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The Influence of Immunological Factors in the Development of Congenital Heart Defects (Literature Review)

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Abstract: The development of CHD is a complex and multifactorial process that genetic factors can interact with other environmental factors such as environmental, epigenetic and behavioral factors. The review provides an analysis of current ideas about the role of immunogenetic factors in the development of CHD and mechanisms for developing approaches to the prevention and treatment of these heart defects in children.

Keywords: congenital heart defects, immunogenetic factors, children, immune regulation genes.

Congenital heart disease (CHD) includes abnormalities of the structure of the heart that occur before birth. Such defects occur in the fetus when it develops in the womb during pregnancy [20].

Congenital heart defects account for almost a third of all major congenital anomalies. It is assumed that the prevalence of CHD births worldwide and over time will vary; however, there is no complete overview [18,13]

The immune system is a functionally interconnected complex of organs, tissues and cells, regulatory peptides that provide protection from foreign antigens, preserve the genetically determined antigenic constancy of the body, its growth and development.

In cases of failure of local protective reactions, inflammation develops, cytokine synthesis increases, they enter the circulation, and the effect manifests itself at the systemic level. The next stage of inflammation begins – a systemic inflammatory reaction - an acute phase response at the body level. In this case, proinflammatory cytokines have an effect on almost all organs and systems of the body involved in the regulation of homeostasis [19].

According to long-term studies, systemic chronic inflammation and immune activation have been identified as crucial factors in the development and progression of the disease, and they have become promising therapeutic targets in cardiovascular diseases [17,23].However, they are not sufficiently evaluated for the treatment of CHD, although recent studies have described several elevated markers associated with inflammation with a prognostic value in HF [4].

The immune system includes innate and adaptive immune strategies to combat host damage associated with pathogens or tissue damage. Along with the activation of innate and adaptive immunity caused by HF itself, dysfunction or absence of central organs of the immune system can affect adaptive immunity in CHD [2].

Immuno-inflammatory reactions mediated by acute phase proteins and proinflammatory cytokines play an important role in the pathophysiology of central and peripheral manifestations of heart failure, forming the basis of the "cytokine" theory of pathogenesis. Information about the

involvement of inflammatory mediators in the pathogenesis of heart failure complements our understanding of the mechanisms of HF development, opening up new prospects for improving the effectiveness of treatment of decompensated patients [22,24].

Immunological factors play an important role in the development of congenital heart defects. These factors are related to the function and response of the immune system during pregnancy and embryo development. Below are some of the key immunological factors that can influence the development of CHD:

1. Autoimmune reactions: Some CHD may be associated with autoimmune reactions of the maternal body. During pregnancy, the mother's immune system must suppress responses to antigens from the paternal genetic material of the fetus. Violations in this process can lead to the development of autoimmune diseases that can affect the development of the fetal heart.
2. Inflammatory reactions: Inflammation may be associated with the development of CHD. Infections and inflammatory processes in the mother during pregnancy can cause the production of cytokines and other inflammatory mediators, which can affect the development of cardiac structures in the embryo.
3. Maternal antibodies: In some cases, maternal antibodies can cross the placental barrier and affect the developing fetal heart. This can happen if the mother has antibodies to antigens that are present on the fetal heart. This can lead to the development of cardiac abnormalities.
4. Genetic variants: Genetic variants related to the function of the immune system in the mother and fetus can also affect the development of CHD. Mutations in genes that control immune responses can affect the formation and function of cells that are involved in the development of the heart.
5. Maternal immunological tolerance: The histocompatibility complex (HLA) in mother and fetus may affect the development of CHD. Abnormalities in histocompatibility between mother and fetus can affect immune system responses and immune cell function.
6. Epigenetic mechanisms: Epigenetic changes during pregnancy may affect the activation or suppression of certain genes associated with heart development. This may be due to environmental influences, including nutrition and exposure to various risk factors.

All these immunological factors can interact with other genetic and environmental factors, determining the risk of developing CHD in the fetus. Research in this area is continuing to better understand the role of immunological factors in the pathogenesis and prevention of congenital heart defects.

These are, first of all, the first months and years of a child's life, when relative immunodeficiency may be detected [2]. In addition, there are two more critical periods, occurring in the 4th-6th years of life and puberty.

In the neonatal period and in the first months of life, the acquired component is characterized by significant immaturity, which is expressed by a reduced ability to form specific antibodies and a lack of immunological memory. Therefore, protection against infections during this period depends mainly on innate immunity [11].

