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The Role of Cytokine Regulation in Obstructive Syndrome of Atypical Genesis in Children

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Abstract. The article presents a review of the literature on the significance and role of cytokines in the course of the disease, their impact on the immune system in acute obstructive bronchitis. The relevance of the problem of acute obstructive bronchitis is associated with the frequency of bacterial complications, the development of life-threatening conditions due to its prevalence in viral infections in children, as well as the presence of atypical bacterial pathogens Acute obstructive bronchitis occurs rather frequently in practice of pediatrician. In many cases pulmonary pathology manifested by bronchial obstruction occurs in early childhood. The disease is more common in young children (20.1%) and more than half of children (57.5%) have two or more recurrent episodes of obstruction. The complexity of etiology and pathogenesis of acute obstructive bronchitis makes the hypothesis of multifactoriality of this pathology most probable. Due to the increasing prevalence of this pathology, further study is an important problem, the solution of which will contribute to the formation of fundamental ideas about the disease.

Keywords: mycoplasma, chlamydia, obstructive bronchitis, cytokines, interleukins.

This review article briefly describes the most common cytokines in acute obstructive bronchitis of atypical etiology.

In parallel with the development of basic research, the use of cytokine determination in the clinic for a variety of pathologies began rapidly. Determination of cytokines in the clinic has various purposes:
-assessment of the severity of the process,
-therapy efficacy,
-prognosis, etc.

Not much time has passed since the first cytokines were described. However, their study has provided an extensive branch of knowledge, cytokinology, which is an integral part of various fields of knowledge and, first of all, immunology, which has given a powerful impetus to the study of these mediators. Cytokinology interfaces with all clinical disciplines, from the etiology and pathogenesis of disease to the prevention and treatment of various pathological conditions. Researchers and clinicians need to navigate the diversity of regulatory molecules and have a clear understanding of the role of each cytokine in the processes under study [6,7,8,10].
The cytokines can be markers of diseases of the immune system because:
-cytokine synthesis supports the main processes of the development of defense reactions;
-many cytokines and their receptors are inducible, and immune activation can be assessed by their appearance in cells;
-most cytokines are soluble circulating mediators, and their concentrations can be easily determined in plasma and other body fluids.
All these facts indicate the importance of determining cytokine levels in the diagnosis of diseases, and this is now actively used by practitioners.
A number of studies have shown that inflammatory cytokines have an important influence on the course of various inflammatory diseases, but the results about their specific role are not always consistent[15,21].

They can be used as biomarkers for indicating or tracking disease or its progress, and they can serve as clinically applicable therapy parameters. However, their precise role is not always clearly defined (IL)-6, IL-1, IL-33, tumor necrosis factor alpha (TNF-α), IL-10 and IL-8[1,21].

Bronchoobstructive syndrome in infants attracts close attention of researchers and practitioners, which is associated with a wide prevalence and heterogeneity of bronchoobstructive syndrome development, and therefore -difficulties in differential diagnosis[5,6,7,10]. In children at an early age in obstructive bronchial diseases, the causative agents of PC virus, parainfluenza viruses of types 1-3, influenza, adenoviruses, coronavirus [1,2,13]. Scientific publications emphasize that among the etiological factors of acute obstructive bronchitis various infectious agents and their combinations, mixt-infections, the significance of which has not been fully studied [19,20]. Pre-morbid background has an important role in the development of OB: perinatal pathology, hypotrophy, a history of allergies, early artificial feeding, respiratory diseases at the age of 6-12 months [11, 45, 47]. Most researchers estimate bronchoobstructive syndrome as a pathophysiological concept characterizing bronchial conduction disorders against the background of acute and chronic respiratory tract diseases [3, 45, 49,50]. The term "atypical" respiratory tract infections was first introduced in 1940 to refer to a group of diseases of unidentified etiology [23,34]. To

date, there is fairly convincing evidence that the combination of intracellular infection with traditional viral and bacterial microflora often creates the most favorable conditions for the emergence and chronicity of diseases such as obstructive bronchitis. Modern nomenclature primarily refers to "atypical" microorganisms of the genus Chlamydophila pneumoniae and Mycoplasma pneumoniae [37, 48]. Some researchers believe that the widespread introduction of effective immunoprophylaxis for pneumococcal, hemophiliac and viral infections in children will most likely cause changes in the etiological structure of the proportion of atypical infections will most likely change in the etiologic structure of respiratory diseases. In their opinion, in some age periods the share of atypical infections in the etiology of acute respiratory tract infections will exceed 50%. All this makes it necessary to study the prevalence of intracellular infections in children and assess their impact on the development of respiratory diseases. [10,22,27,29,30].

