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Research Article

Clinical and Laboratory Characteristics of Acute Respiratory Diseases in Children

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Abstract

The purpose of the study was to determine the cytokine profile that plays a role in the pathogenesis of acute respiratory diseases of various etiologies in children and to analyze the obtained results. 89 patients diagnosed with acute respiratory disease of moderate severity (age 1 month-17 years) were involved in the study. For comparison, 35 children formed the control group. The gender distribution revealed that there were 54 (60.7%) boys and 35 (39.3%) girls in the main group, and 17 (48.6%) boys and 18 (51.4%) girls in the control group.

The children included in the main group were divided into two groups based on the diagnosis: Group I was diagnosed with ARDs (53(59.6%)), Group II (36(40,4%)) was diagnosed with ARDs complicated by other upper respiratory tract diseases (bronchitis, laryngotracheitis, laryngitis, tracheitis).

In the clinical examination, different levels of upper respiratory tract damage syndrome, catarrhal symptoms, fever, cough, rhinitis were more manifested during ARDs.

During the study, the level of pro-inflammatory cytokines (IL-21 and γ- INF, IL-1β, IL-6, IL-18) in the blood serum of patients with ARDs differed depending on the clinical course of the disease in the acute period compared to the control group. Compared to group I, the level of IL-21 and IL-6 increased significantly in group II. The study of the level of pro-inflammatory cytokines in the blood serum of patients with ARDs allows to determine the course and severity of the inflammatory process.

Keywords: Acute Respiratory Diseases; Children; Cytokines

Introduction

Respiratory diseases are one of the most frequent pathologies in childhood and are characterized by the maximum incidence [1-4]. Despite the achievements in pediatrics, cases of recurrence, chronicity and aggravation of respiratory diseases of various etiologies are common in children. Acute repiratory diseases (ARDs) are one of the main reasons of hospitalization in children. High morbidity and mortality associated with acute respiratory infections, being a high epidemic potential, is a serious public health problem in developing countries [5].

The wide spread of the acute respiratory diseases is due to the variety of respiratory viruses and their antigenic variability, their easy spread, the presence of a large number of pneumatic bacteria, the possibility of long-term persistence of pathogens against the background of the age characteristics of immunity. Children, unlike adults, get sick with respiratory diseases more often, and this disease depends on the state of organism's immune system. Recognizing changes in the immune system as a protective and adaptive reaction of the body, importance is attached to the features of the immune system, especially in childhood, in which

the immune system responds inadequately or hyperergically to antigenic stimulation during critical periods of the child's immunological reactivity. However, frequent re-infection in many cases leads to depression of the immune system of organism, disruption of compensatory adaptive mechanisms, dysfunction of the endogenous interferon system, production of inflammatory cytokines, which reduces the effect of the treatment. Thus, the course of the inflammatory process in the lung tissue of the child's organism is related to various factors and differs from each other according to pathogenetic mechanisms and clinical manifestations.

It is known that cytokines play an important role in the pathogenesis of inflammatory diseases. The frequency and severity of acute respiratory infections, in addition to the pathogenic effect of the virus, is associated with a certain type of response of the immune system, the main link of which is cytokines. Cytokines are biologically active substances of protein nature, produced by various immune cells, especially by activated T- and B-lymphocytes and macrophages. Cytokines play an important role in the formation and functional activity of adaptive immunity as inducers and regulators of the immune response. The biological effect of cytokines is related to their activating, proliferative effect, as well as their effect on the differentiation of cells of the immune system. An increase in their activity, as well as a decrease, can lead to the development of pathology. Thus, determination of the level of cytokines in the blood serum in respiratory diseases has diagnostic value for assessing of the severity of the disease [6].

The purpose of the study was to determine the cytokine profile that plays a role in the pathogenesis of acute respiratory diseases of various etiologies in children and to analyze the obtained results.

Materials and Methods of Research

The work was carried out at Educational Therapeutic Clinic of Azerbaijan Medical Unoversity, in 2019-2022. 89 patients with moderately severe course of acute respiratory disease were included in our study. The age of the examined children was between 1 month and 17 years. For comparison, 35 children formed the control group.

The gender distribution revealed that there were 54 (60.7%) boys and 35 (39.3%) girls in the main group, and 17 (48.6%) boys and 18 (51.4%) girls in the control group.

