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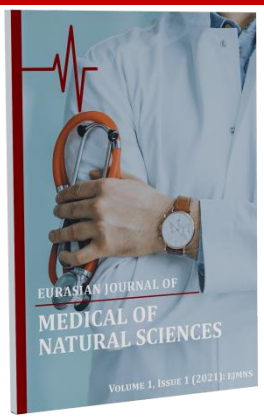

IMPACT OF CONGENITAL HEART DEFECTS ON THE IMMUNE SYSTEM FUNCTION IN INFANTS

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ABSTRACT

The study provides detailed findings from an extensive immunomorphological examination of blood in children with congenital heart defects. It uncovers the distinct patterns of immunodeficiency development that vary based on the specific types of heart defects.

The incidence of cardiovascular disease has been trending rising in recent years. Research indicates that there is a two-fold increase in frequency among children under 14 years old and a 2.5-fold increase in adolescents. All of this suggests that the outcomes of diagnosing CVD illnesses at this age are improving. On the other hand, CHD is sometimes diagnosed too late; in fact, some cases are only identified on their own in teenagers. The literature sources indicate that there is variation in the incidence of occurrence of the most frequent nosological forms of congenital cardiac disease across different age groups. All of these indicates that this child population has a poor detection rate of CHD [1,4].

T-lymphocytes are one of the primary immune system cells. The characteristics of the T-lymphocyte population are diverse. The thymus gland is where most of them are generated. The thymus gland, the immune system's key organ, carries out T-cell differentiation without the need for an antigen [1,8].

According to current research, the body's immunoregulatory functions are carried out by Th1- and Th2-helpers, who collaborate to maintain a balanced physiological state. Any exposure that results in excessive activity will generate a significant immune imbalance, which has negative effects [8,9].

It should be mentioned that, particularly in children, the thymus gland is highly responsive to a variety of exogenous and endogenous factors. The aforementioned conditions have an impact on the thymus gland's structure and function, which compromises the immune system's overall function [1, 5].

Based on a stress factor, hypoxia causes a variety of morphological and functional abnormalities of the thymus. Stress factors have the potential to induce structural and metabolic alterations at the cellular level. Furthermore, a common clinical sign of CHD is hypoxia. Impaired systemic hemodynamics are a common side effect of most CHD in neonates [1,10].

Numerous researchers have worked to date to investigate different forms of immune dysfunction following thymectomy; however, in spite of all of these efforts, the condition of the thymus—the body's primary organ of immunity—and its ability to produce T lymphocytes in the face of dyscirculatory hypoxia continue to be grave issues [3,4].

From the third to the eighth week of pregnancy, a fetus may develop congenital heart disease (CHD) due to a variety of teratogenic causes, the most common of which being the mother's history of infectious infections (60–70%). Despite the fact that the population's access to cardiac surgical care is expanding and increasing quickly and will positively impact survival rates, many physicians continue to prioritize avoiding and treating infectious complications [6,8,11].

Pathologists investigating diverse thymic pathologies come from a variety of medical and biological backgrounds. The thymus gland, the primary organ of the human immune system, is situated in the anterior 1/3 of the upper mediastinum, just behind the sternum [1,7,17].

The body's level of neurohumoral control dictates how CHD develops. Simultaneously, in children, hypofunction of the adrenal glands, thyroid, and thymus is observed during the course of CHD, both in the preoperative and postoperative phases: secondary hypothyroidism is noted, and transient hypocorticism is typical of TGA [2,3,4,12,16].

A vicious cycle often forms in patients with complex forms of congenital cardiac disease as they get older. A common cause of acute respiratory infections is tissue hypoxia, which is exacerbated by blood vessel dysfunction and heart disease. Regular acute respiratory infections cause the body to become less immune, create chronic infection foci, and stunt physical growth. These latter are also among the causes of delayed surgical correction, which raises the possibility of postoperative complications, death, and a decline in life quality [2,3,13,16].

It is well known that T-lymphocytes develop particular roles in the thymus, the immune system's key organ. T-cell maturation is regulated by the thymus gland, a major immuno-endocrine gland. Pre-thymocytes, a subset of stem cells involved in hematopoiesis, go from the bone marrow to the thymus, where they undergo T-lymphocyte development. Mature T-lymphocytes enter the circulation after differentiating [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.).

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)**

Regardless of the kind and severity of the lesion, the examination of cellular immunity revealed a relative lymphocyte shortage in children with congenital heart disease. The absolute number of lymphocytes is slightly lower in white CHD (VSD, ASD), while the most significant reduction in the relative number of lymphocytes is seen in blue defects (TOF, TGA).

A statistically significant deficiency of CD4+-lymphocytes (T-helpers) was also observed in the blood of patients with TOF and TGA, as revealed by analysis of lymphocyte subpopulations. This shortage is made worse following surgical correction (P <0.05). The average relative and absolute numbers of CD4+ cells in 1 μl were 48.6 1.3% and 1644 19.0%, respectively, in the control group.

