

VOLUME LXXVI, ISSUE 3, MARCH 2023

ISSN 0043-5147

E-ISSN 2719-342X

# Wiadomości Lekarskie Medical Advances



Official journal of Polish Medical Association has been published since 1928



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Memory of  
dr Władysław  
Biegański

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The journal *Wiadomości Lekarskie* is cofinanced under Contract No.RCN/SN/0714/2021/1  
by the funds of the Minister of Education and Science



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[www.red-studio.eu](http://www.red-studio.eu)

**Publisher:**

ALUNA Publishing House

ul. Przesmyckiego 29,

05-510 Konstancin – Jeziorna

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## ORIGINAL ARTICLE

# INFLAMMATORY RESPONSE AND METABOLIC ADAPTATION IN CHILDREN WITH ACUTE RESPIRATORY PATHOLOGY

DOI: 10.36740/WLek202303112

Olesya M. Horlenko, Iryna Yu. Pikina, Lyubomyra B. Prylypko, Mariya A. Derbak, Olena V. Debretseni, Kristian O. Debretseni, Ivan I. Myhovych

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## ABSTRACT

**The aim:** To investigate the parameters change of the general immune responds and endocrine metabolism in the children with Acute Respiratory Pathology and their correlational relationship.

**Materials and methods:** The study group included: school-age children (10-14 years old) with a diagnosis of acute respiratory disease (ARI) as a general group of respiratory tract inflammatory diseases, of viral and bacterial origin (n=40), which included local inflammatory lesions of the respiratory tract and presented with acute pharyngitis (60.0%), acute bronchitis (20%), acute tonsillitis (22%) and a control group (n=25), identical in age and sex. The research was conducted at the clinical base of the CNE «UCChH» of the Uzhhorod City Council. General clinical, immunological studies, inflammatory response of the child's body were conducted. Statistical analysis of the results of the examination of patients was carried out using the Statistics for Windows v.10.0 computer program (StatSoft Inc, USA). The evaluation of the obtained results was carried out using parametric and non-parametric methods

**Results:** The inflammatory response parameters of the child's organism present indicative increases in the levels of cytokines with a significant predominance in comparison with the data of the children control group: the level of IL-1 increased in 2 times, IL-4 – in 10 times, IL-6 – in 1.5 times,  $\gamma$ -IFN – in 3 times, TNF- $\alpha$  – in 25 times, Neopterin – in 9 times. The data of the general immune response indicate a 2-times increasing in the level of IgM ( $3.85 \pm 1.89$  g/l,  $p < 0.01$ ) and IgG level increased in 10 times ( $147, 35 \pm 56.12$  g/l,  $p < 0.01$ ). The, according to the obtained data but, in comparison with the data of the control group. There are significant differences in the levels of Leptin ( $p < 0.01$ ), C-peptide ( $p < 0.01$ ), Thyroid stimulating hormone ( $p < 0.01$ ), Free thyroxine ( $p = 0.002$ ). The Leptin level, which is at the upper limit of the reference, the level of Thyroid stimulating hormone at the lower limit of the reference, and the slight predominance of the C-peptide level are noteworthy. Predominance of reliable correlations of pro-inflammatory cytokines IL 1, 4, 6 of varying degrees ( $r = 0.34-0.45$ ) are observed. Only IgG with Free triiodothyronine ( $r = 0.45, p = 0.004$ ), IgE with Thyroid peroxidase antibody ( $r = -0.45, p = 0.004$ ) were identified as statistically significant correlations with high reliability.

**Conclusions:** The obtained date presents the increasing of the levels Cytocines (IL -1,4,6) in 2-10 times. The IgG level increased in 10 times and IgM – in 2 times. The indicators of endocrine metabolism are within the reference values. Reliable correlations of pro-inflammatory cytokines IL 1, 4, 6 of varying degrees ( $r = 0.34-0.45$ ) are observed. IgG with Free triiodothyronine ( $r = 0.45, p = 0.004$ ) have significant reasonableness.