The children included in the main group were divided into two groups based on the diagnosis: Group I was diagnosed with ARDs (53(59.6%)), Group II (36(40,4%)) was diagnosed with ARDs complicated by other upper respiratory tract diseases (bronchitis, laryngotracheitis, laryngitis, tracheitis). Patients were divided by age groups: 4 (4.5%) patients under 1 year, 61 (68.5%) patients in the 1-3 age group, 24 (27.0%) patients in the 3-17 age group.

73 (82.0%) of the examined patients ARDs were urban residents, 16 (18.0%) were regional residents. When studying the seasonality of the disease, it was found that the majority of patients (39.3%, 57.3%) were hospitalized in the autumn-winter period, which is related to the peak of respiratory diseases in the autumn-winter months. Allergic history was positive in most of the complicated ARDs+ patients. 52 examined patients (58.4%) applied to the hospital during the first 3 days of the disease. 33 children (37.1%) were admitted to the hospital on the 4-7th day of the disease, and 4 (4.5%) patients were admitted to the hospital later than the 7th day after the onset of clinical manifestations.

Patients included in the study were selected according to the inclusion and exclusion criteria

- **Inclusion criteria:** Children with acute respiratory disease of moderate severity were included in the study.
- **Exclusion criteria:** bronchial asthma, autoimmune diseases, cystic fibrosis, primary and acquired immune deficiency, hereditary diseases were excluded.

Examination methods included anamnestic, clinical data, instrumental and laboratory examinations, the level of cytokines in blood serum was determined and analyzed. Patients were examined during the acute period of the disease.

Examination methods

The concentration of cytokines IL-21, γ-INF, IL-1ß, IL-6, IL-18 in the blood of the patients included in the research contingent was analyzed by immunoenzyme method (IFA). The concentration of IL-1ß, IL-6 and IL-18 cytokines in blood serum was measured using the «IFA-Best» test system manufactured by «Vektor-Best» (Russian Federation) on the «Stat Fax 303+» device, concentration of IL-21 and γ -İN cytokines was measured using the reagent kit of the company «Invitrogen» (by Thermo Fisher Scientific, USA), on the Medispec 6000 (Microplate Reader RT-6000) device.

Statistical processing

Statistical data processing was carried out using the methods of variation (U-Mann-Whitney), discriminant (Pearson's Chi-square),

correlation (Rho-Spearman), dispersion (F-Fisher and F-S-Fisher-Snedekor tests) tests. All statistical calculations were carried out in MS EXCEL-2019 and IBM Statistics SPSS-26 programs. The null hypothesis was rejected at $p < 0.050$.

Research Results and their Discussion

An accurate assessment of the first stage of the disease on the basis of clinical symptoms of the respiratory tract, as well as an individual approach in the process of examining the patient, makes it possible to predict the further course of the disease. The clinical manifestation of acute respiratory diseases is characterized by polymorphism. So, during the clinical examination, the main symptoms of the patients when applying to the hospital are catarrhal symptoms, cough, fever, rhinorrhea, signs of intoxication has been observed. Fever observed in 56 (62.9%) cases, cough - in 59 (66.3%), rhinorrhea - in 57 (66.0%), weakness - in 71 (79.8%), loss of appetite - in 44 (49.4%), pallor of mucous membranes - in 81 (91.0%) cases (Table 1).

As can be seen from Table 1, there were no signs of intoxication or noticeable dispnea in group I (ARDs group), catarrhal symptoms prevailed in group II (ARDs+ group). During examination, fever was 37.9 ± 0.1^0 C (36.5-39.5) in 66.0% of cases in group I, 37.6 ± 0.2^0 C (36.6-40.0) in 58.3% of cases in group II. SpO_2-96.5 ± 0.2% was observed in group I patients, SpO2-95.9 ± 0.3% in group II patients. Indigestion - diarrhea, vomiting, nausea was mainly observed in group I. Expiratory dispnea and the participation of auxiliary muscles in breathing were observed during bronchoobstructive syndrome in some patients included in group II. The cough was spasmodic, with difficult expectoration. On percussion of the lungs, the presence of a clear percussive sound or a box sound, wheezing and isolated dry or wet crackles were heard on the background of stiff breathing during auscultation.

