS-CoV-2, PID

PD550

T CELL RESPONSE TO SARS-COV-2 IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY AND SELECTIVE IGA DEFICIENCY

POSTER DISPLAY 10: COVID-19

Zane Lucane[1], Baiba Slisere[2], Lota Ozola[3], Natalija Gerula[4], Inta Jaunalksne[4], Dagnija Straupmane[2], Natalja Kurjane[1,4]
[1]Riga Stradins University, Department of Biology And Microbiology, Riga, Latvia, [2]Pauls Stradins Clinical University Hospital, Joint Laboratory, Riga, Latvia, [3]Children's Clinical University Hospital, Department of Pulmonology And Allergology, Riga, Latvia, [4]Pauls Stradins Clinical University Hospital, Outpatient Department, Riga, Latvia

Background and Aims: Patients with primary antibody deficiency (PAD) are at increased risk of severe SARS-CoV-2 infection (Zhu et al., 2020). However, immunogenicity to vaccination could be impaired in these patients (Hagin et al., 2021). Here we describe T cell response to SARS-CoV-2 structural proteins in patients with common variable immunodeficiency (CVID) and selective IgA deficiency.

Methods: WHO clinical progression scale was used to evaluate the severity of Sars-CoV-2 infection. T cell response to Sars-CoV-2 structural proteins was evaluated via the QuantiFERON SARS-CoV-2 assay (no.626715, Qiagen, USA), and antibody response - using Anti-SARS-CoV-2 ELISA (no.2606-9601G, EUROIMMUN, Germany).

Results: In total, 19 patients were included, with 73% being female (median age - 42 (IQR:23) years). Nine patients were diagnosed with CVID and ten patients - with selective IgA deficiency. Seventeen (89%) patients were fully vaccinated, with the median time after vaccination - 151 (IQR:102) days. All vaccinated patients developed a specific T cell response to SARS-CoV-2 structural proteins. We found individual differences in terms of INF-ɣ release by Ag1 ranging from 0.02 IU/mL to 3.50 IU/mL (median 0.46, IQR:0.9), and by Ag2 ranging from 0.23 to over maximal detection (median 0.64, IQR:1.3). T cell response was present in only one of two unvaccinated patients, who had had SARS-CoV-2 infection. No significant difference was identified between the time after vaccination/Sars-Cov-2 infection and T cell response, nor between the WHO scale and T cell response.

Conclusions: In our study all vaccinated patients with PAD were able to develop vaccine-specific T cell response that was detectable several months after vaccination.

Disclosure: Latvian Council of Science project grant Nr. lzp-2020/1–0269.

Keywords: SARS-CoV-2, T cell response, Primary Antibody Deficiency, Common variable immunodeficiency, Selective IgA deficiency

PD551

DECREASED ANTIBODY AVIDITY IN CVID IGG RESPONDERS FOLLOWING A BOOSTER VACCINATION WITH BNT162B2 SARS-COV2 MRNA VACCINE

POSTER DISPLAY 10: COVID-19

Kai Sauerwein[1,2,3], Christoph Geier[3,4,5], Roman Stemberger[3], Hüseyin Akyaman[3], Peter Illes[6], Michael Fischer[1,7], Martha Eibl[2,3], Jolan Walter[8,9,10], Hermann Wolf[3,11]
[1]Danube University Krems, Center of Experimental Medicine, Krems an der Donau, Austria, [2]Biomedizinische Forschung & Bio-Produkte AG, Reserarch Department, Vienna, Austria, [3]Immunology Outpatient Clinic, Research Department, Vienna, Austria, [4]University Medical Center Freiburg, Center For Chronic Immunodeficiency (cci), Freiburg, Germany, [5]University Medical Center Freiburg, Department of Rheumatology And Clinical Immunology, Freiburg, Germany, [6]USF Health, Department of Pediatrics, Tampa, United States of America, [7]Medical University of Vienna, Clinic For Blood Group Serology And Transfusion Medicine, Vienna, Austria, [8]Morsani College of Medicine, University of South Florida, Division of Allergy And Immunology, Department of Pediatrics, Tampa, United States of America, [9]Johns Hopkins All Children's Hospital, St. Petersburg, Division of Allergy/immunology, Department of Pediatrics, St.Petersburg, United States of America, [10]Massachusetts General Hospital for Children, Division of Allergy And Immunology, Boston, United States of America, [11]Sigmund Freud Private University, Medical School, Vienna, Austria

Background and Aims: While previous studies described the production of IgG-antibodies in a subgroup of CVID-patients following mRNA-vaccinations with comirnaty, the quality of these antibodies in terms of binding avidity has not been studied. In this study IgG-antibody titers and avidity were analysed after a third vaccination with bnt162b2 SARS-CoV2 mRNA-vaccine.

Methods: Antibody concentration was analysed by ELISA in CVID-patients responding to the primary vaccination (n=10) and healthy controls (n=39). The binding-avidity of anti-spike antibodies as a measure of antibody quality was investigated using biolayer interferometry in combination with biotin-labelled receptor-binding-domain (RBD) of SARS-CoV2 spike-protein and streptavidin-labelled sensors. Serum-samples were collected at a median of 41 days after vaccination with the bnt167b2 COVID-19 vaccine. Patients and controls gave their informed consent to measure vaccination responses.

Results: A third vaccination led to a significant increase in IgG-antibody titer in healthy controls (Median/IQR [RE/ml]: before: 34.80/21.98; after: 854.5/444.98, n=8) and antibody-avidity was significantly higher compared to serum-samples tested after the second vaccination. In contrast, in CVID-patients antibody-avidity was comparable after the second and third vaccination (Median/IQR [s]: 2nd: 248.76/143.03, n=15; 3rd: 217.00/68.75 , n=8). After the third vaccination both IgG-antibody titers and antibody-avidity were lower in CVID-patients as compared to healthy controls (Median/IQR: HC IgG [RE/ml]: 993 .7/981.60, n=39; CVID IgG: 391.65/458.35, n=10, p<0.0001; HC-Avidity [s]: 306.75/170.90, n=39; CVID-Avidity: 217.00/68.75, n=8, p=0.0062).

Conclusions: In summary, these results show that in CVID patients responding to COVID-19 vaccination spike-specific antibody production after booster-immunization is characterized by decreased IgG-titers and antibody-avidity.

Disclosure: Authors KMTS and MME were employed by the company Biomedizinische Forschung & Bio-Produkte AG that had no role in the design of this study or during its execution, analyses, interpretation of the data and decision to submit the present manuscript. The rem

Keywords: SARS-CoV2, CVID, Antibody Avidity, mRNA Vaccination

PD552

IMPACT of PHYSICAL DISTANCING MEASURES DUE TO THE SARS-COV-2 PANDEMIC ON HUMORAL IMMUNITY IN CHILDREN

POSTER DISPLAY 10: COVID-19

Coralie Mallebranche[1,2], Céline Beauvillain[1,3], Tiffanie Bousser[4], Vannina Giacobbi-Milet[5], Emeline Vinatier[1,3], Julien Lejeune[6], Charline Miot[1,2,3], Isabelle Pellier[1,2]
[1]Univ Angers, Université de Nantes, Inserm, Cnrs, Crci2na, Sfr Icat, ANGERS, France, [2]CHU Angers, Pediatric Immuno-hemato-oncology Unit, Angers, France, [3]CHU Angers, Laboratory of Immunology And Allergology, Angers, France, [4]CH Le Mans, Laboratory of Immunology, Le Mans, France, [5]CH Le Mans, General Pediatric Unit, LE MANS, France, [6]CH Tours, Pediatric Onco-hematology Unit, Tours, France

Background and Aims: After the first year of the SARS-CoV-2 pandemic, the concept of immunity debt arose, consisting in a lack of immune stimulation increasing the susceptibility to future and potentially more severe infections. After the implementation of social distancing measures, the incidence of seasonal community-acquired infections strongly decreased, whereas after COVID restrictions were reduced, their incidence rebound. We hypothesize that the lack of antigenic stimulations due to social distancing could induce a decrease of serum immunoglobulin G (IgG) levels in young children.

Methods: We retrospectively analyze serum IgG levels of French children aged 0 to 10 years before (September 2018-September 2019, group 1) and after (September 2020-September 202, group 2) the first lockdown. We collected results of serum IgG measurement routinely performed in 3 hospitals during these periods of time. We excluded children who received Ig replacement therapy or high dose Ig treatment for auto-immune diseases.

Results: 2292 children were included in our study (n=1156 in group 1, n=1136 in group 2). Overall, serum IgG levels were significantly lower during the second period of time (IgG group 1: 7.55 g/L; IgG group 2: 6.94 g/L, $p<10^{-3}$). After we stratified children on age, a significant decrease persists in the 3-5 years and 5-10 years of age subgroups ($p<10^{-3}$ and p=0.02 respectively).

Conclusions: Our results suggest that social distancing is associated with a decrease of serum IgG level in 3-10 years-old children. Further investigations are needed to determine whether this decrease is inconsequential or contributes to an immunity debt in children.

Disclosure: No.

Keywords: SARS-CoV-2 pandemic, immunity debt, humoral deficiency, social distancing

PD553

SARS-COV-2 VACCINATION ON COMMON VARIABLE IMMUNODEFICIENCY PATIENTS: ANTIBODY NEUTRALIZATION CAPACITY AND CLINICAL FOLLOW-UP.

POSTER DISPLAY 10: COVID-19

Oscar Cabrera-Marante[1], Daniel Arroyo[1], Patricia Almendro-Vázquez[2], Edgar Rodríguez-Frías[1], Daniel E. Pleguezuelo[1], Estela Paz-Artal[1]
[1]University Hospital 12 de Octubre, Immunology, Madrid, Spain, [2]Fundación de investigaciones Biomédicas i+12, Immunology, Madrid, Spain

Background and Aims: Eighteen CVID patients vaccinated against SARS-CoV-2 were prospectively followed-up during 2 years. After analyzing their cellular and humoral response we evaluated the neutralization capacity of those patients with adequate antibody production. Based on these results, we examined the evolution and clinical response to SARS-CoV-2 exposure and COVID-19 diagnosis.

Methods: Measurement of neutralization capacity was done by luciferase assay using VSV-luc pseudotyped replication-deficient viruses transfected with SARS-CoV-2 Spike mutant D614G. The clinical evolution of all CVID patients was recorded for 2 years by monthly evaluation.

Results: After the first dose, among 15 patients who produced anti-S1 antibodies, 9 showed neutralization capacity. After the second dose, three more patients gained neutralizing capacity and six were not able to develop them. In sum, among the global 18 CVID patients cohort, after full vaccination, 83% developed anti-S1 antibodies, but neutralizing antibodies were only recorded in 50% of anti-S1-positive patients. Among the 6 patients who tested SARS-CoV-2-positive during the follow-up, only one underwent severe COVID-19. She required oxygenic support and corticosteroids. Cellular and humoral response after BNT162b2 vaccination had been negative. After the disease, she developed a humoral response against SARS-CoV-2.

Conclusions: After completing the standard COVID-19 vaccination the production of antibodies with neutralizing capacity in CVID is suboptimal, booster doses could be beneficial by enhancing their production. In the infected patient, the absence of cellular and humoral response post-vaccination related to severe COVID-19 and the natural infection provided superior immunogenicity than the vaccine.

Disclosure: This study was supported by the Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation (COVID-19 research call COV20/00181)—cofinanced by the European Development Regional Fund “A way to achieve Europe,” Operative Program Intelligent Gr

Keywords: humoral responses, SARS-CoV-2, COVID-19, Common variable immunodeficiency, vaccines, Infection

PD554

HUMORAL AND CELLULAR IMMUNE RESPONSE TO MRNA SARS-COV-2 VACCINE IN PATIENTS WITH IMPAIRMENT of HUMORAL IMMUNITY

POSTER DISPLAY 10: COVID-19

Ricardo Cuesta Martín De La Cámara[1], Andrea González-Torbay[1], Laura Miguel Berenguel[1], Rebeca Rodríguez Pena[1,2], Eduardo López Granados[1,2,3], Carla Gianelli[1], Lucia Del Pino Molina[1,2,3], Pilar Nozal Aranda[1,2,4], Yadira Bravo Gallego[1,2,3], Cristina Calvo[5], Ana Mendez[5], Jordi Cano Ochando[6,7,8], Carmen Cámara Hijón[1]
[1]University Hospital La Paz, Department of Immunology, Madrid, Spain, [2]Health Institute Carlos III, Ciberer U767, Madrid, Spain, [3]La Paz Institute of Biomedical Research (IdiPAZ, Lymphocyte Pathophysiology In Immunodeficiencies Group, Madrid, Spain, [4]La Paz Institute of Biomedical Research (IdiPAZ), Complement Research Group, Madrid, Spain, [5]University Hospital La Paz, Department of Pediatrics, Madrid, Spain, [6]Icahn School of Medicine at Mount Sinai, Precision Immunology Institute,, New York, United States of America, [7]Centro Nacional de Microbiología, Health Institute Carlos Iii, Madrid, Spain, [8]Icahn School of Medicine at Mount Sinai, Department of Oncological Sciences, New York, United States of America

Background and Aims: While immune response to SARS-CoV-2 after vaccination has been well described in healthy controls, it remains to be correctly characterized in antibody-deficient patients, particularly the spike-specific T cell response. In this study we compare both cellular and humoral responses during and after two doses of SARS-CoV-2 vaccination in patients affected by Bruton agammaglobulinemia (XLA), common variable immunodeficiency (CVID) and hypogammaglobulinemia that does not fit CVID criteria (HG) with a control group of healthy individuals (HC).

Methods: 10 XLA, 32 CVID, 14 HG and 97 HC were assessed in our center before, 20 days after the first dose and 20 days after the second dose. Cellular response was measured by quantifying IFN-γ and IL-2 production after whole blood stimulation with SARS-CoV-2 S and M proteins. Spike-specific IgG quantification was made by chemiluminescence.

Results: Adequate humoral response defined as >260 BAU/ml was impaired in 7/10 XLA patients, 4/32 CVID patients, 13/14 HG patients and none HC. Cellular response is less affected: only 1/10 XLA, 4/32 CVID and 3/14 HG produced <50 pg/ml of IFN-γ. of particular note is the greater immune cellular response in all humoral immunodeficient groups compared to HC. This fact is specially notable for IL-2 response in naïve XLA-patients. No difference of IFN-γ or IL-2 was observed between naïve and recovered patients after the second dose, although it only increased cellular immunity in naïve patients.

Conclusions: Individuals with antibody deficiencies seemingly increased cellular respond after vaccination compared to healthy controls, probably to compensate their impairment of humoral immunity.

Disclosure: No.

Keywords: COVID-19, SARS-CoV-2, T-cell immunity, vaccines, Humoral Immunity

PD555

EVALUATION of THE HUMORAL AND CELLULAR IMMUNE RESPONSES TO THE SARS-COV-2 VACCINE IN PATIENTS WITH PRIMARY OR SECONDARY ANTIBODY DEFICIENCY.

POSTER DISPLAY 10: COVID-19

Arnau Antolí Gil[1,2], Gemma Rocamora Blanch[1,2], Mario Framil Seoane[1,3], Carla Bermúdez Carre[1,2], Virginia Mas Bosch[1,3], Eva Dopico Ponte[4], Raul Rigo Bonnin[5], Francisco Morandeira Rego[1,3], Xavier Solanich Moreno[1,2]
[1]Hospital Universitari de Bellvitge, Adult Primary Immunodeficiency Unit, L'Hospitalet de Llobregat, Spain, [2]Hospital Universitari de Bellvitge, Internal Medicine, L'Hospitalet de Llobregat, Spain, [3]Hospital Universitari de Bellvitge, Immunology Deparment, L'Hospitalet de Llobregat, Spain, [4]Hospital Universitari de Bellvitge, Microbiology Deparment, L'Hospitalet de Llobregat, Spain, [5]Hospital Universitari de Bellvitge, Biochemistry Deparment, L'Hospitalet de Llobregat, Spain

Background and Aims: SARS-CoV-2 vaccines seem safe in immunocompromised patients, but their effectiveness is not yet clearly known. This study aimed to assess the humoral and cellular specific immune response to the SARS-CoV-2 vaccine and the predictors of poor response in patients with primary (PAD) and secondary (SAD) antibody deficiencies, as well as its safety.

Methods: A chemiluminescence immunoassay was used to determine pre- and post- SARS-CoV-2 vaccine antibody levels. The T-cell specific response was assessed by analysing the pre- and post- SARS-CoV-2 vaccination blood samples by a specific whole blood IGRA kit. This study assessed 28 patients with primary antibody immunodeficiencies; 24 multiple sclerosis patients treated with anti-CD20 monoclonal antibodies; and 14 healthy controls.

Results: SARS-CoV-2 vaccines were safe in our immunocompromised patients, although their effectiveness was lower than in healthy individuals. Several PAD patients showed humoral (29%) and cellular (29%) defects, while patients with SAD presented fundamentally humoral response failure (54%). Low IgA values, low CD19+ peripheral B cells, low switched memory B cells, and low CD4+/CD8+ ratio were predictors of inadequate specific antibody response to SARS-CoV-2 vaccine in PAD patients.

Conclusions: SARS-CoV-2 vaccines effectiveness is lower than in healthy individuals. PAD patients could develop impaired humoral and cellular immune responses, while patients with SAD have fundamentally humoral defects.

Disclosure: No.

Keywords: anti-CD20 monoclonal therapies, SARS-CoV-2, SARS-CoV-2 vaccine, Primary Antibody Deficiency, Multiple Sclerosis

PD556

SARS-COV2 SPECIFIC T CELL IMMUNITY IN ANTIBODY DEFICIENT PATIENTS

POSTER DISPLAY 10: COVID-19

Marianna Tzanoudaki[1], Sofia Tantou[1], Theodora Papastamatiou[2], Rediona Kane[1], Virginia Polaki[1], Manolis Liatsis[1]
[1]"Aghia Sophia" Children's Hospital, Dept. of Immunology & Histocompatibility, Athens, Greece, [2]Aglaia Kiriakou Hospital, 2nd Department of Pediatrics of The National And Kapodistrian University of Athens, ATHENS, Greece

Background and Aims: Development of SARS-CoV2 specific immunity post infection or after vaccination is a major issue, even more so for PID patients. T-cell mediated responses constitute the only means of assessing antigen specific immunity in antibody deficient patients (ADp). We aimed to study SARS-CoV2 T cell responses in a cohort of ADp post vaccination or COVID19.

Methods: Commercially available interferon gamma release assay, using 2 tubes with SARS-CoV2 antigen pools, was performed for 8 CVID patients (CVIDp median age 26 years), 1 XLA patient (XLAp, age 6 years) and 10 healthy controls (HC, median age 55 years). History of COVID19 was positive for 3/8 CVIDp, 6/10 HC and for the XLAp. All subjects had received 3 doses of mRNA vaccine. Results (IFNγresp) were expressed as (antigen tube IFNγ concentration)- (unstimulated tube IFNγ concentration).

Results: In HC, median IFNγresp was 0.15 IU/mL and 0.58 IU/mL in each antigen tube, being elevated in the COVID19 + HC group (0.49 IU/mL and 1.59 IU/mL). In CVIDp the respective median IFNγ levels were 0.03 IU/mL and 0.09 IU/mL for all patients and 0.02 IU/mL and 0.07 IU/mL for those with COVID19 history. The XLAp, had IFNγresp 0.11 IU/mL and 0.09 IU/mL. Only one among the CVIDp had IFNγresp levels comparable to those of normal controls

Conclusions: SARS-CoV2 specific T cell immunity seems to be compromised in our patient cohort, even though there were no clinical or laboratory signs of impaired T cell function. Further studies are needed regarding vaccine mediated induction of T cell memory in PID patients.

Disclosure: No.

Keywords: SARS CoV2, T cell immunity, Interferon Gamma Release Assay, CVID

PD557

NEW DIAGNOSES AND TRENDS IN HOSPITAL ADMISSIONS AMONG PRIMARY AND SECONDARY IMMUNODEFICIENCY PATIENTS DURING SARS-COV-2 PANDEMIC

POSTER DISPLAY 10: COVID-19

Sujoy Khan, Rebecca Avison, Sarah Sholtysek, Michelle Day, Tom Rust, Jackie Moor
Castle Hill Hospital, Immunology & Allergy, Cottingham, United Kingdom

Background and Aims: Patients with primary immunodeficiency (PID) and secondary immunodeficiency (SID) disorders have risk of worse outcomes with SARS-CoV-2 infection despite vaccination. We analysed newly identified patients, vaccination rates and outcomes from COVID19 infection among these patients during the pandemic.

Methods: Retrospective review of demographic/clinical data for new referrals diagnosed with PID/SID along with vaccine uptake, COVID19 PCR positivity, clinical outcomes compared with patients on immunoglobulin replacement therapy (IgRT) (March 2020-Dec 2021).

Results: Out of 879 referrals, 87 (10% of referrals) assessed for possible immunodeficiency. 174 referrals closed after electronic advice and guidance or non-attendance. 20 new patients included six PID (3 sIgA deficiency, 2 HGUS, 1 CVID) and 14 SID (6 received anti-CD20/radiotherapy, 8 drug-induced [steroids/anti-epileptic]). Mean(±SD) age (range) PID patients at diagnosis 38(±14) years(25-66 years), and SID patients 62(±13) years(42-82 years). Six of 20 new patients (4 SID) acquired COVID19, and only the CVID patient required IV Sotrovimab. None required hospitalization. Most patients received 3-4 vaccine doses (minimum one dose 95%). 19/64 patients on IgRT acquired COVID19 (total 21 episodes, 15 PID). Eight patients received Regenron/Sotrovimab while one received Paxlovid therapy. Most infections after third vaccination dose. There were six deaths during this time-period [PID (5), SID (1)], one died whilst positive for COVID19 infection. Only one patient had received single vaccine dose, rest had 3-4 doses (minimum one dose 100%).

Conclusions: Referrals for suspected immunodeficiency identified more SID during the pandemic. More PID patients on long-term IgRT acquired COVID19 infection after vaccination indicating ongoing transmissibility of virus and changes in public behaviour.

Disclosure: No.

Keywords: SARS-CoV-2, Secondary Immunodeficiency, COVID19, vaccine, Outcome, primary immunodeficiency

PD558

CELLULAR IMMUNE RESPONSE AFTER A THIRD DOSE of HOMOLOGOUS OR HETEROLOGOUS COVID-19 VACCINE IN BRAZILIAN PATIENTS WITH INBORN ERRORS of IMMUNITY COMPARED TO HEALTHY CONTROLS

POSTER DISPLAY 10: COVID-19

Vitor Gabriel Lopes Da Silva[1], Kathleen E Sullivan[2], Carolina Sanchez Aranda[1], Maria Isabel De Moraes-Pinto[1]
[1]Universidade Federal de São Paulo, Pediatrics, São Paulo, Brazil, [2]The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Pediatrics, Division of Allergy And Immunology, Philadelphia, United States of America

Background and Aims: We investigated cellular immune response after primary vaccination with a 3-dose scheme in Brazilian patients with Inborn Errors of Immunity (IEI) compared to healthy controls (HC).

Methods: 31 IEI (45% male; mean age, 34y) and 55 HC (47% male; mean age, 29y) were immunized with two doses of inactivated SARS-CoV-2 vaccine (CoronaVac), non-replicating viral vectored vaccine (Oxford-AstraZeneca ChAdOx1-nCoV-19) or mRNA vaccine (Pfizer-BioNTech BNT162b2), followed by a third dose of Pfizer. They were sampled one month after the third Pfizer vaccine dose (V1). 22 IEI and 22 HC were also sampled three months later (V2). IEI were: 12 CVID; 6 SAD; 4 PIK3CD; 3 Hyper-IgM Syndrome; 2 XLA; 2 AT; 1 STAT1 Gain-Of-Function and 1 Combined Immunodeficiency. SARS-CoV-2 S1 and nucleocapsid cellular responses were assessed with T-cell ELISpot.

Results: At V1, SARS-CoV-2 T-cell response was positive to S1 in 64.5% of IEI and in 67.3% of HC (p=0.800); to nucleocapsid, in 38.7% of IEI and 34.5% of HC (p=0.700). At V2, S1 positivity was 63.6% of IEI and 81.8% of HC (p=0.176); to nucleocapsid, 31.8% of IEI and 40.9% of HC (p=0.531). A greater but non-significant overall positivity was observed in IEI at V1 with the initial two-dose vaccine schedule of AstraZeneca (70%) and Pfizer (75%) compared to CoronaVac (55.5%) (p=0.630).

Conclusions: IEI patients with predominantly humoral deficiency disorders respond to a 3-dose SARS-CoV-2 immunization with a positive SARS-CoV-2 T-cell response that is maintained for up to three months, similar to HC.

Disclosure: No.

Keywords: Inborn errors of immunity, Primary Immunodeficiencies disorders, SARS-CoV-2, Covid-19 Vaccines, Immunization, Cellular Immunity

PD559

IMPAIRED RESPONSE TO THIRD DOSE COVID-19 MRNA VACCINE IN INBORN ERRORS of IMMUNITY

POSTER DISPLAY 10: COVID-19

Børre Fevang[1], Ragnhild Løken[2], Tonje Skarpengland[2], Ingvild Nordøy[2], Fridtjof Lund-Johansen[3]
[1]Oslo University Hospital, Section of Clinical Immunology And Infectious Diseases, Oslo, Norway, [2]Oslo university hospital, Section of Clinical Immunology And Infectious Diseases, Oslo, Norway, [3]Oslo university hospital, Department of Immunology, Oslo, Norway

Background and Aims: Patients with inborn errors of immunity (IEI) will often have impaired humoral and cellular response to vaccines. During the Covid-19 pandemic mass vaccination that also included IEI-patients were performed and previous studies have shown reduced rate of seroconversion in IEI-patients after two doses of vaccine. We wanted to analyse the effect of a third dose of mRNA Covid-19 vaccine in IEI-patients.