**KEY WORDS:** respiratory tract, cytokines, immunoglobulins, metabolic adaptation, children

Wiad Lek. 2023;76(3):540-547

## INTRODUCTION

Acute respiratory diseases (ARIs) are the most common pathology in the children's infectious diseases structure and are one of the main reasons for hospitalization [1]. ARI, mainly of the upper respiratory tract, is especially common in preschool children [2]. Morbidity in children is quite difficult to estimate, since acute respiratory syndrome is primarily treated in outpatient settings, and epidemiological data are recorded only in severe cases. Numerous clinically mild or asymptomatic forms of ARI remain unaccounted for [3]. Given that common childhood respiratory viruses and SARS-CoV-2 share similar routes of transmission, the combination of measures taken to combat COVID-19 more than halved the number of ARIs in children during the pandemic [4].

Acute throat infections are the sixth leading cause of primary care physician visits. Viruses cause 85 to 95% of throat infections in adults and children under 5 years of age; about 70% are among children aged 5 to 15 years, and the remaining 30% are caused by bacterial pathogens, mainly group A  $\beta$ -hemolytic streptococcus (GAS). According to epidemiological statistics, the incidence of pharyngitis in children reaches 20–50% [4,5]. In healthy children, acute inflammation of the mucous membrane and lymphoid structures of the oropharynx is usually a self-limiting disease, except for episodes caused by GAS. Due to an insufficiently developed immune system, children primarily suffer from SARS and are prone to the development of complications, including bronchitis, pneumonia, sinusitis, otitis. Each

**Table I.** Inflammatory activity indicators

Parameters	Main group (n = 40) M ± m	Control group (n = 25) M ± m	Statistical significance (p)
IL-1 (0-11, pg/ml)	27,63 ± 11,08	2,08 ± 0,49	< 0,01
IL-2 (0-10, pg/ml)	9,61 ± 6,73	0,41 ± 0,05	< 0,01
IL-4 (< 0,5 ng/ml)	5,95 ± 3,16	0,37 ± 0,14	< 0,01
IL-6 (0-10, pg/ml)	16,51 ± 7,22	3,29 ± 0,66	< 0,01
IL-10 (0-20, pg/ml)	14,88 ± 11,91	2,13 ± 0,31	< 0,01
γ-IFN (< 15, pg/ml)	52,92 ± 74,45	5,65 ± 0,85	< 0,01
TNF-α (< 6, pg/ml)	157,21 ± 21,05	3,43 ± 0,47	< 0,01
Neopterin (< 10 nmol/l)	90,43 ± 54,27	6,34 ± 1,14	< 0,01

**Table II.** Indicators of the general immune response

Parameters	Main group (n = 40) M ± m	Control group (n = 25) M ± m	Statistical significance (p)
Ig M (0,31-1,79, g/l)	3,85 ± 1,89	1,05 ± 0,09	< 0,01
Ig G (6,98-15,49, g/l)	147,35 ± 56,12	10,39 ± 0,79	< 0,01
Ig E (до 120 IU/ml)	140,51 ± 64,15	41,71 ± 3,18	< 0,01

year, up to 12 cases of ARI can occur in one child, and the frequency of complications reaches 30% and leads to cases where the use of antibiotics is considered [3,6].

## THE AIM

To investigate the parameters change of the general immune responds and endocrine metabolism in the children with Acute Respiratory Pathology and their correlational relationship.

## MATERIALS AND METHODS

The study group included: school-age children (10-14 years old) with a diagnosis of acute respiratory disease (ARI) as a general group of respiratory tract inflammatory diseases, of viral and bacterial origin (n=40), which included local inflammatory lesions of the respiratory tract and presented with acute pharyngitis (60.0%), acute bronchitis (20%), acute tonsillitis (22%) and a control group (n=25), identical in age and sex. The research was conducted at the clinical base of the CNE

«UCChH» of the Uzhhorod City Council. General clinical, immunological studies, inflammatory response of the child's body were conducted. Statistical analysis of the results of the examination of patients was carried out using the Statistics for Windows v.10.0 computer program (StatSoft Inc, USA). The evaluation of the obtained results was carried out using parametric and non-parametric methods

## RESULTS

Inflammatory diseases of the respiratory tract are characterized by changes in the cytokine chain of homeostasis. During the development of the pathology, the synergism of the action of cytokines is observed, and the cascading nature of the formation of cytokines is also identified. Newly formed cytokines induce the synthesis of other cytokines, stimulate their synthesis, which supports the amplification of the process and the involvement of producer cells in it [7]. The state of the cytokine profile in our study group are represented in table I.

