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Study of Sytokine Profile in Children with Congenital Heart Defects

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Abstract

Congenital heart defects (CHD) without cyanosis are a group of heart abnormalities that do not cause blood to mix between the systemic and pulmonary circles to such an extent as to cause cyanosis or cyanosis.

The study of the interaction of the immune system with pathological processes has limited application in the context of congenital heart defects, since the main causes of these defects are related to the development of the cardiovascular system during the embryonic period, and not to immune mechanisms.

PURPOSE: To study the concentration of cytokines in children with congenital pallid heart defects

PATIENTS AND METHODS: 28 children diagnosed with white CHD were included. The control group consisted of 28 practically healthy children of similar age. The concentration of interleukins and tumor necrosis factor alpha (IL-6, IL-8, TNF-α) in blood serum was determined by enzyme-linked immunosorbent assay using test systems of Vector-Best JSC (Novosibirsk, Russia).

RESULTS: hypersecretion of IL-6, IL-8, TNF-α in patients with CHD was established. An increase in the content of the studied mediators of the immune response may be a protective response of the body to stress and tissue damage, but prolonged expression can lead to pathological changes and affect the development and progression of CHD.

Keywords: congenital heart defects, children, without cyanosis, cytokines, serum, imbalance.

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CONCLUSION: An increase in the content of the studied mediators of the immune response may be a protective response of the body to stress and tissue damage, however, prolonged expression can lead to pathological changes and affect the development and progression of CHD. Further studies and clinical observations are needed to better understand the role of these mediators in CHD pathology.

ACTUALITY: Cyanosis-free congenital heart defects (CHD) are a group of heart abnormalities that do not result in blood mixing between the systemic and pulmonary circles to such an extent as to cause cyanosis or cyanosis. These defects can take different forms and vary in severity.

The study of the interaction of the immune system with pathological processes has limited application in the context of congenital heart defects, since the main causes of these defects are related to the development of cardiovascular diseases

However, immunological mechanisms may play some role in the formation of congenital heart disease. For example, some studies indicate a possible link between congenital heart disease and immune factors, such as maternal immunological responses to infections during pregnancy or autoimmune processes. However, these associations are still the subject of active research, and the precise mechanism by which immune factors may influence the development of congenital heart disease without cyanosis is not fully understood.

It is known that most diseases are associated with increased levels of proinflammatory cytokines. There is an opinion that the chronic inflammatory process can be maintained due to an imbalance of pro- and anti-inflammatory cytokines. Cytokines are biologically active factors, products of many cells of various tissues and organs; they are produced by cells during their life in response to external influences [24].

The main cells that synthesize and secrete immunoregulatory cytokines in the body are T-helper lymphocytes (Th), which differ in phenotype and the range of marker cytokines they produce: Th0 (IL-2), Th1 (IL-2, IFN-γ, TNF- α and TNF-β) (cellular immune response) and Th2 (IL-4, IL-5, IL-6, IL-9, IL-13) (humoral immune response) [6].

Since cytokines and their receptors are synthesized in response to stimulation of cells by antigen, the level of activity of the cytokine system as a whole determines the nature of the body’s response to physiological and pathogenic stimuli [21].

According to modern concepts, an imbalance of Th1/Th2 cytokines can be important in the immunopathogenesis of almost all diseases – infectious and non-infectious [20]. Pro-inflammatory cytokines (IL-1, IL-6, IL-12, TNF-alpha, interferons, chemokines, IL-8, etc.) stimulate the inflammatory response and destroy affected cells and viruses. High levels of these cytokines in the

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blood reflect the activity and severity of the inflammatory process. Inflammation plays an important role in cardiovascular disease, and inflammatory markers can predict future cardiovascular events [11].

Today, according to the literature, there is a growing body of evidence indicating that the level of anti-inflammatory cytokines in the blood demonstrates a significant positive relationship with various types of congenital heart disease [14]

PURPOSE: to study the concentration of cytokines in children with congenital heart defects of the pale type.

MATERIAL AND METHODS: The present study included 28 children with an established diagnosis of white type CHD. The control group consisted of 28 practically healthy boys and girls of the same age. The study involved children aged 1 to 12 years.

Immunological studies of the examined women and men were carried out in the immunoregulation laboratory of the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan. The concentration of interleukins and tumor necrosis factor alpha (IL-6, IL-8, TNF-α) in peripheral blood serum was determined by enzyme-linked immunosorbent assay using test systems of VECTOR-BEST JSC (Russia, Novosibirsk).

