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Association of cough complaints with spirometry, nasal breathing in patients with asthma and allergic rhinitis

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Abstract

Aim: Cough is an important symptom of the combined course of bronchial asthma (BA) and allergic rhinitis (AR) and/or allergic rhinosinusitis (ARS), but the contribution of the pathology of the upper and lower airway to the formation of cough in these patients cannot be considered established. The aim of the study was to evaluate the relationship of cough intensity with indicators of external respiration and nasal respiratory function in children and adolescents with a combined course of BA and AR and/or ARS.

Methods: It was a single-center observational transverse pilot study. The absence and/or presence of cough and its intensity were scored in 122 patients (14.0 [11.0; 16.0] years) using the Sinonasal Outcome Test–22 (SNOT-22). Groups were identified: 1 (n = 29)—no cough (0 points), 2 (n = 72)—mild cough (1–2

points), 3 (n = 21)—moderate cough (3–4 points). Peak nasal inspiratory flow (PNIF) and spirometric parameters were measured.

Results: Assessment of cough by patients using the SNOT-22 test had negative correlations with spirometric indicators: z FEV_1 and z FEV_1/FVC (r = –0.23, P = 0.012 and r = –0.21, P = 0.023, respectively). A positive relationship was noted with changes in FEV_1 in tests with bronchodilators (r = 0.43, P = 0.002) and with the severity of postnasal drip (r = 0.45, P < 0.001 and r = 0.43, P < 0.001, respectively).

Conclusions: Established correlations of cough intensity with spirometry indicators and with symptoms of postnasal drip in patients with combined BA and AR/ARS indicate the participation of both the upper and lower respiratory tract in the formation of cough.

Keywords

Bronchial asthma, allergic rhinitis, allergic rhinosinusitis, cough, spirometry, peak nasal inspiratory flow

Introduction

The main non-infectious causes of cough in children and adolescents are bronchial asthma (BA), as well as pathology of the upper respiratory tract (URT) [1, 2]. Considering that most patients of childhood and adolescence have a combined course of asthma and allergic rhinitis (AR) and/or allergic rhinosinusitis (ARS), the problem of cough in this cohort of patients is especially relevant [3, 4]. It should be noted that these two conditions frequently coexist in the same patient and share numerous pathogenetic and pathophysiological mechanisms [5–7]. According to Marseglia et al. [8], BA and ARS are not simply localized disease processes, but part of a systemic inflammatory disease affecting the respiratory tract.

It is obvious that the genesis of cough in the combined course of BA and AR/ARS may be multifaceted, and associated with the involvement of both the bronchi and the URT in the pathological process, especially in association with a postnasal drip of mucus [9]. This makes it difficult to diagnose and develop effective therapy programs. To date, there have been no comprehensive studies on the relationship of cough severity with objective and subjective parameters reflecting the involvement of various sections of the respiratory tract in the pathological process in children and adolescents with a combined course of BA and AR/ARS. SNOT-22 (Sinonasal Outcome Test-22) is a reliable tool for evaluating sinonasal symptoms. Cough and postnasal drip scores are included in the SNOT-22 questionnaire and thus can be used to assess patients' subjective perceptions of cough. Objective methods reflecting the involvement of the lower respiratory tract (LRT) and URT in the pathological process are spirometry and the study of peak nasal inspiratory flow (PNIF). In the work of Tian et al. [10], a statistically significant association of cough with spirometric parameters and their variability in samples with bronchodilators in asthma patients was demonstrated. However, this study, as well as similar ones, did not take into account the state of the upper airway (UA) and the influence of AR/ARS on cough [10, 11].

We have not found any studies analyzing the relationship between coughing and nasal respiratory function. However, the relationship between cough and URT pathology is beyond doubt, especially in connection with postnasal drip syndrome, which is the subject of a significant number of publications [12, 13]. Currently, this pathological condition is referred to as upper airway cough syndrome (UACS) [12]. We have not found comprehensive studies analyzing the relationship between subjective perception of cough and an objective assessment of the condition of the URT and LRT in children and adolescents with combined asthma and AR/ARS.

In connection with the above, the aim of this study was to evaluate the relationship between the severity of cough and objective indicators of nasal breathing function and spirometry in children and adolescents with a combined course of BA and AR/ARS.