Methods: Patients with IEI were invited to sample serum after the 2nd and 3rd dose of Covid-19 vaccine. We received samples from 177 patients, including patients with CVID (n=110), IgG subclass deficiency (n=13), Brutons agammaglobulinemia (n=5), phagocyte deficiencies (n=9) and combined immunodeficiencies (n=7). Patients received Pfizer-Biontech (n=116), Moderna (n=28) or a combination of those two (n=33). Levels of binding-antibody units (BAU) were analysed using a high throughput flow cytometry bead assay.

Results: Overall, patients had reduced levels of BAU compared to healthy controls both after the 2nd and 3rd dose of mRNA vaccine.

Conclusions: Patients with IEI have impaired serologic response to 2nd and 3rd dose mRNA Covid-19 vaccines compared to healthy controls.

Disclosure: No.

Keywords: Inborn errors of immunity, mrna, COVID-19, vaccine

PD560

CELLULAR AND HUMORAL IMMUNOGENICITY of THE COVID-19 VACCINE AND COVID-19 DISEASE SEVERITY IN INDIVIDUALS LIVING WITH IMMUNODEFICIENCY

POSTER DISPLAY 10: COVID-19

Cliodhna Murray, Jean Dunne, Niall Conlon
St James's Hospital, and Trinity College Dublin School of Medicine, Department of Immunology, Dublin, Ireland

Background and Aims: The development of standardised methods for measuring the COVID-19 vaccine response of individuals with immunodeficiency is of topical interest. We compared the immunogenicity of the 2nd and booster COVID-19 vaccines in individuals with immunodeficiency to healthy controls (HCs). Additionally, the individuals' COVID-19 disease severity was assessed.

Methods: Whole blood was stimulated from 70 participants, and 100 HCs using PepTivator® peptide pool and spike protein and IFN-γ was measured using ELISA. The total antibody titre to SARS-CoV-2 spike protein was measured using the Roche Elecsys®S assay. One vaccine response score was given for a positive antibody level, IFN-γ level to spike protein and peptide stimulation, respectively. Patient characteristics, COVID-19 infection status and IDDA 2.1 'Kaleidoscope' scores were recorded.

Results: 98% of HCs, 89% of individuals with IEI and 79% with SID had an IFN-γ level above the validated reference range to peptide stimulation following the second vaccine. IFN-γ levels increased in patients with IEI following the booster vaccine ($p = 0.047$). 100% of HCs, 70% of individuals with IEI and 63% with SID had detectable spike antibody levels. 57% of those with mild COVID-19 and 11% with moderate/severe COVID-19 showed a response to all modalities. The pre-infection IDDA 2.1 scores were higher in individuals with moderate/severe COVID-19 (19.75 compared to 9.41).

Conclusions: COVID-IGRA is a highly accurate, straightforward and cost-effective assay which can be easily adapted to measure cellular response to COVID-19. The IDDA 2.1 and vaccine response scores may be valuable tools in identifying immunodeficiency patients who may benefit from enhanced vaccination schedules.

Disclosure: No.

Keywords: Covid, diagnostics, Vaccine response, IGRA

PD561

THE USE of COVID SEROLOGY IN THE ASSESSMENT of PATIENTS FOR IMMUNODEFICIENCY

POSTER DISPLAY 10: COVID-19

Tomaz Garcez
Manchester University NHS Foundation Trust, Greater Manchester Immunology Service, Manchester, United Kingdom

Background and Aims: Single centre review of the use of SARS-CoV-2 serology against the spike protein in the assessment of patients with suspected immunodeficiency. Previously clinical immunologists have used various vaccines to test patients referred for suspected antibody immunodeficiency. The COVID-19 pandemic provides an opportunity to use SARS-CoV-2 serology as part of the assessment process.

Methods: Retrospective case note review of adults assessed in the immunology clinic with a SARS-CoV-2 serology result (Elecsys® Anti-SARS-CoV-2 S). The clinical history was classified into severe primary immunodeficiency (PID), mild PID, no immunodeficiency, secondary immunodeficiency and undefined. The serology results were then compared across the groups.

Results: 53 patients were included. 2 had severe primary immunodeficiency, and both had antibody levels below the limit of detection of the assay (<0.4). 21 had mild PID (0 <0.4, 3 <250 and 18 >250), 13 had no immunodeficiency (0 <0.4, 1 <250 and 12 >250), 9 had secondary immunodeficiency (0 <0.4, 2 <250 and 7 >250) and 8 remain undefined (1 <0.4, 5 <250 and 2 >250). 1 patient has a confirmed CARD11 mutation without significant immunodeficiency and had antibody levels >250 All patients with levels <0.4 either had severe primary immunodeficiency or were still under assessment at the time of testing (this patient has subsequently died before completing investigations). of the patients with levels >250 almost all had no detectable immunodeficiency or mild immunodeficiency.

Conclusions: SARS-CoV-2 serology can be used as a measure of B cell / antibody function and helps to categorise patients into more mild versus more severe immunodeficiency categories.

Disclosure: No.

Keywords: Covid, Serology, primary immunodeficiency, B cell defect

PD562

LOWER DISEASE ACTIVITY BUT HIGHER RISK of SEVERE COVID-19 AND HERPES ZOSTER IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS WITH PRE-EXISTING AUTOANTIBODIES NEUTRALISING IFN-ALPHA

POSTER DISPLAY 10: COVID-19

Alexis Mathian[1], Paul Breillat[2], Paul Bastard[3], Karim Dorgham[4], Jean-Laurent Casanova[5], Zahir Amoura[1], Guy Gorochov[6]
[1]APHP, Internal Medicine 2, Paris, France, [2]Sorbonne Université, Immunology, Paris, France, [3]Paris Cité University, Imagine Institute, Paris, France, [4]Inserm, Cimi-paris, Paris, France, [5]Howard Hughes Medical Institute, -, Washington, United States of America, [6]Sorbonne Universite, Immunology, Paris, France

Background and Aims: Type-I interferons (IFNs-I) have potent antiviral effects. IFNs-I are also overproduced in patients with systemic lupus erythematosus (SLE). Auto-antibodies (AAbs) neutralizing IFN-α, -β and/or -ϖ subtypes are strong determinants of hypoxemic COVID-19 pneumonia, but their impact on inflammation remains unknown.

Methods: We retrospectively analyzed a monocentric longitudinal cohort of 609 patients with SLE. Serum AAbs against IFN-α were quantified by ELISA and functionally assessed by abolishment of Madin-Darby bovine kidney cells protection by IFN-α2 against vesicular stomatitis virus challenge. Serum neutralizing activity against IFN-α2, -β and -ϖ was also determined with a reporter luciferase activity. SARS-CoV-2 antibody responses were measured against wild-type spike antigen, while serum-neutralizing activity was assessed against the SARS-CoV-2 historical strain and variants of concerns.

Results: Neutralizing and non-neutralizing anti-IFN-a antibodies are present at a frequency of 3.3% and 8.4%, respectively, in individuals with SLE. AAbs neutralizing IFN-α, unlike non-neutralizing AAbs, are associated with reduced IFN-α serum levels and a reduced likelihood to develop active disease. However, they predispose patients to an increased risk of herpes zoster and severe COVID-19 pneumonia. Severe COVID-19 pneumonia in patients with SLE is mostly associated with combined neutralization of different IFNs-I. Finally, anti-IFN-α AAbs do not interfere with COVID-19 vaccine humoral immunogenicity.

Conclusions: The production of non-neutralizing and neutralizing anti-IFN-I antibodies in SLE is likely to be a consequence of SLE-associated high IFN-I serum levels, with a beneficial effect on disease activity, yet a greater viral risk. This finding reinforces the recommendations for vaccination against SARS-CoV-2 in SLE

Disclosure: No.

Keywords: COVID-19, anti-interferon antibodies, lupus

PD563

AUTOIMMUNITY IN POST-ACUTE SEQUENCE of COVID-19: WHERE DO INTERFERONS FIT IN?

POSTER DISPLAY 10: COVID-19

Zouina Sarfraz[1], Azza Sarfraz[2], Miguel Felix[3], Karla Robles-Velasco[4], Ivan Cherrez-Ojeda[5]
[1]Fatima Jinnah Medical University, Research And Publications, Lahore, Pakistan, [2]Aga Khan University, Pediatrics And Child Health, Karachi, Pakistan, [3]New York City Health + Hospitals, Lincoln, Bronx, NY, USA, Department of Medicine, Bronx, United States of America, [4]Karla Robles-Velasco, MD; Universidad Espíritu Santo, Samborondón, Ecuador, Department of Medicine, Samborondon, Ecuador, [5]Universidad Espíritu Santo, Allergy And Pulmonology, Samborondon, Ecuador

Background and Aims: Post-acute sequelae COVID-19 (PASC) or “long-COVID” syndrome represents 10% of COVID-19 patients yet the contribution of persistent autoimmune activation as underlying pathophysiology remains poorly understood. Recent data is recognizing the intersection of COVID-19 and autoimmunity and is being explored. This systematic review aims to evaluate the immune dysregulation associated with PASC and find meaningful implications for interferon therapy as a treatment modality in this condition.

Methods: Three databases including Pubmed, Scopus, and Embase were searched from December 2019 to August 15, 2022, with keywords including “post-acute,” “long-covid,” “interferon,” and “autoimmune.”

Results: A total of six original investigations were found that reported data on PASC serologically and/or clinically. There are contrasting data both reporting the presence or absence of significantly elevated interferon levels in the acute phase among patients presenting with PASC symptoms. Patients who have received interferon β-1 b-based triple antiviral therapy during hospitalization are not as likely to experience PASC as those who have not while admitted. Anti-interferons are positive in up to 10-15% of patients with PASC alongside other markers of latent autoimmunity and overt autoimmune disease. Three key interferons including IFN-β, IFN-γ, and IFN-λ2/3 have been identified as therapeutic targets for the prevention and treatment of PASC.

Conclusions: Interferon therapy has not been explored in PASC despite having the potential to alleviate the ongoing immune dysregulation in PASC. Well-designed randomized controlled trials are required to assess different interferon therapy as a reasonable choice for PASC.

Disclosure: No.

Keywords: Interferons, Autoimmunity, COVID-19, Post-acute sequelae, Therapeutics

PD564

COVID-19 SEVERITY, CARDIOLOGICAL OUTCOME, AND IMMUNOGENICITY of MRNA VACCINE IN ADULT PATIENTS WITH 22Q11.2DS

POSTER DISPLAY 10: COVID-19

Federica Pulvirenti[1], Carolina Putotto[2], Eva Piano Mortari[3], Sara Terreri[4], Ane Salinas[3], Bianca Laura Cinicola[5,6], Eleonora Sculco[7], Giulia Di Napoli[8], Cinzia Milito[9], Paolo Versacci[10], Bruno Marino[10], Rita Carsetti[3], Isabella Quinti[8]
[1]Regional Reference Centre for Primary Immune Deficiencies, Azienda Ospedaliera Universitaria Policlinico Umberto I, Rome, Italy, Regional Reference Centre For Primary Immune Deficiencies, Azienda Ospedaliera Universitaria Policlinico Umberto I, Rome, Italy, Roma, Italy, [2]Sapienza University of Rome, Materno Infantile E Scienze Uroginecologiche, rome, Italy, [3]Diagnostic Immunology Research Unit, Multimodal Medicine Research Area, Bambino Gesù Children's Hospital, IRCCS; Viale di San Paolo,15, Rome, Italy, Diagnostic Immunology Research Unit, Multimodal Medicine Research Area, Bambino Gesù Children's Hospital, Irccs; Viale Di San Paolo,15, Rome, Italy, Roma, Italy, [4]Bambino Gesù Children's Hospital, IRCCS,, B Cell Unit, Immunology Research Area,, ROMA, Italy, [5]Sapienza University of Rome, Department of Maternal Infantile And Urological Sciences, Rome, Italy, [6]Sapienza University of Rome, Pediatric Immunology And Allergology, Rome, Italy, [7]Sapienza University of Rome, Molecular Medicine, Rome, Italy, [8]Sapienza University of Rome, Molecular Medicine, ROMA, Italy, [9]Università La Sapienza, Department of Molecular Medicine "sapienza" University of Rome, Italy, Roma, Italy, [10]Sapienza University of Rome, Pediatric Cardiology Unit, Department of Pediatrics, Obstetrics And Gynecology,, ROMA, Italy

Background and Aims: The presence of immune defects and heart diseases in patients with 22q11.2 deletion syndrome (DS) represents risk-factor for severe COVID-19. We aimed to analyze if 22q11.2DS-associated conditions impact the COVID-19 severity. As secondary objectives, we analyzed the antibody- and B/T-specific responses after two and three doses of the mRNA-based SARS-CoV-2 vaccine.

Methods: Longitudinal observational study on SARS-Cov-2 outcome in 60 adults with 22q11.2DS. Anti-Spike, and anti-receptor binding domain antibody responses, generation of Spike-specific memory B-cells and Spike-specific T-cells at different time points before and after the mRNA BNT162b2 vaccination were evaluated in sixteen 22q11.2DS patients.

Results: We recorded a 95% rate of vaccination, with almost all patients being immunized with the booster dose. Twenty-one patients had SARS-CoV-2 infection. Three patients were infected before vaccine availability, six after two doses, and twelve after receiving the booster dose. All had a mild infection, except one patient with several comorbidities who died. SARS-CoV-2-infected patients had a more frequently moderate/severe degree of intellectual disability. Despite major congenital heart diseases, COVID-19 did not impact cardiological disease. The BNT162b2 vaccine induced S1-IgG responses, low serum S1-IgA, and the induction of specific memory B cells were slightly impaired. Specific T-cell responses observed in all but one patient were related to lymphocytes, and CD4+ T cell counts.

Conclusions: SARS-CoV-2 infection in patients with 22q11.2DS had a mild course, even in patients with major cardiovascular diseases. Immunization induced Spike-specific IgG responses and generated specific memory B and T cells. The weaker memory responses in patients with lymphopenia suggested the need for additional doses.

Disclosure: No.

Keywords: 22q11.2, COVID-19, mRNA BNT162b2 vaccine, Specific memory B cells, Specific T cells, DiGeorge

INGID

INGID001

AUDIT of ADEQUACY of USE of GGIV IN TIME of CUT IN SUPPLY of PRODUCTS DUE TO COVID19 PANDEMIC. HOW TO HANDLE IT.

POSTER DISPLAY 11: INGID

Maria Angeles Escobar, Javier Carbone, Juana Gil Herrera, Paloma Sanchez Mateos, Marisa Di Natale, Hector Balastegui, Jimena Gómez Pérez, Mercedes Díaz-Luna, Ana Paulina Moncayo Muñoz, Eduardo Fernandez Cruz
GREGORIO MARAÑON HOSPITAL, Immunology, MADRID, Spain

Background and Aims: As a consequence of the health crisis caused by SARS-CoV-2, there was a decrease in blood and plasma donations worldwide. Intravenous immunoglobulins (IVIG) are used for replacement therapy in primary and secondary antibody deficiencies. We aimed to share the multidisciplinary effort which has had to be carried out from a public hospital in Spain to cover all patients individually.

Methods: Since May 2021, clinical histories were carefully reviewed taking into account the diagnosis, number of infections in last 6 months, trough IgG levels, catabolic rates, treatment dose and frequency after which it was decided on an individual basis the potential reduction, spacing of doses or temporary suspension. All patients were being closely monitored every 3 months for the appearance of infectious events or other complications.

Results: of a total of 171 patients receiving IVIG, in 95 (55.29%), due to the previously described criteria, it was decided to maintain the treatment without modifications. In 28 patients (16.47%), the dose was reduced and the frequency of treatment was spaced out. In 31 patients (18.28%) only periodicity was spaced. In 14 patients (8.23%), treatment has been suspended temporarily. In this group prophylactic antibiotic therapy was indicated in patients who had not previously received it. In 3 patients (1.76%) a change of the route of administration from IVIG to facilitated subcutaneous immunologlobulin was performed.

Conclusions: An economic-health crisis can influence treatment of patients. Health professionals, through exhaustive evaluations of patients can handle it in order to avoid further damage.

Disclosure: No.

Keywords: immunology, DEFICIENCY, intravenous immunoglobulins, COVID19, PATIENT, CRISIS

INGID002

READY STEADY GO; A GENERIC TRANSITION TOOL USED IN PATIËNTS WITH PID

INGID SESSION 04: ORAL AND POSTER PRESENTATIONS ON NURSING TOPICS

Linda Van Der Knaap[1], Jelka Van Der Waal[2]
[1]Erasmusmc Sophia's Childerens Hospital, Infectious Diseases And Immunlogy, Rotterdam, Netherlands, [2]Erasmus MC Sophia's Childrens Hospital, Infectious Diseases And Immunology, Rotterdam, Netherlands

Background and Aims: Youth with PID need to take charge in taking care of themselves when they grow older. This might be easier said than done. They lack sometimes in being independent. The aim is to empower youth by making them more aware of the skills they need to develop and to support their independence. We aim by using this tool to make transition experiences more succesful and satisfactory.

Methods: Ready Steady Go (RSG) is a tool developed by University Hospital Southampton, UK and is translated by the University of applied sciences Rotterdam. It helps youth and their parents/ carers to set goals for the future. RSG is a generic program that can be used for all youth (12-18) with a chronic condition and their parents/ carers. From the age of 12 three lists are being processed, one by one (Ready, Steady, Go). Goals are being set with youth and their parents/ carers and a plan is made on how to reach these goals. While following this program youth and parents are stimulated to think about transitionprocess and transfer to adult care. Topics are; Knowledge about illness and treatment, skills for shared decisionmaking and healthy lifestyle, sexual health and other age-related themes, school- and work goals, possible psychosocial problems and understanding transition process to adult care

Results: RSG is in use.

Conclusions: RSG is now embedded in all nursing consultations for patients with PID. Although not officialy studied we can monitor progress in independence in patients. It fits well into our aim to improve transition process.

Disclosure: No.

Keyword: transition in care, transition tool, adolescents,

INGID003

TWENTY YEARS of STEM CELL GENE THERAPY AT GREAT ORMOND STREET HOSPITAL

INGID SESSION 04: ORAL AND POSTER PRESENTATIONS ON NURSING TOPICS

Jinhua Xu-Bayford[1], Gráinne O'Toole[1], Kritika Chetty[1], Claire Booth[1,2]
[1]Great Ormond Street Hospital, Department of Immunology & Gene Therapy, London, United Kingdom, [2]University College London, Division of Infection And Immunity, London, United Kingdom

Background and Aims: Haematopoietic stem cell (HSC) gene therapy offers personalised corrective therapy for patients with devastating inherited diseases. The first UK baby who received gene therapy celebrated his 21st birthday in 2021, 20 years after receiving this pioneer treatment at Great Ormond Street Hospital (GOSH). This abstract offers an insight of our experience from 2001-present.

Methods: A retrospective review of patients treated from 2001-present was conducted in May 2022.

Results: Since 2001, 88 children have been treated with an HSC gene therapy product at GOSH through clinical trials. The scope of diseases treated has rapidly expanded to now include a range of inborn errors of immunity (IEI), as well as haematologic and metabolic conditions, with further indications on the horizon. Several changes have improved patient survival and experiences, including modification of vectors, chemotherapy regimes and personalising treatment according to patient's pre-existing conditions and comorbidities. Our team at GOSH has focused on improving the patient and family pathway. The delivery of information to carers and patients is key to assist them making an informed decision for their child to participate in a clinical trial. Multidisciplinary teamwork facilitates the safe management of patients pre-, peri- and post-gene therapy. Good communication, together with standardised procedures ensure the clinical governance and patient safety of these high-risk procedures.

Conclusions: Supporting patients through this challenging journey is a privilege and highly fulfilling. Engaging with parents and patients at each stage empowers them to have difficult conversations about treatment options in order to progress with patients' complex situations.

Disclosure: No.

Keywords: Therapeutics, HSC Therapy, Clinical Trials, Observational Study, primary immunodeficiencies, gene therapy

INGID004

TRANSITION IN CARE FOR PATIENTS WITH PID

INGID SESSION 04: ORAL AND POSTER PRESENTATIONS ON NURSING TOPICS

Jelka Van Der Waal[1], Marianne Van Der Ent[2], Linda Van Der Knaap[1]
[1]Erasmus MC Sophia's Childrens Hospital, Infectious Diseases And Immunology, Rotterdam, Netherlands, [2]Erasmus mc, Immunology, Rotterdam, Netherlands

Background and Aims: Transitioning from pediatric to adult care is a big change since children and their families know their pediatric team for a long time. With this combined out patient clinic we want to make the transfer more gradual.

Methods: From 12 years on we use the transition tool Ready Steady Go lists (RSG) to prepare children to become more independent. We discuss e.g. skills for health, selfcare and independence. When patients turn 17 we invite them for our transition clinic. Every patient attends two times. One clinic is held in the pediatric, the other in the adult setting . The patient is being seen by the pediatric and the adult team together (doctors and nurses seperately). If the patient has pulmonary problems their pulmonary consultant will join. During this transition period the responsibility lies with the pediatric team. After their second visit the transfer is completed. The transitiontool Hello is been used by the adult nurse after transition as a consecutive to the RSG list.

Results: Although not evaluated formally patients experience tend to be positive. It is helpfull to meet the adult treatment team beforehand. The (pediatric) immunologist and the (pediatric) nurse specialist also find it very usefull to handover the patient in this manner.

Conclusions: The transition clinic is a valuable tool in the whole transition care process. Patients and parents experience it as positive to have a consultation with the familiar and the new team at the same time. We plan to evaluate patients experiences in near future.

Disclosure: No.

Keyword: transition, adolescent, adult, self management, patient centered care, combined out patient clinic

INGID005

LIVED EXPERIENCES of PARENTS AND CHILDREN PARTICIPATING IN EARLY-PHASE CLINICAL TRIALS: EVIDENCE SYNTHESIS.

INGID SESSION 04: ORAL AND POSTER PRESENTATIONS ON NURSING TOPICS

Gráinne O'Toole
GOSH, Gene Therapy, London, United Kingdom

Background and Aims: Scientific advances have resulted in new treatments for paediatric life-limiting diseases.The majority of these treatments are only available if children participate in early-phase clinical trials. Most clinical trial research focuses on safety and physiological outcomes, and little is known about the experiences of parents and children who participate in these trials. Knowledge of the experiences and challenges encountered by participants can highlight areas where further support is needed. The aim of this synthesis was to evaluate existing evidence representing the experiences of children and families who participate in early-phase clinical trials.

Methods: A comprehensive search of two databases CINAHL and PubMed was performed on the 11th November 2021, using keywords which included 'family', 'child', 'paediatric', 'Clinical Trials' and 'experience'. Five qualitative articles were selected as best available evidence to answer this meaning type question.

Results: Five articles examined the experiences of parents and adolescents in early-phase trial participation. Interviews demonstrated pressures felt by parents to advocate for their child's inclusion in trials, as all participants faced a life-limiting disease. Findings were grouped into five themes a) Managing expectations but maintaining hope, b) Motivations to participate, c) Information seeking, d) Logistical impact of trial participation and e) Running out of time.

Conclusions: Literature on parent and child experiences of participating in early-phase trials is scant, with no qualitative research sourced representing the voice of the child. A need for psychological and emotional supports is evident for parents and adolescents. Despite efforts of healthcare professionals' participants can hold unrealistic hope of benefit although efficacy of these trials has not been proven.

Disclosure: No.