Quantitative assessment of the results was carried out by constructing a calibration curve that reflects the dependence of optical density on concentration for the standard antigen and allows comparison of the studied samples with it. Statistical processing of the obtained data was carried out using the computer program “Statistica 6.0”.

The data were statistically processed using conventional approaches and the results are presented as sample mean (M) and standard error of the mean (m); median (Me), characterizing the central tendency, and upper and lower quartiles, characterizing the spread of indicator values among 50% of respondents (Q1-Q3), where Q1 is the 25% percentile, Me is the 50% percentile, Q3 is the 75% percentile. The reliability of differences in mean values (P) of the compared indicators was assessed using the Student's t test (t).

RESULTS AND DISCUSSIONS: Proinflammatory mechanisms of HF are mediated by various cytokines, which can cause cardiomyocyte hypertrophy and apoptosis, fibrosis, and ultimately lead to adverse cardiac remodeling. In this connection, according to the task, the first stage of immunological research was to determine the serum content of the spectrum of pro-inflammatory cytokines in a group of children with white-type congenital heart disease. The results obtained are shown in Table 4.1. below.

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Table 4.1. Level of serum pro-inflammatory cytokines in the examined patients sick children with white type congenital heart disease

Index	M±m, Pg/ml	Me [Q1; Q3]	Min, pg/ml	Max, pg/ml
Control group, n=28				
IL-6	6,25±0,43	5,90 [4,12; 8,82]	2,51	9,70
IL-8	12,66±0,60	12,45 [9,70; 15,67]	9,11	19,13
TNF-α	15,17±0,49	15,22 [13,3; 17,28]	10,63	19,74
White type congenital heart disease (without cyanosis),n=28				
IL-6	22,08±1,09***	21,90 [17,3; 25,2]	12,30	33,12
IL-8	46,82±1,86***	47,30 [37,47; 53,72]	29,71	63,52
TNF-α	56,53±2,82***	53,25 [45,87; 66,80]	32,93	86,52

Note: * - significant compared with the data of the control group (* - P<0.05, ** - P<0.01, *** - P<0.001). Me – median, Q1 (percentile) – 25%, Q3 (percentile) – 75%.

Members of the IL-6 family modulate the immune response and inflammatory activity and are subsequently involved in the development of cardiovascular diseases [5,7,9].

Interleukin-6 (IL-6/IL-6) is a pleiotropic proinflammatory cytokine that can be produced by revitalized T cells, B cells, monocytes, and malignant cells. Macrophages, adipocytes, hematopoietic and endothelial cells are also cellular sources of IL-6 [16].

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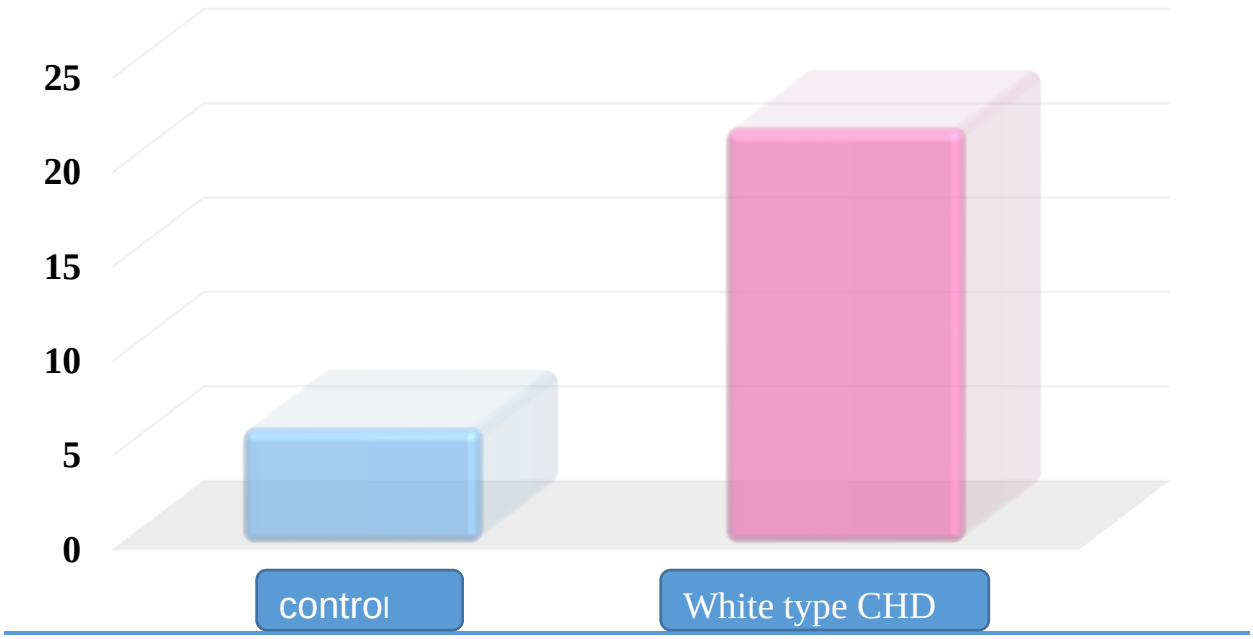