In recent years, with the appearance of new, modern diagnostic methods of infectious diseases, the possibility of differential diagnosis of typical and atypical conditions that cause acute inflammatory pathology of the respiratory organs, including atypical pathogens and, primarily, chlamydia and mycoplasmas, has appeared [18,30,49].

The role of pneumotropic intracellular pathogens in the etiology of obstructive bronchitis in children has increased, with Mycoplasma pneumoniae and Chlamidiae pneumoniae leading the way [23,24]. In the past 10-15 years, Chlamydia pneumonia has been the leading cause of acute bronchitis in school-age children [16,31,47]. In children aged 5-14 years Mycoplasma pneumoniae is the etiologic agent of obstructive bronchitis in 21-35% of cases; in adolescents and persons 19-23 years of age - in 16-20% cases [5, 48]. The parallel circulation of chlamydia and mycoplasmas, the airborne route of transmission, and the high susceptibility of children form the preconditions for the origin of mixed variants of infection. Sources on the current problem are only beginning to accumulate material [4,8].A feature of mycoplasma infection is the cyclicality and periodicity of morbidity increases in 4-7 years. Intracellular pathogens act on the body's immune system and thereby support colonization of the upper and lower airways by other pathogenic flora, especially intracellular microorganisms, encouraging recurrent obstructive bronchitis in children. Mycoplasma, having tropism to the basal membrane of the bronchial cricoid epithelium, as well as its small size and strong adhesive apparatus, is very firmly fixed on the membrane of the bronchial epithelial cell. A differentiating feature of the antigenic structure of mycoplasmas is their poor recognition by the host organism. Chlamidia pneumoniae also has tropism to the epithelial cells of the bronchi and bronchioles. The cell wall structure of chlamydia has an association with Gram-negative bacteria. The pathogen is tropic to the villous epithelium of the bronchi and completely immobilizes the villi within 48 hours of infection. At the same time, the clinical picture may include manifestations of obstructive bronchitis in children [24, 32,35,39,40,43,44].

The study of clinical and serologic variations in the course and outcome of mixed forms of chlamydia-mycoplasma infections shows an extremely valuable and completely unexplored task [34, 35]. They are susceptible to persistence in the child, leading to a prolonged course of the disease, paralyze mucociliary clearance mechanisms, promote bronchial hyperresponsiveness, and worsen immunosuppression [30,31]. Atypical obstructive

bronchitis has inflammatory-toxic edema of cellular interstitium without especially strict localization, poor in cellular elements [7,8,29]. In respiratory mycoplasmosis, there is a significant delay in airway clearance of mucus and extraneous microflora for up to 1 to 3 years after the infection. Decreased respiratory function and ciliary activity of the ciliary epithelium contribute to increased invasiveness of the pathogen, the occurrence of "exogenous" reinfection and pathogenic microflora penetration, mixt-infection, prolonged and chronic course of infectious processes [9,17,33].

