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Changes in Immunological Status in Children with Broncho-Obstructive Syndrome and Bronchial Asthma

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Abstract: It has long been known that the immune system is a component of the homeostatic triangle, which also includes the nervous and endocrine systems. The modern concept of the heterogeneity of the immune response in relation to its cellular and humoral forms, indicating the absence of a single pattern of protection for a particular infection, makes it possible to distinguish among children suffering from a viral or bacterial infection a different dominant mechanism of immune defense - cellular Th1-like, or humoral , Th2-like In most infections, resolution of the pathological process is realized with a mixed type of immune response, including both cellular and humoral forms. protection in the acute phase of the disease. The modern concept of the pathogenesis of bronchial asthma is based on the recognition of the leading role of immune mechanisms in its development. Changes in the immune response found in this disease are considered as a consequence of sensitization of the body and a significant influence on the functioning of genetic and environmental factors. IgE- mediated allergic reactions are leading in the development of bronchial asthma in children.

Key words: immune defense, cytokine dysregulation, cell-mediated immune response, broncho-obstructive syndrome.

Introduction. It has long been known that the immune system is a component of the homeostatic triangle, which also includes the nervous and endocrine systems. If the mutual regulatory relationships between them are not disrupted and all participants in the immune response perform their functions efficiently, the body will adequately respond to any antigens, including microorganisms [1,10,12]. In the occurrence of a secondary immunodeficiency state, which occurs in children with asthma, an important role is played by adaptation processes associated with the adaptation of the child's body to environmental conditions and the development of inflammation in the lungs, which is accompanied by an increase in the functional activity of the pituitary gland and adrenal cortex [1,12]. Frequent respiratory morbidity is a clinical marker of the condition maladjustment of the child's body [13,16]. In this case, there is a suppression of the activity of natural killer cells, which play an important role in maintaining immunological homeostasis [2,5,7]. The morphofunctional immaturity of immune mechanisms in young children causes not only functional immunodeficiencies, but also the early development of immunopathological reactions when exposed to antigenic stimuli on the immune system, especially in the first year of life. Frequent acute respiratory infections in young children contribute to the disruption of the body's adaptive capabilities. A child's immune system cannot be studied without taking into account the peculiarities of its development. Yu. Veltishev identified 5 critical periods in the development of a child's immunobiological reactivity [8,10,11,19]. The first is immediately after birth. The immune system is subject to strong suppressive influences; humoral immunity is provided almost entirely by maternal antibodies. There are many T-lymphocytes in the blood, low NK activity is combined with limited

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synthesis of γ-interferon. The second period is 3-6 months. At this time, passive humoral immunity is weakened due to the catabolism of maternal γ-globulin. The third is the end of the first or second years of life. An intensive switching of the synthesis of IgG class antibodies begins . The fourth period is 4-6 years of life. Levels IgM and IgG in the blood reach the levels of adults, the level of IgA is still low. The fifth period is adolescence.

Puberty leap combined with a decrease in the mass of lymphoid organs. Asthma is a chronic inflammatory disease that can cause significant limitations in the physical, emotional and social aspects of a child's life. Signs of bronchial inflammation persist even during the asymptomatic period of the disease and are the result of changes in the immune system, and their severity correlates with the severity of the disease. The modern concept of the heterogeneity of the immune response in relation to its cellular and humoral forms, indicating the absence of a single pattern of protection for a particular infection, makes it possible to distinguish among children suffering from a viral or bacterial infection a different dominant mechanism of immune defense - cellular Th1-like, or humoral , Th2-like [14]. In most infections, resolution of the pathological process is realized with a mixed type of immune response, including both cellular and humoral forms.