Figure 4.1. IL-6 content in a group of children with white type CHD and control. Note: * - significant compared with the data of the control group (* - P<0.05, ** - P<0.01, * - P<0.001).**

Analysis of the obtained results of IL-6 in the blood serum of examined children with white-type congenital heart disease established statistically significant indicators in comparison with the values of healthy children of the control group. Thus, the serum level of IL-6 expression in the group of children with congenital heart disease without cyanosis was increased by 3.5 times, with an average value of 22.1 ± 1.09 pg/ml, while in children of the control group this value averaged 6.2 ±0.44 pg/ml (P<0.001).

IL-6 is a cytokine that plays an important role in the immune system and inflammatory processes. Elevated levels of IL-6 may be associated with various pathological conditions, including congenital heart defects. The results obtained indicate possible links between IL-6 and congenital heart disease: 1) Congenital heart disease can cause inflammatory reactions in cardiac tissue and blood vessels. IL-6 is an important mediator of inflammation and can be produced by immune cells in response to tissue damage; 2) CHDs can lead to abnormal remodeling of cardiac tissue, including myocardial hypertrophy. IL-6 can stimulate cardiac tissue remodeling processes and participate in the development of hypertrophy; 3) IL-6 also plays an important role in immune regulation and can influence various aspects of the immune response, including immune cell activation and function. Immune dysregulation may be associated with the development of congenital heart disease, and elevated levels of IL-6 may indicate an imbalance in the immune system.

As is known, chemokines are a family of cytokines that cause directed migration of leukocytes along a concentration gradient, which leads to the accumulation of migrating cells in the source of

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chemokine production [19], so the next stage of our research was to study the serum content of IL-8, thereby identifying the role of this mediator of the immune response in congenital heart disease.

IL-8 is a proinflammatory cytokine or chemokine (CXCL8) produced by various cell types, including endothelial cells, peripheral blood monocytes, and vascular smooth muscle cells. IL-8 is encoded by IL8 or CXCL8 [15]. In studies by Kim D.-H.et all (2013) and Takami M. et all (2002), in patients and experimental cell culture models [6,12], they showed that IL-8 is involved in the pathogenesis of cardiovascular diseases, including IHD [12], myocardial infarction (MI) [13], strokes [17] and other diseases. In CVD, IL-8 is involved in all stages of atherosclerosis and the development of coronary artery disease [1,4].

According to the described mechanisms, in normal physiology, macrophages, endothelial cells and epithelial cells produce IL-8 in response to infection or tissue damage, and one of the functions of IL-8 is to induce the chemotaxis of granulocytes, primarily neutrophils, to the affected area [2]. IL-8 signaling in vascular endothelial cells induces cell proliferation, survival and migration [8], which ultimately leads to the formation of new blood vessels [10].

To determine the role and participation of the above chemokine in normal conditions and in various types of congenital heart disease, in our studies we studied serum levels of IL-8, as one of the important mediators of the immune response, which is an activator of the angiogenic response. Comparative results obtained during the study are shown in Table 4.1.

Analysis of the results obtained established a relatively high level of IL-8 in the group of children with white type CHD. Thus, the serum concentration of the studied chemokine in the main group of children was increased by 3.7 times, with an average value of 46.82 ± 1.86 pg/ml, with an individual range from 29.7 to 63.5 pg/ml, whereas in the group In practically healthy children, this indicator was 12.66±0.60 pg/ml ($P<0.001$).

We hypothesize that increased levels of interleukin-8 (IL-8) in congenital heart defects may be explained by several factors: 1) inflammation and immune activation: CHDs cause inflammatory responses in cardiac tissue and blood vessels. IL-8 is a cytokine that plays an important role in the recruitment and activation of inflammatory cells such as neutrophils and macrophages. Elevated levels of IL-8 may reflect activation of the inflammatory process as a result of congenital heart disease; 2) angiogenesis: IL-8 is also involved in the regulation of angiogenesis - the process of formation of new blood vessels. Increased levels of IL-8 may indicate increased activation of angiogenetic mechanisms aimed at compensating for vascular defects; 3) regulation of the immune response: IL-8 can influence the immune response by participating in the regulation of immune cell activity and the production of proinflammatory cytokines. Elevated levels of IL-8 may indicate an imbalance in the immune system, which is likely associated with congenital heart disease without cyanosis.