I group Count		ARDs			
		II group			
		Count	Px2	Pu	
Weakness	Present	44	27	0.355	0.358
Cough	Present	24	35	0.001*	0.001*
Dyspnea	Present	2	7	0.016*	0.017*
Loss of appetite	Present	32	12	0.012*	0.013*
Vomiting	Present	9	0	0.009*	0.010*
Diarrhea	Present	1	0	0.407	0.410
Fever	Present	35	21	0.460	0.463
Rhinorrhea	Present	36	21	0.355	0.357
Throat	Hyperemiya	41	27	0.457	0.552
	Hyperemiya and Hyper-trophy	4	1		

Table 1: Clinical signs observed in patients with ARDs.

Note: The statistical significance of the differences between the indicators of the groups:

$P_{\chi 2}$ -according to Chi-square Pearson test

Pu - according to the Mann-Whitney u test

** - p < 0.050*

During the analysis of the laboratory examinations in the majority of hospitalized children with ARDs, relative lymphocytosis, a slight increase in the level of ESR and CRP was found, but the changes were not statistically significant (Table 2).

		N	Mean	Std. Error	Min	Max	P_F	P_U
Leukocytes q/l	ARD	53	10.2	0.7	3.03	25.82	0.130	0.104
	ARD+	36	12.1	1.2	5.15	44.71		
Neutrophils %	ARD	53	48.0	2.6	2.3	86	0.171	0.168
	ARD+	36	42.5	2.9	8.5	83.7		
Lymphocytes %	ARD	53	39.3	2.3	9.2	74.5	0.005	0.005*
	ARD+	36	49.6	2.8	10.9	81.1		
Erythrocytes q/l	ARD	53	4.67	0.06	3.65	6	0.095	0.155
	ARD+	36	4.84	0.08	4.05	6.22		

Trombocytes q/l	ARD	53	342.4	14.6	135	673	0.311	0.343
	ARD+	36	366.6	19.2	120	640		
Eosinophill %	ARD	53	1.23	0.24	0	7.8	0.205	0.263
	ARD+	35	1.75	0.35	0	8.4		
ESR mm/h	ARD	53	19.4	2.6	2	90	0.667	0.768
	ARD+	35	17.8	2.5	4	85		
CRP mq/l	ARD	43	11.9	3.4	0.05	121.7	0.843	0.670
	ARD+	30	10.9	3.5	0.29	88.1		

Table 2: Comparative analysis of hemogram indicators in ARDs.

***Note:** statistical significance of the difference between the indicators of the groups

PF - According to the F-Fisher criterion.

PU - According to theMann-Whitney U test.

* - «0» hypothesis is rejected.

Taking into account the important role of cytokines in the regulation of inflammatory processes in our study, we examined and analyzed some cytokines (IL-21, γ-INF, IL-1β, IL-6, IL-18) in the blood serum of patients with ARDs in the next stage of our study. For this purpose, the level of anti-inflammatory cytokines IL-21 and γ-INF in blood serum of 56 children, and IL-1β, IL-6, IL-18 in blood serum of 30 children were studied in acute respiratory diseases. During the study, the level of pro-inflammatory cytokines in the blood serum of patients with ARDs differed from those in the control group, depending on the clinical course of the disease in the acute period. It was found that the changes in the cytokine system between the groups varied depending on the diagnosis (Table 3).

	Acute respiratory diseases												**pF**	**pH**
	Control				**I group**				**II group**					
	M	**Me**	**Q1**	**Q3**	**M**	**Me**	**Q1**	**Q3**	**M**	**Me**	**Q1**	**Q3**		
IL-21	10.34	0.00	0.00	12.15	23.26	18.40	13.90	25.10	33.08	24.80	10.60	42.87	0.003*	<0.001*
γ-INF	3.32	3.45	1.15	4.55	6.40	5.80	2.20	10.10	1.95	1.20	0.70	2.60	<0.001*	<0.001*
IL-1β	0.546	0.050	0.000	1.400	1.169	0.500	0.000	2.350	0.914	0.000	0.000	1.900	0.381	0.812
IL-6	1.63	1.10	0.60	1.70	1.79	1.40	0.95	2.65	3.44	2.95	1.00	6.10	0.021*	0.050*
IL-18	231.9	218.0	155.5	310.4	162.3	159.8	47.4	247.4	214.2	199.4	98.2	366.4	0.252	0.254

Table 3: Comparative analysis of cytokine indicators in patients with ARDs.