The immune system is a complex multicomponent mechanism, which is a set of cells in different morphofunctional states. It is for this reason it is very sensitive to the action of various anthropogenic and technogeni factors, which determins the growth of diseases caused by impaired immunological reactivity at the present time [25]. The initiation and development of the immune response is the result of a series of intercellular relationships involving immune cell receptors as well as soluble mediators of immune reactions. It has now been demonstrated that the immune response to various pathogens depends on the interaction of different cell types - macrophages, T and B lymphocytes, natural killer cells.Intracellular pathogens alter the body's immune response and, thus, contribute to DP colonization by other representatives of pathogenic flora, contributing to the recurrence of obstructive bronchitis [10,12,15,18]. During the formation of the immune response, changes in a number of membrane receptors, cytokine and interleukin secretion are observed, which indicates the functional activity of monocytes/macrophages [27]. Tissue macrophages, absorbing microbes, activate and produce cytokines, in particular tumor necrosis factor α (TNF-α) [28]. The macrophage is a unique cell not only because it absorbs microbes, but also because it produces more than 60 biologically active amines, which are regulators of subsystem, intercellular and cell-matrix relationships in the target lesion [27]. Cytokine regulation of target cell functions can be carried out by autocrine, paracrine or endocrine mechanisms [32,33].

The cytokine system includes progenitor cells; soluble cytokines and their antagonists; target cells and their receptors. Producer cells:

1.The main group of cytokine-producing cells in the immune system are lymphocytes. ThO produce a wide range of cytokines in very low concentrations.

Th1 produce IL-2, IFNγ, IL-3, TNFα, which are necessary for the development of cellular immunity reactions (GGT, antiviral, antitumor cytotoxicity, etc.). The set of cytokines secreted by Th2 (IL-4, IL-5, IL-6, IL-10, IL-13, IL-3) determines the development of the humoral immune response. In recent years, a Th3 subpopulation has been described that produces THFβ, which suppresses the function of both Th1 and Th2. T-cytotoxic (CD8+), B-lymphocytes, natural killer cells are weak producers of cytokines.

II. Macrophage-monocytic cells produce cytokines that initiate the immune response and participate in the reaction of inflammation and regeneration.

III. Cells not belonging to the immune system: connective tissue, epithelial, endothelial cells spontaneously, without antigenic stimulation, secrete cytokines supporting hematopoietic cell proliferation and autocrine growth factors (FRF, ERF, TFRβ, etc.) [31-39].

Cytokines with both pro-and anti-inflammatory activity in the development of respiratory diseases, in particular acute obstructive bronchitis, play a certain role, and the balance of

these factors affects the process of this disease. As recent studies show, the negative influence of environmental factors, as a rule, is realized against the background of individual genetic predisposition in almost any pathology known today [2,8]. Changes in a child's body and immune system are linked to the environment. Variations in the environment have an indirect effect on the cytokine system in our bodies. Alterations in cytokine activity cause weakness in children with various allergic diseases of the respiratory system. One of them is obstructive bronchitis.

A special role in the regulation of local protective reactions in tissues is given to cytokines [1, 31]. Cytokine production in response to various exogenous agents is genetically determined. According to the most recent data, differences in the genes that control the body's defense reactions can affect the level of cytokine production and thereby the nature of the development and progression of the immune response [4,7]. Studies in recent years have shown that in the acute inflammatory response, the airway epithelium itself has a prominent and active role, releasing pro-and anti-inflammatory mediators [18].

Epithelial cells have been shown to release mediators such as granulocyte macrophage colony stimulating factor (GMSF), interleukin (IL)-8, 15-hydroxyecosatetraenoic acid (15-HETA), tumor necrosis factor (TNF). In lung diseases cytokines, participating in infectious-inflammatory reactions and allergic response at the level of a specific effector component, have a significant impact on the formation, severity and prognosis of the pathological process [5,7]. Systemic inflammation is a frequent link in the pathogenesis of obstructive lung disease and obesity [19]. During inflammation, all cellular elements are activated and release cytokines -inflammatory cell chemotaxis factors or inflammatory mediators. Cytokines induce an acute inflammatory response and can have immunopathological effects on cells and tissues, ensuring consistency, harmony and completeness of the immune response [1,2,20]. Normally, after the development of a systemic reaction, anti-inflammatory cytokine cascades are released into the systemic bloodstream. The most active are IL-4, IL-10. They also inhibit the secretion of inflammatory phase mediators by macrophages. The body's protection against infection is determined by the following three key points, which influence and define each other: natural resistance, early response and adaptive, or acquired, immunity. After a microbe penetrates the body, protection is determined by a system of cellular and humoral factors [29, 30].