**Table III.** Parameters of endocrine metabolism

Parameters	Main group (n = 40) M ± m	Control group (n = 25) M ± m	Statistical significance (p)
Ferritin (7-140, ng/ml)	62,67 ± 29,92	71,59 ± 10,19	0,16
Adiponectin (5-37, ug/ml)	29,75 ± 8,36	26,28 ± 5,31	0,07
Leptin (2,05-11,09, ng/ml)	10,47 ± 2,93	7,54 ± 0,43	< 0,01
C-peptide (0,81-3,85, ng/ml)	4,56 ± 1,58	1,28 ± 0,12	< 0,01
Free triiodothyronine (1,2 - 2,8, nmol/l)	1,37 ± 0,56	1,32 ± 0,12	0,71
Free thyroxine (12,5 - 21,0, pmol/l)	15,05 ± 1,97	13,72 ± 0,51	0,002
Thyroid stimulating hormone (0,4 - 4,0, mIU/ml)	0,39 ± 0,07	1,98 ± 0,30	< 0,01
Thyroid peroxidase antibody (< 0,9, IU/ml)	0,67 ± 0,49	0,55 ± 0,02	0,20

**Table IV.** Correlation relationships of inflammatory markers

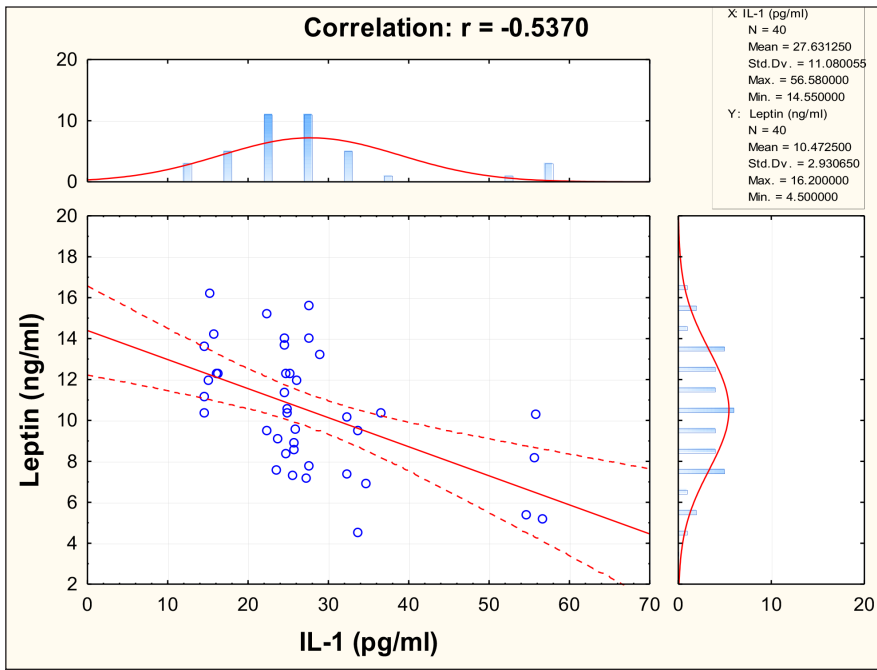
Parameters	Correlation coefficient (r)	Statistical significance (p)
<b>IL-1 npo</b>		
Leptin	-0,54	< 0,01
Thyroid peroxidase antibody	0,35	0,03
<b>IL-4</b>		
γ-IFN	0,34	0,03
IL-10 проти	0,45	0,004
<b>IL-6 npo</b>		
γ-IFN	0,34	0,03
<b>γ-IFN</b>		
IL-4	0,34	0,03
IL-6	0,34	0,03
TNF-α	-0,42	0,007
Leptin	-0,32	0,04