Note: The statistical significance of the differences between the indicators of the groups

P_F – According to the F-Fisher criterion

P_H- According to the H-Kruskal-Wallis criterion

* – «0» hypothesis is rejected

It was clear from the study that the level of IL-21, IL-1β, IL-6 in the main group increased compared to the control group. During the study of the concentration of IL-21, it was found that in the acute period of the disease, in both groups, it increased statistically significantly compared to the corresponding indicators of the control group. In comparison between groups, the level of IL-21

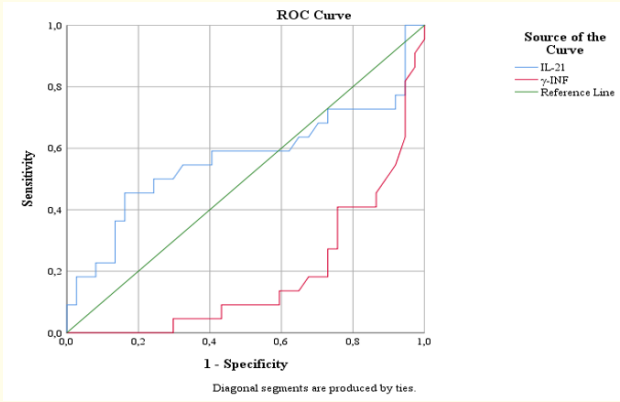
significantly increased in group II. The average value of IL-21 in group I was 23.26 pg/ml, in group II it was 33.08 pg/ml. In the comparison of average structural indicators, the median in group I was 18.40 pg/ml (13.90-25.10 in the 1st and 3rd quartiles), and the median in group II was 24.80 pg/ml (10.60-42,87 in the 1st and 3rd quartiles).

Analysis of the level of γ-INF in blood serum during the study showed that its level in both observation groups was different compared to the corresponding indicators of the control group. In comparison between groups, its level increased in group I and decreased in group II (complicated ARDs+). Thus, the average value of γ-INF in the blood serum of group I cases is 6.40 pg/ml, when comparing the average structural indicators, the median is 5.80 pg/ml (2.20-10.10 in the 1st and 3rd quartiles), In group II, the average value of γ-INF was -1.95 pg/ml, the median was 1.20 pg/ml (0.70-2.60 in the 1st and 3rd quartiles).

As can be seen from the table, the concentration of IL-1β in the blood serum of the examined children increased in the acute period of the disease in both groups, respectively, compared to the indicators of the control group. In group I, the mean value of IL-1β was 1.169 pg/ml, median was 0.500 pg/ml in the comparison of mean structural indicators (0.00-2.350 in the 1st and 3rd quartiles), and in group II the mean value was 0.914 pg/ml, median was 0,000 pg/ml (10.000-1.900 in quartiles 1 and 3). In group I, the mean value of IL-6 was 1.79 pg/ml, in the comparison of average structural indicators, the median was 1.40 pg/ml (0.95-2.65 in the 1st and 3rd quartiles), and in group IL, its mean value was 3.44 pg/ml, median was 2.95 pg/ml (1.00-6.10 in 1st and 3rd quartiles). The concentration of IL-18 in the blood serum in the acute period of the disease in both groups decreased below the limits of the control group.The mean value of IL-18 was 162.3 pg/ml in group I, the median was 159.8 pg/ml in the comparison of average structural indicators (47.4-247.4 in the 1st and 3rd quartiles), in group II (during complicated ARDs+) the mean value was 214.2 pg/ml, the median was 199.4 pg/ml (98.2-366.4 in 1st and 3rd quartiles).

Thus, in the course of the research, it was found that the level of these cytokines in the blood serum was variable depending on the clinical course of the disease.

At the next stage of our research, the ROC curve of the studied cytokine indicators was constructed (Graph 1).