Materials and methods

Study design

Single-center observational transverse pilot. The study was conducted among 122 patients aged 6 to 17 years, of which boys is 73.8% (90/122), they were treated for atopic asthma and had nasal or sinonasal complaints (symptoms) at the Children's City Clinical Hospital No. 1 in Nizhny Novgorod from 2017–2023.

Compliance criteria

Inclusion criteria

(1) The diagnosis of asthma was established in accordance with the applicable international conciliation documents (GINA, 2016–2022) [14];

(2) The presence of nasal or sinonasal complaints and symptoms in patients;

(3) The age of patients from 6 to 17 years old;

(4) Blood oxygen saturation > 96%.

Exclusion criteria

(1) Severe asthma;

(2) Presence of acute infectious diseases and fever;

(3) The presence of diabetes mellitus, autoimmune diseases, oncological diseases and immunodeficiency conditions;

(4) Systemic use of glucocorticoids, the use of angiotensin converting enzyme (ACE) inhibitors;

(5) Smoking;

(6) Pathological changes on the chest X-ray;

(7) The use of immunobiological drugs.

Objective measurements

All children had a symptom complex characteristic of BA and AR; a family history of atopy was assessed. The examination was performed in the autumn-winter period, which minimized the effect of pollen allergens. Treatment of asthma and concomitant diseases of the UA was carried out in accordance with the available conciliation documents [15, 16].

Assessment of sinonasal symptoms

All patients with BA were examined by an otorhinolaryngologist. The diagnosis of AR and ARS was carried out in accordance with existing recommendations. Involvement of the paranasal sinuses in the pathological process was diagnosed using the criteria of the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 [16]. The patients performed a routine otorhinolaryngological examination in combination with a SNOT-22 assessment. SNOT-22 includes 22 questions, each of which is rated on a 6-point scale from 0 to 5 points. The cough intensity in the SNOT-22 test also has a 6-point scale from 0 to 5 points, however, in our study, there were no participants with the maximum number of points (5).

According to the cough assessment data in this study, the children were divided into 3 groups: Group 1: no cough (0 points on SNOT-22), Group 2: mild cough (1–2 points according to SNOT-22), Group 3: cough of moderate intensity (3–4 points according to SNOT-22). There were no patients who had an estimate of 5 points in a symptom cough in this study.

Assessment of nasal respiratory function

PNIF was assessed using a nasal peak flowmeter equipped with a transparent mask (In-Check Nasal, Clement Clarke International Ltd., Harlow, UK). The device uses a tube of variable diameter, calibrated

directly in liters per minute (L/min), as well as a low inertia indicator ring, the position of which after inhalation clearly indicates the maximum flow achieved. PNIF measurements were carried out using the minimum diameter size (S = 7.65 mm^2) in a temperature-controlled room with the patient in a sitting position. Patients were instructed to inhale through their nose with their mouth closed to full lung capacity and exhale through a tightly pressed facial mask without nasal compression. The maneuver was repeated and the largest of the three measurements was recorded with a deviation of up to 10%. Measurements were recorded in accordance with the published 2020 consensus recommendations [16]. Taking into account the dependence of PNIF on spirometric parameters, we introduced the PNIF/FVC (forced vital capacity of the lungs) coefficient, which levels the effect of lung volume on nasal inspiratory flow [17, 18]. However, there are currently no uniform recommendations for assessing nasal flow.

Assessment of the function of external respiration

Spirometric studies were performed using a Masterscreen pneumospirometer (Jaeger, Germany). The following parameters were evaluated: FVC, FEV_1 (l/s): forced expiratory volume in the first second; FEV_1 /FVC: ratio, which is the main spirometry parameter used in the diagnosis of obstructive disorders. The Z-scores (z) of FVC and FEV_1, as well as FEV_1/FVC, were calculated using the Global Lung Function Initiative Calculator (http://gli-calculator.ersnet.org/index.html), created with the support of the European Respiratory Society (https://www.ersnet.org). The change in FEV_1 in bronchodilator tests (FEV_1 after bronchodilator/FEV_1 before bronchodilator) and the change in FEV_1 in physical activity tests (FEV_1 after physical activity/FEV_1 before physical activity) were evaluated. Salbutamol was used as a metered-dose aerosol delivered through a spacer.

