Aspects of the relationship between cognitive dysfunction and bronchial asthma in children and adults

H. Calvo[1], I.Z. Batyrshin[1], N.I. Kubysheva[2], T.I. Eliseeva[3], E.V. Tush[3], E.A. Gorobets[2], R.N. Khramova[3], M.V. Boldina[3], N.A. Geppe[4]

[1]University: Center for Computing Research, Instituto Politécnico Nacional, JD Bátiz e/ MO de Mendizábal s/n, 07738, GAM, Mexico City, Mexico

[2]Kazan Federal University, Kremlyovskaya St, 18, Kazan 420000, Russia,

[3]Federal State Budgetary Educational Institution of Higher Education Privolzhsky Research Medical University, Minin and Pozharsky Square 10/1, Nizhny Novgorod, 603005, Russia,

[4]I.M. Sechenov First Moscow State Medical University (Sechenov University), Trubetskaya st., 8, building 2, Moscow, 119991, Russia,

Hiram Calvo – https://orcid.org/0000-0003-2836-2102

Ildar Batyrshin – https://orcid.org/0000-0003-0241-7902

Nailya Kubysheva – https://orcid.org/0000-0002-5582-5814

Tatyana Eliseeva – https://orcid.org/0000-0002-1769-3670

Elena Tush –https://orcid.org/0000-0002-5961-9794

Elena Gorobets – https://orcid.org/0000-0002-3859-5543

Regina Khramova – https://orcid.org/0000-0002-2396-5054

Marina Boldina – https://orcid.org/0000-0001-8421-0168

Natalia Geppe – https://orcid.org/0000-0003-0547-3686

Corresponding author: Nailya Kubysheva aibolit70@mail.ru

Abstract

Bronchial asthma (BA) can be accompanied by cognitive impairment (CI). However, the relationship between cognitive dysfunction and asthma has not been fully elucidated. Cognitive disorders in patients with asthma largely depend on age, asthma control impairment, the severity of symptoms of the disease, and the duration of its course. The severity of cognitive dysfunction begins to appear already in childhood and increases significantly in adult and elderly patients with asthma. Cognitive impairments can affect adherence to therapy in patients with asthma and negatively affect the achievement of BA control. There is evidence that chronic and acute hypoxia with insufficient control of BA can contribute to the development of cognitive dysfunction. Comorbid conditions also contribute to the enhancement of cognitive dysfunction in patients with asthma. It is known, for example, that asthma is associated with increased levels of depression and anxiety, which may contribute to the development of cognitive dysfunction. Increased body weight may also be a risk factor for cognitive impairment in BA patients. Timely detection of CI and appropriate correction will positively affect the results of therapy. This review examines the features of cognitive dysfunction in patients with BA of different ages, the relationship of CI to the control and duration of the disease, and the impact on the cognitive status of comorbid conditions. This evidence will allow us to streamline our knowledge about the state of cognitive function in patients with asthma for their timely diagnosis, correction, and, ultimately, improvement of BA control.

Keywords: Bronchial asthma, cognitive impairment, children, elderly

List of abbreviations

BA – Bronchial asthma

CI – cognitive impairment

EF – executive function

IQ – intelligence quotient

MoCa – Montreal Cognitive Test

FEV1 – Forced expiratory volume in the first second

MBP – basic protein myelin

MOG – myelin oligodendrocyte glycoprotein

BMI – body mass index

Introduction

Bronchial asthma is a heterogeneous disease characterized by chronic inflammation and airway hyperactivity (GINA, 2022). Patients with asthma are at risk of developing severe symptoms and life-threatening conditions. Currently, there is evidence of asthma's adverse effects on patients' cognitive functions (Irani *et al.*, 2017). Cognitive functions are the brain's higher functions, which include memory, attention, speech, orientation, thinking, counting, executive processes, and planning. Cognitive skills allow each person to solve everyday problems and control the quality of life. At the same time, cognitive deficits reduce feelings of security, work efficiency, and can negatively impact social function and human health. Existing data from diverse populations and research methods demonstrate an association between asthma and cognition, with many patients showing widespread cognitive impairment (Fitzpatrick, 1991; Frol *et al.,* 2013; Irani *et al.*,2017; Moss *et al.*, 2005).