Keywords: Paediatric, Family, Qualitative, Lived Experience, Early phase clinical trials

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Anim Manfred	PD289	**NOVEL HYPERMORPHIC VARIANTS IN IRF2BP2 IDENTIFIED IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY AND AUTOIMMUNITY**	**Poster Display 06: Genetics in IEI**
Antolí Gil Arnau	PD555	**EVALUATION OF THE HUMORAL AND CELLULAR IMMUNE RESPONSES TO THE SARS-COV-2 VACCINE IN PATIENTS WITH PRIMARY OR SECONDARY ANTIBODY DEFICIENCY.**	**Poster Display 10: COVID-19**
Antolí Gil Arnau	PD199	**HYPER-IGD AND PERIODIC FEVER SYNDROME DUE TO TWO VARIANTS IN MEVALONATE KINASE GENE IN A 26-YEAR-OLD PATIENT.**	**Poster Display 05: Autoinflammatory Disorders**
Antonini Lara	PP015	**MISDIAGNOSIS OF PRIMARY IMMUNE THROMBOCYTOPENIA IN CHILDREN AND ADOLESCENTS**	**Poster Discussion 03: Immune Dysregulation**

Antonini Lara	PD107	**LYSO-SPHINGOMYELIN-509 INCREASED IN GRISCELLI SYNDROME TYPE 2**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Arango-Franco Andres Carlos	OC036	**HUMAN INHERITED IL-7 DEFICIENCY IS MILDER THAN IL-7R DEFICIENCY**	**Oral Communications 06: Late Breaking Abstracts**
Arlabosse Tiphaine	PD047	**AN X-CGD PATIENT WITH AGGREGATIBACTER APHROPHILUS CERVICAL LYMPHADENITIS COMPLICATED WITH LEMIERRE SYNDROME**	**Poster Display 03: Biology of Innate Immunity**
Arroyo Daniel	PD553	**SARS-COV-2 VACCINATION ON COMMON VARIABLE IMMUNODEFICIENCY PATIENTS: ANTIBODY NEUTRALIZATION CAPACITY AND CLINICAL FOLLOW-UP.**	**Poster Display 10: COVID-19**
Arroyo Sánchez Daniel	PD539	**IMMUNE RESPONSE AGAINST SARS-COV-2 INFECTION AND VACCINATION IN A CD8 ALPHA CHAIN-DEFICIENT WOMAN**	**Poster Display 10: COVID-19**
Asano Eito	PD389	**PATIENT AND PARENTS UNDERSTANDING AND COMPLIANCE WITH IMMUNOGLOBULIN REPLACEMENT THERAPY FOR ANTIBODY DEFICIENCIES**	**Poster Display 08: Therapy**
Asgari Fatemeh	WP002	**INNOVATIVE PRE-TRANSPLANT CONDITIONINGS FOR IMMUNE DYSREGULATION DISORDERS**	**Working Party 01: Inborn Errors**
Assing Kristian	PD028	**NOVEL CDC42 VARIANT ASSOCIATED WITH SCID-LIKE THYMIC OUTPUT, DECREASED IL-7R SIGNALING, DECREASED T CELL SURVIVAL AND NARROWED TCR REPERTOIRE**	**Poster Display 02: T-Cell Biology**
Assing Kristian	PD263	**T-CELL DEFICIENCY AND NOVEL RNU4ATAC VARIANT FOUND IN SISTERS WITH ROIFMAN SYNDROME**	**Poster Display 06: Genetics in IEI**
Astudillo Andrea Camila	PD194	**TRISOMY 8 INFORMS INFLAMMATORY MECHANISMS IN BEHÇET'S DISEASE**	**Poster Display 05: Autoinflammatory Disorders**
Atschekzei Faranaz	PD065	**EXPLORING THE ROLE OF DNA METHYLATION IN THE PATHOGENESIS OF PAD**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Avison Rebecca	PD557	**NEW DIAGNOSES AND TRENDS IN HOSPITAL ADMISSIONS AMONG PRIMARY AND SECONDARY IMMUNODEFICIENCY PATIENTS DURING SARS-COV-2 PANDEMIC**	**Poster Display 10: COVID-19**
Aygün Aygün Ayşe	PD029	**COMBINED IMMUNODEFICIENCY DUE TO JAK3 MUTATION ASSOCIATED WITH REFRACTORY CMV INFECTION AND BCG-OSİS**	**Poster Display 02: T-Cell Biology**

Babayeva Royala	PD075	**CLINICAL AND IMMUNOLOGICAL EFFECTS OF RUXOLITINIB IN STAT3 GAIN-OF-FUNCTION PATIENTS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Babayeva Royala	PD238	**NOVEL DIAPH1 MUTATION ASSOCIATED WITH COMBINED IMMUNODEFICIENCY AND MICROCEPHALY**	**Poster Display 06: Genetics in IEI**
Backers Lynn	PD305	**ATRIP-DEFICIENT SECKEL SYNDROME PATIENT PRESENTS WITH IMMUNODEFICIENCY**	**Poster Display 07: Genetics Diagnostics**
Baiker Matthias	PD390	**LONG-TERM-OUTCOME OF GROWTH IN PATIENTS WITH MALIGNANT INFANTILE OSTEOPETROSIS (MIOP) AND SEVERE COMBINED IMMUNODEFICIENCY (SCID) AFTER HUMAN STEM CELL TRANSPLANTATION - SINGLE-CENTRE STUDY**	**Poster Display 08: Therapy**
Bajinka Ousman	PD055	**LUNG-BRAIN AXIS: METABOLOMICS AND PATHOLOGICAL CHANGES IN LUNGS AND BRAIN OF RESPIRATORY SYNCYTIAL VIRUS INFECTED MICE**	**Poster Display 03: Biology of Innate Immunity**
Bakhtiar Shahrzad	PD101	**TOWARDS BETTER UNDERSTANDING OF HUMAN LRBA DEFICIENCY SYNDROME**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Baldrich Adrian	PD095	**DONOR-DERIVED TIM-3 DEFICIENCY UNDERLYING POST-TRANSPLANT INFLAMMATORY BOWEL DISEASE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Ballerini Claudia	PD381	**ABATACEPT: A SUCCESSFUL OPTION IN A CHILD WITH LRBA DEFICIENCY**	**Poster Display 08: Therapy**
Baresi Giulia	PP001	**CLINICAL AND IMMUNOLOGICAL OUTCOMES OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR INBORN ERRORS OF IMMUNITY (IEIS): 20 YEARS' EXPERIENCE FROM A 220 PATIENTS' MONOCENTRIC COHORT**	**Poster Discussion 01: Therapies**
Baris Safa	OC040	**SEVERE ALLERGIC DYSREGULATION DUE TO A GAIN OF FUNCTION MUTATION IN THE TRANSCRIPTION FACTOR STAT6**	**Oral Communications 06: Late Breaking Abstracts**
Barman Prabal	PD251	**CLUSTERING OF CASES OF HEREDITARY ANGIOEDEMA IN A DISTRICT IN INDIA: A UNIQUE EXPERIENCE WITH A FOUNDER MUTATION**	**Poster Display 06: Genetics in IEI**
Barman Prabal	PD252	**PHENOTYPE-GENOTYPE CORRELATION OF TWO CHILDREN WITH FOXN1 DEFICIENT SEVERE**	**Poster Display 06: Genetics in IEI**

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Baronio Manuela	PD245	A NOVEL PATHOGENIC MUTATION IN MAGT1 IN X-LINKED MAGNESIUM DEFICIENCY WITH EPSTEIN-BARR VIRUS (EBV) INFECTION AND NEOPLASIA (XMEN) DISEASE	Poster Display 06: Genetics in IEI
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Bataneant Tatiana Mihaela	PD343	CARD11 – ONE GENE, MORE DISEASES	Poster Display 07: Genetics Diagnostics
Bauman M. Bradly	OC005	DOMINANT INTERFERING CARD11 VARIANTS DISRUPT JNK SIGNALING IN T CELLS	Oral Communications Session 01: B Cell T-Cell Biology
Becerra Loaiza Stephania Denisse	PD256	VARIANTS IN TNFSF13B ARE ASSOCIATED WITH COMMON VARIABLE IMMUNODEFICIENCY IN A WESTERN MEXICAN POPULATION.	Poster Display 06: Genetics in IEI
Becerra Loaiza Stephania Denisse	PD260	HLA-G RS66554220 (14-BP INS/DEL) IS NOT ASSOCIATED WITH COMMON VARIABLE IMMUNODEFICIENCY IN A WESTERN MEXICAN POPULATION.	Poster Display 06: Genetics in IEI
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Belevtsev S. Mikhail	WP015	IMMUNODEFICIENCY REGISTRY: A REPORT FROM BELARUS (2007-2021)	Working Party 06: PID Care in Development
Belevtsev S. Mikhail	PD348	LYMPHOPROLIFERATION AT THE ONSET OF PID PATIENTS IN THE REPUBLIC OF BELARUS	Poster Display 07: Genetics Diagnostics
Beltrán Alejandro Jorge	PD488	DESCRIPTION OF PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE AND TOOTH LOSS	Poster Display 09: Other
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Benavides-Nieto Marta	OC002	IMPAIRED LYMPHOCYTE TRAFFICKING AND PLATELET ACTIVATION IN A PATIENT WITH DE NOVO MUTATION IN RAP1B	Oral Communications Session 01: B Cell T-Cell Biology
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benhsaien ibtihal	PD403	**HAPLOIDENTICAL STEM CELL TRANSPLANTATION WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE IN A SEVERE COMBINED IMMUNE DEFICIENCY PATIENT: THE FIRST MOROCCAN CASE**	**Poster Display 08: Therapy**
benhsaien ibtihal	PD407	**MATERNAL T CELL INTERFERS IN HLA TYPING IN SEVERE COMBINED IMMUNODEFICIENCY**	**Poster Display 08: Therapy**
Ben-Mustapha Imen	PD113	**ALPS IN A PATIENT WITH FOXP3 MUTATION: A DIAGNOSTIC CHALLENGE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Bergman Peter	PD547	**SAFETY AND EFFICACY OF THE MRNA BNT162B2 VACCINE AGAINST SARS-COV-2 IN FIVE GROUPS OF IMMUNOCOMPROMISED PATIENTS AND HEALTHY CONTROLS IN A PROSPECTIVE OPEN-LABEL CLINICAL TRIAL**	**Poster Display 10: COVID-19**
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Bhavani SriLakshmi Gandham	PD267	**GENETIC EVALUATION OF INBORN ERRORS OF IMMUNITY IN INDIAN POPULATION**	**Poster Display 06: Genetics in IEI**
Bilgic Eltan Sevgi	PP014	**EXPANDING THE CLINICAL AND IMMUNOLOGICAL PHENOTYPES AND NATURAL HISTORY OF MALT1 DEFICIENCY**	**Poster Discussion 03: Immune Dysregulation**
Bilgic Eltan Sevgi	PD025	**PERSISTENT T LYMPHOPENIA AFTER CARDIAC SURGERY: LONG-TERM FOLLOW-UP WITH DETAILED CLINICAL AND IMMUNOLOGICAL EVALUATION**	**Poster Display 02: T-Cell Biology**
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Blancas Galicia Lizbeth	PD276	**MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE: RETROSPECTIVE CLINICAL AND GENETIC STUDY IN MEXICO**	**Poster Display 06: Genetics in IEI**
Blanco Lobo Pilar	PD085	**MOLECULAR SIGNATURES INDICATING INTERFERON SIGNALING DYSREGULATION AND ESTIMATION OF THE IMPACT OF EX VIVO JANUS KINASE INHIBITION IN DOWN SYNDROME**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Blom Maartje	PD299	**NEWBORN SCREENING FOR X-LINKEND AGAMMAGLOBULINEMIA: THE NEED FOR SECOND-TIER TESTING**	**Poster Display 07: Genetics Diagnostics**
Bludova Viktoriya	PD497	**HYPER IGE SYNDROME (HIES) CAUSED BY BI-ALLELIC HYPOMORPHIC MUTATIONS IN THE STAT3 GENE.**	**Poster Display 09: Other**
Bobcakova Anna	PD459	**KABUKI SYNDROME**	**Poster Display 09: Other**
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Boland Sharisa	PD362	**HRCT SCREENING FOR AIRWAY DISEASE IN PATIENTS WITH PRIMARY ANTIBODY DEFICIENCY: A 10-YEARS PERSPECTIVE FROM A DUTCH TERTIARY CENTER**	**Poster Display 07: Genetics Diagnostics**
Bondarenko Anastasiia	PD414	**ALLOGENIC HSCT IN PID PATIENTS IN UKRAINE**	**Poster Display 08: Therapy**
Bousfiha Ahmed Aziz	PD244	**RETROSPECTIVE STUDY: ABOUT 14 CONFIRMED CASES DIGEORGE**	**Poster Display 06: Genetics in IEI**

Boutboul David	PD320	**THE NEUROLOGICAL SPECTRUM OF ADULT GRISCELLI SYNDROME**	**Poster Display 07: Genetics Diagnostics**
Boutboul David	PD242	**IMMUNE DEFECTS EXPAND THE SPECTRUM OF KBG SYNDROME**	**Poster Display 06: Genetics in IEI**
Boyarchuk Boyarchuk Oksana	PD360	**NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY: FIRST PILOT STUDY IN UKRAINE**	**Poster Display 07: Genetics Diagnostics**
Boyarchuk Boyarchuk Oksana	PD419	**CYCLIC NEUTROPENIA IN A PATIENT WITH SRP54 DEFICIENCY SUCCESSFULLY TREATED WITH G-CSF**	**Poster Display 08: Therapy**
Brasseur Benoit	PD013	**PROBABLE SELECTIVE IGM DEFICIENCY (SIGMD) IN A 3-YEAR-OLD GIRL**	**Poster Display 01: B-Cell Biology**
Brodszki Nicholas	PD396	**SAFETY, TOLERABILITY AND IMMUNOGENICITY OF FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN IN PEDIATRIC PATIENTS WITH PRIMARY IMMUNODEFICIENCIES: FINAL RESULTS FROM A EUROPEAN POST-AUTHORIZATION STUDY**	**Poster Display 08: Therapy**
Bruno Mariolina	OC018	**RECOMBINANT INTERFERON GAMMA RESTORES ALTERED IMMUNOMETABOLISM IN CGD**	**Oral Communications Session 03: Innate Immune Defects**
Bullock Melody	PD393	**A NOVEL APPROACH TO CUSTOMIZING THE FLOW PROFILE FOR THE ADMINISTRATION OF SUBCUTANEOUS IMMUNOGLOBINS TO MINIMIZE OR ELIMINATE SITE REACTIONS – A CASE STUDY**	**Poster Display 08: Therapy**
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Butte J. Manish	PD370	**STUDY DESIGN AND BASELINE CHARACTERISTICS OF A SINGLE ARM, OPEN-LABEL, MULTICENTER, US REGISTRY STUDY OF ELAPEGADEMASE TREATMENT IN PATIENTS WITH ADA-SCID**	**Poster Display 08: Therapy**
Caballero-Oteyza Andrés	PD290	**GENIA DB - THE GENETIC IMMUNOLOGY ADVISOR DATABASE**	**Poster Display 06: Genetics in IEI**
Cabanero-Navalon Marta Dafne	PD082	**DIFFERENTIAL ANALYSIS OF LUNG MICROBIOME IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Cabanero-Navalon Marta Dafne	PD070	**CARDIOVASCULAR COMORBIDITY IN COMMON VARIABLE IMMUNODEFICIENCY: DATA FROM A MULTICENTRE SPANISH COHORT**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**

Cabanero-Navalon Marta Dafne	PD062	**DYSIMMUNE COMPLICATIONS OF COMMON VARIABLE IMMUNODEFICIENCY IN A MULTICENTER SPANISH-BASED COHORT**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Cagdas Ayvaz Deniz	PD234	**EBV RELATED LYMPHAMATOID GRANULOMATOSIS OF CENTRAL NERVOUS SYSTEM IN A PATIENT WITH CD70 DEFICIENCY**	**Poster Display 06: Genetics in IEI**
Camacho-Ordonez Nadezhda	PD117	**EXOME, TRANSCRIPTOME, EPIGENOME, AND PROTEOME ANALYSES IN B CELLS OF PATIENTS WITH NFKB1 IMMUNE DYSREGULATION**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Camacho-Ordonez Nadezhda	PD421	**DO CVID PATIENTS ON SCIG HAVE MORE AUTOIMMUNE THROMBOCYTOPENIC EVENTS THAN CVID PATIENTS ON IVIG?**	**Poster Display 08: Therapy**
Campbell Mollie Tessa	PP033	**RESPIRATORY VIRAL INFECTIONS IN OTHERWISE HEALTHY HUMANS WITH INHERITED IRF7 DEFICIENCY**	**Poster Discussion 06: Innate Immune Defects**
Campos Campos Luiza	WP013	**PHENOTYPE CAPTURE TOOL – A WEB-BASED TOOL TO COLLECT HPO-CODED PHENOTYPE**	**Working Party 04: Registry**
Campos Campos Luiza	PD226	**CHARACTERIZATION OF A LARGE COHORT OF PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY (CVID) USING HUMAN PHENOTYPE ONTOLOGY (HPO)**	**Poster Display 06: Genetics in IEI**
Campos Campos Luiza	PD036	**SKIN MANIFESTATIONS IN ADULTS WITH CHRONIC GRANULOMATOUS DISEASE (CGD) IN THE UNITED KINGDOM**	**Poster Display 03: Biology of Innate Immunity**
CAPILNA EMIL TUDOR	PD364	**HYPER IGE SYNDROME (JOB SYNDROME) IN ROMANIA: A CASE REPORT**	**Poster Display 07: Genetics Diagnostics**
Carrabba Maria	PD518	**THE "BREAKTHROUGH" COVID-19 IN 3-DOSES VACCINATED PATIENTS WITH INBORN ERRORS OF IMMUNITY AND THE EARLY TREATMENT WITH MONOCLONAL ANTIBODIES AND ANTIVIRALS**	**Poster Display 10: COVID-19**
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Carrabba Maria	PD536	**X-LINKED AGAMMAGLOBULINEMIA AND SARS-COV-2**	**Poster Display 10: COVID-19**
Castagnoli Riccardo	PD490	**GUT IMMUNOPATHOLOGICAL SIGNATURES IN HUMANS AND MICE CARRYING RAG1 HYPOMORPHIC MUTATIONS**	**Poster Display 09: Other**
Catelli Arianna	PD336	**THE DARK SIDE OF APDS2: A STORY TOLD THROUGH FDG-PET**	**Poster Display 07: Genetics Diagnostics**

Cay Ezgi	PD450	**A RARE CAUSE OF IMMUNODEFICIENCY : TWO SISTERS WITH DIAGNOSIS OF ADENOSINE DEAMINASE (ADA) ENZYME DEFICIENCY**	**Poster Display 09: Other**
Cay Ezgi	PP013	**HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN CHILDREN WITH GRISCELLI SYNDROME : EXPERIENCE AND OUTCOMES**	**Poster Discussion 03: Immune Dysregulation**
Chacon-Arguedas Daniel	PD035	**BED-TO-BENCH PATIENT-DERIVED T LYMPHOCYTE DEFICIENCY CELL MODELS**	**Poster Display 02: T-Cell Biology**
Chan Max Kam-Kwan	PD042	**P2Y12 IS A NOVEL DRUGGABLE TARGET FOR BLOCKING MACROPHAGE-MYOFIBROBLAST TRANSITION DRIVEN CANCER-ASSOCIATED FIBROBLAST FORMATION IN LUNG CARCINOMA**	**Poster Display 03: Biology of Innate Immunity**
Chandra Anita	PD007	**THE ROLE OF THE STEROID PRODUCING ENZYME CYP11A1 IN B CELL SUBSETS LINKED TO ACTIVATED PI3KDELTA SYNDROME**	**Poster Display 01: B-Cell Biology**
chavoshzadeh zahra	PD430	**VERY EALY ONSET IBD WITH MUTATION IN INTERFERON REGULATORY FACTOR-2 BINDING PROTEIN 2 (IRF2BP2)**	**Poster Display 09: Other**
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Chetty Kritika	PD435	**EYE INVOLVEMENT IN ADENOSINE DEAMINASE (ADA) DEFICIENCY SCID PATIENTS**	**Poster Display 09: Other**
Chovancova Zita	PD335	**ANTIVIRAL ANTIBODIES IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY (CVID)**	**Poster Display 07: Genetics Diagnostics**
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Cicalese Maria Pia	PD412	**GENE THERAPY FOR ADENOSINE DEAMINASE DEFICIENCY: LONG-TERM OUTCOME AND POST-MARKETING EXPERIENCE.**	**Poster Display 08: Therapy**
CINETTO FRANCESCO	PD063	**ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN COMMON VARIABLE IMMUNODEFICIENCY: IMPACT OF B CELL IMPAIRMENT.**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Cinicola Bianca Laura	PD018	**ALLERGIC PHENOTYPE AND FOLLOW-UP OF CHILDREN AND ADOLESCENTS WITH SELECTIVE IGA DEFICIENCY: AN ITALIAN MONOCENTRIC STUDY**	**Poster Display 01: B-Cell Biology**
Cirillo Emilia	PD030	**ANALYSIS OF CIRCULATING MIRNAS TO IDENTIFY PHENOTYPIC VARIABILITY IN ATAXIA TELANGIECTASIA PATIENTS**	**Poster Display 02: T-Cell Biology**

Classen Carl Friedrich	PD058	**RARE – OR NON-LANGERHANS CELL – HISTIOCYTOSES: THE GERMAN COLLECTION AND CONSULTATION SERVICE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
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Colobran Oriol Roger	PD083	**DETECTION AND EVOLUTIONARY DYNAMICS OF SOMATIC VARIANTS CAUSING ALPS IN PERIPHERAL BLOOD SAMPLES WITH HIGH AND LOW DOUBLE-NEGATIVE ALPHA-BETA T CELL COUNTS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Colobran Oriol Roger	PP008	**SOMATIC REVERTANT MOSAICISM CORRELATING WITH CLINICAL IMPROVEMENT IN A PATIENT WITH TNFRSF9 (CD137) DEFICIENCY**	**Poster Discussions 02: Immune Mechanisms**
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Conrey E Peyton	PD032	**PRIMARY IMMUNE REGULATORY DISORDERS (PIRDS) THAT AMPLIFY TCR SIGNALING SHARE PATTERNS OF T CELL EXHAUSTION**	**Poster Display 02: T-Cell Biology**
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Consonni Filippo	PD093	**FADD DEFICIENCY MAY IMPAIR FAS-MEDIATED APOPTOSIS IN THE ABSENCE OF AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS) BIOMARKERS: A RARE, EXPANDING PHENOTYPE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Consonni Filippo	PD068	**INBORN ERRORS OF IMMUNITY (IEI) IN PEDIATRIC HEMATOLOGY DEPARTMENTS: TIME TO INCREASE DIAGNOSTIC AWARENESS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Conti Francesca	PD124	**DOUBLE NEGATIVE B CELLS EXPANSION IN A PEDIATRIC PATIENT WITH**	**Poster Display 04: Immune**

		HYPOGAMMAGLOBULINEMIA AND HIGH FAMILIAL PREDISPOSITION TO AUTOIMMUNITY: IS THERE A LINK?	Dysregulation & Autoimmune Disorders
Conti Francesca	PD508	LIFE-THREATENING COVID-19 PNEUMONIA IN AN 11-YEAR-OLD CHILD WITH AUTOANTIBODIES AGAINST TYPE I IFNS	Poster Display 10: COVID-19
Conti Francesca	PD182	NOVEL INSIGHTS INTO IMMUNE DYSREGULATION- AND HYPER-INFLAMMATION-RELATED NEUROLOGICAL DISORDERS AS SIGNS SUSPICIOUS FOR INBORN ERRORS OF IMMUNITY	Poster Display 05: Autoinflammatory Disorders
Cornish Kevin Spencer Jasper	OC031	A NOVEL INBORN ERROR OF IMMUNITY CAUSED BY MUTATIONS IN NFKBID	Oral Communications Session 05: Novel Defects and Mechanisms
Cucchetti Francesca Martina	PD479	IGG2 DEFICIENCY OR SOMETHING ELSE? A MISLEADING PHENOTYPE OF ACTIVATED PI3-KINASE DELTA SYNDROME TYPE 1	Poster Display 09: Other
Cuesta Martín de la Cámara Ricardo	PD250	NEW HYPOMORPHIC CYBB VARIANT IN A 12 YEARS OLD BOY WITH IBD: FUNCTIONAL ANALYSIS, SEGREGATION STUDY AND CLINICAL INTERPRETATION	Poster Display 06: Genetics in IEI
Cuesta Martín de la Cámara Ricardo	PD554	HUMORAL AND CELLULAR IMMUNE RESPONSE TO MRNA SARS-COV-2 VACCINE IN PATIENTS WITH IMPAIRMENT OF HUMORAL IMMUNITY	Poster Display 10: COVID-19
Cunha DA CUNHA Jose Marcos	PD044	VERY LATE-ONSET CHRONIC GRANULOMATOUS DISEASE: FACT OR ARTIFACT?	Poster Display 03: Biology of Innate Immunity
Cunha Cunha Maria	PD050	A CASE OF STAT-1 GAIN OF FUNCTION MASQUERADING AS AUTOIMMUNE DISEASE	Poster Display 03: Biology of Innate Immunity
Cunha Cunha Maria	PD051	A CASE OF CHRONIC GRANULOMATOUS DISEASE WITH DISSEMINATED INFECTION DUE TO PHAEOACREMONIUM PARASITICUM TREATED WITH VORICONAZOLE	Poster Display 03: Biology of Innate Immunity
Cutajar Jonathan	PD394	THE RESPIRATORY INFECTIOUS BURDEN OF A LARGE COHORT OF ANTIBODY DEFICIENT PATIENTS ON IMMUNOGLOBULIN REPLACEMENT THERAPY	Poster Display 08: Therapy
Dabrowska Leonik Nel	PD246	CONTIGUOUS XP11.4 DELETIONS IN PATIENTS WITH ORNITHINE TRANSCARBAMYLASE DEFICIENCY AND CHRONIC GRANULOMATOUS DISEASE: CLINICAL AND MOLECULAR CHARACTERISTICS OF TWO CASES	Poster Display 06: Genetics in IEI
D'AULERIO ROBERTA	PD011	REVEALING THE MOLECULAR ROLE OF WASP IN THE NUCLEUS OF B CELLS.	Poster Display 01: B-Cell Biology
de Cevins Camille	OC011	SINGLE-CELL TRANSCRIPTOMICS EXPLORATION OF PATIENTS WITH STING-ASSOCIATED	Oral Communications Session 02:

		VASCULOPATHY WITH ONSET IN INFANCY (SAVI)	Autoinflammation and Immune Dysregulation
de Gier Melanie	PD004	MOLECULAR PROFILING OF AUTOIMMUNE MANIFESTATIONS AFTER PEDIATRIC ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION.	Poster Display 01: B-Cell Biology
de Vries de Vries Esther	PD431	MALE-FEMALE DIFFERENCES IN IMMUNOGLOBULIN LEVELS IN PRIMARY ANTIBODY DEFICIENCY (PAD) PATIENTS IN THE UNPAD STUDY	Poster Display 09: Other
Debler Lisa	PD106	AUTOLOGOUS RECONSTITUTION OF T-CELLS WITH COMPLETE NON-T-CELL DONOR CHIMERISM AFTER BONE MARROW TRANSPLANTATION IN A PATIENT WITH APDS1	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
del Pino Molina Lucia	PD012	FUNCTIONAL ASSAYS IN B CELLS TO DETERMINE THE PATHOGENICITY IN ATYPICAL BTK VARIANTS.	Poster Display 01: B-Cell Biology
Delafontaine Selket	PP006	C-TERMINAL DOMAIN COPA MUTATIONS IN SIX CHILDREN FROM THREE UNRELATED FAMILIES WITH AUTOSOMAL DOMINANT COPA SYNDROME	Poster Discussions 02: Immune Mechanisms
DELAGE Laure	PS022	LOW CTLA-4 EXPRESSION BY NBEAL2 DEFICIENT CONVENTIONAL T CELLS AND IMMUNE DYSREGULATION IN GRAY PLATELET SYNDROME.	Parallel Session 11: IEI and Hematological Disease/BM Failure
Dell'Edera Alessandro	PD303	PREVALENCE OF MALIGNANCIES IN AN ITALIAN COHORT OF PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY (CVID): A SINGLE CENTER RETROSPECTIVE STUDY.	Poster Display 07: Genetics Diagnostics
Demir Meryem	PD264	NOVEL CD19 MUTATION CAUSES REMARKABLY LOW B CELL NUMBERS AND P-ANCA POSITIVE IMMUNE-COMPLEX GLOMERULONEPHRITIS	Poster Display 06: Genetics in IEI
Deng Mengyue	PD108	A NOVEL STAT3 GAIN-OF-FUNCTION MUTATION IN FATAL INFANCY-ONSET INTERSTITIAL LUNG DISEASE	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
Deveci Demirbas Nazli	PD378	SUCCESSFUL TREATMENT WITH HAPLOIDENTICAL STEM CELL TRANSPLANTATION AFTER TCRAB/CD19 DEPLETION IN AN ICOS-DEFICIENT PATIENT	Poster Display 08: Therapy
Deveci Demirbas Nazli	PD400	THE VERY FIRST PATIENT OF IL-21 DEFICIENCY SUCCESSFULLY TREATED WITH HEMATOPOETIC STEM CELL TRANSPLANTATION	Poster Display 08: Therapy