Protection in the acute phase of the disease. The modern concept of the pathogenesis of bronchial asthma is based on the recognition of the leading role of immune mechanisms in its development. Changes in the immune response found in this disease are considered as a consequence of sensitization of the body and a significant influence on the functioning of genetic and environmental factors. IgE- mediated allergic reactions are leading in the development of bronchial asthma in children. Their pathogenetic significance is confirmed by the frequent discovery in the anamnesis of such patients of a hereditary predisposition to allergic reactions and diseases, and the presence previously of other manifestations of atopy . At the same time, many children with bronchial asthma show clinical signs of immunological deficiency. These may include: a tendency to frequent acute respiratory diseases of viral origin, the development of chronic lesions, infections, the occurrence of secondary infection of the skin with concomitant atopic dermatitis, and disruption of intestinal microbiocenosis. Imbalance in the immune system and cytokine dysregulation play a significant role in maintaining the chronic inflammatory process and hypoxic state in bronchial asthma in children. Studies of the immunopathogenesis of allergic diseases have shown that a number of cells are involved in the process of allergic inflammation, the interaction of which is regulated by a cascade of cytokines. Different stages of the allergic process are characterized by different cytokine profiles, which determine the direction of action of lymphocytes, monocytes, neutrophils and other cells. The initiating mechanism of chronic inflammation in bronchial asthma is the Thl /Th2 immune imbalance with a disturbance in the cytokine system. The predominance of the Tn2-polarized cytokine profile shapes the immune response and the development of allergic inflammation. Changes in the hypothalamic-pituitary-adrenal system is one of the most important in the development of an allergic reaction.

Normally functioning mechanisms of the immune system prevent the uncontrolled release of cytokines and other inflammatory mediators and ensure an adequate response of the body to inflammation. Pro- and anti-inflammatory ILs simultaneously appear in the blood at the very beginning of inflammation. Under these conditions, they functionally create a balance that determines the favorable course of the inflammatory process and the delimitation of the source of inflammation. Excessive activation of cytokine-producing cells can lead to excessive release of ILs and other inflammatory mediators. The subsequent uncontrolled release of cytokines by over - activated macrophages and other cytokine-producing cells leads to severe consequences. Cytokines, together with other inflammatory mediators, turn from factors of the body’s immune defense into an aggression factor [18]. γ-INF is the most important cytokine for macrophage activation, stimulates phagocytosis, as well as killing neutrophils and natural killer cells, regulates the strength of the immune response, promotes the adhesion of granulocytes to endothelial cells. γ-INF increases and decreases antibody formation, stimulates cellular immune responses, enhances NK activity and

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cytotoxic activity [12,15,16]. Today, the control and regulatory role of INF in maintaining homeostasis is undoubted. In this case, the main identified effects of INF can be divided into antiviral, antimicrobial, antiproliferative , and immunomodulatory. The insufficiency of the reserve capabilities of interferonogenesis , especially in terms of the synthesis of γ-interferon, which provides powerful antiviral protection in the body, despite the normal level of interferon in the blood serum, explains the persistence of a sluggish inflammatory reaction in the child's body even in the absence of clinical signs of acute respiratory infections [6,13,18] . In terms of importance, the INF system approaches the immune system, and in terms of versatility it even surpasses it [19]. γ-INF has the ability to induce apoptosis and is an IL-4 antagonist. IL-4 is a necessary component for IgE production . It is produced by activated T cells (Th-2 type). IL-4 affects resting B cells, making them sensitive to various stimuli: it increases the proliferative activity of T and B lymphocytes . In cases of pneumonia in children without TM, it was noted increased synthesis of IL-4, and in ARVI its level does not change γ-INF enhances the cell-mediated immune response, and IL-4 enhances the humoral response. When the ratio γ-INF/IL-4 = 1, there is a risk of sensitization to inhaled allergens [18].