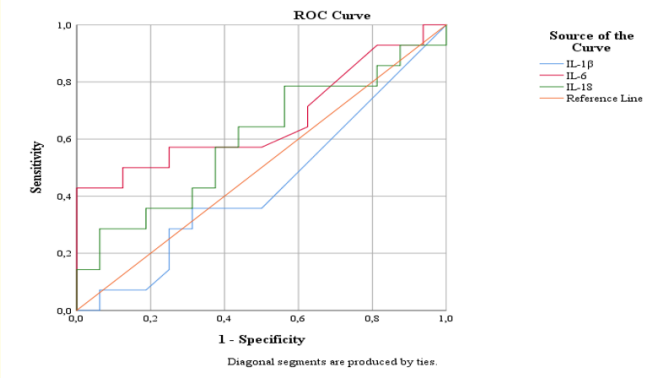
Graph 1: Integral Indicator of ROC-Specificity and Sensitivity of Cytokines IL-21, γ-INF in children with ARDs.

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
IL-21	0.567	0.086	0.393	0.398	0.736
γ-INF	0.185	0.056	<0.001*	0.075	0.294

Table 4: Integral Indicator of ROC-Specificity and Sensitivity of Cytokines IL-21, γ-INF in children with ARDs.

Based on the ROC curve, it was determined that the area of IL-21 was 0.567 ± 0.086; 95% CI: upper and lower bound, 0.398-0.736, respectively; p = 0.393.

γ-INF area was 0.185 ± 0.056; 95% CI: upper and lower bound, 0.075-0.294, respectively; p < 0.001. γ-INF can be evaluated as an indicator with high specificity and sensitivity.



Graph 2: Integral Indicator of ROC-Specificity and Sensitivity of Cytokines IL-1, IL-6, IL-18 in children with ARDs.

Area Under the Curve					
Test Result Variable(s)	**Area**	**Std. Error**	**Asymptotic Sig.**	**Asymptotic 95% Confidence Interval**	
				Lower Bound	**Upper Bound**
IL-1β	0.440	0.107	0.575	0.230	0.649
IL-6	0.667	0.105	0.119	0.462	0.873
IL-18	0.598	0.107	0.360	0.389	0.807

Table 5: Integral Indicator of ROC-Specificity and Sensitivity of Cytokines IL-1, IL-6, IL-18 in children with ARDs.

Based on the ROC curve, it was determined that the area of IL-1β was 0.440 ± 0.107; 95% CI: upper and lower bound, 0.230-0.649, respectively; p = 0.575, area under the ROC curve of IL-6 indicator was 0.667 ± 0.105; 95% CI: upper and lower bound 0.462-0.873; p = 0.119, the area of the ROC curve of IL-18 indicator was 0.598 ± 0.107; 95% CI: upper and lower bound, 0.398-0.807, respectively; p = 0.360, but we could not evaluate these indicators as a statistically significant, diagnostic criterion.

Based on the results of our study, a correlative dependence was determined between a number of clinical signs reflecting inflammation in children with ARDs. In ARDs patients, the patient's condition with temperature: ρ =+ 0.348, p < 0.001; heart rate: ρ =+ 0.323, p = 0.008; loss of appetite: ρ =+ 0.330, p = 0.002; pallor of mucous membrans: ρ =+ 0.233, p = 0.028; CRP: ρ =+ 0.236, p = 0.044 positive relationship was found. Positive correlation was observed between dyspnea and cough ρ =+ 0.239, p = 0.024; fever with SpO_2: ρ =- 0.303, p = 0.005; cor tones p =+ 0.229, p = 0.033; heart rate: ρ =+ 0.303, p = 0.014.

		IL-21	**γ-INF**	**IL-1β**	**IL-6**	**IL-18**
T	ρ (Rho)	0,070	0,124	0,127	-0,081	-0,022
	P	0,599	0,348	0,520	0,681	0,913
SpO2	ρ (Rho)	0,007	0,241	-0,033	0,350	0,245
	P	0,961	0,066	0,867	0,068	0,209
RR	ρ (Rho)	-0,355**	0,002	0,322	-0,279	-0,740*
	P	0,006	0,988	0,437	0,504	0,036
General condition	ρ (Rho)	-0,064	0,015	-0,226	0,075	-0,189
	P	0,629	0,911	0,230	0,694	0,318

Cough	ρ (Rho)	0,103	-0,403**	0,154	-0,047	-0,098
	P	0,439	0,002	0,416	0,807	0,606
Dyspnea	ρ (Rho)	0,068	-0,231	-0,154	-0,258	-0,268
	P	0,607	0,078	0,416	0,169	0,152
Loss of appetite	ρ (Rho)	-0,023	0,115	-0,325	-0,123	-0,057
	P	0,862	0,386	0,080	0,518	0,764
Vomiting	ρ (Rho)	-0,089	0,070	0,119	0,108	0,000
	P	0,501	0,600	0,531	0,571	1,000
Diarrhea	ρ (Rho)	0,000	-0,189			
	P	1,000	0,152			
Rhinorhea	ρ (Rho)	0,008	-0,101	0,084	-0,188	0,212
	P	0,950	0,447	0,659	0,319	0,261

Table 6: Assessment of correlations between some indicators in patients with ARDs.