**Table V.** Correlation relationships of general immune responds parameters

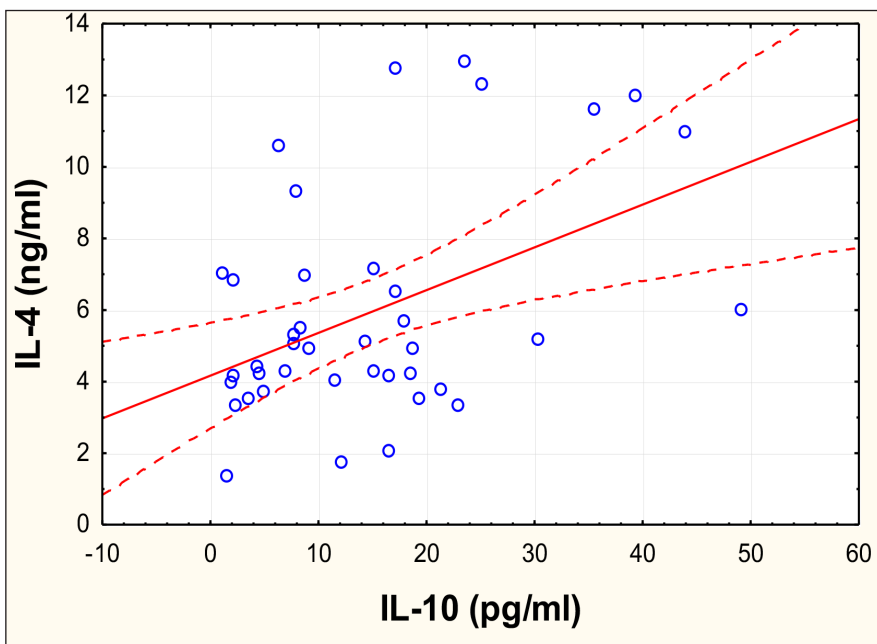
Parameters	Correlation coefficient (r)	Statistical significance (p)
<b>Ig M</b>		
Ferritin	0,33	0,04
Free triiodothyronine	0,33	0,04
<b>Ig G</b>		
Free triiodothyronine	0,45	0,004
<b>Ig E</b>		
Thyroid peroxidase antibody	-0,45	0,004

According to the data in Table I, there are significant increases in the level of the following cytokines with a significant predominance in comparison with the data of the children control group: IL-1 (27,63 ± 11,08 pg/

ml, p < 0,01), IL-4 (5,95 ± 3,16 ng/ml, p < 0,01), IL-6 (16,51 ± 7,22, p < 0,01), γ-IFN (52,92 ± 14,45 pg/ml, p < 0,01), TNF-α (157,21 ± 21,05 pg/ml, p < 0,01), Neopterin (90,43 ± 54,27 nmol/l, p < 0,01). The level of IL-1 increased in



**Fig. 1.** Correlation relationship between the levels of Leptin and IL-1



**Fig. 2.** Correlation relationship between IL-4 and IL-10

2 times, IL-4 – in 10 times, IL-6 – in 1.5 times,  $\gamma$ -IFN – in 3 times, TNF- $\alpha$  – in 25 times, Neopterin – in 9 times. The formation and biological activity of cytokines are interconnected and mutually regulated in response to a irritant. They form the so-called «cytokine cascade», which corresponds to the inflammatory response of the child’s organism and, as a result, the clinical presentation is formed. Regulators of natural resistance – interferons, intelekins 1, 6 and 12, TNF- $\alpha$ , chemokines (IL 8, MCP-1, RANTES, etc.) are the main activators and regulators of nonspecific reactions of the organism to protect it from colonization by carriers of foreign genetic information [8].

The parameters of the general immune response indicators are represented in table II.

As we can see in table II, there is a 2-times increasing in the level of IgM ( $3.85 \pm 1.89$  g/l,  $p < 0.01$ ), which is natural for the growth of their production after the pathogen enters the body. The bactericidal activity of human blood serum largely depends on the level of IgM content. The next, higher stage of humoral immunological reactivity is the IgG molecules formation. Their level is increased in 10 times ( $147, 35 \pm 56.12$  g/l,  $p < 0.01$ ), according to our data. The IgG affinity increases thousands and tens of thousands of times. The presence of immune memory in relation to antibodies of this class