Di Natale Marisa	PD203	**LATE DIAGNOSIS IN ADULTHOOD OF A PATIENT WITH HYPER IMMUNOGLOBULIN D SÍNDROME (HIDS): IMPACT QUALITY OF LIFE.**	**Poster Display 05: Autoinflammatory Disorders**
Díaz-Luna Mercedes	PD543	**STRONG ANTIBODY AND T-CELL RESPONSES AGAINST SARS-COV-2 IN A PATIENT WITH CYTOTOXIC T-LYMPHOCYTE ANTIGEN-4 (CTLA-4) INSUFFICIENCY DUE TO THE NOVEL MUTATION P.GLY142ASP IN CTLA-4.**	**Poster Display 10: COVID-19**
Díaz-Luna Mercedes	PD279	**POLYGENIC CONTRIBUTION IN THE MOLECULAR DIAGNOSIS OF VERY EARLY ONSET INFLAMMATORY BOWEL DISEASE**	**Poster Display 06: Genetics in IEI**
Díaz-Luna Mercedes	PD404	**HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN AS A PROTOCOL FOR LONG-TERM SURVIVAL AFTER LUNG TRANSPLANTATION IN COMMON VARIABLE IMMUNODEFICIENCY**	**Poster Display 08: Therapy**
Diez Jose Maria	PD549	**DYNAMICS OF ANTI-SARS-COV-2 NUCLEOPROTEIN ANTIBODIES IN IGG MEDICINAL PRODUCTS AS A DIRECT REFLECTION OF VIRUS EXPOSURE OF THE DONOR POPULATION: FOLLOW-UP SINCE MARCH 2020**	**Poster Display 10: COVID-19**
Diez Jose Maria	PD546	**ANTI-SARS-COV-2 S ANTIBODIES IN HEALTHY DONOR PLASMA POOLS AND IGG MEDICINAL PRODUCTS: FOLLOW-UP SINCE MARCH 2020**	**Poster Display 10: COVID-19**
Diez Jose Maria	PD443	**CURRENT SEASONAL IGG MEDICINAL PRODUCTS ARE ACTIVE AGAINST EXPECTED FUTURE INFLUENZA VIRUS STRAINS**	**Poster Display 09: Other**
Dinges Svenja Sarah	PS016	**LOSS OF HOXA3 CAUSES LARYNGEAL DYSMORPHIA, THYMIC APLASIA AND SEVERE COMBINED IMMUNODEFICIENCY (SCID)**	**Parallel Session 08: Thymic IEI**
Discardi Claudia	PD326	**IMMUNOLOGICAL AND CLINICAL CHARACTERIZATION OF GASTRIC PATHOLOGY IN COMMON VARIABLE IMMUNODEFICIENCY (CVID) PATIENTS: A SINGLE CENTRE RETROSPECTIVE STUDY.**	**Poster Display 07: Genetics Diagnostics**
Diwakar Lavanya	PD463	**THE LIVED EXPERIENCE OF HEREDITARY ANGIOEDEMA: EXPERIENCES OF MEDICATION USE AND EMERGENCY CARE**	**Poster Display 09: Other**
Diwakar Lavanya	PD447	**THE LIVED EXPERIENCE OF HEREDITARY ANGIOEDEMA: THE RELATIONSHIP BETWEEN ILLNESS REPRESENTATIONS, WELLBEING, QUALITY OF LIFE AND COPING IN PATIENTS WITH HEREDITARY ANGIOEDEMA**	**Poster Display 09: Other**
Dockes Marina	WP012	**LYMPHOPROLIFERATIVE DISEASES IN THE XLP1 SYNDROME**	**Working Party 04: Registry**
Dotta Laura	PD073	**A NOVEL FAMILIAL CASE OF TNFAIP3 MUTATION CAUSES LYMPHOPENIA AND AN**	**Poster Display 04: Immune**

		AUTOINFLAMMATORY DISORDER RESPONSIVE TO ANAKINRA	Dysregulation & Autoimmune Disorders
Dotta Laura	PD249	A NOVEL FRAMESHIFT CXCR4 MUTATION CAUSES A MILDER FORM OF WHIM SYNDROME	Poster Display 06: Genetics in IEI
Drabe Camilla Heldbjerg	PD507	ANTIBODY RESPONSE FOLLOWING THE THIRD AND FOURTH SARS-COV-2 VACCINE DOSE IN INDIVIDUALS WITH COMMON VARIABLE IMMUNODEFICIENCY	Poster Display 10: COVID-19
Driessen Gertjan	PD021	THE EFFECTS OF INTRA UTERINE EXPOSURE TO IMMUNOMODULATING CHEMOTHERAPY ON THE DEVELOPING IMMUNE SYSTEM OF THE INFANT	Poster Display 01: B-Cell Biology
Dubrowinskaja Natalia	PD163	EXPLORING THE DNA METHYLATION PATTERN IN IMMUNE CELLS OF A FAMILY WITH VARIABLE MANIFESTATION OF ICF2 SYNDROME	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
Duncan James Arthur Christopher	PP029	TYPE I INTERFERON MEDIATED NEUROPATHOLOGY IN A MOUSE MODEL OF STAT2 GAIN-OF-FUNCTION	Poster Discussion 06: Innate Immune Defects
Edwards Emily S.J.	PD217	COMBINED IMMUNODEFICIENCY AND IMPAIRED PI3K SIGNALING IN A PATIENT WITH BIALLELIC LCP2 VARIANTS	Poster Display 06: Genetics in IEI
Edwards Emily S.J.	PP007	PREDOMINANTLY ANTIBODY DEFICIENCY AND ENHANCED PI3K SIGNALLING IN B CELLS OF A PATIENT WITH A HETEROZYGOUS MISSENSE VARIANT IN SYK	Poster Discussions 02: Immune Mechanisms
Effner Renate	PD103	IMPROVE UNDERSTANDING OF STAPHYLOCOCCUS AUREUS INFECTION IN STAT3-HYPER IGE SYNDROME	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
Ehl Stephan	PP023	SERUM BIOMARKERS AND DNT PHENOTYPING CAN PREDICT COMPLEX FAS GENE ALTERATIONS IN ALPS-U PATIENTS	Poster Discussion 05: Next Generation Sequencing and Other Diagnostics
Ehlers Lisa	PD266	ADA2 DEFICIENCY MIMICKING ACUTE DISSEMINATED ENCEPHALOMYELITIS	Poster Display 06: Genetics in IEI
El Allam Aicha	PD366	PEDIATRIC REFERENCE RANGES IN THE MOROCCAN POPULATION	Poster Display 07: Genetics Diagnostics
Elkins Megan	PD060	LEUCINE-RICH REPEAT-CONTAINING PROTEIN 8A IS ESSENTIAL FOR T CELL-DRIVEN ACUTE GRAFT VERSUS HOST DISEASE	Poster Display 04: Immune Dysregulation & Autoimmune Disorders

Ellis Natalya	PD417	**CASE REPORT: USE OF PROPHYLACTIC SUBCUTANEOUS C1 ESTERASE INHIBITION FOR HEREDITARY ANGIOEDEMA IN PREGNANCY**	**Poster Display 08: Therapy**
Elmi Abdelsalam Asha	PD162	**VARIANT OF UNKNOWN SIGNIFICANCE IN CARMIL2 RESULTS IN HYPOMORPHIC FUNCTION WITH DECREASED INTERLEUKIN-2 (IL-2) PRODUCTION**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Erkmen Hasret	PD465	**A RIPK1-DEFICIENT PATIENT PRESENTED WITH COMBINED IMMUNODEFICIENCY AND VERY EARLY-ONSET INFLAMMATORY BOWEL DISEASE.**	**Poster Display 09: Other**
Erkmen Hasret	PD481	**A RARE CAUSE OF COMBINED IMMUNODEFICIENCY: ORAI-1 DEFECT**	**Poster Display 09: Other**
Errami Abderrahmane	PD284	**MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASES IN MOROCCAN KINDREDS: CLINICAL, IMMUNOLOGICAL AND GENETIC FEATURES**	**Poster Display 06: Genetics in IEI**
Erwa Hashim Hassan Nahla	PD087	**FEATURES OF IMMUNE DYSREGULATION IN PRIMARY IMMUNODEFICIENCY PATIENTS AT SOBA UNIVERSITY HOSPITAL, KHARTOUM – SUDAN**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
ESCOBAR MARIA ANGELES	INGID001	**AUDIT OF ADEQUACY OF USE OF GGIV IN TIME OF CUT IN SUPPLY OF PRODUCTS DUE TO COVID19 PANDEMIC. HOW TO HANDLE IT.**	**Poster Display 11: INGID**
Farinha Costa Inês	PD116	**NOCARDIA BRAIN ABSCESS AND PULMONARY ASPERGILLOSIS IN AN ADULT PATIENT: DIAGNOSTIC CHALLENGE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Farmand Susan	PD214	**LACK OF STAT3 MODIFIES MACROPHAGE ACTIVATION IN S. AUREUS INFECTION TOWARDS AN ENHANCED INFLAMMATORY PHENOTYPE WITHOUT AFFECTING BACTERIAL CLEARANCE**	**Poster Display 06: Genetics in IEI**
Fasshauer Maria	PD397	**REAL-WORLD UTILIZATION, SAFETY AND PATIENT EXPERIENCE OF 20% SUBCUTANEOUS IMMUNOGLOBULIN IN PATIENTS WITH PRIMARY IMMUNODEFICIENCIES: FINAL DATA FROM THE CORE STUDY**	**Poster Display 08: Therapy**
Fasshauer Maria	PD408	**COMPARISON OF FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN USE BETWEEN PATIENTS WITH PRIMARY OR SECONDARY IMMUNODEFICIENCIES: RESULTS FROM THE FACILITATED IMMUNOGLOBULIN ADMINISTRATION REGISTRY AND OUTCOMES STUDY (FIGARO)**	**Poster Display 08: Therapy**

Fedulkina Andreevna Veronika	PD114	**EXTRACORPOREAL PHOTOPHERESIS AND RENAL TRANSPLANT IMMUNE TOLERANCE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Ferrua Francesca	WP001	**LENTIVIRAL HEMATOPOIETIC STEM AND PROGENITOR CELL GENE THERAPY FOR WISKOTT-ALDRICH SYNDROME: SAFETY AND CLINICAL BENEFIT IN 23 PATIENTS UP TO 10.5 YEARS OF FOLLOW-UP**	**Working Party 01: Inborn Errors**
Fevang Børre	PD559	**IMPAIRED RESPONSE TO THIRD DOSE COVID-19 MRNA VACCINE IN INBORN ERRORS OF IMMUNITY**	**Poster Display 10: COVID-19**
Fischer Marco	PS017	**JAK-INHIBITOR TREATMENT OF INBORN ERRORS OF IMMUNITY WITH DYSREGULATED JAK/STAT SIGNALLING, AN ESID AND EBMT INBORN ERRORS WORKING PARTY STUDY**	**Parallel Session 09: Treatment - Novel/Targeted**
Freeman M. Catherine	PD231	**UNEXPECTED PHENOTYPE OF A KNOWN PATHOGENIC IL2RG VARIANT IN A 38-YEAR-OLD MALE PATIENT**	**Poster Display 06: Genetics in IEI**
Freeman F Alexandra	PD096	**TRACHEAL DIVERTICULUM IN DNSTAT3 HYPER IGE SYNDROME**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Freeman F Alexandra	PD374	**REVERSAL OF SEZARY SYNDROME AND PML THROUGH HEMATOPOIETIC STEM CELL TRANSPLANTATION IN A YOUNG ADULT WITH DOCK8 DEFICIENCY**	**Poster Display 08: Therapy**
Freiberger Tomas	PD270	**DIFFERENT PATTERNS OF IMMUNE SYSTEM ACTIVATION IN HEREDITARY ANGIOEDEMA BASED ON DISEASE SEVERITY**	**Poster Display 06: Genetics in IEI**
Fritsch-Stork Ruth	PD144	**SJÖGREN-LIKE SYNDROME, MULTIPLE AUTOIMMUNE DISEASES, THYMOMA AND GENETIC VARIANTS IN AIRE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Fuentes Isela Elma	PD170	**THE NEXT GREAT MASQUERADER: FOUR PATIENTS WITH ACTIVATING PIK3CD MUTATIONS AND DIVERSE PHENOTYPES**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Fusaro Mathieu	PP018	**LCK GAIN OF FUNCTION VARIANT IN TWO SIBLINGS WITH SEVERE CD8 T CELL LYMPHOPENIA**	**Poster Discussion 04: T Cell & B Cell Biology**

Gacem Ourida	PD052	**INFECTIONS WITH REPEATED SUPPURATION THINK ABOUT PRIMARY IMMUNODEFICIENCY: CASE REPORT**	**Poster Display 03: Biology of Innate Immunity**
Gámez-Díaz Laura	OC009	**LRBA DRIVES ACTIN CYTOSKELETON DYNAMICS THROUGH INTERACTION WITH MYOSIN-9**	**Oral Communications Session 02: Autoinflammation and Immune Dysregulation**
Gámez-Díaz Laura	PP012	**DISSECTING THE ROLE OF LRBA IN AUTOPHAGY AND ITS IMPACT ON ANTIGEN PRESENTATION**	**Poster Discussion 03: Immune Dysregulation**
Gangadharan Gangadharan Harikrishnan	PD120	**PRIMARY IMMUNODEFICIENCY DISORDERS PRESENTING WITH AUTOIMMUNE MANIFESTATIONS IN THE ADULT INTERNAL MEDICINE WARD OF A TERTIARY CARE CENTRE IN SOUTH INDIA- A CASE SERIES.**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Gangadharan Gangadharan Harikrishnan	PD202	**NEONATAL ONSET MULTISYSTEM INFLAMMATORY DISEASE (NOMID)- A SERIES OF TWO PATIENTS FROM A TERTIARY CARE CENTER IN NORTH INDIA.**	**Poster Display 05: Autoinflammatory Disorders**
Garcez Tomaz	PD561	**THE USE OF COVID SEROLOGY IN THE ASSESSMENT OF PATIENTS FOR IMMUNODEFICIENCY**	**Poster Display 10: COVID-19**
Garcia-Prat Marina	PD209	**CAN WE PREDICT WHEN TO EVALUATE CVID GENETICALLY?**	**Poster Display 06: Genetics in IEI**
García-Soidán Ana	PD283	**COEXISTENCE OF TNFRSF13B AND IL2RG MUTATIONS IN A PATIENT WITH CVID**	**Poster Display 06: Genetics in IEI**
Gardner Logan	PD094	**DEVELOPMENT OF LYMPHOMATOID GRANULOMATOSIS IN DEFICIENCY OF ADENOSINE DEAMINASE 2 WITH UNCONTROLLED EBV INFECTION**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Gattorno Marco	OC012	**AN UPDATE OF THE INTERNATIONAL REGISTRY ON COVID-19 RELATED HYPERINFLAMMATION IN CHILDREN AND YOUNG ADULTS (HYPERPED-COVID)**	**Oral Communications Session 02: Autoinflammation and Immune Dysregulation**
Geier B. Christoph	OC001	**LOSS-OF-FUNCTION MUTATIONS IN PDLIM1 ABROGATE TH17 DIFFERENTIATION BY T-CELL EXHAUSTION IN HUMANS AND MICE**	**Oral Communications Session 01: B Cell T-Cell Biology**
Gemici Karaaslan Hatice Betul	PD436	**CHRONIC RHINOSINUSITIS IN PEDIATRIC PATIENTS WITH PRIMARY IMMUNODEFICIENCY**	**Poster Display 09: Other**
Gemici Karaaslan Hatice Betul	PD241	**MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASES; A SMALL COHORT WITH DIFFERENT DIAGNOSES**	**Poster Display 06: Genetics in IEI**

Germer Matthias	PD509	**EMERGENCE OF SARS-COV-2 ANTIBODIES IN AN INTRAVENOUS IMMUNOGLOBULIN PREPARATION**	**Poster Display 10: COVID-19**
Ghosh Sujal	PD359	**BALLER-GEROLD SYNDROME – RECQL4 PATIENT IDENTIFIED BY TREC NEWBORN SCREENING**	**Poster Display 07: Genetics Diagnostics**
Ghosh Sujal	PD069	**MHV68 INFECTION CAUSES A DISTINCT LUNG PHENOTYPE IN ITK-/- DEFICIENT MICE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Giardino Giuliana	PD261	**COMBINED IMMUNE-DEFICIENCY IN A YOUNG BOY WITH ADNP VARIANT: EXPANDING THE PHENOTIPIC SPECTRUM OF HELSMOORTEL-VAN DER AA SYNDROME**	**Poster Display 06: Genetics in IEI**
Giardino Giuliana	PD462	**A NOVEL WASP SPLICE-SITE MUTATION IN A PATIENT WITH WISKOTT-ALDRICH SYNDROME**	**Poster Display 09: Other**
Giardino Giuliana	PD432	**DEFINITION OF THE ROLE OF MIRNA IN THE CLINICAL VARIABILITY OF 22Q11.2DS**	**Poster Display 09: Other**
Giardino Giuliana	PD193	**SUCCESSFUL USE OF SECUKINUMAB IN A PATIENT WITH SYNOVITIS, ACNE, PUSTOLOSIS, HYPEROSTOSIS, OSTEITIS (SAPHO) SYNDROME**	**Poster Display 05: Autoinflammatory Disorders**
Giardino Giuliana	PD229	**INTRA AND INTER-FAMILIAL CLINICAL VARIABILITY IN PATIENTS WITH 22Q11.2 DELETION SYNDROME: GENOTYPE TO PHENOTYPE CORRELATION**	**Poster Display 06: Genetics in IEI**
Giardino Giuliana	PD375	**SUCCESSFUL TREATMENT OF DRUG-RESISTANT CHRONIC COLITIS WITH TGF-BETA2-CONTAINING HYDROLYSATE FORMULATION IN A PATIENT WITH X-LINKED LYMPHOPROLIFERATIVE SYNDROME TYPE 1 FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION**	**Poster Display 08: Therapy**
Givol Or	PD139	**ICF1 PATIENTS TREATED WITH IVIG, THE IMPORTANCE OF EARLY RECOGNITION AND INITIATION OF TREATMENT AS SEEN IN TWO CASE STUDIES.**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Gkantaras Antonios	PD100	**FAMILY HISTORY OF IMMUNE DYSREGULATION IN A GREEK COHORT OF PATIENTS WITH PAEDIATRIC-ONSET COMMON VARIABLE IMMUNODEFICIENCY DISORDERS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Gkantaras Antonios	PD314	**INITIAL PRESENTING MANIFESTATIONS OF PAEDIATRIC-ONSET COMMON VARIABLE IMMUNODEFICIENCY DISORDERS: A 20-YEAR EXPERIENCE OF TWO GREEK REFERRAL CENTRES**	**Poster Display 07: Genetics Diagnostics**

Gkantaras Antonios	PD172	**SYSTEMS BIOLOGY AND MACHINE LEARNING APPROACHES IDENTIFY COMMON VARIABLE IMMUNODEFICIENCY PATIENTS WITH IMMUNE DYSREGULATION MANIFESTATIONS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Glashoff H Richard	PD131	**NOVEL IL12RB1 VARIANT ASSOCIATED WITH SEVERE TUBERCULOSIS IN A SOUTH AFRICAN FAMILY**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Goda Rayan	PD090	**FUNCTIONAL ASSESSMENT OF IMMUNOLOGICAL RESPONSE IN TWO PATIENTS WITH IL-10RA MUTATION PRESENTING WITH EARLY-ONSET INFLAMMATORY BOWEL DISEASE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Goddard Sarah	PD372	**SURVEY OF COMPLEX MULTI-SYSTEM COMMON VARIABLE IMMUNODEFICIENCY PRESENTATION, INVESTIGATION AND TREATMENT IN 15 CENTRES IN THE UNITED KINGDOM**	**Poster Display 08: Therapy**
GOEL SUMIT	PD079	**LYMPHOCYTE PROLIFERATION ASSAY BY FLOW-CYTOMETRY: OUR EXPERIENCE FROM CHANDIGARH, NORTH INDIA**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Goffard Jean-Christophe	WP004	**EXPLORING THE OLIGOGENIC ASPECTS OF COMMON VARIABLE IMMUNODEFICIENCIES USING ORVAL**	**Working Party 02: Genetics**
Goldacker Sigune	PD401	**TREATMENT OF CAMPYLOBACTER ENTERITIS IN COMMON VARIABLE IMMUNODEFICIENCY - A MONOCENTRIC EXPERIENCE**	**Poster Display 08: Therapy**
Golwala Mohammedi Zainab	PP024	**USE OF EX VIVO T CELL DIFFERENTIATION ASSAYS IN THERAPEUTIC MANAGEMENT OF GENETICALLY UNDEFINED T-B+NK+ SEVERE COMBINED IMMUNODEFICIENCY (SCID)**	**Poster Discussion 05: Next Generation Sequencing and Other Diagnostics**
Gomez Hernandez Noemi	PD350	**MYCOBACTERIUM ABCESSUS IN A PATIENT WITH ARPC1B MUTATION**	**Poster Display 07: Genetics Diagnostics**
Gomez Hernandez Noemi	PD409	**OTHER USES IMMUNOGLOBULIN INTRAVENOUS IN PATIENT WHIT GATA 2 DEFICIENCY .**	**Poster Display 08: Therapy**
gómez pérez gómez jimena	PD015	**SPLENECTOMY FOR THE TREATMENT OF A CVID PATIENT WITH REFRACTORY CHRONIC PANCITOPENIA AND HETEROZYGOUS ALLELIC VARIANT IN THE CR2 GENE**	**Poster Display 01: B-Cell Biology**
González Torbay Andrea	PD235	**NEW APPROACHES IN THE GENETIC DIAGNOSIS OF PRIMARY IMMUNODEFICIENCIES: DEVELOPMENT OF A NEW STRATEGY FOR THE EVALUATION OF CNVS THROUGH NGS**	**Poster Display 06: Genetics in IEI**

González-Torbay Andrea	PD399	OUTCOMES OF DIFFERENT THERAPEUTIC APPROACHES FOR ADA-SCID: A SINGLE CENTER EXPERIENCE	Poster Display 08: Therapy
Goretzki Adrian	PD455	PLASMA DONATIONS AND PLASMA-DERIVED PRODUCTS. SITUATION IN POLAND IN COMPARISON TO OTHER EU COUNTRIES	Poster Display 09: Other
Gorochov Guy	PD562	LOWER DISEASE ACTIVITY BUT HIGHER RISK OF SEVERE COVID-19 AND HERPES ZOSTER IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS WITH PRE-EXISTING AUTOANTIBODIES NEUTRALISING IFN-ALPHA	Poster Display 10: COVID-19
Gothe Florian	PS014	ABERRANT INFLAMMATORY RESPONSES TO TYPE I INTERFERON IN STAT2 OR IRF9 DEFICIENCY	Parallel Session 07: Autoinflammatory Diseases
Goyal Taru	PD135	A DIAGNOSTIC ODYSSEY IN A FEMALE ADOLESCENT WITH RECURRENT SINOPULMONARY INFECTIONS AND POLYARTHRITIS	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
Gray Edgar Paul	PD210	TNFAIP3 DELETIONS BECOME CLINICALLY APPARENT WITH IN TRANS EXPRESSION OF THE HYPOMORPHIC DENISOVAN-DERIVED ADAPTIVELY INTROGRESSED I207L ALLELE	Poster Display 06: Genetics in IEI
Griffin Griffin Helen	PD221	PROVIDING A GENETIC DIAGNOSIS FOR GENOMICS ENGLAND 100,000 GENOMES PROJECT PARTICIPANTS WITH AN INBORN ERROR OF IMMUNITY	Poster Display 06: Genetics in IEI
Griffin Griffin Helen	PP027	SPLICING DEFECT DUE TO A SYNONYMOUS MUTATION IN DOCK2 CAUSING DOCK2 DEFICIENCY	Poster Discussion 05: Next Generation Sequencing and Other Diagnostics
Grimbacher Bodo	PD422	THE GAIN REGISTRY – A NEW PROSPECTIVE STUDY FOR PATIENTS WITH MULTI-ORGAN AUTOIMMUNITY	Poster Display 09: Other
Grimbacher Bodo	PP031	DETRIMENTAL NFKB1 MISSENSE VARIANTS AFFECTING THE REL-HOMOLOGY DOMAIN OF P105/P50	Poster Discussion 06: Innate Immune Defects
Guarnieri Valentina	PD297	A TRIPLE NEWBORN SCREENING STRATEGY FOR INBORN ERRORS OF IMMUNITY: A RETROSPECTIVE STUDY OVER 10-YEARS IN TUSCANY	Poster Display 07: Genetics Diagnostics
Guerra fabiola	PD424	ABNORMAL B CELL MATURATION AND INCREASED TRANSITIONAL B CELLS IN CBL SYNDROME	Poster Display 09: Other
Gülez Nesrin	PD292	GENETIC DIAGNOSIS OF INBORN ERRORS OF IMMUNITY: A SINGLE TERTIARY CENTER EXPERIENCE IN TURKEY	Poster Display 06: Genetics in IEI

