Cognitive impairment in patients with bronchial asthma

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The course of bronchial asthma (BA) may be accompanied by cognitive impairment. However, the relationship between cognitive dysfunction and asthma has not been fully elucidated, nor has it been fully established what causes cognitive impairment in patients with asthma. There is an opinion that transient hypoxia and persistent systemic inflammation with insufficient control of bronchial asthma may be accompanied by neurotoxicity in relation to the hippocampus and indirectly lead to deterioration of cognitive functions. Comorbid conditions, such as obesity, allergic rhinitis, depressive states, can increase cognitive dysfunction in asthmatics. The review considers the pathophysiology of cognitive dysfunction in patients with bronchial asthma, as well as the impact of comorbid conditions on the cognitive status. This information will allow us to systematize the available knowledge about the state of cognitive functions in asthma for their timely detection, correction, and, ultimately, optimization of the management of these patients.

Keywords: ***bronchial asthma; cognitive impairment***

Bronchial asthma (BA) is a common chronic inflammatory disease of the respiratory tract with the risk of developing severe symptoms and life—threatening conditions [1]. Asthma affects the lungs, but can adversely affect brain function, which in turn can lead to depression and cognitive impairment [2]. Cognitive functions are the highest functions of the brain, which include memory, attention, speech, orientation, thinking, counting, executive processes and planning.

Literature data indicate the presence of cognitive disorders of varying degrees in more than half of patients with asthma, especially with severe, uncontrolled, prolonged course of the disease [2-4]. Cognitive impairments, in turn, can lead to insufficient control of BA due to non-compliance with the treatment regimen by patients.

The natural course of BA can contribute to the formation of brain hypoxia. Hypoxia is one of the important risk factors for changes in brain function and the development of cognitive disorders. Acute and chronic hypoxia can cause impairment of cognitive functions such as attention, thinking speed, learning and memory [5,6]. The unfavorable effect of chronic or intermittent hypoxia on development, behavior and academic performance occurred in children even with moderate levels of oxygen desaturation [7]. It has also been shown that hypoxia caused by severe exacerbations affects the decrease in executive function in BA patients [8].

The reason for the development of cerebral hypoxia may be sleep disturbance and sleep apnea, which is characteristic of many patients with asthma. Insufficient control of asthma is the cause of nocturnal awakenings, breathing disorders during sleep, which also has an adverse effect on cognitive functions [9]. It has been shown that sleep apnea can lead to impaired spatial memory, learning, neuronal death, and brain gliosis [10,11]. Children with BA who were prone to developing intermittent hypoxia and sleep apnea had lower IQ scores, problems with concentration, hand-eye coordination, and mental set flexibility [7]. In patients with asthma, against the background of a decrease in blood oxygen saturation, deterioration of cognitive functions such as digit substitution and sequential subtraction was noted [3].

Oxygen levels can decrease during acute or severe asthma attacks and cause diffuse cerebral hypoxia, anoxic brain injury, and changes in baseline arterial hemoglobin oxygen saturation, which can affect cognitive function [12]. Hypoxia can lead to damage to neurons and severe neurological disorders [5].

Damage to neurons can be manifested by structural damage and atrophy of neurons, and functionally by neurocognitive impairment. Asthma increases the risk of hypoxic events, especially in vulnerable areas of the brain with high metabolic needs, for example, in the hippocampus [13,14].

The hippocampus is most susceptible to hypoxia and is the predominant nervous structure involved in memory and learning processes [13,14]. Studies on BA models in animals have shown the chronic inflammation of the respiratory tract leads to activation of microglia, loss of neurons in the hippocampus [13,14].

One of the key mediators of the response to hypoxia is the hypoxia-induced factor (HIF). The expression of HIF-1α and HIF-2β was increased in the hippocampus and cerebral cortex of mice with the BA model, who simultaneously had memory deficits and morphological changes at synaptic levels in the cortex and hippocampus [15]. In patients with asthma, a relationship was found between hippocampal volume and cognitive function [16], and a decrease in the volume of the right and left hippocampus was also found in some asthmatics [17].