Note

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Discussion

It is known that respiratory infections can weaken the functional activity of the immune system in children, cause a prolonged course of the inflammatory process and the transition to a chronic form, and become complicated.

During our study, most of the patients with ARDs were children of early age (1-3 years). According to many authors, early childhood is known as the period of maximum risk for infectious diseases. According to Kushnarev M.V., Luss L.V. and co-authors, the highest incidence of ARDs is observed in young children and is characterized by a number of severe complications (pneumonia, bronchiolitis) [7,8]. The mechanisms underlying this are unknown, but are thought to be related to an imbalance in host defense responses resulting from the functional immaturity of the immune system in this age group. Thus, the anatomical and physiological structure of the respiratory organs, the characteristics of the adaptation period, the immaturity of general and local immunity, the insufficient formation of specific and nonspecific protection factors in children at this age are predisposing factors for the development of respiratory diseases.

The clinical characteristics of the patients examined in our study reflect the clinical course of acute respiratory diseases. Thus, during the clinical comparison, different levels of upper respiratory tract damage syndrome, catarrhal symptoms, and rhinitis were observed in patients with ARDs. Common main symptoms in both comparison groups were fever (56(62.9%)), cough (59(66.3%)), rhinorrhea (57(66.0%)). Expiratory dyspnea and the involvement of auxiliary muscles in breathing were observed during the accompanying bronchoobstructive syndrome in some patients included in the complicated ARDs+ group. The cough was spasmodic, with difficult expectoration. Many researchers have also noted the presence of typical symptoms in patients with ARDs [9-11].

Laboratory examinations of the majority of hospitalized children revealed relative leukocytosis, lymphocytosis, a slight increase in the level of CRP and ESR, and eosinophilia in allergic children. But it was not significant. However, these laboratory indicators are in common with the studied pathology. Choi E. (2018) and colleagues came to similar conclusions in their research [3].

In recent years, disruption of the activity of cytokines, which has an important role in the pathogenesis of respiratory diseases, has been noted by many authors [6,13]. During our study, the change in the level of pro-inflammatory cytokines in the blood serum of children with ARDs, the imbalance between them, which

affects the immune component cells during the acute period of the disease, affects the formation of the early immune response and the activity of inflammation. Changes in the levels of these cytokines in respiratory diseases can be considered a component of the immune response that suppresses viral replication and virulence activity, and a clinical-diagnostic criterion of the inflammatory process.

During the study, IL-21, IL-1β, IL-6 increased in both groups compared to the control group. A high increase in the concentration of cytokines in blood serum in patients is directly related to the activity of the inflammatory process. Compared between groups, the level of IL-21, IL-6 increased significantly in patients with complicated ARDs+. As the clinical course of the disease worsens, the difference between these indicators increases. We think that the significant increase in the levels of pro-inflammatory cytokines in the examined patients can be considered an important factor in the pathogenetic mechanism of the exacerbation of the inflammatory process.

In our previous studies, we noted an increase in the mean IL-21 levels in respiratory diseases [13]. Literary data showing the role of IL-21 in respiratory diseases in children are almost rare. IL-21 is one of the multifunctional cytokines synthesized by T-helpers, follicular T cells including Th17, NK cells (natural killers) [12,14]. It plays an important role in inflammatory responses by participating in the proliferation and differentiation of cells of the immune system, especially T-lymphocytes and their subpopulations that perform various functions, as well as B-lymphocytes. One of the specific functions of IL-21 is increasing the phagocytic and bacteriocytic activity of macrophages, accelerating the synthesis of a number of pro-inflammatory cytokines, as a result of which the functional activity of both cellular and humoral immune factors increases. IL-21 is involved in immune reactions occurring in allergic diseases. Elevation of its level increases the secretion of B-lymphocytes and mast cells, the production of eosinophils [15]. On the other hand, IL-21 induces the differentiation of Th0 cells towards Th2, which increases the production of cytokines (IL-4, IL-5) that play a role in allergic processes. During our study, allergic symptoms were observed in the majority of patients included in group II, and the increase of IL-21 in this group indicates its role in immune reactions occurring in allergic diseases. We observed this again in our research work. However, despite elevated mean serum IL-21 levels, no correlation was noted with clinical parameters such as fever, cough, and malaise. In our view, IL-21 is a component of the antiviral immune response that controls viral replication and viral clearance. Presumably, this is due to the fact that IL-21 plays a certain role in the development of a whole set of clinical symptoms that lead to the aggravation of the disease.