Gumusburun Reyhan	PD442	**CLINICAL AND IMMUNOLOGICAL CHARACTERISTICS OF FIVE PATIENTS WITH PROTEIN-LOSING ENTEROPATHIES AND IMMUNODEFICIENCIES**	**Poster Display 09: Other**
Gutiérrez-Zepeda Melissa Bricia	PD278	**ASSOCIATION OF RS1799889 (-675 4G/5G) IN SERPINE1 (PAI-1) GENE WITH COMMON VARIABLE IMMUNODEFICIENCY PATIENTS.**	**Poster Display 06: Genetics in IEI**
Haefner Verena	OC015	**INVESTIGATING THE PATHOPHYSIOLOGY OF LUNG DISEASE IN STAT3-HYPER IGE SYNDROME**	**Oral Communications Session 03: Innate Immune Defects**
Hagin David	PD165	**A NOVEL NFKB1 SPLICE VARIANT PRESENTING WITH MULTIPLE LYMPHOCYTIC BONE LESIONS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Hagin David	PD156	**LATE DIAGNOSIS OF ALPK1 PATHOGENIC VARIANT CAUSING ROSAH SYNDROME**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Hagl Beate	PP009	**ALVEOLAR ORGANOIDS AS A HUMAN MODEL TO STUDY LUNG DISEASE IN STAT3-HYPER-IGE SYNDROME**	**Poster Discussions 02: Immune Mechanisms**
Haji Khodaverdi Khani Hedieh	PD151	**A CD122 DEFICIENCY CASE PRESENTED WITH HEMOLYTIC ANEMIA AND LUPUS VULGARIS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Hancioglu Gonca	PD167	**DOWN SYNDROME; A COMBINED IMMUNODEFICIENCY WITH IMMUNE DYSREGULATION!**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Haskologlu Sule	PD309	**THE ROLE AND SIGNIFICANCE OF FLOW CYTOMETRIC ANALYSIS IN THE EARLY DIAGNOSIS OF INBORN ERRORS OF IMMUNITY (IEI)**	**Poster Display 07: Genetics Diagnostics**
Haskologlu Sule	PD247	**THE IMPORTANCE OF GENETIC ANALYSES IN THE DIAGNOSIS OF INBORN ERRORS OF IMMUNITY (IEI)**	**Poster Display 06: Genetics in IEI**
Haskologlu Sule	PD468	**CLINICAL, LABORATORY FEATURES, TREATMENT AND OUTCOME IN CHRONIC GRANULOMATOUS DISEASE (CGD)**	**Poster Display 09: Other**
He Minghui	PP022	**OVERACTIVE WASP IN X-LINKED NEUTROPENIA LEADS TO ABERRANT B CELL DIVISION WITH DECREASED IG SWITCHING AND ACCELERATED PLASMA CELL GENERATION**	**Poster Discussion 04: T Cell & B Cell Biology**

Heinz Laura Johanna	PD222	**SEVERE VZV CNS INFECTION - A ROLE FOR AUTOPHAGY?**	**Poster Display 06: Genetics in IEI**
Hernandez Peralta Mariana	PD293	**SCREENING OF ELANE GENE IN PATIENS WITH NEUTROPENIA AND THEIR PARENTS**	**Poster Display 06: Genetics in IEI**
Hernandez-Trujillo Vivian	PD204	**DIVERSE CLINICAL PRESENTATION OF HEREDITARY ALPHA TRYPTASEMIA IN SIBLINGS**	**Poster Display 05: Autoinflammatory Disorders**
Heropolitanska-Pliszka edyta	PD365	**FAST AND COST-EFFECTIVE FLOW CYTOMETRIC METHOD TO DISCRIMINATE PATIENTS WITH ATOPIC DERMATITIS AND HYPER-IGE SYNDROME**	**Poster Display 07: Genetics Diagnostics**
Hoeller Sonja	PD112	**EFFICACY AND SAFETY OF A SUBCUTANEOUS HUMAN IMMUNOGLOBULIN (20% SCIG - NEWNORM) IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES – DESIGN OF A PHASE 3 STUDY**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Hon-Balla Borbala Bernadett	PD098	**STAT3 GOF SYNDROME WITH HYPOGAMMAGLOBULINEMIA, LYMPHOPROLIFERATION AND RECURRENT INFECTION PHENOTYPE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
HONDA-OZAKI 尾崎 FUMIKO	PD183	**PATHOPHYSIOLOGICAL ANALYSIS AND THERAPEUTIC EXPLORATION USING PSTPIP1-ASSOCIATED MYELOID-RELATED PROTEINEMIA INFLAMMATION (PAMI) SYNDROME DISEASE-SPECIFIC INDUCED PLURIPOTENT STEM CELL MODEL**	**Poster Display 05: Autoinflammatory Disorders**
Horner Clare Emily	PP017	**AGE ASSOCIATED B-CELLS AS A PREDICTOR OF RESPONSE TO BNT162B2 IN PEOPLE WITH INBORN ERRORS OF IMMUNITY**	**Poster Discussion 04: T Cell & B Cell Biology**
Hoste Levi	PD109	**WHOLE BLOOD TCR VB21.3 STAINING AS A DIAGNOSTIC TEST FOR MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN: A PROOF-OF-CONCEPT STUDY**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Hoste Levi	PD538	**DELAYED PRESENTATIONS OF SEVERE COMBINED IMMUNODEFICIENCY DURING THE SARS-COV-2 PANDEMIC**	**Poster Display 10: COVID-19**
Hoste Levi	PD132	**AUTOIMMUNE LOSS OF ENTERO-ENDOCRINE CELLS IS A HALLMARK APECED MANIFESTATION THAT RESULTS IN SEVERE MALABSORPTION BUT CAN RECOVER WITH IMMUNE SUPPRESSANTS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Howley Evey	PD384	**IMPACT OF EARLY DIAGNOSIS OF CONGENITAL ATHYMIA ON THE EUROPEAN THYMUS TRANSPLANTATION PROGRAMME.**	**Poster Display 08: Therapy**

Hsu P Amy	OC017	**IMMUNOGENETICS ASSOCIATED WITH SEVERE COCCIDIOIDOMYCOSIS**	**Oral Communications Session 03: Innate Immune Defects**
Hsu P Amy	OC014	**RAC2 MUTATIONS AND IMMUNE DEFICIENCY – FUNCTIONAL SPECTRUM OF AN INTERNATIONAL COHORT**	**Oral Communications Session 02: Autoinflammation and Immune Dysregulation**
Hu Lili	PD524	**ANTIVIRAL ROLE OF AUTOPHAGY IN PATIENTS WITH CRITICAL COVID-19**	**Poster Display 10: COVID-19**
Huibers Manon	PD233	**IMPLEMENTATION OF EARLY NEXT-GENERATION SEQUENCING FOR INBORN ERRORS OF IMMUNITY: DIAGNOSTIC YIELD AND CLINICAL IMPLICATIONS IN DUTCH GENOME DIAGNOSTIC CENTERS**	**Poster Display 06: Genetics in IEI**
Hupfer Robin	PP026	**SP110 EXPRESSION ANALYSIS FACILITATES THE DETECTION OF HUMAN PATIENTS WITH TYPE I INTERFERON SIGNATURES**	**Poster Discussion 05: Next Generation Sequencing and Other Diagnostics**
IJspeert Hanna	PD216	**CLINICAL HETEROGENEITY IN A FAMILY WITH A GAIN-OF-FUNCTION VARIANT IN IKBKB: DOES SP110 FUNCTION AS A MODIFIER GENE?**	**Poster Display 06: Genetics in IEI**
Inan Dilan	PD277	**DEFINITION OF GATA2 DEFICIENCY IN A FAMILY AFTER EVALUATION OF A BOY WITH RECURRENT AND RESISTANT PULMONARY DISEASE**	**Poster Display 06: Genetics in IEI**
Inoue Kento	PD311	**CLINICAL AND GENETIC CHARACTERIZATION OF JAPANESE PATIENTS WITH ARTEMIS DEFICIENCY**	**Poster Display 07: Genetics Diagnostics**
Invernizzi Andrea Antonella	PD153	**REPORT OF A NOVEL VARIANT IN AIRE GENE IN TWO SIBLINGS FROM ARGENTINA**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Islamoglu Candan	PD495	**A CASE DIAGNOSED WITH COCKAYNE SYNDROME WHILE INVESTIGATING PRIMARY IMMUNODEFICIENCY**	**Poster Display 09: Other**
Jacobsen Maria Eva	OC007	**UNEXPECTEDLY LOW PROPORTION OF DONOR B CELLS ALLOWS FOR B-CELL FUNCTION POST HSCT IN PATIENTS WITH B-POS SCID**	**Oral Communications Session 01: B Cell T-Cell Biology**
Jesenak Milos	PD192	**FAMILIAL MEDITERRANEAN FEVER IN THE CENTRAL EUROPE – EXPERIENCE FROM SLOVAKIA AS AN INSPIRATION FOR DISEASES AWARENESS IN CEE REGION**	**Poster Display 05: Autoinflammatory Disorders**
Jimenez Portillo Ana Lucia	PD331	**JOB-LIKE PHENOTYPE ASSOCIATED TO PHOSPHOGLUCOMUTASE 3(PGM3) COMPOUND**	**Poster Display 07: Genetics Diagnostics**

		HETEROZYGOUS MUTATIONS IN MONOZYGOTIC TWINS	
Jimenez Portillo Ana Lucia	PD198	VEXAS SYNDROME A NEWCOMER IN AUTOINFLAMMATORY DISEASE	Poster Display 05: Autoinflammatory Disorders
Jindal Kumar Ankur	PD006	T CELL ABNORMALITIES IN PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA	Poster Display 01: B-Cell Biology
Johansson Pegah	PD313	CLINICAL ASSAYS TO VALIDATE THE SIGNIFICANCE OF UNKNOWN VARIANTS IN DNA REPAIR GENES IN PATIENTS WITH IMMUNODEFICIENCY.	Poster Display 07: Genetics Diagnostics
Jørgensen Eg Sofie	PD522	VARIANTS IN SSRP1, MRPS25 AND EXOSC8 MAY INCREASE SUSCEPTIBILITY TO CRITICAL COVID-19	Poster Display 10: COVID-19
JOSHI JOSHI VIBHU	PD195	PERIODIC FEVER, APTHOUS STOMATITIS, PHARYNGITIS AND ADENITIS (PFAPA) SYNDROME – OUR EXPERIENCE FROM TERTIARY CARE CENTRE IN NORTH INDIA	Poster Display 05: Autoinflammatory Disorders
Jurcut Jurcut Ciprian	PD325	DOUBLE HETEROZYGOUS RAB27A MUTATIONS IN A YOUNG MAN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS – THE ROLE OF GENETIC TESTING FOR THE GRISCELLI SYNDROME	Poster Display 07: Genetics Diagnostics
Kacar Mark	PD357	DIFFERENTIAL DIAGNOSIS OF COUGH AND DYSPNOEA IN GATA2 DEFICIENCY - A CASE REPORT	Poster Display 07: Genetics Diagnostics
Kairienė Kairienė Ignė	PD122	MANAGEMENT OF AUTOIMMUNE ENTEROPATHY AND ENDOCRINOPATHY – SUSCEPTIBILITY TO CHRONIC INFECTIONS SYNDROME	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
Kaliuzhnaia Anatolyevna Tatiana	PD498	CLINICAL CASE OF SUCCESSFUL VACCINATION OF A CHILD WITH INCOMPLETE DI GIORGI SYNDROME	Poster Display 09: Other
Kan Andy Ka Chun	PD377	TEN-YEAR TRENDS OF IMMUNOGLOBULIN USE, BURDEN OF ADULT ANTIBODY DEFICIENCY AND FEASIBILITY OF SUBCUTANEOUS IMMUNOGLOBULIN (SCIG) REPLACEMENT IN HONG KONG	Poster Display 08: Therapy
Kang M Elizabeth	OC025	ALLOGENEIC TRANSPLANTATION FOR HIGH RISK PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE (CGD)	Oral Communications Session 04: Therapy
Karabağ Çıtlak Hilal	PD526	A RARE CASE OF IMMUNODEFICIENCY-ICF 1 SYNDROME DIAGNOSED FOLLOWING COVID-19 INFECTION	Poster Display 10: COVID-19

Karaca Edeer Neslihan	PD482	**PROGNOSTIC ROLE OF PRESEPSIN, NEOPTERIN, AND PROCALCITONIN IN SEPSIS IN INBORN ERRORS OF IMMUNITY**	**Poster Display 09: Other**
Karaca Edeer Neslihan	PD253	**SEVERE COMBINED IMMUNODEFICIENCIES: EXPANDING THE MUTATION SPECTRUM IN TURKEY AND IDENTIFICATION OF 4 NOVEL VARIANTS**	**Poster Display 06: Genetics in IEI**
Karakulska-Prystupiuk Marta Ewa	PD405	**MONOMAC SYNDROME PATIENT WITH NOVEL GATA2 MUTATION SUCCESSFULLY TREATED BY ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION- A CASE REPORT**	**Poster Display 08: Therapy**
Karali Yasin	PD145	**EVALUATION OF OUR PATIENTS WITH HYPOGAMMAGLOBULINEMIA DIAGNOSED WITH ATOPIC DERMATITIS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Karanovic Karanovic Boris	PD049	**ADULT SIBLINGS WITH INBORN ERROR OF IMMUNITY CAUSED BY TYK2 DEFICIENCY**	**Poster Display 03: Biology of Innate Immunity**
Kaustio Meri	OC033	**HETEROZYGOUS LOSS OF MAP4K1 ENCODING FOR HEMATOPOIETIC PROGENITOR KINASE 1 (HPK1), A NEGATIVE REGULATOR OF TCR SIGNALING, CAN LEAD TO IMMUNE DYSREGULATION**	**Oral Communications Session 05: Novel Defects and Mechanisms**
Keller Bärbel	PD014	**T-CELL-DERIVED FACTORS ARE CRUCIAL FOR THE EXPANSION OF T-BETHIGHCD21LOW B CELLS**	**Poster Display 01: B-Cell Biology**
khanbabaee Ghamartaj	PD078	**DEMOGRAPHIC, CLINICAL, AND IMMUNOLOGICAL FEATURES IN COMBINED IMMUNODEFICIENCY PATIENTS WITH AND WITHOUT PULMONARY COMPLICATIONS: A RETROSPECTIVE MULTICENTER STUDY FROM IRAN**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Khoreva Anna	WP016	**PROSPECTIVE STUDY OF EFFICACY AND SAFETY OF ROMIPLOSTIM VERSUS ELTROMBOPAG IN PATIENTS WITH WISKOTT-ALDRICH SYNDROME .**	**Working Party 06: PID Care in Development**
Kilic Sara Sebnem	PD081	**NEUROLOGICAL INVOLVEMENT IN PRIMARY IMMUNODEFICIENCIES**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Kilic Sara Sebnem	PD046	**NEUROCOGNITIVE EVALUATION OF PATIENTS WITH DI GEORGE SYNDROME**	**Poster Display 03: Biology of Innate Immunity**

Kilic Sara Sebnem	PD228	**RECOMBINASE ACTIVATING GENE DEFECTS, PHENOTYPIC DIVERSITY: TWO CENTERS' EXPERIENCE FROM TURKEY**	**Poster Display 06: Genetics in IEI**
Kim kyung-Ran	PD451	**MALIGNANCY IN PATIENTS WITH INBORN ERRORS OF IMMUNITY**	**Poster Display 09: Other**
Kim kyung-Ran	PD258	**WHOLE-GENOME SEQUENCING REVEALED A NOVEL BTK VARIANT IN PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA**	**Poster Display 06: Genetics in IEI**
Kim kyung-Ran	PD461	**A PATIENT WITH STAT3 LOSS-OF-FUNCTION PRESENTS PERSISTENT HUMAN PAPILLOMAVIRUS SKIN INFECTION**	**Poster Display 09: Other**
King Alejandra	PD080	**PUSTULAR PSORIASIS AS CLINICAL PRESENTATION IN A BOY WITH X- LINKED INHIBITOR OF APOPTOSIS (XIAP) MUTATION: A CASE REPORT**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Kinoshita Hannah	PP002	**DONOR-DERIVED VIRUS-SPECIFIC T CELL INFUSION FOR TREATMENT AND PROPHYLAXIS OF VIRUS INFECTIONS POST-HEMATOPOIETIC STEM CELL TRANSPLANT**	**Poster Discussion 01: Therapies**
Klocperk Adam	OC004	**DISTINCT CD8 T CELL POPULATIONS WITH DIFFERENTIAL EXHAUSTION PROFILES ASSOCIATE WITH SECONDARY COMPLICATIONS IN COMMON VARIABLE IMMUNODEFICIENCY**	**Oral Communications Session 01: B Cell T-Cell Biology**
Knopf Nina-Christine	PD061	**NEW INSIGHTS INTO IKBKB- GOF-DISEASE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Kokron Maria Cristina	PD515	**ANTIBODY AND CELLULAR IMMUNE RESPONSE TO COVID-19 INFECTION AND/OR IMMUNIZATION IN CVID PATIENTS**	**Poster Display 10: COVID-19**
Kolijn Kolijn Pieter Martijn	PD427	**EARLY DETECTION OF NON-HODGKIN LYMPHOMA AND LEUKEMIA IN PATIENTS WITH CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY THROUGH IMMUNOGENETIC SEQUENCING**	**Poster Display 09: Other**
Köppen Christoph Julius	PS009	**IMMUNE TOLERANCE DEFECTS IN INDIVIDUALS WITH PATHOGENIC MUTATIONS IN THE KAPPA LIGHT CHAIN**	**Parallel Session 05: B and T Cell Tolerance Checkpoints**
Köppen Christoph Julius	PD223	**OPPORTUNISTIC INFECTION AND IMMUNE-DYSREGULATION ASSOCIATED WITH A NOVEL FRAMESHIFT MUTATION IN SMAD3**	**Poster Display 06: Genetics in IEI**
Körholz Julia	PD186	**A FAMILY WITH A DE NOVO LOF-VARIANT IN TNFAIP3 SHOWING DISTINCT PHENOTYPES**	**Poster Display 05: Autoinflammatory Disorders**

Körholz Julia	PD225	**NEWS FROM THE CVID-SPECTRUM: NOVEL MUTATION AND EXPANDING PHENOTYPE IN IRF2BP2 DEFICIENCY**	**Poster Display 06: Genetics in IEI**
Koumas Koumas Laura	PD347	**INTERPRETATION OF HETEROGENEOUS TNFRSF13B MUTATION POSES A CHALLENGE IN THE CLINICAL SETTING**	**Poster Display 07: Genetics Diagnostics**
Krausz Mate	PD141	**NO OBVIOUS ASSOCIATION BETWEEN COMMON INFECTIONS AND DISEASE ONSET OR SEVERITY IN CTLA-4 INSUFFICIENCY**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Krausz Mate	OC008	**THE ABACHAI CLINICAL TRIAL PROTOCOL: SAFETY AND EFFICACY OF ABATACEPT (S.C.) IN PATIENTS WITH CTLA-4 INSUFFICIENCY OR LRBA-DEFICIENCY – ESTABLISHMENT OF A DISEASE-SPECIFIC SCORING SYSTEM**	**Oral Communications Session 02: Autoinflammation and Immune Dysregulation**
Krausz Mate	PS007	**PATIENTS WITH CTLA-4 INSUFFICIENCY HAVE DISTINCT INTESTINAL MICROBIOME SIGNATURES**	**Parallel Session 04: IEI and Microbiome**
Kreins Yema Alexandra	PS015	**LONG-TERM OUTCOMES AFTER THYMUS TRANSPLANTATION IN COMPLETE DIGEORGE SYNDROME**	**Parallel Session 08: Thymic IEI**
kristal eyal	PD437	**HYPOPARATHYROIDISM RETARDATION AND DYSMORPHISM SYNDROME DUE TO MUTATIONS IN TUBULIN-SPECIFIC CHAPERONE E GENE AS A CAUSE OF COMBINED IMMUNE DEFICIENCY**	**Poster Display 09: Other**
Kurjane Natalja	PD550	**T CELL RESPONSE TO SARS-COV-2 IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY AND SELECTIVE IGA DEFICIENCY**	**Poster Display 10: COVID-19**
Kutukculer Necil	PD271	**PRIMARY IMMUNE REGULATORY DISORDERS (PIRD): EXPANDING THE MUTATION SPECTRUM IN TURKEY AND IDENTIFICATION OF SEVEN NOVEL VARIANTS**	**Poster Display 06: Genetics in IEI**
Kuzmenko Natalia	PD212	**GENETIC CHARACTERISTICS OF A LARGE PEDIATRIC COHORT OF PATIENTS WITH INBORN ERRORS OF IMMUNITY (IEI): SINGLE-CENTER EXPERIENCE FROM 2012 TO 2021**	**Poster Display 06: Genetics in IEI**
Laberko Alexandra	PD429	**RISKS OF BCG INFECTION IN PRIMARY IMMUNODEFICIENCIES PATIENTS VACCINATED WITH THE RUSSIAN BCG STRAIN.**	**Poster Display 09: Other**
Laberko Alexandra	WP011	**ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION ACTIVITY FOR INBORN ERRORS OF IMMUNITY (IEI) IN RUSSIAN FEDERATION**	**Working Party 04: Registry**
Ladj Mohamed.Samir	PD355	**PERITONEAL PSEUDO TUMOR TUBERCULOSIS COMPLICATING HLA-DR DEFICIENCY**	**Poster Display 07: Genetics Diagnostics**

Ladj Mohamed.Samir	PD330	**CHRONIC SALMONELLA MENINGOENCEPHALITIS REVEALING AN EXPRESSION DEFICIT OF HLA - DR MOLECULES**	**Poster Display 07: Genetics Diagnostics**
Ladj Mohamed.Samir	PD126	**GRISCELLI SYNDROME: RARE NEONATAL SYNDROME OF HEMOPHAGOCYTOSIS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Ladj Mohamed.Samir	PD352	**ATAXIA TELANGIECTASIA: ABOUT TWO BROTHERS**	**Poster Display 07: Genetics Diagnostics**
Ladj Mohamed.Samir	PD346	**SEVERE IMMUNE DEFICIENCY DISCOVERED FOLLOWING BILATERAL PNEUMOPATHY: A CASE REPORT**	**Poster Display 07: Genetics Diagnostics**
Lanciarotta Alison	PD367	**IMMUNE RECONSTITUTION (IR) AFTER HSCT PERFORMED WITH AN INNOVATIVE METHOD OF GRAFT MANIPULATION IN CHILDREN WITH PRIMARY IMMUNODEFICIENCIES (PIDS) AND PRIMARY IMMUNE DYSREGULATION DISEASES (PIRDS)**	**Poster Display 08: Therapy**
lazarevic dragana	PD201	**THE CLINICAL PRESENTATION OF HYPERIMMUNOGLOBULIN D SYNDROME**	**Poster Display 05: Autoinflammatory Disorders**
Leahy Timothy Ronan	PD149	**IMMUNODEFICIENCY IN A PATIENT WITH NOONAN SYNDROME 13; A NOVEL IMMUNO-TOROPATHY?**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Ledig Svea	OC027	**ETOPOSIDE FOR PRIMARY HLH – BETTER THAN ITS REPUTATION.**	**Oral Communications Session 04: Therapy**
Lee Lee Yu Nee	PD457	**WHAT WE CAN LEARN FROM TRG AND IGH REPERTOIRE ANALYSES IN PATIENTS WITH WISKOTT-ALDRICH SYNDROME (WAS)**	**Poster Display 09: Other**
Lehtonen Johanna	PD224	**GENOME SEQUENCING REVEALS CCDC88A VARIANTS UNDERLYING MALFORMATIONS OF CORTICAL DEVELOPMENT, PROFOUND DEVELOPMENTAL DELAY, EPILEPSY, AND IMMUNE DYSFUNCTION**	**Poster Display 06: Genetics in IEI**
Leonardi Lucia	PD169	**IMMUNE DYSREGULATION IN KABUKI SYNDROME: A CASE REPORT**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Leslie Natalie	PD475	**TRANSFERRING PATIENTS TO SUBCUTANEOUS HOME THERAPY DUE TO IMMUNOGLOBULIN SHORTAGE FOLLOWING A GLOBAL PANDEMIC.**	**Poster Display 09: Other**
Lévy Romain	PD023	**HUMAN CARMIL2 DEFICIENCY UNDERLIES A BROADER IMMUNOLOGICAL AND CLINICAL**	**Poster Display 02: T-Cell Biology**

		PHENOTYPE THAN CD28 DEFICIENCY: AN INTERNATIONAL STUDY OF A COHORT OF 89 PATIENTS	
Lévy Romain	PD420	PROLONGED REMISSION OF AZOLE-RESISTANT LUNG ASPERGILLOSIS WITH OLOROFIM, IN AN ADOLESCENT WITH X-LINKED CHRONIC GRANULOMATOUS DISEASE	Poster Display 08: Therapy
Li Zhaoyang	PD382	POPULATION PHARMACOKINETICS OF IMMUNOGLOBULIN G AFTER INTRAVENOUS, CONVENTIONAL SUBCUTANEOUS OR FACILITATED SUBCUTANEOUS ADMINISTRATION IN IMMUNOGLOBULIN-NAÏVE PATIENTS WITH PRIMARY IMMUNODEFICIENCIES	Poster Display 08: Therapy
Liquidano-Perez Eduardo	PD091	CLINICAL, IMMUNOLOGICAL, AND GENETIC FEATURES OF A MEXICAN COHORT OF PATIENTS WITH DOCK8 DEFICIENCY.	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
Liquidano-Perez Eduardo	PD476	LYMPHOMATOID GRANULOMATOSIS IN A PATIENT WITH DOCK8 DEFICIENCY	Poster Display 09: Other
Liu Zhiyong	OC038	HUMAN INHERITED RIPK3 DEFICIENCY IN HERPES SIMPLEX ENCEPHALITIS	Oral Communications 06: Late Breaking Abstracts
Lodi Lorenzo	PD111	STAT3-CONFUSION-OF-FUNCTION: BEYOND THE LOSS AND GAIN DUALISM.	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
LOPES DA SILVA VITOR GABRIEL	PD532	INCIDENCE AND CLINICAL CHARACTERISTICS OF SARS-COV-2 INFECTION IN PATIENTS WITH INBORN ERRORS OF IMMUNITY AFTER COVID-19 IMMUNIZATION IN A BRAZILIAN REFERENCE CENTER	Poster Display 10: COVID-19
LOPES DA SILVA VITOR GABRIEL	PD558	CELLULAR IMMUNE RESPONSE AFTER A THIRD DOSE OF HOMOLOGOUS OR HETEROLOGOUS COVID-19 VACCINE IN BRAZILIAN PATIENTS WITH INBORN ERRORS OF IMMUNITY COMPARED TO HEALTHY CONTROLS	Poster Display 10: COVID-19
Lowe M David	PD410	A CHARACTERISATION OF CHRONIC CAMPYLOBACTER INFECTION IN COMMON VARIABLE IMMUNODEFICIENCY PATIENTS.	Poster Display 08: Therapy
Lui Lui Victor	OC006	HYPOMORPHIC LCK MUTANT RESULTS IN IMMUNODEFICIENCY AND INTESTINAL INFLAMMATION	Oral Communications Session 01: B Cell T-Cell Biology
Luka Marine	PP010	TYPE 1 IFN REGULATION OF HIF1A SWITCHES ENERGY METABOLISM ENHANCING	Poster Discussions 02: Immune Mechanisms