Children with congenital heart disease had lower CD4+ lymphocyte counts across the board, according to a study of these parameters. Simultaneously, a more profound relative value deficit is observed at TOF -37.0□3.5% and TGA -32.0□5.5% (P<0.01). Regardless of the kind of congenital abnormalities or hemodynamic problems, a statistically significant deficit in all CHD studies was shown through the analysis of absolute values. Simultaneously, TGA shows the greatest insufficiency, measuring 1320 13.0 in 1 μl (P<0.01).

The type of congenital cardiac disease in children was found to influence the multidirectional alterations in the concentration of CD8+-lymphocytes (also known as cytotoxic/T-suppressor lymphocytes). In comparison to control values of 23.4□1.5%, the relative number of CD8+ cells was statistically substantially lower in ASD-19.5□1.0% and higher in TOF-29.9□2.0% and TGA-28.2□1.0% (P<0.01). Compared to the control group, which had a VSD of 291±11.0 in 1 μl and an ASD of 344±14.0 in 11 μl, the absolute value of CD8+ cells decreased (P<0.01). Furthermore, it was discovered that TOF significantly increased the absolute number of CD8+ cells to 434±11.0 per 1 μl (P <0.01). Simultaneously, there is a propensity for its value to rise to 410 ± 6.0 in 1 μl in TMS patients. 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.

A measure of the immune system's health, the immunoregulatory index (IRI) (CD4/CD8) reveals some of the alterations occurring within the body. IRI in children with congenital heart disease during the time before surgical repair was shown to be within the normal range of 1.13-1.98. In addition, prior to surgically correcting the VSD, the CD4/CD8 index in our research was -1.8□0.14, the ASD was 2.0±0.16, the TOF was 1.2±0.13, and the TGA was 1.1±0.2.

Additionally, following CHD surgical repair, IRI increased somewhat, falling between 1.6 and 2.4.

The relative value of CD4+ lymphocytes is found to be significantly lower after surgical correction of VSD, at 29.9□1.7% vs control values of 48.6□1.3%, and indicators prior to surgical correction are found to be 41.3□2.1%. This results in an IRI in dynamics of - 1.6□0.16 compared to baseline -1.84□0.14. The development of pulmonary hypertension and the stress factor associated with VSD prior to surgery, along with the development of secondary immunodeficiency as a result of thymectomy during sternotomy to gain access to the heart during surgical repair, all contribute to the explanation of this illness.

An rise in IRI to - 2.4±0.45 was observed with surgical treatment of ASD, indicating the possibility of bacterial and/or viral infection in the postoperative phase.

When compared to the initial values before to surgical correction, which were 1.2 ± 0.13 and 1.1 ± 0.2, respectively, a positive shift in IRI was observed with blue CHD: with TOF- it

increases to 1.6±0.26 and with TGA up to 1.5□0.7. This indicates the significance of hypoxemia in the immune system's implementation in CHD.

It was fascinating to examine the quantity of CD16+ lymphocytes during the investigation, as these cells possess characteristics of both NK and T cells. It is possible to assess the presence of autoimmune and oncological diseases, as well as acute and/or chronic ones, by studying its concentration.

Before the surgical correction, VSD-29.3□1.1%, DMPP-22.5□1.0%, and TMS-28.8□1.7% had statistically significant increases in the relative and absolute numbers of CD16+ lymphocytes compared to the indicators of the control group, which were 14.0□1.5%. Simultaneously, its concentration is 13.8□1.1% and tends to decline in individuals with TF.

All patients had a rise in CD16+ lymphocytes following surgical repair of their CHD, a sign of the body's reaction to the procedure.

Depending on the type of CHD and how long the course has taken, indicators of cellular immunity show their characteristics. It was shown that there was a deficit in the entire lymphocyte pool, irrespective of the kind of CHD. The most severe lack of CD4+ lymphocytes (T-helpers) and an increase in CD8+ lymphocytes (T-suppressors/cytotoxic lymphocytes) are the characteristics of the blue forms of CHD (TOF and TGA) ($p < 0.01$). T-lymphocytes and T-lymphocytes/helpers are lacking in the context of elevated suppressor activity in TOF and TGA.

Conclusions: The development of innate and adaptive immune deficiencies has been linked to surgical treatment of congenital heart disease (CHD) with partial or total thymus ectomy. This conclusion is supported by the study's collected and presented data. The development of tissue respiration disorders and immunological insufficiency, which in turn greatly deteriorate patients' conditions and lessen the efficacy of conservative therapy for hemodynamic disorders, are both facilitated by the presence of CHD, particularly blue ones. As a result, the surgical treatment of congestive heart failure is delayed. Immunodeficiency in children is a result of heart surgery with thymectomy, hypoxemia in CHD, and circulation problems.

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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