Cytokine Status of Children with Chronic Tonsillitis and Adenoiditis Associated with Cytomegalovirus and Epstein Barr Virus.

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Annotation
Chronic tonsillitis is one of the main problems of otolaryngology and pediatrics and accounts for 54% according to some authors [1,2,14,15]. Hypertrophy of the pharyngeal tonsils occurs according to different authors and ranges from 3.5 to 8% at the age of 2-15 years and plays a leading role in the formation of the inflammatory process [4,6,7].An increase in the pharyngeal tonsil leads to difficulty in nasal breathing, hearing loss, snoring, frequent colds, and a decrease in immunity [4,9]. Palchun V.T. et al. [2018] studied and confirmed the features of the functioning of the palatine tonsil in normal and chronic inflammation, for this they used the method of autoradiography, which allows assessing the histoarchitectonics of the pharyngeal tonsil, as well as determining the functional activity of microbes that live in the parenchyma of the tonsils.

Keywords: Chronic tonsillitis, otolaryngology, Cytomegalovirus, onsillopharyngitis, chronic inflammation.

Introduction. .
The pharyngeal tonsil, being part of the lymphoepithelial ring, forms the formation of the body's defense system, the dysfunction of which leads to pathological processes for other organs, especially for the cardiovascular system, joints, and the homeostasis system. [1,5,8,12,13,16].
The mechanisms of causal factors, the pathogenesis of HT and its complications are multifaceted, and therefore research on this problem is being intensively carried out around the world. The main cause of chronic inflammation in the pharyngeal tonsil is viruses and bacteria. [16]
Cytomegalovirus (CMV) is an extremely common virus that affects people of all ages and forms a lifelong persistence in the body of an infected person. It is believed that in most cases persistence begins in the early years of life and proceeds latently, without a pronounced pathological effect on the health of the infected person. On the other hand, it has been proven that the persistence of the virus can be accompanied by chronic inflammation, form a variety of numerous immune dysfunctions and determine the development of secondary immune, autoimmune and degenerative disorders. Various kinds of immunocompromising can lead to relapses of virus reproduction and diverse clinical manifestations affecting any organs and systems at any age.
Cytokines are regulatory proteins produced by nucleated cells. Cytokines regulate a complex of pathophysiological changes when pathogens enter the body. Currently, about 2000 individual polypeptide substances belong to cytokines. Cytokines regulate the body's defense responses, both locally after contact with a pathogen, and so-called receptors, which are called pattern recognition.

The receptors are located in the cells of the innate immune system. Pro-inflammatory cytokines are always produced in the focus of inflammation, followed by their effect on almost all cells that are involved in the development of inflammation. In the process of a specific immune response, macrophages produce a number of cytokines: IL -2, IL -4, IL -6, IL -10, TNF -β.

A special property of CMVI is the ability to cause depression in almost all parts of the immune system, to sharply inhibit the production of interferons (IFN), primarily IFN-α. The introduction of CMV leads to immune restructuring in the form of a decrease in the response of lymphocytes to viruses due to the inhibition of antigen expression by macrophages, suppression of the proliferative activity of lymphocytes (which correlates with the severity of the disease), inhibition of phagocytic activity and the completion of phagocytosis [7].

With Epstein-Barr acute tonsillopharyngitis, as with tonsillopharyngitis of another etiology, there is an acute onset, febrile fever, and a pronounced intoxication syndrome. Distinctive features are the presence of difficulty in nasal breathing without discharge from the nasal passages due to swelling of the lymphoid tissue, an increase in all groups of cervical lymph nodes, superficial fibrin plaque on the tonsils, hepatosplenomegaly (which develops gradually and may not be detected on the first day of the disease). In a laboratory examination, there may be leukocytosis or leukopenia, lymphocytosis, monocytosis are characteristic, however, the presence of atypical mononuclear cells is diagnosed only in 83% of patients and may also not be detected at the onset of infection.

During the period of active reproduction, the virus produces an IL-10-like protein that suppresses T-cell immunity, the function of cytotoxic lymphocytes, macrophages, and disrupts all stages of the functioning of natural killers (that is, the most important antiviral defense systems). Another viral protein (BI3) can also suppress T-cell immunity and block the activity of killer cells (through downregulation of interleukin-12). Another property of EBV, as well as other herpes viruses, is its high mutability, which allows it to avoid the effects of specific immunoglobulins (which were produced for the virus before its mutation) and cells of the host's immune system for a certain time. Thus, the reproduction of EBV in the human body can be the cause of the aggravation (appearance) of secondary immunodeficiency. [3,17].