		INFLAMMATION THROUGH CYTOKINE PRODUCTION IN AGS	
Lukke Mari-Liis	PD302	THE DIAGNOSTIC YIELD OF NEXT-GENERATION SEQUENCING INCLUDING NONCODING VARIANTS AND HIGH-RESOLUTION CNV ANALYSIS IN THE DIAGNOSIS OF INBORN ERRORS OF IMMUNITY	Poster Display 07: Genetics Diagnostics
Mach Ondrej	PD428	PROLONGED EXCRETION OF POLIOVIRUS AMONG INDIVIDUALS WITH PRIMARY IMMUNODEFICIENCY DISORDERS	Poster Display 09: Other
Mach-Tomalska Monika	PD349	DIFFERENT CLINICAL PRESENTATION OF CHRONIC GRANULOMATOUS DISEASE - INTRICATE PATHWAYS TO DIAGNOSIS	Poster Display 07: Genetics Diagnostics
Mackeh Rafah	PD076	A DIFFERENTIAL ROLE FOR STK4/MST1 IN RESTING AND PROLIFERATING T CELLS.	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
Maier Felix	PD440	POSITIVE INFLUENCE OF CHEMOTHERAPY FOR A SECONDARY MALIGNANCY ON MYELOID ENGRAFTMENT IN A SCID-PATIENT AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION	Poster Display 09: Other
Mailer K Reiner	PD086	FULL-LENGTH FOXP3 PRECEDES EXPRESSION OF OTHER ISOFORMS IN HUMAN THYMOCYTES AND NAIVE T CELLS	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
Maimaris Jesmeen	PD318	DIAGNOSIS OF IMMUNODEFICIENCY USING TYPHIM VI IN CHILDREN IMMUNISED WITH PNEUMOCOCCAL CONJUGATE VACCINE	Poster Display 07: Genetics Diagnostics
Maimaris Jesmeen	OC039	AUTOSOMAL DOMINANT STAT6 GAIN OF FUNCTION CAUSES ATOPY ASSOCIATED WITH LYMPHOMA	Oral Communications 06: Late Breaking Abstracts
MALLEBRANCHE Coralie	PD552	IMPACT OF PHYSICAL DISTANCING MEASURES DUE TO THE SARS-COV-2 PANDEMIC ON HUMORAL IMMUNITY IN CHILDREN	Poster Display 10: COVID-19
Manolache Elena Anca	PD341	NIJMEGEN SYNDROME IN AN ADULT PATIENT - THE ROLE OF EARLY DIAGNOSTIC	Poster Display 07: Genetics Diagnostics
Manolache Elena Anca	PD342	ADA DEFICIENCY DIAGNOSED IN AN ADULT WOMEN – THE IMPORTANCE OF THE GENETIC TESTING	Poster Display 07: Genetics Diagnostics
Manusama Rebekka Olivia	PD110	T-CELL ABERRANCIES IN CVID CORRELATE WITH PRO-INFLAMMATORY MONOCYTE GENE EXPRESSION, AND ARE AGGRAVATED IN THE PRESENCE OF AUTOIMMUNE COMPLICATIONS	Poster Display 04: Immune Dysregulation & Autoimmune Disorders

Marcus Mandelblit Nufar	PD504	**SARS-COV-2 SYMPTOMATIC REINFECTION AMONG PATIENTS WITH PRIMARY ANTIBODY DEFICIENCY**	**Poster Display 10: COVID-19**
Marcus Mandelblit Nufar	PD001	**NEUTROPENIA IN X-LINKED AGAMMAGLOBULINEMIA PATIENTS MAY BE A MORE COMMON PRESENTING FEATURE THAN PREVIOUSLY REPORTED, AND WARRANTS A HIGH INDEX OF SUSPICION AND IMMUNE EVALUATION**	**Poster Display 01: B-Cell Biology**
Markelj Gasper	PD376	**PRETRANSPLANT USE OF VIRUS SPECIFIC T CELLS FOR EBV+ LYMPHOPROLIFERATION IN AN ARPC1B DEFICIENT PATIENT**	**Poster Display 08: Therapy**
Markelj Gasper	PD275	**NETHERTON SYNDROME PATIENTS IN SLOVENIA**	**Poster Display 06: Genetics in IEI**
Markocsy Adam	PD317	**OUR EXPERIENCES WITH CLINICAL MANIFESTATION OF PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY FROM SPECIALISED CENTRE FOR PRIMARY IMMUNODEFICIENCIES IN MARTIN, SLOVAKIA**	**Poster Display 07: Genetics Diagnostics**
Martini Beatrice	PD243	**THE IMPACT OF A NOVEL NFKB2 GENE VARIANT ON CVID CLINICAL SPECTRUM: A NON-CANONICAL NF-KB PATHWAY HAPLOINSUFFICIENCY?**	**Poster Display 06: Genetics in IEI**
Martín-Nalda Andrea	PD329	**NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY (SCID) IN EUROPE: FIVE-YEARS´ EXPERIENCE IN CATALONIA**	**Poster Display 07: Genetics Diagnostics**
Matuozzo Daniela	PS019	**RECESSIVE INBORN ERRORS OF TYPE I IFN IMMUNITY IN CHILDREN WITH COVID-19 PNEUMONIA**	**Parallel Session 10: COVID-19 in IEI**
Mauracher Alexis Andrea	PS005	**CIS Junior: ALTERED STAT1 SIGNALLING YIELDS CD8+ T CELL DYSFUNCTION IN INBORN ERRORS OF IMMUNITY**	**Parallel Session 03: IEI in the World (IAPIDS Session)**
MAZEROLLES Fabienne	PD031	**PD-L1 IS EXPRESSED ON HUMAN ACTIVATED NAIVE EFFECTOR CD4+ T CELLS. REGULATION BY DENDRITIC CELLS AND REGULATORY CD4+ T CELLS**	**Poster Display 02: T-Cell Biology**
McDowell Joe	PD064	**EVALUATING THE USE OF RUXOLITINIB TO TREAT STAT1 GAIN OF FUNCTION DRIVEN PRIMARY IMMUNODEFICIENCY**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
McKenna McKenna Alexander	OC016	**PATHOGENESIS OF STAT1 GAIN-OF-FUNCTION PRIMARY IMMUNODEFICIENCY**	**Oral Communications Session 03: Innate Immune Defects**
McKenna McKenna Alexander	PP028	**SIGNIFICANT MUTATION-SPECIFIC VARIATION IN DISEASE SEVERITY AND OUTCOME FOR PATIENTS WITH STAT1 GOF MUTATIONS**	**Poster Discussion 05: Next Generation**

			Sequencing and Other Diagnostics
Megino Rebeca F	PD033	**P.Y153X CD247 VARIANT IS STABLE IN IMMORTALIZED T CELLS AND FORMS CD247 HETERODIMERS**	**Poster Display 02: T-Cell Biology**
Mekki Najla	PD123	**IGG SUBCLASS DEFICIENCY DUE TO NOVEL HETEROZYGOUS NFKB1 MUTATION REVEALED BY ADULT ONSET OF PYODERMA GANGRENOSUM IN TWO SIBLINGS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Mekki Najla	PD281	**CLINICAL AND IMMUNOGENETIC FEATURES OF WISKOTT-ALDRICH SYNDROME IN FIVE UNRELATED TUNISIAN PATIENTS**	**Poster Display 06: Genetics in IEI**
Mekki Najla	PD027	**COMBINED IMMUNODEFICIENCY ASSOCIATED WITH NOVEL HOMOZYGOUS DNMT3B MUTATION**	**Poster Display 02: T-Cell Biology**
Mekki Najla	PD467	**CLINICAL, IMMUNOLOGICAL AND MOLECULAR FEATURES OF 132 CHRONIC GRANULOMATOUS DISEASE PATIENTS**	**Poster Display 09: Other**
Melamed Isaac	PD142	**COMBINED C1-ESTERASE INHIBITOR DEFICIENCY AND ALPHA-1 ANTITRYPSIN DEFICIENCY: A NEW PLAYER IN NEURO-IMMUNE DISEASE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Melamed Isaac	PD084	**EFFICACY OF IVIG IN PATIENTS WITH PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME (PANS)**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Mensa-Vilaro Anna	PD181	**EARLY-ONSET AUTOINFLAMMATORY DISEASE RESEMBLING CRYOPYRINOPATHY DUE TO SOMATIC NLRC4 MOSAICISM**	**Poster Display 05: Autoinflammatory Disorders**
Mesdaghi Mehrnaz	PD337	**CHRONIC GRANULOMATOSIS DISEASE WITH AN UNUSUAL DHR PATTERN AND NBT RESULT**	**Poster Display 07: Genetics Diagnostics**
Messelink Alice Marianne	PD300	**DEVELOPMENT OF A SCREENING ALGORITHM FOR THE EARLY DETECTION OF PRIMARY ANTIBODY DEFICIENCIES IN PRIMARY CARE**	**Poster Display 07: Genetics Diagnostics**
Mihailova Snezhina	PD232	**GENETIC CHARACTERISTIC OF PATIENTS FROM BULGARIAN PID REGISTRY**	**Poster Display 06: Genetics in IEI**
Milota Tomas	PD510	**COVID-19 SEVERITY AND POSTVACCINATION OUTCOMES AFTER BNT162B2 VACCINE ADMINISTRATION IN PATIENTS WITH INBORN ERRORS OF IMMUNITY**	**Poster Display 10: COVID-19**
Miot Charline	PD433	**LONG-TERM OUTCOME OF MILD WAS/XLT PATIENTS: EXPERIENCE FROM THE FRENCH**	**Poster Display 09: Other**

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Miot Charline	PD426	MAGT1 DEFICIENCY CAUSES A PROMINENT PLATELETS DYSFUNCTION THROUGH IMPAIRMENT OF MEMBRANE GLYCOPROTEINS N-GLYCOSYLATION	Poster Display 09: Other
Mir Adhora	PD191	AN UNUSUAL PRESENTATION OF FAMILIAL MEDITERRANEAN FEVER WITH FEATURES OF BEHÇET'S DISEASE: A CASE REPORT AND LITERATURE REVIEW	Poster Display 05: Autoinflammatory Disorders
Mistry Anoop	PD016	INHERITED CD19 DEFICIENCY IMPAIRS SIGNALLING IN PLASMA CELLS.	Poster Display 01: B-Cell Biology
Mogensen Trine	PS020	IDENTIFICATION OF HOST GENETIC VARIANTS IN THE CYTOSOLIC DNA SENSOR POL III IN PATIENTS WITH CRITICAL COVID-19	Parallel Session 10: COVID-19 in IEI
Mohamed Mohamed Kauzar	PD542	CELLULAR AND HUMORAL IMMUNOGENICITY OF S1 NEOANTIGEN OF SARS-COV-2 VACCINES IN PATIENTS WITH SYSTEMIC AUTOIMMUNE RHEUMATIC DISEASES	Poster Display 10: COVID-19
Mok Hoi Ping	PD034	MUTATIONS IN CARMIL2 ARE ASSOCIATED WITH PARTIAL T CELL DEFECTS AND INFECTION WITH MYCOBACTERIUM MICROTI	Poster Display 02: T-Cell Biology
Momenilandi Paris Mana	OC037	INHERITED FLT3 LIGAND (FLT3LG) DEFICIENCY UNDERLIES SEVERE CUTANEOUS PAPILLOMAVIRUS INFECTION	Oral Communications 06: Late Breaking Abstracts
Morales Garcia Carmen	PD262	NOVEL COMPOUND HETEROZYGOUS VARIANTS IN THE HELLS GENE CAUSE IMMUNODEFICIENCY–CENTROMERIC INSTABILITY–FACIAL ANOMALIES SYNDROME	Poster Display 06: Genetics in IEI
Moreno Yanino Solange Andrea	OC010	IMPACT OF CASPASE 10 MUTATIONS IN AUTOIMUNE LYMPHOPROLIFERATIVE SYNDROME OUTCOME	Oral Communications Session 02: Autoinflammation and Immune Dysregulation
Morris C Emma	OC028	THERAPEUTIC GENE EDITING OF T CELLS CORRECTS CTLA4 INSUFFICIENCY.	Oral Communications Session 04: Therapy
Mortellaro Alessandra	PS021	CHARACTERIZATION OF HEMATOPOIETIC STEM CELL FUNCTIONS IN PATIENTS WITH ADENOSINE DEAMINASE 2 DEFICIENCY	Parallel Session 11: IEI and Hematological Disease/BM Failure
MOSES WAISWA	PD119	IMPLICATIONS FOR THE DIAGNOSTIC APPROACH IN PEDIATRIC COMMON VARIABLE IMMUNODEFICIENCY:	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
Mukhina Anna	PD392	SCHIMKE IMMUNO-OSSEOUS DYSPLASIA: ANALYSIS OF A COHORT OF RUSSIAN PATIENTS.	Poster Display 08: Therapy

Muñoz García Raquel	PD255	**SHWACHMAN–DIAMOND-LIKE SYNDROME: DIAGNOSTIC CHALLENGE**	**Poster Display 06: Genetics in IEI**
Murray Cliodhna	PD560	**CELLULAR AND HUMORAL IMMUNOGENICITY OF THE COVID-19 VACCINE AND COVID-19 DISEASE SEVERITY IN INDIVIDUALS LIVING WITH IMMUNODEFICIENCY**	**Poster Display 10: COVID-19**
Muscianisi Francesco	PD345	**EVALUATION OF TOTAL SERUM IGE LEVELS AMONG A COHORT OF ATOPIC PATIENTS WITH PRIMARY ANTIBODY DEFICIENCY**	**Poster Display 07: Genetics Diagnostics**
Nabiyeva Cevik Nadira	PD003	**CLINICAL AND IMMUNOLOGICAL CHARACTERISTICS OF PATIENTS WITH NFKB1 AND NFKB2 DEFICIENCY**	**Poster Display 01: B-Cell Biology**
Nadeau Marc-Antoine	PD529	**COVID-19 INFECTION TREATED WITH MONOCLONAL ANTIBODIES IN 5 PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA**	**Poster Display 10: COVID-19**
Naesens Leslie	OC021	**GTF3A DEFICIENCY IN HUMANS PREDISPOSES TO HERPES SIMPLEX ENCEPHALITIS BY ABROGATING TRANSCRIPTION OF THE HOST-DERIVED RIG-I LIGAND RNA5SP141**	**Oral Communications Session 03: Innate Immune Defects**
Nasrullayeva Gulnara	PD328	**CHARACTERISTICS OF THE CYTOKINE STATUS IN NEWBORNS WITH INTRAUTERINE INFECTIONS.**	**Poster Display 07: Genetics Diagnostics**
Nath Navdeep	PD369	**ALLOGENEIC HAEMATOPOIETC STEM CELL TRANSPLANTATION OUTCOME IN OLDEST KNOWN SURVIVING PATIENTS WITH WISKOTT ALDRICH SYNDROME IN THE UK.**	**Poster Display 08: Therapy**
Nazarpack Fatemeh Fatemeh	PD477	**THE PREVALENCE OF HYPOALBUMINEMIA AMONG PATIENTS WITH COMBINED IMMUNODEFICIENCY: A MULTI-CENTER SURVEY FROM IRAN**	**Poster Display 09: Other**
Neehus Anna-Lena	PD254	**CHRONIC GRANULOMATOUS-LIKE PRESENTATION OF A PATIENT WITH AUTOSOMAL RECESSIVE PKCΔ DEFICIENCY**	**Poster Display 06: Genetics in IEI**
Neirinck Jana	PD319	**THE EUROFLOW PID ORIENTATION TUBE (PIDOT) IN THE DIAGNOSTIC WORK-UP OF PRIMARY IMMUNODEFICIENCY: DAILY PRACTICE PERFORMANCE IN A TERTIARY UNIVERSITY HOSPITAL**	**Poster Display 07: Genetics Diagnostics**
Neven Benedicte	WP003	**LATE-ONSET ENTERIC VIRUS INFECTION ASSOCIATED WITH HEPATITIS (EVAH) IN TRANSPLANTED SCID PATIENTS**	**Working Party 01: Inborn Errors**
Nguyen Nguyen Thi Phuong Mai	PD351	**A NOVEL MUTATION IN CD40LG GENE CAUSING HYPER IGM SYNDROME IN VIETNAMESE FAMILY**	**Poster Display 07: Genetics Diagnostics**
Nguyen Thi Van Anh	PD072	**RITUXIMAB TREATMENT FOR AUTOIMMUNE ENCEPHALITIS OF IMMUNE DYSREGULATION,**	**Poster Display 04: Immune Dysregulation &**

		POLYENDOCRINOPATHY X-LINKED SYNDROME: CASE REPORT	Autoimmune Disorders
Nishimura Madoka	PD456	TREC BASED NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY DISEASE IN KUMAMOTO: RESULTS OF THE FIRST THREE YEARS	Poster Display 09: Other
Noma Kosuke	WP006	CHRONIC MUCOCUTANEOUS CANDIDIASIS DISEASE DUE TO A NOVEL DUPLICATION MUTATION OF IL17RC	Working Party 02: Genetics
O Farrill Romanillos Maria Patricia	PD147	LIVER DISORDERS IN ADULTS PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
O Farrill Romanillos Maria Patricia	PD358	GOOD'S SYNDROME A PHENOCOPY OF A COMPLEX PRESENTATION	Poster Display 07: Genetics Diagnostics
O Farrill Romanillos Maria Patricia	PD143	GOOD'S SYNDROME; ABOUT A CASE	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
O Farrill Romanillos Maria Patricia	PD130	SECONDARY HEMOPHAGOCYTIC SYNDROME DUE TO HODGKIN LYMPHOMA IN A PATIENT WITH CVID	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
Önalan Tuğba	PD519	RELATIONSHIP BETWEEN SWITCHED MEMORY B-CELL LEVELS AND THE CLINICAL COURSE OF COVID-19 IN CVID PATIENTS	Poster Display 10: COVID-19
Orange Scott Jordan	PD054	AN ELF4 HYPOMORPHIC VARIANT RESULTS IN NATURAL KILLER CELL DEFICIENCY	Poster Display 03: Biology of Innate Immunity
O'Toole Gráinne	INGID005	LIVED EXPERIENCES OF PARENTS AND CHILDREN PARTICIPATING IN EARLY-PHASE CLINICAL TRIALS: EVIDENCE SYNTHESIS.	INGID session 04: Oral and Poster Presentations on Nursing Topics
Ott de Bruin M Lisa	PP020	PERSISTENT HYPOGAMMAGLOBULINEMIA AFTER RECEIVING RITUXIMAB POST-HSCT IS NOT CAUSED BY AN INTRINSIC B-CELL DEFECT	Poster Discussion 04: T Cell & B Cell Biology
Ouair Hind	PD344	ANALYSIS OF THE DIHYDRORHODAMINE ASSAY IN THE DIAGNOSIS OF CHRONIC GRANULOMATOUS DISEASE	Poster Display 07: Genetics Diagnostics
Ouair Hind	PD197	COPA DEFECT: ABOUT 2 MOROCCAN PATIENTS	Poster Display 05: Autoinflammatory Disorders

Ouair Hind	PD471	**LATE ONSET COMBINED IMMUNODEFICIENCY: ABOUT 4 CASES**	**Poster Display 09: Other**
Ouair Hind	PD448	**PEDIATRIC ARPC1B DEFICIENCY A CASE SERIES OF FOUR CHILDREN IN MOROCCO**	**Poster Display 09: Other**
OUEDERNI OUEDERNI Monia	PD385	**HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PRIMARY IMMUNODEFICIENCIES**	**Poster Display 08: Therapy**
OUEDERNI OUEDERNI Monia	PD503	**RESPIRATORY DISORDERS IN COMMON VARIABLE IMMUNODEFICIENCY**	**Poster Display 09: Other**
OUEDERNI OUEDERNI Monia	PD502	**PREDICTIVE FACTORS OF PRIMARY HEMOPHAGOCYTOSIS LYMPHOHISTIOCYTOSIS**	**Poster Display 09: Other**
OUEDERNI OUEDERNI Monia	PD174	**PRIMARY IMMUNODEFICIENCIES IN CHILDHOOD AUTOIMMUNE HEMOLYTIC ANEMIA AND EVANS SYNDROME: WHICH PREVALENCE?**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Oxelius I Vivi-Anne	PD294	**TITLE: EXCLUDED IGG SUBCLASS GENES IN SEVERE VIRAL INFECTIONS AND PRIMARY IMMUNODEFICIENCIES (PIDS)**	**Poster Display 06: Genetics in IEI**
Özdemir Öner	PD045	**PRIMARY IMMUNODEFICIENCY IN COMBINATION WITH FALLOT TETRALOGY AND THROMBOCYTOPENIA IN A PATIENT WITH JACOBSEN SYNDROME; CASE REPORT**	**Poster Display 03: Biology of Innate Immunity**
Özdemir Öner	PD528	**COURSE OF COVID-19 IN PATIENTS WITH PREDOMINANTLY ANTIBODY DEFICIENCIES**	**Poster Display 10: COVID-19**
Özdemir Öner	PD540	**RECURRENT SARS-COV-2 INFECTION IN A CHILD WITH PREDOMINANTLY ANTIBODY DEFICIENCY; CASE REPORT**	**Poster Display 10: COVID-19**
Özdemiral Cansu	PD211	**THE SPECTRUM OF INBORN ERRORS OF IMMUNITY IN PATIENTS WITH EBV FROM TURKEY**	**Poster Display 06: Genetics in IEI**
Pachlopnik Schmid Jana	PD088	**PERFORIN-INDEPENDENT CYTOTOXICITY ENHANCED BY CYTOKINE COMPLEXES**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Pacillo Lucia	PD140	**THYROID CARCINOMA IN TWO PATIENTS WITH ATAXIA-TELANGIECTASIA: RADIOSENSITIVITY AND USE OF RADIOIODINE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Pacillo Lucia	OC020	**A NOVEL HETEROZYGOUS GERMLINE STAT6 VARIANT AS A LIKELY MONOGENIC CAUSE OF A NOVEL PRIMARY ATOPIC DISORDER**	**Oral Communications Session 03: Innate Immune Defects**

Pacillo Lucia	PP034	**IDENTIFICATION OF A COMPOUND HETEROZYGOUS MUTATION IN DUOX2 GENE IN A INFANT AFFECTED BY IBD**	**Poster Discussion 06: Innate Immune Defects**
Pacillo Lucia	PD129	**SUCCESSFUL TREATMENT WITH MYCOPHENOLATE MOPHETILE OF RELAPSING/REFRACTORY IMMUNE THROMBOCYTOPENIA IN FOUR PATIENTS WITH DEL22Q11.2 SYNDROME**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Palma Martin Alejandro	PD213	**THE EXPANDING SPECTRUM OF WAS-RELATED DISORDERS: AN INTERMEDIATE CLINICAL PHENOTYPE BETWEEN WISKOTT ALDRICH SYNDROME AND X-LINKED NEUTROPENIA CAUSED BY THE NOVEL WAS R431W MUTATION**	**Poster Display 06: Genetics in IEI**
Palterer Boaz	PD230	**DUPLICATION OF CD70 AND 4-1BBL CAUSES IMMUNODEFICIENCY AND IMMUNODYSREGULATION**	**Poster Display 06: Genetics in IEI**
Papa Papa Riccardo	PD280	**LACK OF PERIPHERAL T CELLS REVEALING A NOVEL CD3E MUTATION IN A FAMILY WITH MULTIPLE INFANT DEATHS**	**Poster Display 06: Genetics in IEI**
Papadopoulou-Alataki Efimia	PD190	**EVALUATION OF THE RISK FOR VASCULAR DAMAGE IN CHILDREN AND YOUND ADULTS WITH FAMILIAL MEDITERRANEAN FEVER**	**Poster Display 05: Autoinflammatory Disorders**
PAPASTAMATIOU ΠΑΠΑΣΤΑΜΑΤΙΟΥ THEODORA	PD048	**A DIAGNOSIS OF VERY EARLY-ONSET OF CHRONIC GRANULOMATOUS DISEASE (CGD) IN A NEONATE**	**Poster Display 03: Biology of Innate Immunity**
PAPASTAMATIOU ΠΑΠΑΣΤΑΜΑΤΙΟΥ THEODORA	PD537	**MEASUREMENT OF SARS-COV-2 ABS IN PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA (XLA) RECEIVING IMMUNOGLOBULIN PRODUCTS**	**Poster Display 10: COVID-19**
PAPASTAMATIOU ΠΑΠΑΣΤΑΜΑΤΙΟΥ THEODORA	PD517	**ANTIBODY RESPONSES FOLLOWING COVID-19 VACCINATION IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY (CVID)**	**Poster Display 10: COVID-19**
Parackova Zuzana	PD053	**IMPAIRED TOLEROGENIC DENDRITIC CELLS QUALITIES AS A CAUSE OF AUTOIMMUNE COMPLICATIONS IN PATIENTS WITH STAT1-GAIN-OF-FUNCTION MUTATIONS**	**Poster Display 03: Biology of Innate Immunity**
Parra-Martínez Parra-Martínez Alba	PD219	**CLINICAL AND FUNCTIONAL EVALUATION OF E57K HYPOMORPHIC MUTATION IN IKBKG GENE**	**Poster Display 06: Genetics in IEI**
Pathmanandavel Karrnan	PD158	**MEMORY RESPONSES TO SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 VACCINATION IN PATIENTS WITH HYPER-IMMUNOGLOBULIN E SYNDROMES**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Payne Kathryn	PD002	**DISSECTING GERMINAL CENTER B CELL RESPONSES IN COMMON VARIABLE IMMUNODEFICIENCY**	**Poster Display 01: B-Cell Biology**

