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Cytokine Status and Humoral Immunity Depending on the Recurrence Rate of Obstructive Bronchitis in Children

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Abstract To study the state of immunity in children depending on the frequency of recurrence of obstructive bronchitis Changes in the child's organism and its immunity are interrelated with the environment. Changes in the environment indirectly affect the system of cytokines in our body.The change in the activity of cytokines causes the appearance of mildness in children with various allergic diseases of the respiratory system. One of these is obstructive bronchitis.

Keywords Obstructive bronchitis, Cytokines, Interleukin, Immunoglobulin

1. Introduction

The immune system is a complex multicomponent mechanism, which is a set of cells in different morphofunctional state. It is for this reason that it is very sensitive to the action of various anthropogenic and technogenic factors, which determines at the present stage the growth of diseases caused by a violation of immunological reactivity. The subject of ecological and immunological research is the study of the state of immunity in various conditions of human life [1]. 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 are introduced into the macroorganism [10]. Usually, after the development of a systemic reaction, cascades of anti-inflammatory cytokines are released into the systemic circulation. The most active are IL-4, IL-10. They inhibit the secretion of inflammatory phase mediators by macrophages. Excessive, due to gross dysregulation, production of mediators of the anti-inflammatory phase is called "compensatory anti-inflammatory response syndrome" (CARS). The main sign of CARS development is a decrease (less than 30%) in the activity of the surface complex of hladr monocytes receptors and a significant decrease in the ability of monocytes to produce TNF-α and IL-6 in response to damage. The formation of this syndrome leads to the development of immunodeficiency, which is accompanied by a high probability of progression of the infectious process or occurrence of severe superinfection [3,4,5]. At the heart of the mechanisms of anti-infection protection are complex relationships between the host and the pathogen. Polymorphism and diversity of protection factors determine its main mechanisms [2]. The body's defense against infection is determined by the following three key points that affect and define each other: natural resistance, early response, and adaptive, or acquired, immunity. After the penetration of the microbe into the body, the protection is determined by the system of cellular and humoral factors of natural resistance. In the immune response, everything begins and ends with phagocytosis.

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2. Page Layout

The participation of primary cells allows, figuratively speaking A. N. Mayansky, "to gain time for adaptive adjustment of immunity" [7]. Tissue macrophages, absorbing microbes, activate and synthesize cytokines, in particular tumor necrosis factor α (TNF-α) [9]. Macrophage is a unique cell not only because it absorbs microbes, but also because it produces more than 60 biologically active amines, hus being a regulator of intersystem, intercellular and cell-matrix relationships in the lesion. The system of phagocytes mononuclear cells in addition to aggressive functions implements and reparative function, helping to limit inflammation and delimitation of the focus of inflammation [8]. 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 responses. During the development of the immune response, changes in a number of membrane receptors, secretion of cytokines and interleukins are observed, which indicates the functional activity of monocytes/macrophages [6].

The results of immunological examination of children under 1 year with OB showed a significant increase in the level of IL - 4 and IL-8 in the blood (table.1).

An increase in IL - 4 levels was established regardless of the period and frequency of OB in children under 1 year. In OB, it was significantly increased by 3.7 times in the period of exacerbation-31.6±2.15 PG/ml (P<0.001), and has a slight tendency to decrease to 28.6±1.72 PG/ml (P<0.001) in the period of clinical remission, while maintaining reliability with respect to control-8.5±0.40 PG/ml.

In the acute phase of ROB of IL - 4 increased 3.5-fold -30,1±1,50 PG/ml (P<0.001) compared to the control -8,5±0,40 PG/ml. And in the period of remission ROB revealed increased IL - 4 3.8-fold: to 32.3=1,69 PG/ml (P<0.001). Taking into account the proven fact that IL-4 suppresses the proinflammatory activity of macrophages and their secretion of IL-1, tumor necrosis factor and IL-6 and thus has an anti-inflammatory effect, the results of studies indicate a strain of immunity and the continuation of the anti-inflammatory reaction of the body even in clinical remission, especially ROB. Consequently, the synthesis of IL-4 depends on the frequency of relapse.

The level of IL-8 in the blood in the acute phase of OB is increased by 1.5 times-22.2±1.38 PG/ml (P<0.001) compared to the control of 14.5±0.66 PG/ml. And during remission of OB is within 19.4±1.12 PG/ml, with a tendency to decrease (P<0.001). There was a characteristic increase in IL-8 during clinical remission of ROB: its concentration increased by 1.65 times (24.0±1.27 PG / ml, P<0.001) relative to the control values of -14.5±0.66 PG/ml.