According to a number of studies, a significant proportion of asthmatics (up to 54%) have a different degree of CI, especially patients with a severe and prolonged disease course (Esmaeel & Aly, 2019; Irani *et al.*, 2017). Caldera-Alvarado *et al.* been shown that there is a 78% increased risk of cognitive impairment in patients with asthma (Caldera-Alvarado *et al.*, 2013).

Currently, research on the role of cognitive dysfunction in asthma is increasing since these disorders may cause non-compliance with the treatment of the disease. In addition, CI in asthmatics can cause serious damage to the patient's physical and mental health, affecting his quality of life and placing a heavy burden on his family and society. It has been shown that in patients with asthma, impaired cognitive functions such as goal setting, data collection, decision-making, productivity, and self-efficacy lead to mismanagement and lack of improvement of the disease (Creer, 2008).

Age, educational status, duration and severity of asthma, and general health may be associated with the development of cognitive disorders in asthma patients (Blackman & Gurka, 2007; Dunleavy & Baade, 1980; Haq Satti *et al.*, 2022; Rhyou *et al.*, 2021).

Cognitive impairment in asthmatic children

Cognitive impairment in patients with BA can manifest itself at an early age. Asthmatic children are at high risk of cognitive and psychological maladjustment. It was noted that 35% of children aged 9 to 14 years with severe bronchial asthma had a neuropsychological behavioral deficit in memorizing spatial configurations and random memory (Dunleavy & Baade, 1980).

Children with asthma are more likely to have problems with concentration of attention and behavioral disorders (Blackman & Gurka, 2007). Attention is one of the key components of cognitive function. Attention is characterized by such indicators as attention span (volume), switching, allocation, concentration, and duration concentration. A defect in the function of attention leads to difficulties in the preparation and implementation of plans and tasks. A number of studies have shown a decrease in concentration in asthmatics children compared to healthy children (Koinis-Mitchell *et al.*, 2009; Zhu *et al.*, 2023).

Nedelska *et al*. found an inability to focus attention, decreasing both the attention span and the level of sustained attention in examined children (10-17 years old) with asthma (Nedelska *et al.*, 2020). In addition, this work showed that, especially in boys with asthma with an uncontrolled course, exacerbation, and duration of the disease for more than 5 years, moderate manifestations of cognitive disorders appear in the form of disturbances in various forms of attention.

Impaired attention and information processing speed are strong predictors of the accuracy of perception of asthma symptoms in children, which can lead to negative consequences of disease management. Koinis-Mitchell *et al.* previously found a link between better attention skills and more accurate monitoring of symptoms in children (Koinis-Mitchell *et al.*, 2009). The authors suggested that children distracted by external stimuli were less likely to pay attention to asthma symptoms, thereby minimizing the likelihood of their perception as serious symptoms of the disease.

A defect in the attention function leads to difficulties in making and executing plans and completing tasks. It was found that a decrease in the level of attention in children with mild and moderate asthma (aged 6-12 years) was associated with differences in neuropsychological functioning, wide-range memory assessment and learning (Annett *et al.*,2007; Nedelska *et al.*, 2020). Guo et al. revealed impaired attention and memory function in asthmatic adolescent mice, which was associated with chronic hypoxia due to bronchial obstruction (Guo *et al.*, 2013).

Attention deficit is the main cause of learning difficulties for school-age children and poor academic performance. Senter *et al.* found that asthma was associated with worse academic performance during one school year (Senter *et al.*, 2021). This association strengthened over time as students with asthma continued to fall behind, especially among those with more severe asthma.

Schoolchildren with persistent asthma were found to have decreased performance measures and executive function (EF), strongly associated with adherence to treatment in these patients (Sonney & Kathleen, 2019). EFs are among the numerous cognitive processes contributing to planning, organization, monitoring, and self-regulation of goal-directed behavior (Best *et al.*, 2011, Huizinga *et al.*, 2006). At the suggestion of Miyake *et al.*, the EF consists of three main processes: braking, renewal, and switching. Inhibition refers to the ability to suppress automatic, predisposed responses or interfering stimuli (Miyake *et al.*, 2000). Updating is related to working memory and represents the ability to track, process, and update information relevant to specific tasks. Switching refers to cognitive flexibility, which implies switching between several tasks, adapting one's behavior, and thinking to new and unexpected situations. Impairment of executive functions forms difficulties in organizing and memorizing tasks, concentrating attention when solving problems, performing labor-intensive actions, controlling emotions, and planning for the future (Fitzpatrick *et al.*, 1991).