Peirano. Lucia	PD150	**TOXOPLASMOSIS OCULAR IN GOOD SYNDROME. A CASE REPORT.**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Pello Eetu	PD161	**EARLY CHILDHOOD LYMPHOCYTE COUNTS IN THE PREDICTION OF CLINICAL COURSE IN CARTILAGE-HAIR HYPOPLASIA – A LONGITUDINAL STUDY OF 32 PATIENTS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Peñafiel Vicuña Peñafiel Ana Karen	PD478	**CHRONIC GRANULOMATOUS DISEASE IN THE MAYAN ETHNIC GROUP**	**Poster Display 09: Other**
Pereira Helena Pires	PD316	**AN ATYPICAL LYMPHOMA PRESENTATION IN SCID**	**Poster Display 07: Genetics Diagnostics**
Perez-Andres Martin	PD308	**NEW AGE-MATCHED CRITERIA BETTER IDENTIFY LATE-ONSET COMBINED IMMUNODEFICIENCY AMONG PATIENTS WITH A DIAGNOSIS OF COMMON VARIABLE IMMUNODEFICIENCY**	**Poster Display 07: Genetics Diagnostics**
Perez-Andres Martin	PD434	**IMMUNE CELL PROFILING OF FIVE GOOD SYNDROME PATIENTS**	**Poster Display 09: Other**
Perez-Andres Martin	PS001	**AUTOIMMUNE CYTOPENIAS AND INTERSTITIAL LUNG DISEASE ARE ASSOCIATED WITH EXPANDED TH1 CELLS IN LOCID AND CVID PATIENTS**	**Parallel Session 01: Immune Dysregulation in CVID**
Perinetti Casoni Giovanna	PD040	**ABNORMAL NK CELL DIFFERENTIATION IN A DEF6 DEFICIENT PATIENT**	**Poster Display 03: Biology of Innate Immunity**
Petit Françoise Audrey	PP005	**IMPACT OF GRAFT FUNCTION ON HEALTH STATUS AND QUALITY OF LIFE IN 112 LONG TERM SURVIVORS WHO RECEIVED AN HSCT FOR A PID**	**Poster Discussion 01: Therapies**
Petit Françoise Audrey	PD269	**IKZF 1,2 AND 3 TRANSCRIPTION FACTOR FAMILY AND AUTO-IMMUNE CYTOPENIA IN THE OBS'CEREVANCE FRENCH COHORT : A NOVEL ENTITY ?**	**Poster Display 06: Genetics in IEI**
Petrovicova Otilia	PD525	**MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN ASSOCIATED WITH COVID-19 INFECTION (EXPERIENCE OF ONE CENTRE)**	**Poster Display 10: COVID-19**
Pignata Claudio	PD148	**CASE REPORT: RARE SOLID TUMORS IN A PATIENT WITH WISKOTT ALDRICH SYNDROME AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Pignata Claudio	PD019	**CHARACTERIZATION OF CLINICAL AND IMMUNOLOGICAL FEATURES OF PATIENTS**	**Poster Display 01: B-Cell Biology**

		WITH ANTIBODIES DEFICIENCY SECONDARY TO DIFFERENT CAUSES.	
Pignata Claudio	PD136	**IMPACT OF THE USE OF JAK INHIBITORS ON METABOLIC CONTROL IN PATIENTS WITH INBORN ERRORS OF IMMUNITUY AND DIABETES MELLITUS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Pilania Rakesh Kumar	PD180	**HUMAN DEFICIENCY OF ADENOSINE DEAMINASE 2 - MYRIAD FACES IN A FAMILY!**	**Poster Display 05: Autoinflammatory Disorders**
Poggi Lucie	PS018	**GENE EDITING OF APDS1 T CELLS**	**Parallel Session 09: Treatment - Novel/Targeted**
Pons Berta	PD043	**ASSESSMENT OF THE IN VITRO IMMUNOMODULATORY CAPACITY OF INTRAVENOUS IMMUNOGLOBULIN USING A NEW DEVELOPED AND VALIDATED METHOD**	**Poster Display 03: Biology of Innate Immunity**
Pons Berta	PD391	**CHARACTERIZATION OF IMMUNOGLOBULIN G ANTIBODIES AGAINST HUMAN CRIMEAN CONGO HEMORRHAGIC FEVER VIRUS IN INTRAVENOUS IMMUNOGLOBULINS SAMPLES**	**Poster Display 08: Therapy**
Ponsford Mark	PD363	**FAILURE TO MOUNT A DETECTABLE HUMORAL VACCINE RESPONSE – A NEW DIAGNOSTIC TOOL TO SUPPORT DIAGNOSIS OF HYPOGAMMAGLOBULINAEMIA?**	**Poster Display 07: Genetics Diagnostics**
Porta Fulvio	PD333	**A PECULIAR DIAGNOSTIC PATTERN IN AN ADA SCID CHILD**	**Poster Display 07: Genetics Diagnostics**
Porta Fulvio	PD105	**HSCT IN CGD PATIENTS: NOT ALWAYS AN EASY TREATMENT**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Porta Fulvio	PD173	**RECOMBINANT ADA ENZYME REPLACEMENT THERAPY (ERT) IN PATIENTS AFTER LONG TERM TREATMENT**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Pulvirenti Federica	PD516	**IMMUNE RESPONSE AFTER FULL IMMUNIZATION FOLLOWED BY A BOOSTER DOSE OF BNT162B2 MRNA COVID-19 VACCINE IN PATIENTS WITH 22Q11.2 DELETION SYNDROME**	**Poster Display 10: COVID-19**
Pulvirenti Federica	PD506	**T-CELL DEFECTS ASSOCIATED TO LACK OF SPIKE-SPECIFIC ANTIBODIES AFTER BNT162B2 FULL IMMUNIZATION FOLLOWED BY A BOOSTER DOSE IN PATIENTS WITH COMMON VARIABLE IMMUNE DEFICIENCIES**	**Poster Display 10: COVID-19**

Pulvirenti Federica	PD564	**COVID-19 SEVERITY, CARDIOLOGICAL OUTCOME, AND IMMUNOGENICITY OF MRNA VACCINE IN ADULT PATIENTS WITH 22Q11.2DS**	**Poster Display 10: COVID-19**
Pulvirenti Federica	PD022	**CHARACTERISATION OF IMMUNE DEFECT IN COMMON VARIABLE IMMUNODEFICIENCY BY COMBINING ANTI-SPIKE ANTIBODIES AND SPECIFIC-MEMORY B-CELLS RESPONSE TO BNT162B2 IMMUNISATION**	**Poster Display 01: B-Cell Biology**
Quintero Ramos Antonio	PD259	**RS34557412 IN TNFRSF13B GENE AS A PROTECTOR FACTOR IN COMMON VARIABLE IMMUNODEFICIENCY IN A WESTERN MEXICAN POPULATION.**	**Poster Display 06: Genetics in IEI**
Radwan Nesrine	PD446	**HEALTH-RELATED QUALITY OF LIFE AMONG CHILDREN WITH INBORN ERRORS OF IMMUNITY AT AIN SHAMS SPECIALIZED CHILDREN HOSPITAL, CAIRO, EGYPT : A CROSS SECTIONAL STUDY**	**Poster Display 09: Other**
Ramirez Jose Neftali	PD071	**TRANSCRIPTOME-, PROTEOME- AND CHROMATIN ACCESSIBILITY ANALYSIS IN NAIVE B CELLS OF PATIENTS HARBORING THE C104R MUTATION IN TACI**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Ramsay Isobel	PD418	**PASSIVE IMMUNISATION AGAINST SARS-COV-2 BY IMMUNOGLOBULIN REPLACEMENT THERAPY**	**Poster Display 08: Therapy**
Rantanen Rea	PD024	**EFFECT OF EARLY THYMECTOMY ON LATER HEALTH**	**Poster Display 02: T-Cell Biology**
Rao V. Koneti	OC023	**INTERIM SAFETY AND EFFICACY ANALYSIS OF AN ONGOING LONG-TERM OPEN-LABEL EXTENSION STUDY OF LENIOLISIB FOR PATIENTS WITH ACTIVATED PI3K DELTA SYNDROME (APDS) THROUGH DECEMBER 2021**	**Oral Communications Session 04: Therapy**
Raposo A.S.F. Alexandre	PP025	**GENE REGULATORY MODULES DEFINING HUMAN THYMIC REGULATORY T CELLS HELP DECIPHERING THE CONTRIBUTION OF MULTIPLE VARIANTS TO PIDS**	**Poster Discussion 05: Next Generation Sequencing and Other Diagnostics**
Renner Ellen	PD373	**TO CURE LUNG DISEASE IN STAT3-HYPER IGE SYNDROME (STAT3-HIES)**	**Poster Display 08: Therapy**
RILLER RILLER Quentin	PP030	**HETEROZYGOUS DELETERIOUS MUTATION OF CHUK IN A PATIENT WITH IMMUNODEFICIENCY, AUTOIMMUNITY AND LYMPHOMA**	**Poster Discussion 06: Innate Immune Defects**
Rivalta Beatrice	PD152	**PREMATURE GRAYING OF HAIR AS IMMUNODISREGULATION FEATURES ASSOCIATED WITH RAG DEFICIENCY**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**

Rivalta Beatrice	PP004	**PERSISTENT HYPOGAMMAGLOBULINEMIA POST RITUXIMAB: AN UNDERLYING PRIMITIVE IMMUNODEFICIENCY?**	**Poster Discussion 01: Therapies**
Rivière G. Jacques	PD368	**REPURPOSING DRUGS FOR ORPHAN DISEASES: DUPILUMAB FOR AD HIES-RELATED DERMATITIS AND BENRALIZUMAB FOR SEVERE EOSINOPHILIC CYSTITIS IN CGD**	**Poster Display 08: Therapy**
Robertson Nic	PD026	**MUTATIONS ASSOCIATED WITH CARTILAGE-HAIR HYPOPLASIA IMPAIR RIBOSOME SYNTHESIS**	**Poster Display 02: T-Cell Biology**
Rodina Yulia	PD371	**INTERFERON GAMMA (IFNG) INHIBITOR EMAPALUMAB IS EFFECTIVE AND SAFE IN TREATMENT OF PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (P-HLH) IN CHILDREN**	**Poster Display 08: Therapy**
Rodina Yulia	PD074	**CLINICAL CHARACTERISTICS AND RESPONSE TO ABATACEPT TREATMENT IN A GROUP OF PATIENTS WITH LRBA AND CTLA4 DEFICIENCIES (A.K.A T-REGOPATHIES)**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Rodina Yulia	PD187	**HEMATOLOGIC MANIFESTATIONS IN A GROUP OF PATIENTS WITH MONOGENIC AUTOINFLAMMATORY DISEASES (AID): SINGLE CENTER EXPERIENCE**	**Poster Display 05: Autoinflammatory Disorders**
Rodina Yulia	PD179	**SIMULTANEOUS KIDNEY TRANSPLANTATION AND HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) WITH TCR ALPHA/BETA DEPLETION IN A PATIENT WITH DNASE2 DEFICIENCY**	**Poster Display 05: Autoinflammatory Disorders**
Rodrigo Riestra Maria	OC035	**BIALLELIC MUTATION IN DNA POLYMERASE DELTA 3 AS A NOVEL CAUSE OF SEVERE COMBINED IMMUNODEFICIENCY WITH DEVELOPMENTAL DEFECTS**	**Oral Communications Session 05: Novel Defects and Mechanisms**
Rodriguez Johanna Ivon	PD487	**INFLUENCE OF SEX DIFFERENCES ON THE DISTRIBUTION OF DIFFERENT LEUKOCYTE POPULATIONS**	**Poster Display 09: Other**
Roels Marie Louise Lisa	PD521	**IFNAR2 HAPLOINSUFFICIENCY IN A CASE OF SEVERE COVID-19**	**Poster Display 10: COVID-19**
Rosain Jeremie	OC042	**HUMAN IRF1 GOVERNS PHAGOCYTIC IFN-GAMMA IMMUNITY TO MYCOBACTERIA BUT NOT CELL-INTRINSIC IFN-ALPHA/BETA IMMUNITY TO VIRUSES**	**Oral Communications 06: Late Breaking Abstracts**
Rossmanith Raphael	PD438	**A NOVEL ERCC2 MUTATION IS ASSOCIATED WITH IMPAIRED NUCLEOTIDE EXCISION REPAIR (NER), HYPOGAMMAGLOBULINEMIA AND ALTERED COMPOSITION OF LYMPHOCYTE SUBPOPULATIONS IN A TRICHOTHIODYSTROPHY (TTD) PATIENT**	**Poster Display 09: Other**

Runken Chris Michael	PD387	**A CLINICAL TRIAL DATA REVIEW OF TOLERABILITY TO SUBCUTANEOUS IMMUNOGLOBULIN PRODUCTS USED TO TREAT PRIMARY IMMUNODEFICIENCY**	**Poster Display 08: Therapy**
Sacco Keith	PD441	**PREVALENCE OF COCCIDIOIDOMYCOSIS IN PRIMARY IMMUNODEFICIENCY: DATA FROM THE USIDNET REGISTRY**	**Poster Display 09: Other**
Sacco Keith	PD460	**XLA LIFE: AN ADVOCACY GROUP FOR X-LINKED AGAMMAGLOBULINEMIA**	**Poster Display 09: Other**
Sakovich S. Inga	PD041	**NEUTROPHIL FUNCTION AND ADAPTIVE IMMUNE SYSTEM ABNORMALITIES IN LAD I AND LAD III DEFICIENT PATIENTS**	**Poster Display 03: Biology of Innate Immunity**
Sakovich S. Inga	PD273	**SLAVIC FOUNDER MUTATION P.S44R IN IL7RA GENE IN CHILDREN WITH POSTMORTEM DIAGNOSIS SEVERE COMBINED IMMUNODEFICIENCY**	**Poster Display 06: Genetics in IEI**
Sakovich S. Inga	WP014	**SLAVIC FOUNDER MUTATION IN UNC13D GENE IN PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS FROM BELARUS AND UKRAINE**	**Working Party 06: PID Care in Development**
Sakovich S. Inga	PD282	**NEW CASE OF CDC42 DEFICIENCY WITH ADDITIONAL PATHOGENIC VARIANTS IN UNC13D AND DNAH8 GENES**	**Poster Display 06: Genetics in IEI**
Sakura Fumiaki	PS024	**A PROTEOME-BASED APPROACH FOR THE DIAGNOSIS OF INBORN ERRORS OF IMMUNITY**	**Parallel Session 12: Artificial Intelligence in IEI**
Salih Mohammed Hussein Hiba	PD168	**PUNCTATE INNER CHOROIDOPATHY IN A PATIENT WITH COMMON VARIABLE IMMUNODEFECIENCY ASSOCIATED WITH POINT MUTATION IN THE TUMOUR NECROSIS FACTOR RECEPTOR SUPERFAMILY 13B (TNFRSF13B) GENE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Salvati Lorenzo	PD092	**DISSEMINATED NOCARDIOSIS AND ANTI-GM-CSF ANTIBODIES.**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
SANCHEZ ARANDA CAROLINA	PD395	**EXPERIENCE IN PATIENTS WITH INBORN ERRORS OF IMMUNITY (IEI) WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)**	**Poster Display 08: Therapy**
SANCHEZ ARANDA CAROLINA	PD323	**NBS EXPERIENC - KNOWING THE INCIDENCE OF SCID IN BRAZIL**	**Poster Display 07: Genetics Diagnostics**
SANCHEZ ARANDA CAROLINA	PD017	**X-LINKED AGAMMAGLOBULINEMIA (XLA) AND PYODERMA GANGRENOSUM (PG)**	**Poster Display 01: B-Cell Biology**

SANCHEZ ARANDA CAROLINA	PD128	**EFFICACY AND SAFETY OF RAPAMYCIN IN CHILDREN WITH APDS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
SANCHEZ ARANDA CAROLINA	PD310	**VERY-EARLY ONSET INFLAMMATORY BOWEL DISEASE (VEO-IBD): A CLINICAL AND LABORATORY APPROACH**	**Poster Display 07: Genetics Diagnostics**
Sánchez-Ramón Silvia	PD240	**CLINICAL AND IMMUNOLOGICAL FEATURES OF BCL10 DEFICIENCIES**	**Poster Display 06: Genetics in IEI**
Sanchi .	PD489	**AUTOIMMUNE MANIFESTATIONS IN A LARGE MULTI-CENTRE COHORT OF PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY IN INDIA.**	**Poster Display 09: Other**
Sanchi .	PD286	**GENETIC PROFILE OF PATIENTS WITH HEREDITARY ANGIOEDEMA AT A TERTIARY CARE REFERRAL HOSPITAL IN NORTH INDIA**	**Poster Display 06: Genetics in IEI**
Sande James Obondo	PD483	**PRIMARY IMMUNODEFICIENCY DISORDERS IN UGANDA: EVALUATION OF KNOWLEDGE ON CLINICAL AND LABORATORY DIAGNOSIS**	**Poster Display 09: Other**
Santangeli Enrico	PD157	**LONG-TERM CLINICAL AND IMMUNOLOGICAL OUTCOME OF 12 PATIENTS WITH X-LINKED THROMBOCYTOPENIA: A SINGLE CENTRE EXPERIENCE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Santilli Veronica	PD413	**SAFETY AND EFFICACY OF PAXLOVID IN CHILDREN WITH PRIMARY IMMUNODEFICIENCY AFFECTED BY SARS-COV-2 INFECTION: A CASE SERIES.**	**Poster Display 08: Therapy**
Sarfraz Zouina	PD416	**WHAT DO WE KNOW SO FAR ABOUT THE SAFETY AND EFFICACY OF THE IGE-TARGETED BIOLOGIC OMALIZUMAB FOR CHRONIC URTICARIA? A META-ANALYSIS**	**Poster Display 08: Therapy**
Sarfraz Zouina	PD563	**AUTOIMMUNITY IN POST-ACUTE SEQUENCE OF COVID-19: WHERE DO INTERFERONS FIT IN?**	**Poster Display 10: COVID-19**
Sauerwein M.T. Kai	PD551	**DECREASED ANTIBODY AVIDITY IN CVID IGG RESPONDERS FOLLOWING A BOOSTER VACCINATION WITH BNT162B2 SARS-COV2 MRNA VACCINE**	**Poster Display 10: COVID-19**
Savic Sinisa	PS004	**A HIGH-THROUGHPUT AMPLICON SCREEN FOR SOMATIC UBA1 VARIANTS IN CYTOPENIC AND GIANT CELL ARTERITIS COHORTS**	**Parallel Session 02: IEI Phenocopies**
Savic Sinisa	PD208	**PREVALENCE OF CFTR VARIANTS IN PID PATIENTS WITH BRONCHIECTASIS - AN IMPORTANT MODIFYING CO-FACTOR**	**Poster Display 06: Genetics in IEI**

Savic Sinisa	OC032	**NOVEL PRIMARY IMMUNODEFICIENCY ASSOCIATED WITH BIALLELIC VARIANTS IN CWF19L2**	**Oral Communications Session 05: Novel Defects and Mechanisms**
Scarpa Riccardo	PD520	**IMPACT OF HYPOGAMMAGLOBULINEMIA ON THE COURSE OF COVID-19 IN A NON-INTENSIVE CARE SETTING: A SINGLE-CENTER RETROSPECTIVE COHORT STUDY.**	**Poster Display 10: COVID-19**
Schiavo Ebe	PD115	**IMMUNE DYSREGULATION IN CHILDREN WITH INHERITED BONE MARROW FAILURE SYNDROME AND REFRACTORY CYTOPENIA OF CHILDHOOD: PERIPHERAL IMMUNOPHENOTYPING AS POTENTIAL TOOL FOR DIFFERENTIAL DIAGNOSIS**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Schuetz Catharina	PD398	**IKAROS- GLIDING THROUGH AN EASY TRANSPLANT COURSE**	**Poster Display 08: Therapy**
Schulze J. Janika	PD332	**REAL-TIME PCR BASED QUANTITATIVE EPIGENETIC IMMUNE CELL PROFILING OF PATIENTS WITH PRIMARY AND SECONDARY IMMUNE DEFECTS**	**Poster Display 07: Genetics Diagnostics**
Schumann Emma	PD315	**FACS-BASED EVALUATION OF T-CELL FUNCTION IN CHILDREN WITH STIMULI BEYOND MITOGENS**	**Poster Display 07: Genetics Diagnostics**
Schütze Kerstin	PS002	**MAP KINASE ACTIVATING DEATH DOMAIN (MADD) DEFICIENCY IS A NOVEL CAUSE OF IMPAIRED LYMPHOCYTE CYTOTOXICITY**	**Parallel Session 01: Immune Dysregulation in CVID**
Schwartzberg Lee Pamela	OC003	**ALTERED T CELL DIFFERENTIATION ASSOCIATED WITH ACTIVATED PI3 KINASE DELTA**	**Oral Communications Session 01: B Cell T-Cell Biology**
seghrouchni Fouad	PD361	**IMMUNOLOGICAL AND CLINICAL ANALYSIS IN PATIENTS WITH SEVERE COMBINED IMMUNODEFICIENCY IN MOROCCO**	**Poster Display 07: Genetics Diagnostics**
Seidel G Markus	PS023	**UNSUPERVISED PHENOTYPE EXPRESSION PROFILING AND LONGITUDINAL MONITORING IN INBORN ERRORS OF IMMUNITY WITH IMMUNE DYSREGULATION BY MEANS OF THE IDDA2.1 'KALEIDOSCOPE' SCORE**	**Parallel Session 12: Artificial Intelligence in IEI**
Seidel G Markus	PD146	**THE INTESTINAL MICROBIOME IN HEALTH AND DISEASE OF 150 CHILDREN AND ADOLESCENTS WITH OR WITHOUT PRIMARY IMMUNODEFICIENCY OR AUTOIMMUNITY**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Selmanovic Velma	PD501	**RUPTURED CEREBRAL MYCOTIC ANEURISMS AS A PRESENTING SIGN OF PRIMARY IMMUNODEFICIENCY IN A 17Y OLD GIRL WITH HISTORY OF CONGENITAL HEART DISEASE**	**Poster Display 09: Other**

Seminario Gisela Analia	PD512	**COVID-19 VACCINATION AND NATURAL INFECTION'S RESPONSES IN A COHORT OF PATIENTS WITH INBORN ERROR OF IMMUNITY FROM ARGENTINA**	**Poster Display 10: COVID-19**
Seminario Gisela Analia	PD287	**PATIENT WITH GRANULOMAS, RECURRENT INFECTIONS AND ENTEROPATHY. ASSOCIATION OF DEFECTS IN TAP2 AND NOD2.**	**Poster Display 06: Genetics in IEI**
Sendel Anton	PD527	**UNDERLYING GENETIC CAUSES IN YOUNG PATIENTS TREATED WITH INTENSIVE CARE FOR SEVERE COVID-19**	**Poster Display 10: COVID-19**
SETIA PRIYANKA	PD125	**TREND OF DNTS IN ALPS AND ALPS-LIKE DISORDER.**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Sgrulletti Mayla	PD138	**IS A PID OR A SID? THE TROUBLED DILEMMA**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Shamshirgaran Yasaman	PD104	**DEVELOPMENT OF A REPORTER-BASED ASSAY TO QUANTIFY NHEJ/HR RATIO IN PRIMARY T-CELLS USING TRANSIENT TRANSFECTION**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Shanbhag Mohite Kaustubh Rachna	PS006	**APSID Junior: AUTOIMMUNITY IN A LARGE COHORT OF INBORN ERRORS OF IMMUNITY! – EXPERIENCE FROM A TERTIARY CARE CENTER IN SOUTH INDIA**	**Parallel Session 03: IEI in the World (IAPIDS Session)**
Shapero Mara	PD454	**A SERIES OF THREE ADULT PATIENTS WITH CHRONIC RHINOSINUSITIS AND PATHOGENIC MUTATIONS IN CYSTIC FIBROSIS OR PRIMARY CILIARY DYSKINESIA GENES**	**Poster Display 09: Other**
sharifinejad niusha	PD164	**AUTOIMMUNITY IN MONOGENIC COMBINED IMMUNE DEFICIENCIES WITH ASSOCIATED OR SYNDROMIC FEATURES**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Sharma Saniya	PD356	**IMMUNOPHENOTYPIC ABERRANCIES IN PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY**	**Poster Display 07: Genetics Diagnostics**
Shields M Adrian	PD513	**IMPACT OF VACCINATION ON HOSPITALISATION AND MORTALITY FROM COVID-19 IN PATIENTS WITH PRIMARY AND SECONDARY IMMUNODEFICIENCY: THE UNITED KINGDOM EXPERIENCE.**	**Poster Display 10: COVID-19**