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One of the key proinflammatory cytokines that has been widely studied as a potential biomarker associated with heart failure is TNFα [3].

Tumor necrosis factor α (TNFα/TNFα) is a member of a family of immunologically significant proteins, a proinflammatory cytokine with a wide spectrum of activity. The main producers of TNFα are monocytes and macrophages. It is also secreted by neutrophils, endothelial and epithelial cells, eosinophils, mast cells, B and T lymphocytes when they are involved in the inflammatory process [23].

TNFα normally plays a fundamental physiological role in immunoregulation, but in some cases it can have a pathological effect, taking part in the development and progression of inflammation, microvascular hypercoagulation, hemodynamic disorders and metabolic exhaustion (cachexia) in various human diseases of both infectious and non-infectious nature [18].

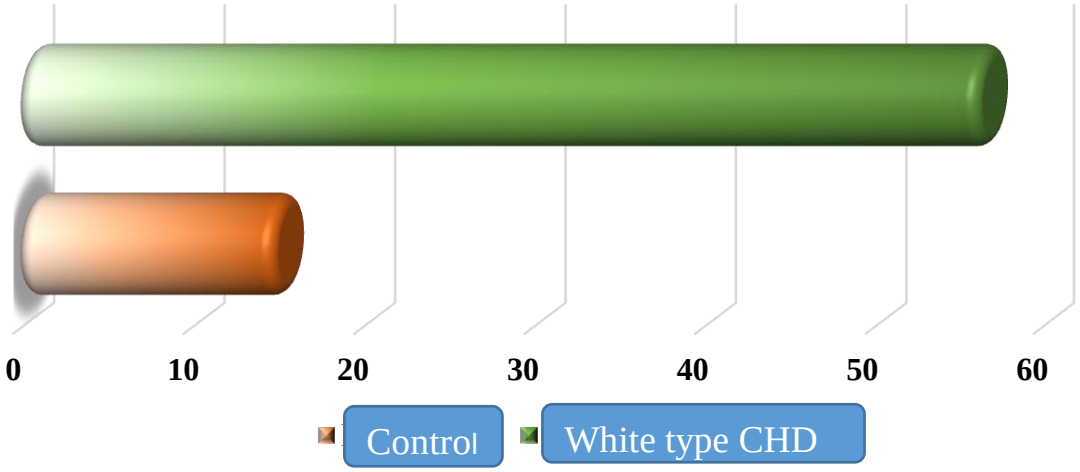


Figure 4.3. TNFα content in examined children with white type CHD and in the control group. Note: * - significant compared with the data of the control group (* - P<0.05, ** - P<0.01, * - P<0.001).**

A comparative assessment of the serum level of TNFα presented in Fig. 4.3. revealed significantly significant results in the group of children with congenital heart disease without cyanosis. Thus, the synthesis of cachexin in the group of sick babies with white-type congenital heart disease increased 3.7 times, and on average amounted to 56.53 ± 2.82 pg/ml, ranging from 32.9 to 86.5 pg/ml, while in the group of healthy babies this indicator was 15.17±0.49 pg/ml (P<0.001) Table 4.1.

An increased serum level of TNFα in the group of examined children with congenital heart disease without cyanosis indicates that cardiac cachexia syndrome has probably developed in children with chronic congestive heart failure or chronic hypoxemia, and may indicate several facts: 1) TNF-α is an important mediator of inflammation and can be produced immune cells in response to tissue damage; 2) TNF-α may be involved in these remodeling processes and contribute to the development

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of fibrosis and hypertrophy. Increased levels of TNF-α may reflect its participation in pathological changes in cardiac tissue in congenital heart defects; 3) TNF-α is one of the key cytokines regulating the immune response, and its increased levels may be associated with this imbalance.

CONCLUSION: Thus, the increase in the levels of the studied pro-inflammatory cytokines in white-type congenital heart disease is the result of a complex relationship between pathological changes in the heart, stressful conditions, activation of the immune system and compensatory mechanisms of the body. Therefore, additional research is required to fully understand the mechanisms of this process and the possibility of using pro-inflammatory cytokines in the diagnosis and treatment of congenital heart disease.

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