The obtained results indicate that the dynamic changes in the concentration of the studied cytokines depending on the frequency of relapse show the continuation of active synthesis of both proinflammatory (IL-1, IL-6, IL-8, TNF-α) and anti-inflammatory cytokines (IL-4) during clinical remission. And on the basis of their concentration it is possible to state the activity of anti-inflammatory immune response of the body and predict the next relapse.

The increase in IL-6 concentration in clinical remission of OB in children under 1 year by 1.1 times (64.6±4.37 PG / ml) in relation to the control-59.1±2.79 PG/ml and the decrease in TNF-α at the same time by 1.5 times reaching a concentration of 16.9±0.88 PG/ml (P<0.001) confirms the activation of the hypothalamic-pituitary-adrenal system for the regulation of the inflammatory process.

The studies found a characteristic increase in the concentration of all studied cytokines during clinical remission of ROB, which indicates the continuation of the active immune response and confirms the compensatory anti-inflammatory response. Available results of our research show a trend towards reduction of concentration of IL -6 as in OB and ROB (56,8±3,65 and 57.5±2,67) in relation to the control of 59.1± and 2.79 PG/ml shows a lack of respect for their synthesis with a frequency of recurrence. At the same time, the level of TNF-α was also significantly reduced at 21.0±1.46 PG/ml as compared to the control group - 23.8±1.02 PG/ml, and repeated relapses of OB contributed to normalization with a tendency to increase its concentration to control values -23.9±1.15 PG/ml.

This condition proves the ability of TNF-α to activate cells by changing their phenotype. Consequently, the decrease in Il-6 and TNF-α synthesis in OB regardless of the frequency of relapse indicates the beginning of the formation of immunodeficiency and adverse course of OB in children under 1 year.

Table 1. Cytokine profile of blood of patients with obstructive bronchitis under the age of 1 year

Indicator	Control group (n=50)	OB (n=40)		ROB (n=42)	
		Acute phase (n=40)	Remission (n=14)	Acute phase (n=42)	Remission (n=10)
IL-1 PG/ml	53,5±2,21	56,2±3,95	48,72±2,99	57,4±2,81	59,8±3,84
IL -4 PG/ml	8,5±0,40	31,6±2,15***	28,6±1,72***	30,1±1,50***	32,3±1,69***
IL -6 PG/ml	59,1±2,79	56,8±3,65	64,6±4,37	57,5±2,67	61,3±3,24
IL -8 PG/ml	14,5±0,66	22,2±1,38***	19,4±1,12***	22,8±1,20***	24,0±1,27***
TNF-α PG/ml	23,8±1,02	21,0±1,46	16,9±0,88***	23,9±1,15	25,1±1,35

Note: * - differences relative to control group data are significant

Table 2. Cytokine profile of blood of patients with obstructive bronchitis at the age of 1-3 years

Indicator	Control group (n=50)	OB (n=19)		ROB (n=34)	
		Acute phase (n=19)	Remission (n=8)	Acute phase (n=34)	Remission (n=18)
IL -1 PG/ml	78,3±3,57	77,0±4,31	81,9±3,98	81,8±4,93	94,1±5,93*
IL -4 PG/ml	8,1±0,34	31,6±1,28***	30,6±1,85***	33,1±1,53***	34,9±1,73***
IL -6 PG/ml	78,1±3,64	79,1±4,04	83,3±6,00	74,8±3,17	86,6±4,22
IL -8 PG/ml	14,9±0,69	22,4±1,11***	21,6±1,09***	23,4±1,04***	24,8±1,34***
TNF-ά PG/ml	25,9±1,14	21,4±1,00**	17,9±1,43***	24,4±0,89	27,5±1,52

Note: * - differences relative to control group data are significant
(*- P<0.05, * * - P<0.01, * * * - P<0.001

The study of blood cytokines of patients with OB in children aged 1 to 3 years showed a significant increase in the concentration of IL - 4, IL-8 and a decrease in TNF-α (table.2).

A 4-fold increase in IL-4 was found during exacerbation and remission in both OB and ROB in children aged 1-3 years (P<0.001). IL -8 was increased by 1.5 times in periods of exacerbation and remission in both OB and ROB (P<0.001). TNF-α was significantly reduced-21,4±1,00 PG / ml (P<0,01) versus control-25,9±1,14 PG/ml in the acute phase of OB, and the remission period of its reduction below control reaches 17,9±1,43 PG / ml (P<0,01).