In newborns, the content of components of the complement system C1, C2, C3, C4 in the blood is about 2 times lower than in adults, the processes of activation of the complement system are weakened, especially along an alternative pathway. All this determines the low opsonic activity of their blood. The production of interleukins and interferons in newborns is also lower than in adults. Phagocytosis in children of this age often turns out to be incomplete, phagocyte migration and chemotaxis are less pronounced, and the production of a factor inhibiting macrophage migration is reduced. In addition, the blast transformation reaction is weak, and the activity of T-cytotoxic lymphocytes and NK cells is low. During the period of life between the 2nd and 6th months, the child's own IgG synthesis is weak. The primary immune response is manifested by

the synthesis of IgM class antibodies. By the end of the first year of life, the IgG content is approximately 50-60%, and IdA is only about 30% of the content of these antibodies, respectively, in adults. Secretory immunoglobulins of class Ig A appear in[12].

Currently, it is recognized that the types of immune response are associated with the predominant participation of T-lymphocyte clones of the first type (Th1) or second type (Th2) helper cells, which differ in the spectra of cytokines produced and the role in stimulating the immune response by cellular or humoral type. There are a number of diseases associated with Th1 and Th2 lymphocytes [15]. The dependence of various forms of cardiovascular diseases on immune factors has been convincingly proved in the publications of domestic and foreign authors. A hypothesis on the role of humoral immunity factors in the development of cardiac arrhythmias and conduction is proposed. An increase in the blood content of immunoglobulins of classes A and G, along with an immunoregulatory imbalance of T and B lymphocytes in patients with cardiac arrhythmia, has been described [15].e

In recent decades, in clinical cardiology, in order to assess the immune characteristics of cardiac activity, particular attention has been paid to the study of subpopulations of CD4, CD8, CD19 lymphocytes, circulating immune complexes (CIC), as well as the state of levels of immunoglobulins M and G and IgG subclasses [12].

In recent years, an idea has been formed about the possible pathogenetic role of immune factors, in particular autoantibodies, to various myocardial structures in the development of cardiac arrhythmias [18]. Autoantibodies are involved in the clearance of the body from the products of natural catabolism and are involved in the regulation of many physiological functions. Hyperproduction of autoantibodies may be a secondary adaptive (sanogenic) reaction of the immune system induced by primary organ damage. No matter how one interprets the role of

Some of the cytokines that have been implicated in the pathogenesis of HF are TNF-α, INF-γ, IL-1β, IL-6, IL-17 and IL-18. These pro-inflammatory cytokines can induce both hypertrophy, fibrosis, and apoptosis of cardiomyocytes and contribute to further inflammation in the myocardium. The role of TNF-α in the pathogenesis of CHF was first recognized in 1990 and aroused interest in investigating the role of inflammation in CHF. TNF-α has been shown to induce dysfunction, hypertrophy and fibrosis of cardiomyocytes, negative inotropic effects, leading to ventricular dilation and further death [4,14].

One of the criteria for the development of pathology of the cardiovascular system in children may be indicators of autoimmune reactions. It is known that with the development of the infectious process in the body, the production of antibodies to heart antigens, etc. is noted. organs, as well as an increase in their titer as the pathological process decompensates [15]. Chronic fetal hypoxia on the background of somatic and infectious pathology in the mother may cause a violation of the immune balance and the appearance of sensitization to tissue proteins [14]. In the presence of cardiac pathology in children (CHD, posthypoxic cardiopathy), elevated levels of antibodies to cardioproteins of various fractions are detected in the blood serum. The presence of elevated levels of antibodies to cardioproteins in healthy children is a risk criterion for their development of cardiopathology [10,15]. British scientists have published a study conducted on large groups of adult patients with Eisenmenger syndrome, in which various pro-inflammatory factors and markers of endothelial dysfunction in the blood were determined. At the same time, the concentration of inflammatory mediators in the blood (interleukin-6, tumor necrosis factor-α) and C-reactive protein in plasma were significantly increased in this syndrome.

In the studies of Kotlukova N.P. (2010), an increase in the expression of interleukin-1 and tumor necrosis factor- α in lymphocytes was found in patients with CHD and left-right shunt. Proinflammatory cytokines are involved in the formation of pulmonary hypertension and heart failure in CHD with left-right shunt in the early stages of the disease (the first year of life), which indicates their importance in the remodeling of the pulmonary vascular bed and myocardium.

Proinflammatory cytokines can have an adverse effect on myocardial function [7]. Consequently, in children with heart diseases, various immunological disorders associated with the activation of Th1 or Th2 clones of T lymphocytes, their imbalance and an increase in proinflammatory cytokines, as well as the production of autoantibodies, changes in the levels of immunoglobulins and their subclasses can be determined. In children with cardiac pathology, along with immunological disorders, it is necessary to take into account the biochemical changes occurring in the body.

A number of studies by foreign authors have established that the relationship between immunology and heart disease lies in the fact that structural CHD is associated with a decrease in the number of immune cells and their maturity. In particular, granulocyte activity against bacterial infections, T- and B-lymphocyte levels, naive T-cell production, and levels of excisional circles of T-cell receptors (TREC)[9], IgA, and IgG are reduced in children with CHD. complement levels and levels, as well as enhancement of the function of suppressor T cells[15,18].

