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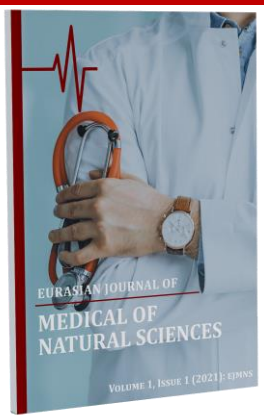

FUNCTIONING OF IMMUNE SYSTEM OF BABIES WITH CONGENITAL HEART DEFECTS

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ABSTRACT
The paper presents the results of a comprehensive immunomorphological study of blood in children with congenital heart defects. The features of the development of an immunodeficiency state depending on the types of defect were revealed.

In recent years, there has been an upward trend in the incidence of cardiovascular disease. For example, studies show an increase in frequency of 2 times in children under 14 years of age, and 2.5 times in adolescents. All this indicates an improvement in the results of diagnosing CVD diseases at this age. However, there is a late diagnosis of CHD, some of which are spontaneously detected only in adolescents. According to literature sources, the frequency of occurrence of the most common nosological forms of congenital heart disease in different age periods is diverse. All this testifies to the low detection rate of CHD in this group of children [1,4].

One of the main cells of adaptive immunity are T-lymphocytes. The population of T-lymphocytes has heterogeneous properties. Most of them are formed in the thymus gland. The thymus gland, as the central organ of immunity, conducts antigen-independent differentiation of *T*-cells [1,8].

Modern literature says that Th_1- and Th_2-helpers perform immunoregulatory processes in the body, and they interact in a harmonious physiological state. Excessive activity caused by any exposure will lead to a serious imbalance of immunity, which has adverse consequences [8,9].

It should be noted that the thymus gland is extremely sensitive to various exogenous and endogenous influences, especially in childhood. The impact of the above factors leads to a violation of the structure of the thymus gland and, as a result, its function, which causes dysfunction of the immune system as a whole [1,5].

Hypoxia leads to various types of morphological and functional disorders of the thymus, which are based on a stress factor. The stress factor can lead to the development of metabolic and structural changes down to the cellular level. In addition, hypoxia is a frequent clinical manifestation of CHD. Most CHD in children in the neonatal period is accompanied by impaired systemic hemodynamics [1,10].

To date, the work of many researchers is aimed at studying various types of immune dysfunction after thymectomy, but, despite all these studies, the state of the thymus, as the central organ of immunity, and providing the body with T-lymphocytes under conditions of dyscirculatory hypoxia, remains an urgent problem today [3,9].

From the 3rd to the 8th week of pregnancy, various teratogenic factors, especially past infectious diseases of the mother, the share of which is 60-70%, can cause the formation of CHD in the fetus. Despite the fact that the possibilities of cardiac surgical care for the population are rapidly growing and developing, they will favorably affect the prognosis of survival, the problems of preventing and combating infectious complications still remain on the agenda of many doctors [6,8,11].

Specialists from various medical and biological areas are interested in studying various pathological conditions of the thymus. The thymus gland is located in the anterior 1/3 of the upper mediastinum directly behind the sternum and, as the main organ of the human immune system, has a lobed structure [1,7,17].

The state of neurohumoral regulation of the body determines the course of CHD. At the same time, in children, both in the preoperative and postoperative periods, the course of CHD is accompanied by dysfunction of the thyroid and thymus, as well as hypofunction of the adrenal glands: secondary hypothyroidism is observed, and transient hypocorticism is characteristic of TGA [2,3,4,12,16].

For complex types of congenital heart disease, with the age of patients, the formation of a vicious circle is characteristic. The presence of heart disease and blood vessels contributes to tissue hypoxia, which, in turn, contributes to frequent acute respiratory infections. Frequent acute respiratory infections lead to a decrease in immunity and the formation of foci of chronic infection, as well as to a delay in physical development. The latter, in turn, are one of the reasons for late surgical correction, resulting in a high risk of postoperative complications, mortality and reduced quality of life [2,3,13,16].

It is known that T-lymphocytes acquire specific functions in the central organ of the immune system, the thymus. The thymus gland, as a central immuno-endocrine gland, performs the control function of T-cell maturation. Stem cells involved in hematopoiesis, in particular, pre-thymocytes, migrate from the bone marrow to the thymus, then the process of differentiation of T-lymphocytes begins. After differentiation, mature T-lymphocytes enter the bloodstream [8,14,15].

Purpose of the study: to study and evaluate the main indicators of cellular immunity in children with congenital heart defects in the dynamics of surgical correction.

Materials and methods: 142 sick children with CHD aged from 1 month to 18 years, hospitalized in the period from 2018-2021 in the Bukhara Regional Children's Multidisciplinary Hospital, to the Department of Pediatric Cardiology were involved in the clinical study. The exclusion criteria for the selection of patients were: endocrine and immunological diseases in parents, congenital heart disease with Down's syndrome. The control group consisted of 30 healthy children (16 boys and 14 girls).