In the acute phase ROB in the blood of children aged 1-3 years, there has been insignificant increase in IL-1 - 81,8±4,93 PG/ml vs control-78,3±3,57 PG/ml, and s the phase of clinical remission ROB IL -1 significantly increased by 1.2 times -94,1±of 5.93 PG/ml (P<0.05). It is also noted simultaneous increase of concentration of IL -6 in the period of remission as in OB-83,3±6,00 PG/ml and ROB-86,6±4,22 PG/ml vs control-78,1±3,64 PG/ml. the results of the research prove the change in the regulation of the hypothalamic - pituitary - adrenal axis, as evidenced by the increase of concentration of IL -6 in the period of clinical remission OB. Consequently, an increase in the level of IL-6 in the blood of examined patients with OB shows the simultaneous presence of severe inflammatory processes and infections.

The study of nonspecific protection factor revealed a slight functional insufficiency of phagocytes. There was a decrease in phagocytosis both in the acute phase-52.1±3.28%, and in the period of remission of OOB-49.6±2.72% in patients under the age of 1 year, with respect to the control of 53.1±3.05%. This phenomenon is also observed in ROB during periods of exacerbation and remission, respectively 50.7±2.60% and 51.0±2.67% (table.3.).

A study of the concentrations of the main classes of immunoglobulins G, A, M and E. As a result, a tendency to increase the synthesis of Ig A, M and G in OB and ROB was established in comparison with the control group. The study of concentrations of the main classes of immunoglobulins depending on the frequency of relapse revealed a significant increase in the synthesis of IgM in OB and ROB, 96.6±5.91 mg% and 109.6±5.36 mg%, respectively.

It is known that this type of antibodies is produced against infectious agents, activates complement and enhances phagocytosis. Increased IgM synthesis in the group of children with OB is associated with the addition of the infectious process. Very important properties of Ig M are the involvement of phagocytic cells in the location of the antigen or in the focus of infection and activation of phagocytosis.

IgG is the primary antibody of the secondary immune response. Being thymus-dependent, IgG is produced only with the mandatory participation of T-lymphocytes.

There was a significant increase in IgG concentration at ROB -1027.7±59.36 mg% (P<0.05) compared to the control group - 855.7±35.97 mg%.

And there was also an increase in the concentration of IgA: so, in the blood of sick children up to 1 year with OB, the concentration of IgA increases in the period of exacerbation by 1.4 times (118.4±7.69 mg%) relative to the control - 85.2±5.09 mg% (P<0.001) with a tendency to decrease during remission. And with ROB on the background of increasing its concentration by 1.4 times in the acute phase (117.0±6.29 mg%, P<0.001), it tends to increase to 1.5 times - 127.9±7.13 mg% (P<0.001) during clinical remission.

Table 3. Indicators of phagocytosis and humoral immunity in the blood of patients with obstructive bronchitis under the age of 1 year

Indicator	Control group (n=22)	OB (n=40)		ROB (n=42)	
		Acute phase (n=40)	Remission (n=14)	Acute phase (n=42)	Remission (n=10)
Phagocytosis %	53,1±3,05	52,1±3,28	49,6±2,72	50,7±2,60	51,0±2,67
IgA mg%	85,2±5,09	118,4±7,69***	110,3±7,15**	117,0±6,29***	127,9±7,13***
IgM mg%	73,7±3,86	96,6±5,91**	116,0±8,95***	109,6±5,36***	91,9±5,61**
IgG mg%	855,7±35,97	989,5±62,4	957,4±46,3	1027,7±59,4*	1031,7±50,78**
IgE mg%	23,0±1,01	20,7±1,43	19,6±1,28*	20,6±0,96	19,7±1,06*

Note: * - differences relative to control group data are significant
(*- P<0.05, * * - P<0.01, * * * - P<0.001)

Table 4. Indicators of phagocytosis and humoral immunity in the blood of patients with obstructive bronchitis at the age of 1-3 years

Indicator	Control group (n=50)	OB (n=19)		ROB (n=34)	
		Acute phase (n=19)	Remission (n=8)	Acute phase (n=34)	Remission (n=18)
Phagocytosis %	51,4±2,59	53,0±2,93	51,7±2,78	51,4±2,38	52,1±2,81
IgA mg%	86,1±4,75	120,9±6,48***	111,5±5,17***	129,2±5,85***	132,5±6,54***
IgM mg%	74,0±4,00	108,8±5,30***	118,6±4,95***	110,9±5,80***	101,6±6,52***
IgG mg%	845,0±45,57	1019,0±48,90*	1003,1±60,90*	1032,7±42,87**	1039,9±59,78*
IgE mg%	21,7±1,11	22,0±1,25	20,3±1,21	22,4±1,07	19,6±1,14

Note: * - differences relative to control group data are significant
(*- P<0.05, * * - P<0.01, * * * - P<0.001)

The study of blood of sick children up to 1 year with OB shows a low concentration of IgE in the acute phase and a significant decrease in remission in both OB-19.6±1.28 mg% (P<0.05) and ROB-19.7±1.06 mg% (P<0.05) with respect to the control-23.0±1.01 mg%, which proves the presence of an infectious process in OB and the absence of allergies at the same time.