Executive function is an important factor in the self/co-management of children with asthma. Lower performance in processes such as inhibition, sustained attention, working memory, and processing speed has been found in some children with asthma (aged 6–14 years) (Hajek *et al.*, 2014). A decrease below the norm in EF indicators may be a reason of low adherence to treatment in these patients with BA, which may lead to the progression of the disease (Hajek *et al.*, 2014). Treatment adherence implies self-regulation by taking medications on time and planning and organizing therapeutic events. Regression analysis showed that 16% of children had deviations in adherence to asthma treatment (Sonney & Kathleen, 2019). Thus, executive functions and adherence to treatment may be interrelated, which underlines the need for further development of personalized approaches in treating asthmatic children, taking into account their cognitive abilities. Correction of executive function may provide a new way to improve the independent/collaborative management of patients with asthma.

Several researchers have found that some asthmatic children have lower cognitive abilities concerning general intelligence. Gaffari et al. reported that there was a noticeable difference in IQ scores in children with asthma aged 6 and 10 years (Ghaffari *et al.*, 2014). Asthmatic children are at risk of developing intermittent hypoxia and sleep apnea, which have been observed to correlate with lower IQ scores (Bass *et al.*, 2004; Mahmoud *et al.*, 2020). Indicators of general intelligence in children with asthma were closely related to the severity of the disease (Mahmoud *et al.*, 2020). A significant decrease in IQ was recorded against the background of an increase in the severity of asthma, and a lower IQ index was characteristic of 45% of children with severe asthma. In addition, a significant negative correlation was found between the frequency of symptoms of the disease and IQ (Mahmoud *et al.*, 2020). Thus, one of the tasks of managing children with asthma to improve their quality of life is to determine and correct indicators of general intelligence if they go beyond the norm.

The relationship of cognitive impairment and asthma in adult patients

The prevalence of cognitive dysfunction increases with age in BA patients and is widely represented in elderly asthmatics. Cognitive impairment is a major problem in this category of patients because it can lead to unreliable or systematically biased self-reports of disease control. It was found older people with asthma (mean age 74 years) had worse attention and executive function scores than controls without lung disease (Moss *et al.*, 2005). Rajabi *et al*. also reported impaired inhibition, attention, and switching in adults with asthma (Rajabi *et al.*, 2017). Other researchers revealed that asthmatics aged 55 and older had low scores on the Montreal Cognitive Test (MoCa), which indicated mild or severe cognitive impairment (Bozek *et al.*, 2010). In this category of patients, cognitive indicators improved one year after therapy and significantly correlated with asthma control and FEV1, indicating CI's role in the progression of the disease and airway obstruction.

Middle-aged asthma is also associated with the frequency of cognitive impairment and the development of dementia, while the risk increased even more with exacerbations and hospitalization (Chen *et al.*, 2014; Peng *et al*., 2014; Rusanen *et al.*, 2013). High levels of synaptic degeneration biomarkers such as neurogranin and α-synuclein in the cerebrospinal fluid against the background of progression of the degree of CI in patients with severe asthma have been found (Nair *et al.*, 2022). Neurogranin is a postsynaptic protein that plays an important role in synaptic plasticity and memory consolidation and is a candidate biomarker with the high specificity of Alzheimer's disease (Kester *et al.*, 2015). Increased levels of this protein in patients with severe asthma may be a factor in the development of cognitive decline (Kester *et al.*, 2015). The elevated amount of α-synuclein may also indicate synaptic degeneration (Nair *et al.*, 2022). In patients with severe asthma, a relationship was found between the concentrations of these markers and vascular risk. These associations may indicate a high risk of developing cerebrovascular-mediated damage to the nervous system and neurodegeneration with increasing severity of the disease.

Older adults are most prone to worse control and outcome of the disease, which can lead to a high risk of hospitalization and a worse quality of life associated with asthma (Federman *et al.*, 2019; Hartert *et al.*, 2002; Krauskopf *et al.*, 2013; Talreja & Baptist, 2011). Impairment of working memory can be a predictor of self-report of non-compliance with the regime. Cognitive dysfunction significantly affects the asthma patient's self-control, depending on the severity of the cognitive impairment and the complexity of tasks. It was shown that elderly patients with impaired memory and general cognitive functioning had the lowest odds of compliance with the treatment regimen, low adherence to treatment, and insufficient perception of asthma symptoms (Becker *et al.*, 2022; Krauskopf *et al.*, 2013; Stilley *et al.*, 2010).