Blood test

All participants underwent peripheral blood assessment on an empty stomach in the morning before treatment. In our work, we performed a peripheral blood analysis by counting the absolute number of eosinophils on an automatic hematological analyzer of the XS series (XS-1000i/XS-800i, SYSMEX CORPORATION, Japan). Determination of the level of total serum immunoglobulin E (IgE) was performed using the IgE-ELISA-Best test systems, manufactured by Vector-Best JSC, Russia, on the automated enzyme immunoassay analyzer ALISEI-QS, RADIM GROUP, Italy.

Statistical analysis

The principles of calculating the sample size: the calculation of the sample size was not carried out beforehand. Methods of processing missing data: there were no missing data in the study.

Methods of statistical data analysis

Statistical analysis was performed using Statgraphics Centurion v.16 (Statgraphics Technologies, Inc., The Plains, Virginia, USA). Quantitative indicators were evaluated for compliance with the normal distribution using the Shapiro-Wilk criterion (with fewer than 50 subjects) or the Kolmogorov-Smirnov criterion (with more than 50 subjects), as well as indicators of asymmetry and kurtosis. The data is presented in the form of Me [Q1; Q3], where Me is the median, [Q1; Q3] is 1st and 3rd quartiles in the case of an abnormal distribution of quantities, and in the form of M ± σ, where M is the mean value, σ is the standard deviation in the case of their normal distribution. The Mann-Whitney criterion was used to compare quantitative variables in two independent groups. The differences between the two dependent groups were determined using Wilcoxon's *W*-test. Correlation analysis was performed for normally distributed variables using the Pearson correlation coefficient and for abnormally distributed variables using Spearman's rank correlation coefficient. Categorical data were described with absolute values and percentages. The differences were evaluated using Pearson's χ^2 criterion. If the number of expected observations in any of the cells of the four-field table was less than 10, the exact Fisher criterion was used to assess the significance of the differences. The differences were considered statistically significant at $P < 0.05$.

Results

The study involved 122 patients aged 14.0 [11.0; 16.0] years, boys 73.8% (90/122). The clinical characteristics of the study group are shown in Table 1. Boys and girls were comparable according to the z-criteria of anthropometric parameters (z height: 0.40 [–0.25; 1.22] vs. 0.64 [–0.12; 1.15], $P = 0.662$; z BMI (body mass index): 0.01 ± 0.98 vs. 0.53 ± 1.17, $P = 0.214$).

Table 1. Clinical characteristics of patients

Parameters	Values (n_{total} = 122)
Age, year	14.0 [11.0; 16.0]
z Height	0.42 [–0.25; 1.16]
z BMI	0.24 ± 1.04
z FVC	1.11 ± 1.31
z FEV_1	0.31 ± 1.23
z FEV_1/FVC	–1.01 ± 1.26
Change of FEV_1 in tests with bronchodilator, $n = 50$	1.12 ± 0.11
PNIF, L/min	44.64 ± 13.49
PNIF/FVC	11.05 [7.89; 14.40]
Eosinophils, 10^9/L	0.28 [0.14; 0.50]
IgE, ME/mL	180.01 [81.55; 384.01]
SNOT-22, scores	16.0 [10.0; 24.0]
Postnasal discharge, scores	1.0 [0.0; 2.0]
Cough, scores	2.0 [1.0; 2.0]
Cough, scores	
0: no	23.8% (29/122)
1–2: low intensity	59.0% (72/122)
3–4: medium intensity	17.2% (21/122)

z BMI: z-score body mass index; z Height: z-score height; PNIF: peak nasal inspiratory flow; FVC: forced vital capacity of the lungs; FEV_1: forced expiratory volume in the first second; SNOT-22: Sinonasal Outcome Test-22; IgE: immunoglobulin E. The data is presented in the form of Me [Q1; Q3], where Me is the median, [Q1; Q3] is 1st and 3rd quartiles in the case of an abnormal distribution of quantities, and in the form of M ± σ, where M is the mean value, σ is the standard deviation in the case of their normal distribution

The statistically significant expected negative correlation between the assessment of cough and spirometric parameters reflecting bronchial patency, including z FEV_1 and z FEV_1/FVC ($r = –0.23$, $P = 0.012$, $r = –0.21$, $P = 0.023$, respectively), was revealed (Table 2). The reversibility of bronchial obstruction in tests with bronchodilators increased statistically significantly with increased cough, $r = 0.43$, $P = 0.002$.