Traditionally, the following groups of cytokines are distinguished in accordance with their biological effects.

1) Interleukins (IL-1 to IL-18) are secretory regulatory proteins of the immune system that mediate the immune system and its connection to other body systems;

2) Interferons (IFNα, IFNβ, IFNγ) are antiviral proteins with pronounced immunoregulatory and antitumor effects;

3)Tumor necrosis factors (TNFα, TNFβ -lymphotoxin) are cytokines with cytotoxic and regulatory effects;

4)Colony-stimulating factors (CSF) are stimulators of growth and differentiation of hematopoietic cells;

5)Chemokines are chemoattractants for leukocytes;

In this article, review some of the following cytokines of inflammation.

IL-1, IL-6, TNF-α, IL-8, and other cytokines produced by macrophages during the early inducible response are proinflammatory cytokines. Their action completely determines the development of the inflammatory process that develops when microbes enter the macroorganism [35-39].

IL-1α, and -β bind to a single IL-1 receptor (called IL-1R1) and are pro-inflammatory cytokines produced mainly by monocytes, macrophages and fibroblasts. The IL-1 receptor antagonist (IL-1RN or IL-1RA) binds to IL-1R and inhibits both IL-1α and -β binding, neutralizes their activity, and thus acts as an endogenous counterregulatory mechanism[24].

Interleukin 1β is the predominant form of IL-1. It is a multifunctional cytokine with a broad spectrum of action, plays a key role in the development and regulation of nonspecific defense and specific immunity, one of the first to be included in the body's defense response to pathogenic factors. The main producers of IL-1β are macrophages and monocytes. Lymphocytes and fibroblasts may also participate in the synthesis of this cytokine. IL-1β plays an essential role in the pathogenesis of obstructive bronchitis. In this pathology, IL-1β synthesis is not reduced, but their functional activity decreases. IL-1β suppresses the development of B-lymphocytes and participates in the choice of hemopoiesis direction between myelo-and B-lymphopoiesis (in favor of the first) [29-34].

Interleukin-2 (IL-2) the main immunological role of IL-2 is to regulate the specific (antigen-dependent) immune response by stimulating the proliferation and differentiation of immune cells involved in its implementation [20,21]. The main endogenous producers of IL-2 are CD4+- activated Th1 (90%), CD8+ (10%). IL-2 has a relatively narrow spectrum of targets and objects: T- and B-lymphocytes, NK cells. It is a growth and differentiation factor for them.IL-2 promotes the function of T helper, increasing the production of γ-interferon, prevents the development of immunological tolerance, is able to cancel it. IL-2 serves as a growth and differentiation factor for T-killers. On B-lymphocytes, IL-2 acts as a growth factor and can increase the synthesis of IgM, IgG, IgA. IL-2 also affects monocytes by increasing the generation of reactive oxygen species and peroxides, as well as the process of hematopoiesis. It increases the formation of eosinophils and platelets, but suppresses myeloid and erythroid hematopoiesis, promotes the development of extramedullary foci of hematopoiesis [20,37,38,40,50].

Interleukin-4 (IL-4) this lymphokine (molecular weight 15-20 kDa) is produced by T cells (Th2) and is a differentiation factor for T- and B-lymphocytes. IL-4 has the strongest effect on the regulation of the formation of other cytokines through participation in numerous biological processes-immune response and inflammatory reactions.IL-4 limits macrophage synthesis of proinflammatory IL-1b, 6, 8,12, TNFa, formation of highly active oxygen metabolites, nitrogen. It serves as a cofactor in the proliferation of resting B-lymphocytes and also it induces the synthesis of IgE and IgG4 in these cells. IL-4 is known to be able to generate the activity of lymphokinactivated cells and enhance the antitumor activity of macrophages. Dysregulation of IL-4 secretion is key in the development of allergopathology. Increased IgE synthesis in response to IL-4 stimulation leads to increased IgE-stimulated cytokine synthesis by mast cells capable of producing IL-4, IL-5, IL-6.