Shields M Adrian	PD514	**IMMUNOGENICITY OF A THIRD PRIMARY SARS-COV-2 VACCINATION IN PATIENTS WITH ANTIBODY DEFICIENCY: A COV-AD STUDY UPDATE**	**Poster Display 10: COVID-19**
Sil Archan	PD449	**MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE MASQUERADING AS HISTIOCYTOSIS**	**Poster Display 09: Other**
Sil Archan	PD496	**MYCOBACTERIAL INFECTIONS IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE: AN EXPERIENCE FROM NORTH INDIA**	**Poster Display 09: Other**
Simão Raimundo Diana	PD118	**ADA2 DEFICIENCY MANIFESTING AS SEVERE NEUTROPENIA, RECURRENT FEVER AND LYMPHOPROLIFERATION**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Sindram Elena	PD298	**ASSESSING THE FUNCTIONAL RELEVANCE OF CTLA4 VARIANTS: THE EXPERIENCE OF THE CENTER FOR CHRONIC IMMUNODEFICIENCY IN FREIBURG, GERMANY**	**Poster Display 07: Genetics Diagnostics**
Sivadasan Anju	PD166	**NEUROINFLAMMATORY LESIONS IN CVID**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Skouboe Kelder Morten	PP032	**LIFE-THREATENING VIRAL DISEASE IN A NOVEL FORM OF AUTOSOMAL RECESSIVE IFNAR2 DEFICIENCY IN THE ARCTIC**	**Poster Discussion 06: Innate Immune Defects**
Smieszek Paulina Sandra	PD523	**ELEVATED LEVELS OF CXCL16 IN SEVERE COVID-19 PATIENTS: EFFECTS ON MORTALITY**	**Poster Display 10: COVID-19**
Smits Bas	OC041	**HETEROZYGOUS VARIANTS IN THE DNA-BINDING DOMAIN OF C-MYB MAY AFFECT NORMAL B/T CELL DEVELOPMENT**	**Oral Communications 06: Late Breaking Abstracts**
Smits Bas	PD160	**THE EFFECTIVITY AND TOXICITY OF STEROIDS AS FIRST LINE TREATMENT FOR GRANULOMATOUS LYMPHOCYTIC INTERSTITIAL LUNG DISEASE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Sobh Ali	PD530	**COVID-19 IN PATIENTS WITH INBORN ERRORS OF IMMUNITY; THE EGYPTIAN EXPERIENCE**	**Poster Display 10: COVID-19**
Sobh Ali	PD534	**MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN DURING COVID-19 PANDEMIC IN EGYPT: A SINGLE-CENTRE EXPERIENCE**	**Poster Display 10: COVID-19**
Somech Raz	PS012	**LESSONS LEARNED FROM FIVE YEARS OF NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY (SCID) IN ISRAEL**	**Parallel Session 06: IEI Newborn Screening**

Somech Raz	PD220	**MUTATIONS IN SLP76 ASSOCIATED WITH SEVERE IMMUNODEFICIENCY INCLUDING EBV-RELATED LYMPHOMA**	**Poster Display 06: Genetics in IEI**
Somogyi Vivien	PD464	**INTERSTITIAL LUNG DISEASE IN CVID (GLILD): CLINICAL PRESENTATION AND COMPARISON TO CVID WITHOUT ILD**	**Poster Display 09: Other**
SÖNMEZ EZGİ	PD354	**A CASE OF LATE DİAGNOSIS IMMUNODEFICIENCY: GOOD'S SYNDROME**	**Poster Display 07: Genetics Diagnostics**
Soomann Maarja	PS011	**NEWBORN SCREENING IN SWITZERLAND: TRECS AND KRECS**	**Parallel Session 06: IEI Newborn Screening**
Soomann Maarja	PP011	**CONGENITAL ATHYMIA AS A FEATURE OF DIGEORGE SYNDROME IN PATIENTS WITH MONOGENIC TBX1 DEFICIENCY**	**Poster Discussions 02: Immune Mechanisms**
Sorin Boris	PS013	**SHARPIN HETEROZYGOUS MUTATION IS RESPONSIBLE FOR AUTOIMMUNITY, INFLAMMATORY MANIFESTATIONS AND PRIMARY IMMUNE DEFICIENCY**	**Parallel Session 07: Autoinflammatory Diseases**
Spaan András	OC034	**HUMAN OTULIN HAPLOINSUFFICIENCY IMPAIRS CELL-INTRINSIC IMMUNITY TO STAPHYLOCOCCAL ALPHA-TOXIN**	**Oral Communications Session 05: Novel Defects and Mechanisms**
Sprissler Jasmin	PD425	**RAG1/2 EXPRESSION DISCRIMINATES IPSC-DERIVED NK CELL DEVELOPMENT**	**Poster Display 09: Other**
Staels Frederik	PD248	**A NOVEL HOMOZYGOUS STOP MUTATION IN IL23R CAUSES MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE**	**Poster Display 06: Genetics in IEI**
Staniek Julian	PD008	**NON-APOPTOTIC FAS SIGNALING CONTROLS CD40-DEPENDENT MTOR ACTIVATION AND BALANCES EXTRAFOLLICULAR VERSUS GERMINAL CENTER FATE IN HUMAN B CELLS**	**Poster Display 01: B-Cell Biology**
Staudacher Olga	PD321	**COMBINED IMMUNODEFICIENCY (CID) IS MISSED BY NEWBORN SCREENING FOR T CELL RECEPTOR EXCISION CIRCLES (TREC) IN IMMUNODEFICIENCY CENTROMERIC INSTABILITY AND FACIAL ANOMALIES (ICF)**	**Poster Display 07: Genetics Diagnostics**
Steiner Sophie	PD535	**SARS-COV-2 VACCINATION IN CVID ELICITS A ROBUST T CELL RESPONSE BUT FORMATION OF B CELL MEMORY IS IMPAIRED DESPITE THE PRESENCE OF CIRCULATING ANTIBODIES**	**Poster Display 10: COVID-19**
Steinhart Christine	PD411	**SAFETY ANALYSIS OF ALLOGENEIC PROCESSED THYMUS TISSUE-AGDC TREATMENT IN PATIENTS WITH CONGENITAL ATHYMIA**	**Poster Display 08: Therapy**
Stewart O'Jay	WP005	**RESOLVING INCOMPLETE PENETRANCE IN PRIMARY IMMUNODEFICIENCIES (PIDS): VIA MONOALLELIC EXPRESSION (MAE)**	**Working Party 02: Genetics**

Stojanovic R Maja	PD531	**COVID-19 IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY - SINGLE CENTER EXPERIENCE**	**Poster Display 10: COVID-19**
Stracuzzi Stracuzzi Marta	PD415	**ROLE OF BOOSTER DOSE IN A X-LINKED AGAMMAGLOBULINEMIA ADOLESCENT SARS-COV-2 INFECTED**	**Poster Display 08: Therapy**
Strohmeier Valentina	PS008	**INTERFERON-DRIVEN IMMUNE DYSREGULATION IN COMMON VARIABLE IMMUNODEFICIENCY ASSOCIATED ENTEROPATHY IS EXACERBATED BY NOROVIRUS INFECTION**	**Parallel Session 04: IEI and Microbiome**
Sviridova Alekseevna Daria	PD304	**PATHOGENIC LANDSCAPE IN GENES OF PRIMARY IMMUNODEFICIENCIES**	**Poster Display 07: Genetics Diagnostics**
Tadros Susan	PD379	**USE OF TOFACITINIB IN THE TREATMENT OF THREE ADULT PATIENTS WITH GAIN-OF-FUNCTION MUTATIONS IN STAT-1**	**Poster Display 08: Therapy**
Tajik Shaghayegh	PD494	**MOLECULAR FINDINGS AND CLINICAL MANIFESTATIONS IN NINE IRANIAN CHILDREN WITH GRISCELLI SYNDROME TYPE 2**	**Poster Display 09: Other**
Takada Sanami	PP019	**CHARACTERIZING AND UNRAVELLING THE VARIABLE SPECTRUM OF IMMUNOGLOBULIN DEFICIENCY IN ATAXIA TELANGIECTASIA**	**Poster Discussion 04: T Cell & B Cell Biology**
Tanita Kay	PD010	**A NOVEL SLC39A7 VARIANT AND ZIP7 DISORDER IN A B-CELL DEFICIENT JAPANESE GIRL**	**Poster Display 01: B-Cell Biology**
Tantou Sofia	PD474	**THROMBOCYTOPENIA AS INITIAL PRESENTATION IN PATIENTS WITH INBORN ERRORS OF IMMUNITY**	**Poster Display 09: Other**
Tejada Pilar Maria	PD102	**CASE REPORT: MORE THAN AN ALPS PHENOTYPE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Teocchi Marcelo	PP016	**EFFECTS OF THE HETEROZYGOUS TNFRSF13B P.C104R VARIANT ON THE EXPRESSION OF APOPTOSIS-ASSOCIATED GENES IN THREE UNRELATED PATIENTS WITH DIFFERENT DEGREES OF CLINICAL PENETRANCE**	**Poster Discussion 03: Immune Dysregulation**
Teocchi Marcelo	PD406	**CLINICAL CONDITION DETERIORATION IN A LIKELY DOCK8 DEFICIENCY IRANIAN PATIENT WHO UNDERWENT A DONOR RELATED-HSCT COMPLICATED IN CHRONIC GRAFT VERSUS HOST DISEASE (GVHD)**	**Poster Display 08: Therapy**
TEPETAM FATMA MERVE	PD207	**A CURIOUS DIAGNOSIS, MELKERSSON-ROSENTHAL SYNDROME PRESENTING AS DRUG ALLERGY**	**Poster Display 05: Autoinflammatory Disorders**

Tesakov Ivan	PD423	**PLATELET DYSFUCTION IN PATIENTS WITH SHWACHMAN-DIAMOND SYNDROME**	**Poster Display 09: Other**
Tessarin Giulio	PD268	**CLINICAL AND IMMUNOLOGICAL ANALYSIS OF A LARGE KINDRED AFFECTED BY AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS) DUE TO A NOVEL TNFRSF6 MUTATION DISPLAYING AGE DEPENDENT DISEASE ACTIVITY**	**Poster Display 06: Genetics in IEI**
Thouenon Romane	OC030	**AN IRF4 MUTATION AFFECTING THE INTERFERON ACTIVATION DOMAIN IS ASSOCIATED TO AN AUTOSOMAL DOMINANT PRIMARY B CELL IMMUNODEFICIENCY**	**Oral Communications Session 05: Novel Defects and Mechanisms**
Tomacinschii Tomacinschii Cristina	PD458	**IMAGING CHEST FEATURES IN INBORN ERRORS OF IMMUNITY**	**Poster Display 09: Other**
Tomacinschii Tomacinschii Cristina	PD484	**SPECTRUM OF DISEASE MANIFESTATIONS IN PEDIATRIC PATIENTS WITH WISKOTT-ALDRICH SYNDROME**	**Poster Display 09: Other**
Tomacinschii Tomacinschii Cristina	PD473	**GENOTYPE-PHENOTYPE CORRELATION IN A CHILD WITH WISKOTT ALDRICH SYNDROME**	**Poster Display 09: Other**
Topyildiz Ezgi	PD533	**IMMUNOLOGICAL EVALUATION OF PEDIATRIC COVID-19 CASE**	**Poster Display 10: COVID-19**
Torpiano Paul	PD469	**IMMUNODEFICIENCY-CENTROMERIC INSTABILITY-FACIAL ANOMALIES SYNDROME 4 PRESENTING IN THE NEONATAL PERIOD WITH SEVERE IUGR, RESPIRATORY DISTRESS, AND CONGENITAL HEART DISEASE**	**Poster Display 09: Other**
Torpiano Paul	PD486	**OUTCOMES IN PATIENTS WITH SCHIMKE'S IMMUNO-OSSEOUS DYSPLASIA – A REGISTRY-BASED INTERNATIONAL SURVEY**	**Poster Display 09: Other**
Torpiano Paul	PD295	**CLARIFYING MIRAGES - A DILEMMA LEADING TO A DIAGNOSIS**	**Poster Display 06: Genetics in IEI**
Touzot Fabien	OC019	**NOX2-DERIVED ROS CONTROL THE INFLAMMATORY RESPONSE BY REGULATING GASDERMIN D CLEAVAGE**	**Oral Communications Session 03: Innate Immune Defects**
Trizzino Antonino	PD480	**HYPOGAMMAGLOBULINEMIA WHICH HELPS TO EXPLAIN A DIFFICULT INTERPRETATION OF A MICROCYTIC ANEMIA**	**Poster Display 09: Other**
Tromp Alexandra Maloe Samantha	PD089	**TREATMENT OF AN HLH-MIMIC DISEASE BASED ON HAVCR2 VARIANTS WITH ABSENT TIM-3 EXPRESSION**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Tsilifis Christo	OC024	**ALLOGENEIC HSCT FOR STAT3-DN HYPER IGE SYNDROME – AN INTERNATIONAL SURVEY**	**Oral Communications Session 04: Therapy**

Tsilifis Christo	PD491	**POOR HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH STAT3-DN HYPER-IGE SYNDROME: PRELIMINARY RESULTS OF AN INTERNATIONAL MULTICENTRIC STUDY**	**Poster Display 09: Other**
Tsilifis Christo	PD492	**RESPIRATORY AND DERMATOLOGICAL SYMPTOMS AND QUALITY OF LIFE IN PATIENTS WITH STAT3-DN HYPER-IGE SYNDROME: PRELIMINARY RESULTS OF AN INTERNATIONAL MULTICENTRIC STUDY**	**Poster Display 09: Other**
TUNAKAN DALGIÇ CEYDA	PD265	**A CASE OF CVID CLINICAL OVERLAPS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA PRESENTING WITH MUTATIONS IN BOTH EPHB4 AND INPP5D GENES**	**Poster Display 06: Genetics in IEI**
Tuovinen Anna Elina	PD227	**CHARACTERIZATION OF EXPANDED GAMMA DELTA T CELLS FROM ATYPICAL X-SCID PATIENT REVEALS PRESERVED FUNCTION AND IL2RG-MEDIATED SIGNALING**	**Poster Display 06: Genetics in IEI**
Tusseau Maud	OC013	**EXOME SEQUENCING IN EARLY-ONSET OR FAMILIAL SYSTEMIC LUPUS ERYTHEMATOSUS**	**Oral Communications Session 02: Autoinflammation and Immune Dysregulation**
Tyagi Rahul	PD009	**GENETIC BASIS OF COMMON VARIABLE IMMUNODEFICIENCY (CVID): A MULTICENTRE EXPERIENCE FROM INDIA.**	**Poster Display 01: B-Cell Biology**
Tzanoudaki Marianna	PD334	**EARLY WISKOTT-ALDRICH SYNDROME DIAGNOSIS DUE TO INCREASED AWARENESS OF PID IN A GENERAL PEDIATRIC CLINIC**	**Poster Display 07: Genetics Diagnostics**
Tzanoudaki Marianna	PD306	**INDETERMINATE INTERFERON GAMMA RELEASE TUBERCULOSIS ASSAY AS A WARNING SIGN FOR PID**	**Poster Display 07: Genetics Diagnostics**
Tzanoudaki Marianna	PD338	**STUDY OF IMMUNOGLOBULIN SUBCLASS EXPRESSION ON B CELLS: INITIAL EXPERIENCE FROM ITS IMPLEMENTATION IN CLINICAL PRACTICE**	**Poster Display 07: Genetics Diagnostics**
Tzanoudaki Marianna	PD077	**IMPLEMENTATION OF A FUNCTIONAL IL-10R MEDIATED CYTOKINE INHIBITION ASSAY IN CLINICAL PRACTICE**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Tzanoudaki Marianna	PD556	**SARS-COV2 SPECIFIC T CELL IMMUNITY IN ANTIBODY DEFICIENT PATIENTS**	**Poster Display 10: COVID-19**
Ueki Masahiro	PD177	**HYPER-INFLAMMATION AND JUVENILE MYELOMONOCYTIC LEUKEMIA LIKE MANIFESTATIONS ARE ATTRIBUTABLE TO GM-CSF AND IL-3 HYPERSENSITIVITY IN A PATIENT**	**Poster Display 05: Autoinflammatory Disorders**

		WITH NEMO DEFICIENCY BY DEEP INTRONIC BASE SUBSTITUTION	
Unninayar Dana	PD493	SEROLOGICAL RESPONSE OF ADULT AND PEDIATRIC PATIENTS WITH PRIMARY AND SECONDARY IMMUNODEFICIENCY TO SARS-COV2 BNT16B2 AND MRNA-1273 VACCINES, AND BREAKTHROUGH INFECTIONS IN CANADA	Poster Display 09: Other
van Coller Ansia	PD067	ABERRANT T-BET EXPRESSION IN PATIENTS WITH SUSPECTED MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE IN SOUTH AFRICA	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
van der Burg Mirjam	PD020	IL-7 RECEPTOR SIGNALING DRIVES HUMAN B-CELL PRECURSOR DIFFERENTIATION AND EXPANSION.	Poster Display 01: B-Cell Biology
van der Knaap Linda	INGID002	READY STEADY GO; A GENERIC TRANSITION TOOL USED IN PATIËNTS WITH PID	INGID session 04: Oral and Poster Presentations on Nursing Topics
van der Made Ivan Caspar	PS010	HYPERMORPHIC HETEROZYGOUS VARIANTS IN ZAP70 UNDERLIE AUTOIMMUNE DISEASE	Parallel Session 05: B and T Cell Tolerance Checkpoints
van der Waal Jelka	INGID004	TRANSITION IN CARE FOR PATIENTS WITH PID	INGID session 04: Oral and Poster Presentations on Nursing Topics
van Leeuwen Leane	PD511	IMMUNOGENICITY OF THE MRNA-1273 COVID-19 VACCINE IN ADULT PATIENTS WITH INBORN ERRORS OF IMMUNITY : SIGNIFICANT DECLINE IN BINDING ANTIBODY LEVELS SIX MONTHS AFTER VACCINATION	Poster Display 10: COVID-19
van Leeuwen Leane	PD548	SARS-COV-2 BOOSTER VACCINATION IN PATIENTS WITH COMMON VARIABLE IMMUNE DEFICIENCY: USEFULL OR USELESS?	Poster Display 10: COVID-19
van Stigt Charlotte Astrid	PD057	SUBTLE DIFFERENCES DUE TO IMMUNE DYSREGULATION IN SOLUBLE SURFACE MARKERS AND CELL COUNTS IN COMMON VARIABLE IMMUNE DEFICIENCY	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
Vargas Cely Samir Fabio	PD184	AN UNUSUAL CASE OF HEPATOMEGALY, PANCYTOPENIA AND AUTOINFLAMMATORY SYNDROME IN A COLOMBIAN GIRL: ABOUT A CASE OF PSTPIP1-ASSOCIATED MYELOID-RELATED PROTEINEMIA INFLAMMATORY (PAMI) SYNDROME	Poster Display 05: Autoinflammatory Disorders
Vargas Cely Samir Fabio	PD121	SEVERE AUTOIMMUNITY TRAITS IN A COLOMBIAN BOY: A NOVEL NRAS MUTATION C.182A>G (P.Q61R) CAUSING RAS-ASSOCIATED	Poster Display 04: Immune Dysregulation &

		AUTOIMMUNE LEUKOPROLIFERATIVE DISEASE (RALD)	Autoimmune Disorders
Venavides Venavides Wendy	PD340	FROM THE CLINICAL PHENOTYPE TO THE MOLECULAR DIAGNOSIS: FIRST YEAR OF EXPERIENCE IN A PEDIATRIC HOSPITAL IN EL SALVADOR WITH MOLECULAR DIAGNOSIS IN PID	Poster Display 07: Genetics Diagnostics
Verhoeven Dorit	PD038	CHARACTERIZATION OF A NOVEL HETEROZYGOUS TICAM1/TRIF MUTATION IN A SINGLE FAMILY	Poster Display 03: Biology of Innate Immunity
Vieira Calixto Rhaissa	PD236	A DE NOVO THR325ARG MUTATION IN CDCA7 CAUSES IMMUNODEFICIENCY, CENTROMERIC REGION INSTABILITY, FACIAL ANOMALIES SYNDROME, AND DEFECTIVE B AND T CELL DIFFERENTIATION	Poster Display 06: Genetics in IEI
Vieira Calixto Rhaissa	PP003	FLOW CYTOMETRY-BASED DRUG SCREENING TO FIND DRUG CANDIDATES THAT RESTORE WASP IN MEGAKARYOCYTE AND PLATELET FUNCTION	Poster Discussion 01: Therapies
Villa Mariana	PD339	LIFE-CHANGING TREATMENT AFTER A LATE DIAGNOSIS OF CHAPLE SYNDROME. CASE REPORT.	Poster Display 07: Genetics Diagnostics
Volokha Alla	PD470	MYELODYSPLASTIC SYNDROME AND HEBO DEFICIENCY	Poster Display 09: Other
Volpi Stefano	PD189	CLINICAL CHARACTERIZATION AND TYPE I INTERFERON ACTIVATION OF A COHORT OF PATIENTS WITH UNDEFINED INFLAMMATORY SYNDROMES FROM THE EUROFEVER REGISTRY	Poster Display 05: Autoinflammatory Disorders
Vorsteveld E Emil	PD037	IDENTIFICATION OF POTENTIAL CORE FUNCTIONS IN HUMAN IMMUNE RESPONSES OF GENES WITH PREVIOUSLY UNKNOWN FUNCTION	Poster Display 03: Biology of Innate Immunity
Wahren Borgström Emilie	PD388	THREE ADULT CASES OF STAT1 GAIN-OF-FUNCTION WITH CHRONIC MUCOCUTANEOUS CANDIDIASIS TREATED WITH JAK INHIBITORS	Poster Display 08: Therapy
Walkiewicz-Yvon Magdalena	PD288	FOXI3 HAPLOINSUFFICIENCY CONTRIBUTES TO LOW T CELL RECEPTOR EXCISION CIRCLES AND T CELL LYMPHOPENIA.	Poster Display 06: Genetics in IEI
Wang wang Yating	PD544	IMPACT OF DNA REPAIR DEFECTS ON SARS-COV-2 INFECTION IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY	Poster Display 10: COVID-19
Weitering Johan Thomas	PD324	IN-DEPTH PHENOTYPING OF THE T-CELL SYSTEM OF A ZAP-70-DEFICIENT PATIENT POST-HSCT IN CONTEXT OF MIXED CHIMERISM	Poster Display 07: Genetics Diagnostics
Withers Elizabeth Sarah	PD175	CHARACTERISATION OF A MUTANT SAMHD1 ZEBRAFISH MODEL IMPLICATES DYSREGULATION OF CHOLESTEROL	Poster Display 05: Autoinflammatory Disorders

		BIOSYNTHESIS IN AICARDI-GOUTIÈRES SYNDROME	
Wolff S. B. Anette	PS003	IS THE PRESENCE OF CYTOKINE-AUTOANTIBODIES IN PATIENTS WITH ENDOCRINE AUTOIMMUNE DISORDERS POINTING TO AN UNDERLYING MONOGENIC ETIOLOGY?	Parallel Session 02: IEI Phenocopies
Wong Chi Yan Jane	PD452	EFFICACY AND IMPACT OF CASCADE SCREENING AND EVALUATION OF HAE (CASE-HAE)	Poster Display 09: Other
Wouters Marjon	PD176	LONGITUDINAL IFN SCORES AND CLINICAL STATE IN FOUR ADA2 PATIENTS	Poster Display 05: Autoinflammatory Disorders
Xu-Bayford Jinhua	INGID003	TWENTY YEARS OF STEM CELL GENE THERAPY AT GREAT ORMOND STREET HOSPITAL	INGID session 04: Oral and Poster Presentations on Nursing Topics
Yaakoubi Roukaya	PD274	NEXT GENERATION SEQUENCING HELPS TO DISTINGUISH A DOCK8 DEFICIENCY FROM AD-HYPER IGE SYNDROME FORM	Poster Display 06: Genetics in IEI
Yasaei Mehrdad	PD272	A NOVEL MUTATION IN NSMCE3 GENE IN AN IRANIAN INFANT WITH COMBINED IMMUNODEFICIENCY.	Poster Display 06: Genetics in IEI
Yılmaz Çölkesen Ümmügülsüm	PD137	THE RELATIONSHIP BETWEEN AUTOIMMUNE DISEASES AND SERUM BASAL IGE LEVELS IN CVID PATIENTS	Poster Display 04: Immune Dysregulation & Autoimmune Disorders
Yukhacheva Daria	OC022	COMPARISON OF EFFICACY AND SAFETY OF IL-1 RECEPTOR INHIBITOR (ANAKINRA) AND STEROIDS (PREDNISOLONE) IN TREATMENT OF GRANULOMATOUS COMPLICATIONS IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE	Oral Communications Session 04: Therapy
Yukhacheva Daria	PD322	INFLAMMATORY BOWEL DISEASE (IBD) IN PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA (XLA) RECEIVING INTRAVENOUS IMMUNOGLOBULIN (IVIG) THERAPY	Poster Display 07: Genetics Diagnostics
Zecevic Gordana Milica	PD541	SEVERE COURSE OF SARS-COV-2 PNEUMONIA IN A PATIENT WITH PATHOLOGICAL HETEROZYGOUS VARIANT IN RAG1 GENE	Poster Display 10: COVID-19
Zeuner Albrecht Rainald	PD185	REGRESSION OF SEVERE CARDIAC AA-AMYLOIDOSIS UNDER 5-YEAR TREATMENT WITH ANAKINRA IN A PATIENT WITH DOUBLE-HOMOCYGOTE FMF-MUTATIONS(C.2080A>G; C.605G>A).	Poster Display 05: Autoinflammatory Disorders

Zhang Yue	PD353	**DEFICIENCY OF ADENOSINE DEAMINASE IN CHILDREN: THE FIRST CASE SERIES FROM CHINA**	**Poster Display 07: Genetics Diagnostics**
Zhang Yue	PD327	**X-LINKED CHRONIC GRANULOMATOUS DISEASE SECONDARY TO SKEWED X CHROMOSOME INACTIVATION IN FEMALE PATIENTS**	**Poster Display 07: Genetics Diagnostics**
Zhou Z.Z	PD097	**ROLE OF STAT3 GAIN-OF-FUNCTION VARIANT IN THE DEVELOPMENT AND TREATMENT OF CYSTOID MACULAR EDEMA**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**
Zmajkovicova Katarina	PD066	**CASE STUDY: A NOVEL CXCR4 P.SER346PROFS*12 VARIANT IN A CHILD WITH WHIM SYNDROME**	**Poster Display 04: Immune Dysregulation & Autoimmune Disorders**