Of the total number of those hospitalized with congenital heart disease, there were more boys - 73 (51.4±0.2%) than girls - 69 (48.6±0.3%). Of these, children with VSD were 45 (31.7%), ASD - 32 (22.5%), TOF - 33 (23.2%) and TGA - 32 (22.5%) children.

To study the state of cellular immunity in patients with CHD who underwent surgical correction followed by thymectomy, an immunological blood test was performed.

Immunological studies were held at the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan (Tashkent).T-lymphocytes were determined by ELISA: young thymocytes ($CD3^+$-, $CD4^+$-, $CD8^+$-)-participating in antigen-independent differentiation of T-cells, natural killers (EK-$CD16^+$), lymphocytes of early ($CD25^+$) and late activation ($CD95^+$).

Results and discussion:

According to the data received characteristic immune imbalance in CHD in children ($p<0.001$) (Table 1.).

The analysis of cellular immunity showed a relative deficiency of lymphocytes in congenital heart disease in children, regardless of the type and type of defect. There is the most profound deficit in the relative number of lymphocytes in blue defects (TOF, TGA), and the absolute number of lymphocytes is somewhat more reduced in white CHD (VSD, ASD).

Analysis of lymphocyte subpopulations also showed a statistically significant deficiency of $CD4^+$-lymphocytes (*T*-helpers) in the blood of patients with TOF and TGA, which is even more aggravated after surgical correction ($P<0.05$). In the control group, the relative number of $CD4^+$-lymphocytes averaged 48.6±1.3%, and absolute 1644±19.0 in 1 μl.

Table 1

Indicators of cellular immunity in congenital heart defects in children, depending on the period of surgical correction, (M ± m)

Blood indicators	Control Group n=30	Type of UPU							
		white				blue			
		VSD		ASD		TOF		TGA	
		Before n=45	After n=30	Before n= 32	After n=22	Before n=33	After n=21	Before n= 32	**After n=21**
Lymphocytes, %	33.4±1.5	31.4±1.6	22.3±1.4	30.2±2.1	23.3±1.8	28.0 ± 1.5	19.0±1.5	27.2± 1.3	**21±0.5**
Lymphocytes, abs.	3150±30.6	2733±eighteen	18780 ±12	2897± 17.0	1988±21.0	2980 ±12.0	2290± 14.0	2900 ±13.0	**21500±12.5**
CD4⁺, %	48.6±1.3	41.3±2.1 *	29.9±1.7*	38.8±2.5*	27.3±1.9*	37.0 ±3.5*	28.0±3.3*	32.0± 5.5*	**26.0± 3.0***
CD4⁺, abs	1644±19.0	1456±12.0*	1112± 6.0*	1387±11.0*	1098±9.0*	1480 ±7.7*	1210± 9.0*	1320 ±13.0 *	**1010 ±7.0***
CD8⁺, %	23.4±1.5	22.4±1.3	18.7±1.5*	19.5±1.0*	11.5±1.8*	29.9 ±2.0*	17.5± 2.0*	28.2± 1.0*	**17.7± 1.8***
CD8⁺, abs	391 ± 11.0	288 ± 11.0*	235± 10.0*	344 ± 14.0*	317± 11.0*	434± 11.0*	224±13.0*	410± 6.0	**224± 7.0***
CD4/CD8	2.1 ± 0.16	1.8± 0.14	1.6± 0.16	2.0±0.16	2.4±0.45	1.2 ± 0.13	1.6± 0.26	1.1 ± 0.2	**1.5± 0.7**

CD16⁺, %	14.0±1.5	29.3±1.1	69.6±1.8	22.5±1.0	33.0±1.1	13.8±1.1	28.5±1.1	28.8±1.7	**37.5±1.0**
CD16⁺, abs	210 ± 9.0	334±7.0	518±6.0	293 ± 7.0	401±11.0	202 ± 11.0	314±7.2	317 ± 7.0	**423±11.0**
Note: * Values are significant in relation to the control group (P<0.05) ** Values are significant in relation to the group before treatment (P<0.01)									

The analysis of parameters of CD4+-lymphocytes in children with congenital heart disease showed their decrease in all groups. At the same time, a deeper deficit of the relative value is noted at TOF -37.0±3.5% and TGA - 32.0±5.5% (P<0.01). The analysis of absolute values made it possible to establish a statistically significant deficit in all studied CHD, regardless of hemodynamic disturbances and the type of congenital malformations. At the same time, the deepest deficiency is observed with TGA - 1320±13.0 in 1 μl (P<0.01).