Interleukin-6 (IL-6) is a small glycoprotein (21 kDa) produced by cells of the innate immune system (e.g., macrophages, dendritic cells, mast cells, neutrophils), but also by B

cells and, to a lesser extent, by some effector CD4 Th cells. Moreover, IL-6 is also secreted by endothelial cells, fibroblasts, astrocytes, epithelial cells and a number of malignant cells [16,21,58]. Although a wide variety of stimuli can induce the production of IL-6 by these cells, common to most of them is their effect in causing stress or cell damage (e.g., UV irradiation, microbial products, viruses, or other proinflammatory cytokines). Serum IL-6 levels have been shown to be elevated in a number of inflammatory diseases. But have not been fully studied in acute obstructive bronchitis of chlamydial and mycoplasma etiology. As a result, IL-6 has long been considered a common marker of inflammation along with TNFα and IL-1β, two other classic inflammatory cytokines [5,21,57]. However, IL-6 is not just a proinflammatory marker, but an active factor that contributes to the pathogenesis of some inflammatory diseases, such as rheumatoid arthritis, and is a successful target for some of these diseases [3,4,5,11,17,18,51].

Interleukin-10 (IL-10) is an immunomodulatory cytokine that is considered to be a powerful anti-inflammatory and resolution-promoting factor in many model systems [23,56].

IL-10 is secreted by various cell types, including T cells, B cells, macrophages, mast cells, eosinophils, and dendritic cells [18,55]. In addition, it inhibits the proliferative response of T cells to antigens and mitogens, and suppresses the secretion by activated monocytes of IL-1β, TNF and IL-6. At the same time, IL-10 stimulates Ig secretion by B cells. IL-10 can stimulate the synthesis of IgE. In its inhibitory effect on cellular immunity, IL-10 is synergistic with IL-4. Studies have shown that the systemic and local IL-10 response has pathophysiological significance in some malignant neoplasms, infectious diseases, autoimmune diseases and atopic disorders [17,54]. IL-10 can function as an antiregulatory cytokine, whereby LPS-induced IL-10 can suppress the expression of proinflammatory cytokines as well as suppress pattern recognition receptor signaling [17, 23, 30,53].

Tumor necrosis factor alpha (TNFα) is the most widely studied pleiotropic cytokine of the TNF family. There are three main directions of TNFα action:

- cytotoxic, directed at tumor cells or cells affected by viruses;
- immunomodulatory and anti-inflammatory, caused by activation of macrophages, neutrophils, eosinophils and endothelial cells;
- effects on metabolism, which can lead to hyperglycemia, bone resorption and increased muscle glycogenolysis, i.e. the cachexia seen in some parasitic infections [51,52].

Under pathophysiological conditions, the generation of TNFα at high levels leads to the development of inflammatory responses, which are hallmarks of many diseases. Of the various lung diseases, TNFα is involved in the pathogenesis of asthma, chronic bronchitis (CB), chronic obstructive pulmonary disease (COPD), acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). In addition to its primary role in inflammatory events, there is increasing evidence of TNFα involvement in cytotoxicity [11]. Thus, pharmacological agents that can inhibit TNFα production or block its biological action may have potential therapeutic value against a wide range of diseases. Despite some immunological side effects, therapeutic strategies against TNFα represent an important breakthrough in the treatment of inflammatory diseases and may play a role in lung diseases characterized by inflammation and cell death [22,41,44,45, 50, 51].

Cytokines have a regulatory function and their effects depend on their concentration in the circulation and in the tissues. Treatment requires individualized approaches to cytokine or anticytokine therapy based on the study of the immunopathogenesis of the disease [34, 36,38,39].

Thus, the growth trend of acute respiratory diseases in children and their role in the development of bronchoobstruction, high risk ofrecurrence of obstructive bronchitis and the possibility of bronchial asthma, a variety of immune disorders in thispathology determine the relevance of the study of factors and mechanisms of obstructive bronchitis formation in children with infectionsrespiratory tract [40-45].

Despite numerous achievements in the study, many problems still remain unresolved, which requires combining the efforts and research of both scientists and physicians in the study of bronchoobstructive syndrome of atypical genesis.

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