Table 2. Correlations between cough assessment scores and spirometric parameters, indicators of nasal respiratory function, indicators of SNOT-22, and anthropometric parameters (all, *n* = 122)

Parameters	Cough (scores)	
	r	***P*-value**
z FVC	–0.06	0.516
z FEV_1	–0.23	0.012
z FEV_1/FVC	–0.21	0.023
Change of FEV_1 in tests with bronchodilator, $n = 50$	0.43	0.002
PNIF, L/min	–0.11	0.239
PNIF/FVC	–0.16	0.083
PNIF/FVC (without children with polyps in the cavity of the nasal passages), n =114	–0.18	0.056
Eosinophils, 10^9/L	0.27	0.004
Total IgE, ME/mL	0.15	0.150
SNOT-22, score	0.45	< 0.001
Postnasal discharge, score	0.43	< 0.001

PNIF: peak nasal inspiratory flow; FVC: forced vital capacity of the lungs; FEV_1: forced expiratory volume in the first second; SNOT-22: Sinonasal Outcome Test-22; IgE: immunoglobulin E

In this study, we did not establish a statistically significant relationship between nasal respiratory function and cough intensity in patients, $r = -0.16$, $P > 0.05$. However, after excluding 8 patients from the sample who had polypous changes in the nasal mucosa, a weak negative relationship was revealed, having the character of a trend, $r = -0.18$, $P = 0.056$. At the same time, both the severity of sinonasal symptoms in general and the severity of the symptom of postnasal mucus drip had a direct relationship with the subjective perception of cough by patients ($r = 0.45$, $P < 0.001$ and $r = 0.43$, $P < 0.001$, respectively). The absolute eosinophil count in peripheral blood had a direct statistically significant relationship with the severity of cough ($r = 0.27$, $P = 0.004$), while no statistically significant relationships with the level of total serum IgE were found.

A comparison of clinical, functional, and laboratory parameters in patients with no cough, mild cough, and moderate cough demonstrated patterns generally consistent with the results of regression analysis (Table 3). Spirometric parameters reflecting bronchial patency, including both z FEV_1 and z FEV_1/FVC, had statistically significant differences in patients of these groups, with the highest values of these indicators occurring in patients with no cough and the lowest in patients with moderate cough. Changes in FEV_1 in bronchodilator tests were the least pronounced in patients with no cough and most pronounced in patients with moderate cough; the differences were statistically significant ($P = 0.033$ and $P = 0.024$, respectively). However, there were no statistically significant differences in the values of PNIF in children with different cough severity in the analyzed sample. The ratio of PNIF to FVC (PNIF/FVC) was slightly lower in patients with moderate intensity cough, but the differences were only trending, $P = 0.089$. The exclusion of patients with polyps in the lumen of the nasal passages from the sample was accompanied by the appearance of statistically significant differences in the PNIF/FVC ratio in patients of the three analyzed groups with minimal values of this indicator in children with moderate cough, $P = 0.035$. The values of SNOT-22 both in general and in terms of the severity of the postnasal mucus drainage symptom increased progressively with increasing cough severity, all $P < 0.001$. We did not find statistically significant differences in the absolute eosinophil count in peripheral blood and serum total IgE in patients of the analyzed groups in this sample, however, the median values of the absolute eosinophil count increased with increasing severity of cough.

Table 3. Comparison of clinical, functional, and laboratory data depending on cough intensity