Cytokines produced by Th 1 provide the development of cellular defense mechanisms, and Th 2 synthesize immunomediators that activate B-lymphocytes, stimulate their differentiation into plasma cells and the synthesis of antibodies by them. Disruption of the balance between anti-inflammatory and pro-inflammatory immune responses, which is carried out by the interaction of various cytokines, can lead to mucosal damage. [9,18].

Purpose of the study To study the cytokine status of patients with chronic tonsillitis associated with cytomegalovirus infection and Epstein-Barr virus, to assess the effectiveness of conservative treatment.

Materials and research methods. Clinical observation was carried out in 76 patients with chronic tonsillitis (CT) compensated form and 40 patients with chronic adenoiditis aged 4 to 14 years, was carried out inpatient and outpatient on the basis of the multidisciplinary clinic of Samara State Medical University in the department of otorhinolaryngology and the children's department.

In addition to general clinical methods of studying children with chronic tonsillitis and adenoiditis, methods of molecular biological research were used to confirm the presence of CMV in the blood - the detection of DNA and RNA in biological material. The amount of CMV DNA in the whole blood of the examined was determined, the DNA of the human herpes virus type 4 (EBV) was determined in peripheral blood samples by PCR with hybridization-fluorescence detection in the "real time" mode. ELISA diagnostics: cytokine level: IL-1β, IFNy, IL-6, IL-8, IL-10.

Given the presence of CMVI and EBV, along with standard therapy, patients were prescribed Groprinosin as an antiviral therapy. Children were prescribed at a daily dose of 50 mg/kg of body weight for 3–4 doses for 5–7 days, then for children older than 7 years VIFERON® 500,000 IU 1 suppository 2 times a day every 12 hours daily for 5 days. children under 7 years VIFERON® 150,000 IU 1 suppository 2 times a day every 12 hours daily for 5 days, after a 5-day break, the patients were prescribed a second course of groprinosin and Viferon according to the above scheme. The effectiveness of therapy was assessed by the dynamics and rate of regression of

clinical symptoms and laboratory parameters, including the content of cytokines. Given the slight discrepancies in indicators between cytomegalovirus infection and Epstein Bar virus, we analyzed them in a single group.

Results and its discussion. To assess the cytokine profile, we examined the content of cytokines before and after treatment in children with chronic tonsillitis and chronic adenoiditis associated with CMVI and EBV. The results of the examination of the level of cytokines in children with CT associated with CMVI and EBV are presented in Table 4.1.

Table 1.

Levels of cytokines in patients with chronic tonsillitis associated with EBV, CMVI before and after treatment

Studied indicators (reference values in parentheses)	**Groups of sick children**		
	Before treatment pg/ml)	**After treatment** pg/ml	R
IL- 1β (0-11 pg/ml)	2 1 , 91±3.38	6.38±2.94	p<0.05
IL-6 (0-10 pg/ml)	19.43±2.97	7.65±2.39	p<0.05
IL - 8 (0-10 pg/ml)	18.90±3.65	7.02±2.79	p<0.05
IL - 10 (0-31 pg/ml)	16.71±1.64	6.22±0.99	p<0.05
IFN-γ (0-15 pg/ml)	21.53±4.08	10.78±3.40	p<0.05

Note: p-significance of differences before and after treatment

The results of the study of the level of cytokines with chronic tonsillitis associated with CMVI and EBV revealed a significant increase in IL - 1β, IL -6, IL -8, IL -10, IFN - γ before treatment.

As shown in Table 1, before treatment, there was an increase in IL - 1β to 2 1, 91±3.38 pg/ml, compared with the reference values, the significance of the difference was p<0.05.

Our studies also revealed an increase in IL -6 values before treatment of 19.43±2.97 pg/ml almost 2 times, if we take the upper limits of the reference values, the significance of the difference was also p<0.05.

The level of IL -10 was within the reference values before treatment and amounted to 18.90±3.65 pg/ml. There is also an increase in the amount of IL -8 and IFN -γ 18.90±3.65 pg/ml ; 21.53±4.08 pg/ml resp. It should be noted that all indicators were significantly significant.

To evaluate the effectiveness of treatment, we analyzed the levels of cytokines after treatment. After the standard treatment with the inclusion of the drug groprinosin and viferon according to the scheme, the levels of cytokines in children with chronic tonsillitis associated with CMVI and EBV, which are also presented in Table 1.

After treatment, there was a decrease in the level of IL - 1β to 6.38±2.94 pg/ml, compared with the values before treatment, the significance of the difference was p<0.05.