Analysis of the concentration of CD8⁺-lymphocytes (*T*-suppressors/cytotoxic lymphocytes) showed multidirectional changes depending on the type of congenital heart disease in children. The relative number of CD8⁺ lymphocytes was statistically significantly reduced in ASD-19.5±1.0% and increased with TOF - 29.9±2.0% and TGA- 28.2±1.0% vs control values - 23.4±1.5% (P<0.01). The absolute value of CD8+-lymphocytes showed a decrease in VSD 288±11.0 in 1 μl and ASD 344±14.0 in 11 μl, relative to the control 391±11.0 in 1 μl (P<0.01). And with TOF, a statistically significant increase in the absolute number of CD8⁺-lymphocytes was found to 434±11.0 per 1 μl (P <0.01). At the same time, in patients with TMS, there is a tendency to increase its value to 410 ± 6.0 in 1 μl. This implies that the concentration of CD8⁺-lymphocytes (*T*-suppressors/cytotoxic lymphocytes) depends on the type and type of congenital heart disease in children. With blue CHD, developing hypoxia and hypoxemia is accompanied by a transient increase in the level of CD8⁺-lymphocytes (*T*-suppressors/cytotoxic lymphocytes), which confirms the tension of the immune system.

The immunoregulatory index (IRI) (CD4/CD8), as an indicator of the state of the immune system, shows some of the changes taking place in the body. In studies in children with CHD in the period before surgical correction, IRI was in the range of 1.13-1.98, which corresponds to normal values. At the same time, in our studies, the CD4/CD8 index in the period before surgical correction of the VSD was -1.8±0.14, with ASD 2.0±0.16, TOF-1.2±0.13 and with TGA-1.1±0.2.

And after surgical correction of CHD, IRI was in the range of 1.6-2.4, that is, there was a slight increase in it.

It has been established that IRI in dynamics after surgical correction of VSD decreases to - 1.6±0.16 compared to baseline -1.84±0.14, which is observed as a result of a significant decrease in the relative value of CD4⁺-lymphocytes 29.9±1.7% vs control values - 48.6±1.3% and indicators before surgical correction 41.3±2.1%. This condition is explained by the development of pulmonary hypertension and the stress factor in VSD in the period before surgery, as well as the development of secondary immunodeficiency as a result of thymectomy during sternotomy for access to the heart during surgical correction.

During surgical correction of ASD, an increase in IRI to - 2.4±0.45 was noted, which indicates the likelihood of developing a bacterial and/or viral infection in the postoperative period.

A positive shift of IRI was revealed with blue CHD: with TOF- it rises to 1.6±0.26 and with TGA up to 1.5±0.7, in relation to the initial values before surgical correction, respectively, 1.2 ± 0.13 and 1.1 ± 0.2, which confirms the importance of hypoxemia in the implementation of immunity in CHD.

During the study, it was interesting to study the number of $CD16^+$-lymphocytes, which have the properties of both T-lymphocytes and NK cells. The study of its concentration makes it possible to judge the presence of acute and / or chronic diseases, as well as autoimmune and oncological ones.

In the period before surgical correction, a statistically significant increase in the relative and absolute number of $CD16^+$-lymphocytes was found in VSD-29.3±1.1%, DMPP-22.5±1.0% and TMS-28.8±1.7%, in relation to the indicators of the control group 14.0±1.5%. At the same time, in patients with TF, its concentration is 13.8±1.1% tended to decrease.

After surgical correction of CHD, all patients showed an increase in the level of $CD16^+$-lymphocytes, which indicates the body's response to surgical intervention.

Indicators of cellular immunity, depending on the duration of the course and the type of CHD, illustrate their features. A deficiency of the total pool of lymphocytes was established, regardless of the type and type of CHD. For blue types of CHD (TOF and TGA) are characterized by the most profound deficiency of CD4+-lymphocytes (T-helpers) and an increase in $CD8^+$-lymphocytes (T-suppressors/cytotoxic lymphocytes) ($p < 0.01$). Against the background of increased suppressor activity in TOF and TGA, there is a deficiency of *T*-lymphocytes and *T*-lymphocytes/helpers.

Conclusions: Based on the obtained and presented results of the study, it was found that surgical correction of CHD with partial or complete removal of the thymus contributes to the development of innate and adaptive immunity deficiency. The presence of CHD, especially blue ones, contributes to the development of tissue respiration disorders and the formation of immunological insufficiency, which in turn significantly worsens the condition of patients, reduces the effectiveness of conservative therapy for hemodynamic disorders. In turn, this leads to a delay in the surgical treatment of CHD. Circulatory disorders, hypoxemia in CHD and cardiac surgery followed by thymectomy contribute to the development of immunodeficiency in children.

In this way, all established data proves the need not only for immunocorrection in the postoperative period, but also for improving the methods of surgical correction of CHD.

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