INF-γ is a cytokine with strong immunomodulatory, anti-inflammatory, antiproliferative, antibacterial and antiviral effects [16]. γ-INF, the main mediator of cellular immunity, has an antiviral effect on infected cells, locally activates dendritic cells, macrophages, NK cells, stimulates the differentiation of T-lymphocytes in the direction of Th1, inhibits Th2 cells [17]. Its high level usually indicates an effective immune response. According to Pierce C.A. and co-authors [18], the increase of γ-IFN in children leads to the formation of an early immune response. We think that the increase of γ-INF in group I is due to its properties. However, the concentration of γ-INF in the blood serum of patients in the II group decreased. In our opinion, this is due to the deficiency of cellular immunity during relapsing acute respiratory diseases. It is known that repeated respiratory diseases also lead to a weakening of endogenous γ-INF functional activity in the child's organism. A decrease in γ-IFN leads to a weakening of the immune system, especially cell-type immunity and phagocytic activity of macrophages, an increase in susceptibility to various viral infections [13], and therefore its rise was not expected. γ-IFN can be considered a component of the antiviral immune response that suppresses viral replication and virulence activity, and a clinical and diagnostic criterion of the inflammatory process [19,20].

In our study, the level of IL-1 and IL-6 increased compared to the control group. IL-1, affecting cells of the immune component, T- and B-lymphocytes, macrophages, monocytes, neutrophils, NK-cells, and others, is involved in innate and adaptive immune responses of the organism [21]. IL-1β, IL-6, being endogenous pyrogens, have the properties of a neuroendocrine hormone that affects the centers of the hypothalamus and pituitary gland and causes of fever, loss of appetite, sleep disorders, and weakness.

IL-6 is a pro-inflammatory cytokine with high biological activity and plays an important role in innate and acquired immune responses [22]. The pro-inflammatory cytokine IL-6, which plays a role in the pathogenesis of inflammatory diseases and affects its course, is considered one of the main regulators of

immune response and hemopoiesis. IL-6 increases the expression of adhesion molecules by increasing the permeability of vascular walls, such as IL-1, resulting in the release of small molecule inflammatory mediators such as prostaglandins, biologically active substances are released and cause an increase in the inflammatory process. In allergic diseases, IL-6 is involved in the differentiation and proliferation of effector T lymphocytes, and in the final differentiation of B-lymphocytes in cells that produce immunoglobulins. We think that the increase of IL-6 in group II compared to group I is due to its properties. Our study is consistent with many literature data. Miromanova G.A., Smirnov, I.E. and others showed the increase of IL-1β, IL-6 in patients with ARDs [23,24].

During our study, no increase in IL-18 was observed in patients with acute respiratory disease. It is known that IL-18 is a broad-spectrum glycoprotein that plays a role in the formation of the innate and adaptive immune response [25]. In addition, IL-18 contributes to lower antiviral defense as an immunosuppressive factor that helps shift immune responses from Th1 to Th2 type during inflammation, suggesting that it plays a dual role during inflammation. We think that the relative decrease of the level of IL-18 during our study compared to the control group is due to this characteristic of it.

Conclusion

Thus, according to the results of the study, determination of the level of IL-21, IL-1, IL-6 and γ-NF is important in the pathogenesis of acute respiratory diseases depending on the clinical course. During our research, it became clear that the change in the amount of cytokines responsible for immunity is a sign of cytokine imbalance. According to the above, the study of the level of cytokines, the analysis of the results shows the importance in the diagnosis of respiratory diseases and the development of new effective treatment methods.

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