It is known about changes in the levels of hippocampal metabolites in BA [16]. In particular, in this category of patients, a relationship was established between the degree of cognitive impairment and a decrease in the concentration of N-acetylaspartate and glutamate in the hippocampus. N-acetylaspartate is considered one of the most reliable markers of damage to the nervous system even with mild cognitive impairment; lower levels of it can predict a decrease in cognitive functions and structural deficiency of the hippocampus [16].

The observed metabolic changes in the hippocampus are also associated with a violation of synaptic plasticity. In the study [18], patients with asthma had a decrease in the number of synaptic vesicles, which was combined with a deterioration in spatial learning and memory.

Asthma may be associated with functional and structural disorders of other areas of the brain. Neuroimaging in adult patients with asthma using diffusion-weighted MRI showed significant changes in the microstructure of the white matter, similar in degree and magnitude to those in neurodegenerative diseases [19]. This negative character of changes in white matter correlate with the concentration of GFAP in the blood plasma of patients with asthma.

Many patients with BA are characterized by depressive and anxiety disorders [20,21]. In these patients, there was a significant increase in the level of the main protein myelin and myelin oligodendrocyte glycoprotein (MOG) associated with white matter damage [20]. MOG values negatively correlated with the results of the Montreal Cognitive Test (MoCA), which may indicate that in patients with asthma, white matter damage is accompanied by cognitive changes.

In the study [22], an increase in regional homogeneity of the bilateral occipital lobe and the bilateral sensorimotor region was registered in patients with asthma and concomitant depression. In addition, in some patients with BA, a relationship was found between a decrease in the volume of gray matter of the right superior temporal gyrus and a deterioration in concentration [23].

Cognitive impairment in patients with asthma can be aggravated in conditions of comorbid pathology, including obesity, allergic rhinitis, allergic rhinosinusitis and other diseases. Obesity is an independent factor in the development of cognitive impairment. A positive correlation between the body mass index and the values of the Short Mental Status Assessment Scale (MMSE) in children with asthma is described in [24]. A positive association of body mass index and values of the Montreal Cognitive Test was also found in adult patients with asthma [25].

It is assumed that the effect of asthma on the brain is mediated by inflammatory and neuroinflammatory processes [26]. The development of neuroinflammation may be due to the induction of allergens on the sensory fibers of the vagus nerve, whose signal is projected to the nuclei of a solitary pathway and from there to several areas of the brain [27,28]. Allergens can also indirectly stimulate inflammatory reactions in the brain, enhance activity and functional connectivity in the chain of the anterior cingulate cortex and basolateral amygdala,

which contributes to the development of anxiety states [29]. Asthma can lead to neuroinflammation through microglia activation and increased levels of TNFα and IL-1β in the hippocampus and prefrontal cortex [13,14]. Activation of the leukotriene pathway during inflammation of the respiratory tract in asthma also contributes to the violation of the BBB, activation of microglia, the development of neurotoxicity and a decrease in cognitive functions [30].

T2 cells that produce pro-inflammatory cytokines both in the respiratory tract and at the systemic level play an important role in the pathogenesis of allergic asthma inflammation [31]. The cytokines secreted by these cells are able to penetrate through the BBB into the brain tissue, into the pericentricular structures and induce the production and enhanced release of phlogogenic mediators in them [28,32]. Excessive secretion of inflammatory mediators in the brain can stimulate the activation of neurons through the interaction of cytokines with neurons and glia [33,34], which contributes to the development of neuroinflammation and cognitive disorders.

Thus, in addition to the leading role of inflammatory processes in the respiratory tract, cognitive disorders become essential in the development of BA due to impaired functional activity of the brain and the formation of neuroinflammation. Given the development of nervous system dysfunction in patients with asthma, it has been proposed to consider asthma as a secondary neurological disease [35].

The totality of data available in the scientific literature indicates that the adverse effect of BA on brain health requires new approaches in the management of this disease and personalized therapeutic measures. Correction of cognitive impairment will influence adherence to BA treatment, which is necessary to achieve good control over the disease.

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