A decrease in lung function indicators can also affect the development of CI. As is known, with age, the values of FEV1 can decrease and be associated with various indicators and the rate of cognitive decline (Anstey *et al.*, 2004; Carroll *et al.*, 2011). For example, in BA patients over 60 years of age, poor asthma control and FEV1 values of less than 70% were found to be significantly associated with low measures of cognitive function (Ray *et al.*, 2015).

The relationship between cognitive impairment and the duration and control of the disease

The development of CI is significantly influenced by the duration and control of asthma. Haq Satti *et al*. when testing the British Columbia Cognitive Complaints Questionnaire in patients with asthma showed a close relationship between cognitive decline and disease duration (more than five years) in more than half of asthmatics (Haq Satti *et al.*, 2022). In the study Visilo *et al.*, in persons with moderate to severe asthma after five years of the disease, there was a deterioration in short-term verbal memory, a decrease in the speed of sensorimotor reactions, working capacity, active and volume of attention, speech activity (Vizilo *et al.*, 2008). Significant defects in executive functions (switching settings, inhibition, and concentration of attention) were also found in patients with BA with an average age of 26 years and five years of illness (Rajabi *et al.*, 2017).

Impairment of disease control is of no small importance in the development of cognitive dysfunction. Multivariate analysis showed a moderate association between asthma control, airway obstruction, and the degree of CI in individuals with BA (Ray *et al.*, 2015). J.L. Kroll *et al*. found that the degree of asthma control was significantly correlated with the results of the MoCA test (Kroll *et al.*, 2018). Thus, insufficient control of the disease may be associated with a decrease in cognitive function in patients with BA.

The effect of depression and obesity on cognitive impairment in patients with asthma

Cognitive impairment in BA patients can be aggravated by comorbid pathologies, including depression, obesity, and other diseases. Asthmatics often suffer from depression and anxiety, which causes severity in disease control and negatively affects the quality of life (Fritzsche *et al.*, 2010; Hsu *et al.*, 2020; Zielinski & Brown, 2003). The cause of these conditions in patients with asthma may be anxiety due to periodic attacks of airway obstruction. A number of studies have shown the prevalence of depression in asthma was up to 32% and anxiety conditions from 34% to 47 % (Renzi-Lomholt *et al.*, 2023). Depression occurs already in mild to moderate asthma, but most often develops in more severe disease. This state may also be associated with frequent hospitalizations, exacerbation of the disease, and taking corticosteroids (Kullowatz *et al.*, 2007).

Depression and anxiety symptoms may also be accompanied by cognitive impairment in asthmatic patients (Bratek *et al.*, 2015; Lu *et al.*, 2022). Lu et al. demonstrated that individuals with asthma and depression had the highest incidence of cognitive deficits compared to patients with asthma alone (Lu *et al.*, 2022). It was also noted that cognitive decline and the level of anxiety-depressive symptoms become more pronounced as lung disease progresses (Bratek *et al.*, 2015). Violations in the field of attention, orientation, visual-spatial, and executive functions were revealed in this category of persons (Lu *et al.*, 2022). In these patients, an increased value of the basic protein myelin (MBP) and myelin oligodendrocyte glycoprotein (MOG), which are markers of damage to the white matter of the brain, was found. Measures of cognitive deficits was negatively correlated with MOG, which indicates that white matter damage can lead to cognitive changes in patients with asthma and depression.

According to some authors, excessive or prolonged production of proinflammatory cytokines in asthmatics in the airway can cause not only chronic systemic inflammation, but also lead to anxiety and depressive states (Salim *et al.*, 2012). Hyperproduction of cytokines in the respiratory tract of patients with asthma can induce the release of proinflammatory mediators in the brain, which contributes to the development of neuroinflammation, depressive and cognitive disorders (Chen *et al.*, 2014; Rusanen *et al.*, 2013).