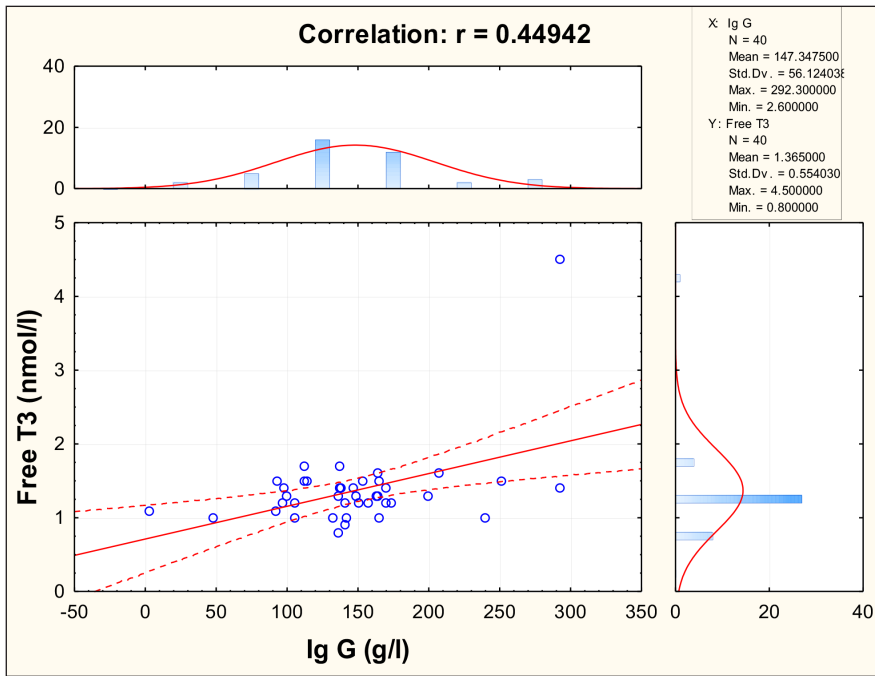


Fig. 3. Correlation relationship between Free T3 and Ig G

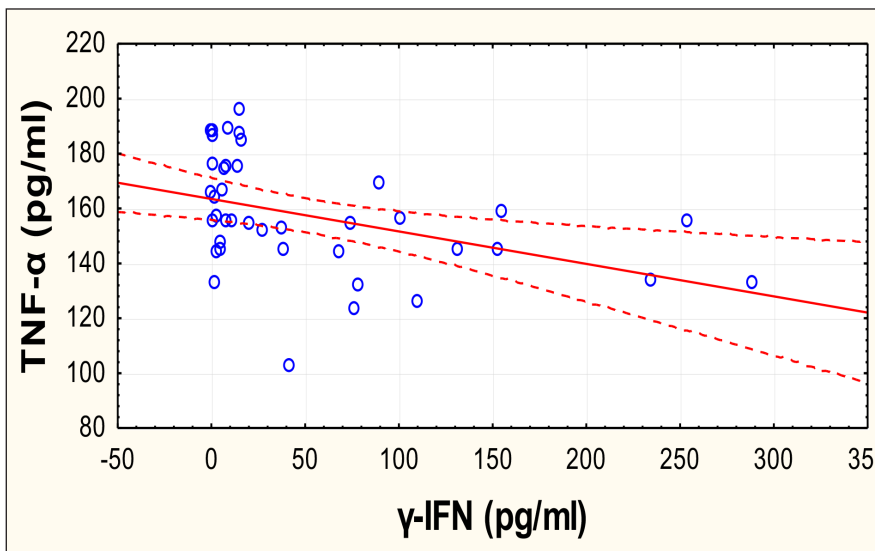


Fig. 4. Correlation relationship between TNF-α and γ-IFN

enables the body to dramatically increase its production, if necessary. The synthesis of IgM is switched to IgG in the process of the immune response. Switching from IgM to IgG is also necessary to regulate the level of production of specific antibodies. Since IgM, unlike IgG, does not have an inhibitory effect on the synthesis of class M immunoglobulins [8]. The level of IgE is slightly higher than the reference values, but it is 3.5 times higher than the level of children in the control group ( $140.51 \pm 64.15$  IU/ml vs.  $41.71 \pm 3.18$  IU/ml,  $p < 0.01$ ). It is believed that the main role of IgE is the protection of mucous membranes due to the induction of a local inflammatory reaction, according to the literature. This causes an inflammatory reaction.