Parameters	Group 1 ($n = 29$)	Group 2 ($n = 72$)	Group 3 ($n = 21$)	*P*-value
z FVC	1.15 ± 1.25	1.14 ± 1.41	0.98 ± 1.08	0.876
z FEV_1	0.64 ± 0.98	0.35 ± 1.26	–0.28 ± 1.28	0.028
z FEV_1/FVC	–0.67 ± 1.18	–0.97 ± 1.31	–1.65 ± 1.03	0.022
Changes of FEV_1 in tests with salbutamol, $n = 50$	1.06 ± 0.05	1.10 ± 0.09	1.19 ± 0.15	0.024
PNIF, L/min	45.53 ± 12.33	45.73 ± 13.10	39.67 ± 15.73	0.179
PNIF/FVC	10.52 [8.63; 14.85]	11.65 [8.58; 14.97]	9.72 [6.91; 11.95]	0.089
PNIF/FVC (without children with polyps in the cavity of the nasal passages), $n = 114$	10.95 [8.86; 15.72]	12.11 [8.98; 15.11]	9.27 [6.91; 11.95]	0.035
SNOT-22, score	0.0 [0.0; 1.0]	2.0 [0.0; 2.0]	2.0 [1.0; 3.0]	< 0.001
Postnasal discharge, score	0.0 [0.0; 1.0]	2.0 [0.0; 2.0]	2.0 [2.0; 3.0]	< 0.001
Eosinophils, 10^9/L	0.19 [0.10; 0.32]	0.29 [0.15; 0.60]	0.35 [0.16; 0.50]	0.132
Total IgE, ME/mL	182.69 [86.83; 298.43]	173.50 [81.55; 356.70]	187.58 [62.20; 724.69]	0.685

Group 1: no cough (0 points on SNOT-22); Group 2: mild cough (1–2 points according to SNOT-22); Group 3: cough of moderate intensity (3–4 points according to SNOT-22). PNIF: peak nasal inspiratory flow; FVC: forced vital capacity of the lungs; FEV_1: forced expiratory volume in the first second; SNOT-22: Sinonasal Outcome Test-22; IgE: immunoglobulin E. The data is presented in the form of Me [Q1; Q3], where Me is the median, [Q1; Q3] is 1st and 3rd quartiles in the case of an abnormal distribution of quantities, and in the form of M ± σ, where M is the mean value, σ is the standard deviation in the case of their normal distribution

Discussion

In this study, for the first time, a comprehensive objective examination of 122 pediatric and adolescent patients with a combination of BA and AR was conducted from the standpoint of the absence/presence and severity of cough. Spirometry parameters, flow variability in tests with bronchodilators, and nasal

breathing function indicators were determined in these patients. It was found that subjective cough assessment by the SNOT-22 test had statistically significant correlations with spirometric parameters, including z FEV_1 and z FEV_1/FVC (all $P < 0.05$). At the same time, the greatest relationship was noted between the severity of cough and the bronchodilation coefficient in the bronchodilator test for the reversibility of bronchial obstruction. In our study, no statistically significant relationships were found between cough severity and the parameters of nasal respiratory function, either when analyzing the absolute values of PNIF (L/min) or when analyzing the PNIF/FVC ratio. However, when excluding from the sample patients with polypous changes in the sinonasal mucosa (fixed nasal obstruction), we obtained a weakly negative correlation between PNIF/FVC and cough severity.

It should be noted that cough severity showed a significant direct relationship with postnasal drip symptoms. Cough severity was also significantly associated with systemic eosinophilia but not with serum IgE levels. Comparison of patient groups by cough severity confirms the patterns identified during correlation analysis. Thus, cough in BA and AR patients has a more pronounced relationship with external respiratory parameters compared to nasal respiratory function. However, this opinion cannot be final, since there are currently no generally accepted normative data for PNIF taking into account age, gender, and ethnicity, in contrast to spirometric parameters, the expected values of which are well documented. At the same time, cough in patients with a combination of BA and AR has a relationship with symptoms of postnasal drip. The revealed relationship between cough severity and the levels of systemic biomarkers of T2 inflammation, including the eosinophils count in peripheral blood, seems to indicate the involvement of allergic inflammation in the genesis of cough in these patients.

The obtained results indicate a relationship between the cough severity in patients with a decrease in their bronchial patency and an increase in the variability of airway obstruction. Our data are consistent with the results of studies by Tian et al. [10], who demonstrated a statistically significant relationship between cough intensity and decreased bronchial patency and FEV_1 variability in bronchodilator tests.

BA and UA pathology are currently considered to be the leading non-infectious causes of prolonged cough [19]. Cough is known to be a common symptom of both asthma and AR/ARS. In patients with a combined course of BA and AR, which is currently viewed as systemic pathology [20], cough may both have bronchogenic genesis and also reflect pathology of the UA [12, 21]. The procedure for identifying the main potential causes of cough and the extent of their involvement remains unclear [22]. The published recommendations of the American College of Thoracic Physicians for the diagnosis and treatment of chronic cough recommend an integrative approach that takes into account both “upper airway cough syndrome” and asthma [23]. However, these recommendations do not determine the multifactorial causes of cough in patients with combined BA and AR [23, 24].