A change in nutritional status in patients with BA may also be one of the possible mechanisms for developing cognitive impairment. In itself, obesity affects the change in cognitive functions. It is noted that increased obesity may be associated with a decrease in executive function in children, adolescents and adults (Smith *et al.*, 2011). A positive correlation was found between body mass index ((BMI) and measures of cognitive function in children with asthma and obesity (Habib *et al.*, 2020). A positive association between body mass index and MoCA values was also found in adult asthma patients in the work of Mourad et al. (Mourad *et al.*, 2017). Potential risk factors for cognitive dysfunction in obesity may be impaired regulation of insulin and glucose, systemic and central inflammation, and increased brain atrophy (Cunningham *et al.*, 2009; Nameni *et al.*, 2017; Smith *et al.*, 2011). Thus, obesity in combination with asthma can have an aggravating effect on the development of cognitive impairment.

Hsu et al. demonstrated that overweight may also be associated with depression in patients with asthma (Hsu *et al.*, 2020). This study showed that depression can potentiate the negative impact of obesity on airway obstruction mediated by vagus nerve displacement. According to the assumption of these authors, asthmatic children with obesity and depressive states are more difficult to control the disease and react poorly to traditional methods of treatment, which requires additional therapeutic approaches taking into account these comorbid diseases.

The role of obesity in the development of cognitive impairment in patients with asthma is currently not fully defined and a wider and more comprehensive study of the relationship between overweight and neurocognitive disorders in this disease is required.

The role of hypoxia in the development of cognitive impairment in patients with bronchial asthma

Bronchial stenosis caused by asthma can lead to the formation of brain hypoxia. The brain is more sensitive to oxygen, so hypoxia becomes one of the important risk factors in the deviation of brain function and the development of cognitive disorders. The hypoxic factor is one of the causes of violations of such cognitive areas as attention, speed of thinking, learning, and memory (Guo *et al.*, 2013; Qaid *et al.*, 2017; Wang *et al.*, 2021). The unfavorable effect of chronic or intermittent hypoxia on development, behavior, and academic performance were noted in children, even with moderate levels of oxygen desaturation (Bass *et al.*, 2004). The hypoxic factor can also have a negative impact on executive function decline in patients with bronchial asthma, especially those with a history of severe exacerbations (Sonney *et al.*, 2019).

In addition to airway obstruction, the cause of the development of brain hypoxia may also be sleep disturbance and night apnea, characteristic of many asthmatics. Insufficient control over asthma can cause night awakenings and sleep breathing disorders, which adversely affect cognitive functions (Banasiak *et al.*, 2016; O'Brien & Gozal, 2002;). Sleep apnea has been shown to lead to impaired spatial memory, learning, neuronal death, and gliosis in the brain (Gozal *et al.*, 2001; Row *et al.*, 2002). Asthmatic children prone to developing intermittent hypoxia and sleep apnea had lower IQ scores, problems with concentration, hand-eye coordination, and mental set flexibility (Bass *et al.*, 2004).

Blood oxygenation is crucial for the functional activity of the brain. Airway obstruction in asthma can lead to varying degrees of hypoxemia. Asthmatics may experience intermittent and prolonged periods of hypoxemia, especially during poorly controlled asthma or exacerbations. Oxygen levels can decrease during acute or severe asthma attacks and cause diffuse cerebral hypoxia, anoxic brain damage, and changes in the initial arterial hemoglobin oxygen saturation level, which can affect cognitive functions (Brannan & Lougheed, 2012). In work Moss *et al*. (Moss *et al.*, 2005), there was a deterioration in such cognitive functions as the replacement of digit symbols and sequential subtraction in asthmaticss with with reduced blood oxygen saturation. In this study, 44.1% of participants also have been observed an association of cognitive impairment and decreased lung function and disease duration. The hypoxic factor can damage neurons and affect their biochemical changes (Vargas Becerra, 2009). Damage to neurons can be manifested by structural damage and atrophy of neurons and functional neurocognitive disorders in BA patients.

Conclusion

The totality of recently obtained literature data indicates that in asthma, neurocognitive disorders become essential in developing the disease, in addition to the leading role of inflammatory processes in the respiratory tract. The unfavorable effect of cognitive impairment in patients with asthma on the control and course of the disease requires new approaches to managing this disease and implementing personalized therapeutic measures.

Correction of cognitive impairments will not only optimize the overall quality of life, but can also directly affect the prognosis of the disease in patients with asthma. In addition, improvements in cognitive function may affect adherence to treatment, which is necessary to achieve good asthma control.

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Conflict of Interest

The authors declare no conflict of interest.

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