The study of the parameters of phagocytosis and humoral immunity in the blood of children with OB at the age of 1-3 years showed a significant increase in the concentration of IgA, IgM and IgG. It was characterized by an increase in IgA 1.4 times in the acute phase-120.9±6.48 mg% (P<0.001) and 1, 54 times in exacerbation of ROB - 129.2±5.85 mg% versus control-86.1±4.75 mg%. During remission, it significantly increased at ROB-132.5±6.54 mg% (P<0.001) (table.4).

IgM parameters in children aged 1-3 years with OB and ROB during exacerbation were significantly increased by 1.5 times: 108.8±5.30 mg% and 110.9±5.80 mg%, respectively (P<0.001). And during remission, it increases to 118.6±4.95 mg% (P<0.001) in OB and to 101.6±6.52 mg% (P<0.001) in ROB vs. control-74.0±4.00 mg%.

At the same time, there was a significant increase in IgG concentration by 1.2 times in the acute phase of OOB-1019.0±48.90 mg% (P<0.001) and 1.3 times in the exacerbation of ROB - 1032.7±42.87 mg% (P<0.001). And in remission ROB its concentration reaches 1039,9±59,78 mg% (P<0.001) vs control-845,0±of 45.57 mg%.

Indicators of phagocytosis and IgE in the blood of patients aged 1-3 years with OB and ROB were at the level of control values in both exacerbation and remission.

Thus, in children under 1 year of age, the blood level of IL-4 increased by 3.7 times, IL - 8 by 1.5 times, IgA by 1.4 times, and IgM by 1.4 times (P<0.001). When ROB children under 1year the increase in serum IL -4 3.5-fold, IL-8 1.65 times, IgA 1.4-fold, IgM 1.2 times and IgG in 1.1 times (P<0.001).

The established decrease in the synthesis of IL-6 and TNF-a regardless of the recurrence rate indicates the beginning of the formation of immunodeficiency and its unfavorable course (the risk of formation of bronchial hyperreactivity) in children under 1 year.

In children aged 1-3 years, the increase in blood IL -4 4.0 times, IL-8 - 1.5 times, IgA 1.4 times, IgM 1.5 times and IgG 1.2 times (P<0.001) in both OB and ROB.

Consequently, the results indicate the features of the formation of adaptive immune response in children with OB, which is manifested by a pronounced immunological imbalance depending on the frequency of relapse of AM, which contributes to the development of secondary immunodeficiency.

For a comparative assessment of the significance of the humoral status in the prediction of recurrence OB the study of IgA, IgM, IgG and IgE in the saliva of 135 children: 59 children with OB (1 group), 76 sick children with ROB (2 group) and 50 healthy children.

As a result of the analysis of the content of immunoglobulins in the saliva of sick children with OB, it was found that the concentrations of IgM and IgG in both groups exceed the upper limit of the concentration range of these indicators in the group of healthy children (table.5).

The concentration of IgM in saliva is characterized by an increase of 1.5 times in the acute phase of OB-0.05±0.002 mg% (P<0.001) and 2.0 times in exacerbation of ROB -0.069±0.004 mg% (P<0.001) versus control-0.033±0.002 mg%, indicating another relapse of the infectious process.

Salivary IgG was also increased 1.8 times in the acute phase by -0.042±0.002 mg% (P<0.001) and 1.6 times in ROB by 0.036±0.002 mg% (P<0.001) versus control by 0.023±0.001 mg%.