Thus, disruption of the production, secretion and reception of anti-inflammatory cytokines leads to profound defects in anti-infective defense, up to the development of "immunological paralysis", and aggravates the direct damaging effect of the microorganism and their toxins on lung tissue. The normal functioning of the immune system is based on the balance of Th1 and Th2 based on the equal production of their regulatory cytokines, therefore, excessive activation of any of the types of T - helper clones can direct the immune response along one of the alternative options, and chronic imbalance of their activation leads to the development of immune pathology.The formation of the atopic phenotype occurs already in the antenatal period, while IgE_mediated antigen-specific reactions can occur in utero. Maternal IgE and IgG , as well as cytokines of amniotic fluid, in combination with the presence of an allergen in the fetoplacental environment, are possible factors in the formation of Th1, Th2 responses to environmental antigens in the fetus. According to modern data, the process of developing atopy or differentiation of the neonatal immune system along the Th2 pathway begins even before the birth of the child. This occurs due to a number of physiological changes occurring in the body of a pregnant woman [12]. It has been proven that at certain stages of intrauterine development, the fetus can swallow and absorb amniotic fluid containing cytokines and allergens, thereby stimulating its own T-lymphocytes to a certain, namely, Th2 type of immune response. In addition, the skin and lungs of the fetus take part in the process of intrauterine contact with allergens. The skin of the fetus, being in direct contact with the amniotic fluid throughout pregnancy, can present some of the substances contained in it as antigens (AGs). Some amniotic fluid usually contains fetal fluid from the lungs due to minor aspiration during pregnancy. Such primary contact of the fetal immune system with certain antigens can directly influence the nature of the child's immune response in the postnatal period.

Thus, maternal IgE and IgG , as well as cytokines of amniotic fluid, in combination with the presence of an allergen in the fetal environment, are possible factors in the formation of a Th1-Th2 response to environmental antigens in the fetus. Obviously, interaction at the level of mother - placenta - fetus, being currently in the focus of scientific interests, carries a potential answer to the question about the possibility of primary prevention of bronchial asthma and atopy in general [14]. Currently, among the possible reasons for the decrease in the level of T-lymphocytes, the mechanism of their damage, such as apoptosis, is considered. Apoptosis is programmed cell death that occurs unnoticed by the microenvironment. If mass death of cells of a multicellular organism by the mechanism of necrosis is often associated with the death of the entire organism, then cell death by the mechanism of apoptosis is considered rather as a condition for the normal existence of the organism. In its most general form, the purpose of apoptosis is to determine the size and "architecture" of the organism, which is manifested in: maintaining a constant number of cells; in determining the shape of an organism and its parts; in ensuring the correct ratio of the number of cells of different types; in the removal of genetically defective cells. Insufficient manifestation of apoptosis is reflected in the processes of morphogenesis, elimination of cells with genetic defects, the formation of self-tolerance and

manifests itself in the form of various developmental defects, autoimmune processes and malignant tumors. Excessive accumulation of apoptotic cells due to a violation of their utilization by phagocytes with the participation of complement leads to the fact that, firstly , self-antigens on the surface of apoptotic cells are recognized as foreign, and secondly, the spectrum of dominant cytokines changes from pro-inflammatory to anti-inflammatory, which contributes to long-term maintenance Th2 type immune response. There is a hypothesis about “altruistic self-destruction” of cells - when cells react to a viral infection by activating apoptosis in order to prevent viral replication. Some viruses block apoptosis, creating optimal conditions for their own reproduction [19]. In relation to infectious pathology caused by bacterial pathogens, apoptosis performs the function of protecting the macroorganism. The death of infected cells followed by the elimination of destroyed cells and microorganisms by cells of the immune system helps prevent the spread of the infectious process.

In recent years, the possibility of inducing cell apoptosis through specialized receptors has been intensively studied. These receptors include, in particular, the Fas receptor (CD95). An increase in the number of CD95 cells may reflect not only proliferation, but also the inability of cells to initiate a cell death program under the influence of factors that normally cause apoptosis. Excessive apoptosis of lymphocytes leads to a breakdown of the body's defense mechanisms.

Consultation. Thus, the analysis of the literature data showed that today the problem of broncho-obstructive syndrome and bronchial asthma in children is relevant and constantly studied. Few works are devoted to the study of the state of activation markers and cytokine status in BOS and bronchial asthma, criteria for the transformation of BOS into bronchial asthma have not been developed, and there are no works devoted to long-term prospective observation of children with repeated episodes of BOS in history.

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