The obtained results of Parameters of endocrine metabolism are given in table III.

According to the obtained data, the parameters of endocrine metabolism are within the reference values, but, in comparison with the control group data, there are significant differences in the levels of Leptin ( $p < 0.01$ ), C-peptide ( $p < 0.01$ ), Thyroid stimulating hormone ( $p < 0.01$ ), Free thyroxine ( $p = 0.002$ ). The Leptin level, which is at the upper limit of the reference, the level of Thyroid stimulating hormone at the lower limit of the reference, and the slight predominance of the C-peptide level are noteworthy.

Adiponectin and Leptin are the main adipokines secreted by adipose tissue. Their role has been established not only in obesity, but also in the production of inflammatory cytokines [10], which identified by our study. The C-peptide level increasing is also presented in the the articles of the researchers. C-peptide, originally

thought to be inert, can modulate the inflammatory response in conditions of endotoxemia and ischemia reperfusion. However, the spectrum of its biological action is unclear. Scientists suggest that exogenous administration of C-peptide can modulate pro- and anti-inflammatory signaling pathways and thus reduce lung inflammation [11].

The obtained results of correlation analysis are given in table IV.

There is a predominance of correlations of pro-inflammatory cytokines II (1,4,6) of varying degrees ( $r=0.34-0.45$ ), according to the data in table IV. Also, the cascading of induction of cytokine synthesis by producer cells is clearly expressed. Consideration of correlations is no less important parameters of the general immune response (table V).

Only IgG with Free triiodothyronine ( $r=0.45, p=0.004$ ), IgE with Thyroid peroxidase antibody ( $r=-0.45, p=0.004$ ) were identified with high reliability as statistically significant correlations. We proceed to the consideration of correlograms. The correlation relationship between the levels of Leptin and IL-1 is presented in the correlogram (Fig. 1).

IL-1 is one of the main mediators of the non-specific protective factors activation, especially during inflammation. IL-1 activates the endothelium of vessels, which helps to increase the ability of endothelial cells to bind of blood leukocytes and thereby promote their migration to the center of inflammation, increases the neutrophils mobility, the phagocytes and NK activity, the generation of bactericidal substances, activates a number of cells in the area of inflammation, which leads to increased production of many cytokines, prostaglandins, collagen, fibronectin. It induces the formation of some proteins of acute inflammation – C-reactive, mannose-binding, etc. IL-1 plays an important role in the implementation of intersystem interaction, especially with the neuro-endocrine system [8] The biological effect of Leptin is to directly or indirectly affect hematopoiesis, immunity. It is a proven fact that leptin level increasing stimulates the production of somatotropic and sex hormones, as well as thyroid hormones. Glucocorticoids, Insulin, Estrogens, Tumor Necrosis factor  $\alpha$ , Interleukin-1 to stimulate the synthesis and secretion of Leptin by adipocytes [12]. That is, by our study, a negative reliable correlation can be traced, which corresponds to the scientific studies of many scientists, and signified about metabolic adaptation disorder in children with acute respiratory pathology.

The correlogram of the interleukins between IL-4 and IL-10 are given in Fig. 2. IL-4 has anti-inflammatory activity, which is due to its ability to suppress the secretion of pro-inflammatory cytokines by macrophages – IL-1, IL-6,

TNF. Its presence stimulates the activity of macrophages and monocytes. IL 4 is involved in the formation of the focus of inflammation. Interleukin 10 (IL-10) has been known since 1989, it was called «the factor that inhibits the synthesis of cytokines». The positive correlation of the data in our study indicates the synergism of the action of interleukins 4,10. The following correlogram is informative for consideration too, which presents the relationship between free T3 and IgG (Fig. 3).

In the development of a pathological condition, in particular, acute respiratory pathology, both the immune and thyroid systems are involved. There is evidence of the involvement of cells of the immune system in the regulation of the activity of the thyroid gland [13]. Our data show about the reliable positive relationships of these links of homeostasis. Presentation of the correlogram of the relationship between  $\gamma$ -IFN and TNF- $\alpha$  are illustrated in Fig. 4.