Table 5. The content of immunoglobulins in the saliva of children under the age of 1 year with obstructive bronchitis

Indicator	Control group (n=50)	OB (n=40)		ROB (n=42)	
		Acute phase (n=40)	Remission (n=14)	Acute phase (n=42)	Remission (n=10)
IgA mg%	0,568±0,027	0,173±0,007***	0,23±0,015***	0,306±0,018***	0,308±0,014***
IgM mg%	0,033±0,002	0,05±0,002***	0,041±0,003*	0,069±0,004***	0,025±0,001***
IgG mg%	0,023±0,001	0,042±0,002***	0,028±0,002*	0,036±0,002***	0,037±0,002***
IgE mg%	0,87±0,049	0,2±0,010***	0,22±0,015***	0,3±0,016***	0,26±0,014***

Note: * - differences relative to control group data are significant
(*- P<0.05, * * - P<0.01, * * * - P<0.001)

Table 6. The content of immunoglobulins in the saliva of children aged 1-3 years with obstructive bronchitis

Indicator	Control group (n=50)	OB (n=19)		ROB (n=34)	
		Acute phase (n=19)	Remission (n=8)	Acute phase (n=34)	Remission (n=18)
IgA mg%	0,582±0,032	0,179±0,009***	0,26±0,016***	0,338±0,016***	0,344±0,018***
IgM mg%	0,034±0,002	0,034±0,002	0,035±0,002	0,071±0,004***	0,030±0,002
IgG mg%	0,027±0,001	0,044±0,002***	0,023±0,002	0,033±0,002**	0,036±0,002***
IgE mg%	0,900±0,049	0,33±0,020***	0,27±0,015***	0,37±0,016***	0,270±0,017***

Note: * - differences relative to control group data are significant
(*- P<0.05, * * - P<0.01, * * * - P<0.001)

The decrease of IgA concentration in 3.3 times in saliva during exacerbation OB - 0,173±0,007 mg% (P<0.001) and 1.8 times at ROB - 0,306±0,018 mg% (P<0.001) relative to control-0,568±0.027 mg%.

The study of saliva of sick children up to 1 year with OB as well as in the blood shows a low concentration of IgE independent of the period of the disease: there is a 4-fold decrease in OB-0.2±0.010 mg% (P<0.001), and a 3-fold decrease in ROB-0.3±0.016 mg% (P<0.001) with respect to the control-0.87±0.049 mg%.

Distinctive data were obtained in the study of these immunoglobulins in saliva in patients with OB at the age of 1-3 years (table.6).

When assessing the condition of patients with OB at the age of 1-3 years, there was a significant decrease in the level Of IgA and Ig E in saliva, regardless of the frequency of relapse of OB (table.6).

As a result of the comparative analysis of the content of immunoglobulins in blood and saliva of sick children aged 1-3 years it is established that at ROB IgM in saliva increases in 2 times more - 0,071±0,004 mg% (P<0,001) in relation to indicators of control - 0,034±0,002 mg%.

IgG is significantly increased both at the OB-0.044±0.002 mg% (P<0.001) and at the ROB-0.033±0.002 mg% (P<0.01) versus the control-0.027±0.001 mg%.

Thus, for young children (1-3 years) with ROB is characterized by a significant 2-fold increase in IgM, IgG and a decrease in IgA and IgE in the saliva of sick children against the background of normal phagocytosis in the blood.

Comparative analysis of humoral immunity indicators in children with OB under the age of 1 year showed a significant increase in IgM concentration by 2, 0 times, IgG by 1.6 times and a decrease in IgE level by 3.0 times in both blood and saliva.

There was a characteristic imbalance in the concentration of IgA in patients with OB under the age of 1 year, so when increasing its concentration in the blood by 1.8 times, there was a sharp decrease in saliva by 3.3 times, and in ROB - by 1.8 times.

This phenomenon indicates a significant value of the level of secretory IgA in the early diagnosis and prediction of the next relapse OB children under 1 year (P<0.001).

Comparative evaluation of humoral immunity parameters in the blood and saliva of young children (1-3 years) revealed an unambiguous increase in IgM and IgG levels in the studied biological media. The increase of IgA in blood by 1.5 times against the background of normal values of IgE in OB in young children was established. A secretory IgA and IgE were reduced by 3.0 times (P<0.001).

3. Conclusions

The degree of involvement of various inflammatory regulators in the formation and progression of obstructive bronchitis in young children remains insufficiently studied, so the study of the dynamics of cytokine production and humoral immunity factors systemically and locally is important to optimize the diagnosis and prediction of its recurrence.

Consequently, the indicators of secretory IgA and IgE serve as an indicator of early diagnosis and relapse in children of early (1-3 years) age. To predict the next relapse of OB in children under the age of 1 year, the diagnostic indicator is the concentration of secretory IgA, and for sick children with OB at the age of 1-3 years, indicators of early diagnosis and relapse of OB are the indicators of secretory IgA and IgE.

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