The relationship between cough and nasal pathology in our study had a more complex structure. In the initial sample, we did not find a statistically significant relationship between nasal respiratory function and cough intensity in patients with combined BA and AR. However, after excluding 8 patients from the sample, who had polypous changes in the nasal mucosa of the nasal cavity, a weak negative correlation appeared, having the character of a trend ($P = 0.056$). Thus, it seems an increase in coughing may be associated with amplified nasal congestion, but with the exclusion of organic causes of nasal obstruction. We have not found any publications between nasal respiratory function and cough in patients. Both the magnitude of sinonasal symptoms in general and the severity of postnasal drip syndrome demonstrated the expected direct statistically significant relationship with the subjective perception of cough by patients. The data obtained are consistent with most of the publications available on this topic, indicating the high importance of UACS in the genesis of cough in a significant proportion of patients, which was summarized in a recent review by Donaldson AM [12].

The positive correlation of cough severity with the absolute eosinophil count in peripheral blood obtained in our work may point to the role of eosinophilic inflammation in the mechanisms of cough development in patients with combined BA and AR/ARS. This is consistent with the work of Diver et al. [25] and emphasizes the systemic nature of this disease [21]. The data obtained suggest that cough in patients

with a combined course of BA and AR/ARS is a reflection of systemic pathology. Accordingly, its treatment should take into account the effects on the URT and LRT and on the systemic aspects of allergic inflammation. Accordingly, its treatment should take into account the effects on the URT and LRT and on the systemic aspects of allergic inflammation [26].

In some patients, the use of topical anti-inflammatory agents in the form of nasal and inhaled steroids may be supplemented by the use of systemic therapy, including immunobiological drugs such as omalizumab [27] or anti-IL-5 molecules [28].

The single-center and cross-sectional nature of our study is recognized as a limitation of the study. Other limitations are the lack of analysis of abnormalities in the development of nasal structures that can affect nasal flow and the lack of analysis by gender (in this study, we did not divide the sample into boys and girls, although we mainly used standard values for age and gender). In addition, we did not analyze the combination of other factors influencing cough. In the future, the study of these factors will require, perhaps, the use of modern machine learning methods.

The relationship between cough intensity and spirometry and postnasal congestion syndrome in patients with a combination of BA and AR/ARS has been established. These correlations indicate the involvement of both the URT and LRT in the formation of cough in this category of patients.

Abbreviations

AR: allergic rhinitis

ARS: allergic rhinosinusitis

BA: bronchial asthma

FEV_1: forced expiratory volume in the first second

FVC: forced vital capacity of the lungs

LRT: lower respiratory tract

PNIF: peak nasal inspiratory flow

SNOT-22: Sinonasal Outcome Test-22

UA: upper airway

UACS: upper airway cough syndrome

URT: upper respiratory tract

Declarations

Author contributions

RNK: Conceptualization, Resources, Investigation, Methodology, Writing—original draft, Writing—review & editing. SVK: Conceptualization, Resources, Investigation, Methodology, Validation, Visualization, Writing—original draft, Writing—review & editing. ASK: Data curation, Resources, Software, Writing—original draft. KVG: Data curation, Investigation, Methodology, Writing—original draft. DYO: Conceptualization, Methodology, Writing—review & editing. AAK: Data curation, Resources, Software, Writing—original draft. AAS: Data curation, Software. GSI: Data curation, Software, Writing—review & editing. MAK: Data curation, Software, Validation, Writing—original draft. NIK: Writing—review & editing. OVK: Resources, Writing—review & editing. VVN: Writing—review & editing. VAB: Methodology, Writing—review & editing. NAG: Methodology, Writing—review & editing. TIE: Conceptualization, Investigation, Formal analysis, Supervision, Resources, Writing—original draft, Writing—review & editing.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The study was performed in accordance with the Helsinki Declaration (2013) and approved by the Ethics Committee of the Volga Region Research Medical University (Protocol No. 13 dated 10.10.2016).

Consent to participate

All participants and all primary caregivers provided written informed consent.

Consent to publication

Not applicable.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request (Nailya I. Kubysheva, aibolit70@mail.ru).

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