TNF- $\alpha$  appears in blood serum during infectious diseases, cancer and some non-infectious pathologies,. The spectrum of biological action of TNF is very wide. The main ones are the lysis of tumor, transformed and virus-infected cells and the regulation of many organism functions. It was shown that the activity of macrophages is closely related to the presence of TNF- $\alpha$  in the cell membrane, the amount of which increases sharply after IFN treatment.  $\gamma$ -IFN has antiviral activity – it inhibits the reproduction of some viruses. This action may be due to the induction of  $\gamma$ -IFN. In many cases, the action of tumor necrosis factor is more pronounced when interacting with  $\gamma$ -IFN and IL-1 [8,9]. The obtained data of our study are coherent with the available scientific developments and trends and are confirmed by the negative correlation data: TNF- $\alpha$  and  $\gamma$ -IFN  $r=-0.42, P=0.007$ .

## DISCUSSION

Acute respiratory infections are the cause of high morbidity in children. Innate and adaptive immune responses to microorganisms are critical for maintaining a healthy respiratory system and preventing respiratory disease. High morbidity and mortality are the result of inadequate, incorrect or excessive immunity. The formation and biological activity of cytokines indicate interconnected and mutually regulated actions in response to a irritant. They form the so-called «cytokine cascade», which corresponds to the inflammatory response of the child's organism and, as a result, the clinical presentation is formed. Regulators of natural resistance – interferons, inteleukins 1, 6 and 12, TNF- $\alpha$ , chemokines (IL 8, MCP-1, RANTES, etc.) are the main activators and regulators of nonspecific reactions of the body to protect it from colonization by carriers of



foreign genetic information [8]. Indicators of endocrine metabolism also pay attention. Their role has been established not only in obesity, but also in the production of inflammatory cytokines [10], which can be seen in our study. The C-peptide level increasing is also coherent with other scientific researchers. C-peptide, originally thought to be inert, can modulate the inflammatory response in conditions of endotoxemia and ischemia reperfusion. The understanding of pathochemical and pathophysiological changes in acute respiratory diseases is in a constant dynamic process. The obtained data of our research indicate disorders of immunological and metabolic adaptation of the child's organism systems during the infectious process, which require adequate methods of diagnosis, treatment and effective ways of prevention.

## CONCLUSIONS

1. The inflammatory response parameters of the child's organism present indicative increases in the levels of cytokines with a significant predominance in comparison with the data of the children control group: the level of IL-1 increased in 2 times, IL-4 – in 10 times, IL-6 – in 1.5 times,  $\gamma$ -IFN – in 3 times, TNF- $\alpha$  – in 25 times, Neopterin – in 9 times.
2. The data of the general immune response indicate a 2-times increasing in the level of IgM ( $3.85 \pm 1.89$ ,  $p < 0.01$ ), which is natural for the growth of their production after the pathogen enters the body. The IgG affinity increases thousands and tens of thousands of times. The IgG level increased in 10 times ( $147, 35 \pm 56.12$  g/l,  $p < 0.01$ ), according to our data.
3. The indicators of endocrine metabolism are within the reference values, according to the obtained data but, in comparison with the data of the control group. There are significant differences in the levels of Leptin ( $p < 0.01$ ), C-peptide ( $p < 0.01$ ), Thyroid stimulating hormone ( $p < 0.01$ ), Free thyroxine ( $p = 0.002$ ). The Leptin level, which is at the upper limit of the reference, the level of Thyroid stimulating hormone at the lower limit of the reference, and the slight predominance of the C-peptide level are noteworthy.
4. Predominance of reliable correlations of pro-inflammatory cytokines IL 1, 4, 6 of varying degrees ( $r = 0.34-0.45$ ) are observed. The cascading of induction of cytokine synthesis by producer cells is also pronounced. Only IgG with Free triiodothyronine ( $r = 0.45, p = 0.004$ ), IgE with Thyroid peroxidase antibody ( $r = -0.45, p = 0.004$ ) were identified as statistically significant correlations with high reliability.

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**Conflict of interest:**

*The Authors declare no conflict of interest*

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**Received:** 20.08.2022**Accepted:** 17.02.2023

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**A** – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

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