It was also revealed a decrease in IL -6 after treatment of 7.65±2.39 pg/ml almost 2 times, if we take the upper limits of the reference values, the significance of the difference was also p<0.05.

The level of IL -10 was within the reference values after treatment and amounted to 6.22±0.99 pg/ml. There is also a decrease in the amount of IL -8 and IFN -γ 7.02±2.79 pg/ml ; 10.78±3.40pg/ml resp. It should be noted that all indicators were significantly significant.

Based on the results of the study, an increase in the level of cytokines in the blood before treatment was established: the level of IL - 1β, IL -6 by 1.9 times, IL -8 by 1.8 times, IL -10 within the reference values, IFN - γ in 1.5 times. (p<0.05).

Thus, based on the results of the study, a significant decrease and normalization of the blood levels of the above mentioned cytokines in children with chronic tonsillitis associated with CMVI and EBV after treatment was also established.

Analysis of the results of the study of the level of cytokines with chronic adenoiditis associated with CMVI and EBV revealed a significant increase in IL -10, IFN - γ, IL - 1β, IL -6, IL -8, before and after treatment is presented in table 2..

Table 2.

Levels of cytokines in patients with chronic adenoiditis associated with EBV, CMVI before and after treatment

Studied indicators	**Groups of sick children**		
	Before treatment	**After treatment**	**p<0.05**
IL- 1β (0-11 pg/ml)	22, 15±2.38	7.20±1.52	p<0.05
IL-6 (0-10 pg/ml)	19.22±2.41	5.13±2.49	p<0.05
IL-8 (0-10 pg/ml)	20.97±2.63	3.12±1.53	p<0.05
IL-10 (0-31 pg/ml)	17.22±0.94	8.02±3.21	p<0.05
IFN-γ (0-15 pg/ml)	16.23±2.18	10.78±3.40	p<0.05

P-significance of differences before and after treatment.

As shown in Table 2, before treatment, there was an increase in IL - 1β to 22.15 ±2.38 pg/ml, compared with the reference values, the significance of the difference was p<0.05.

An increase in IL -6 before treatment was also revealed , 19.22±2.41 pg/ml, almost 2 times, if we take the upper limits of the reference values, the significance of the difference was also p<0.05.

The level of IL -10 was within the reference values before treatment and amounted to 17.22±0.94 pg/ml. There is also a significant increase in the amount of IL -8 and IFN -γ 20.97±2.63 pg/ml ; 16.23±2.18 pg/ml resp. Thus, based on the results of the study, it was found that in children the level of cytokines increases in the blood before treatment: the levels of IL - 1β, IL -8, IL -10 by 2 times, IFN - γ by 1 times, and the level of IL -10 was within the reference values (p<0.05).

To assess the effectiveness of treatment, we also analyzed the levels of cytokines after treatment in children with chronic adenoiditis associated with CMVI and EBV . After the standard treatment with the inclusion of the drug groprinosin, the levels of cytokines in children in this contingent of children are presented in Table 4.2. After treatment, there was a decrease in the level of IL - 1β to 7.20±1.52 pg/ml, compared with the values before treatment, the significance of the difference was p<0.05.

It was also revealed a decrease and normalization of IL -6 after treatment of 5.13±2.49 pg/ml, the significance of the difference was also p<0.05.

The level of IL -10 was within the reference values after treatment and amounted to 8.02±3.21 pg/ml. There is also a decrease in the number of IL -8 and IFN -γ 3.12±1.53; 10.78±3.40 pg/ml ; resp. It should be noted that all indicators were significantly significant.

When analyzing the ratios of pro-inflammatory and anti-inflammatory cytokines, their significant increase was revealed due to the predominance of the production of pro-inflammatory cytokines over anti-inflammatory ones. The data are presented in table 3.

Table 3

Ratios of cytokine levels in chronic tonsillitis and adenoiditis in children

Studied indicators	**Before treatment**	**After treatment**	R
IL-6/IL-10	19.32/16.96 (1.14)	6.39/7.12 (0.89)	p<0.05
IL-8/IL-10	19.93/16.96 (1.17)	5.07/7.12 (0.71)	p<0.05

P-*significance of differences before and after treatment.*

Conclusions . Thus, based on the results of the study, a significant decrease and normalization of the blood level after treatment compared to the treatment of the studied cytokines in children with chronic adenoiditis and tonsillitis associated with CMVI and EBV was established, which, along with positive clinical dynamics, indicates the effectiveness of the proposed therapy. .

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