Such an immune profile becomes clinically significant, since children with structural CHD have an increased incidence of contact with common pathogens, such as respiratory syncytial virus (RSV), and an increased risk of developing bronchopneumonia or other infectious complications. In RSV bronchiolitis, the presence of CHD can lead to a decrease in oxygen saturation, an increase in the length of hospital stay, the likelihood of hospitalization in the intensive care unit and up to a 25-fold increase in the risk of mortality. In addition, in premature infants, CHD is associated with an increased risk of sepsis [6], while up to 35% of late-onset neonatal sepsis is detected in children with an open ductus arteriosus (OAP). These children are more likely to develop recurrent sepsis, which requires longer ventilation time and hospital stay[19]. One explanation for immune complications is the altered anatomy of children with CHD, especially changes in the small circle of blood circulation. For example, in children with shunts from left to right, where increased right-sided blood flow can cause pulmonary edema or cyanotic heart disease, RSV may initially be more severe[7]. However, an increase in the severity of respiratory diseases can also be caused by a shift in immune responses. This is observed in children with CHD who develop bronchopneumonia (PD), who then experience an exaggerated increase in both B and T cells in addition to the expected increase in the number of CD3+ and CD8+ cells [17].

As is known, CHD can be a consequence of immune disorders in the mother–embryo system and/or constitutional disorders in regulatory systems, including those associated with Toll-like receptors (TLR), cytokines and their receptors. In the study, Shabaldin A.V. et al. (2022) associations between cytokine and TLR genes with congenital heart defects in children were studied. The examined 188 children had CHD: septal CHD – 98 children, heart valve defects – 17 children, tetrad of Fallot – 15 children, aortic coarctation – 10 children, fetal drains – 32 children, a single ventricle of the heart – 9 children and abnormal pulmonary vein drains – 7 children. It has been established that the determination of congenital heart defects is associated with the genes of immune regulation. In particular, the missen mutation TLR6 rs5743810, which was a predictor of congenital heart valve defects, is of particular importance. The formation of congenital heart valve defects and aortic coarctation is determined by the intergenic interactions of TLR2 rs5743708 with TLR6 rs5743810 and TLR2 rs5743708 with TLR6 rs3775073, respectively. For congenital heart valve defects, such polymorphic gene regions were IL6 rs2069827, IL6R rs2229238 and IL8 rs4073, and for aortic coarctation – IL6R rs2228145, IL8 rs4073. The formation of septal congenital heart defects is associated with the general contribution of polymorphic variants of TLR and cytokine genes to the determination of this pathology[21]. A missense mutation in the TLR4 gene rs4986790 and the TNF mutation rs1799964 have a combined effect on this process, leading to increased synthesis of the TNFa molecule. The contribution of the interaction of TLR genes and cytokines to the formation of CHD is generally insignificant [9].

Thus, it is important to note that the development of CHD is a complex and multifactorial process, and immunological factors can interact with other environmental factors such as environmental, epigenetic and behavioral factors to determine the risk and nature of CHD in a particular child. Research in this area is continuing to better understand the role of immunogenetic factors in the development of CHD and to develop approaches to the prevention and treatment of these heart defects.

LITERATURES:

1. Alekseev L.P., Dedov I.I., Khaitov R.M., etc. The clinical significance of the determination of HLA(DRB1) genotypes associated with predisposition or resistance to type 1 diabetes mellitus in various ethnic groups of Russia. diabetes. – 2007. – vol. 10, No. 2. – pp. 2-5.
2. Age-related features of immunity in children. Lecture for doctors - Moscow: Anita-Press LLC, 2008. -36 p., Prakhov A.V.
3. Degtyareva E.A., Zhdanova O.I., Mukhanov O.A. [et al.] Immune and infectious risk factors of pathological transformation of the "sports heart" in children's and youth sports // Russian Bulletin of perinatology and Pediatrics. - 2010 – No. 3 - pp. 47-51.
4. Diagnosis and treatment of chronic heart failure in children and adolescents. Methodological recommendations of the Association of Pediatric Cardiologists of Russia. - M., 2010. - 80 p.
5. Kiseleva A.N., Zaitseva G.A., Isaeva N.V. and others. Features of polymorphism of genes of the HLA system in disorders of reproduction processes // Vestn. akush.(gin. – 2014. – No. 3. –pp. 16-19.
6. N. P. Shabalov Children's diseases 6th edition, revised and expanded, in two volumes. Volume 2. (Accessed 11/22/2020)
7. Saperova E. V., Vakhlova I. V. Congenital heart defects in children: prevalence, risk factors, mortality.//Issues of modern pediatrics. 2017; 16 (2): 126–133. doi: 10.15690/vsp. v16i2.1713
8. Tsepokina A.V., Shabaldin A.V., Litvinova N.A., Shmulevich S.A. THE ROLE OF POLYMORPHIC VARIANTS OF HLA6DRB1* IN THE DEVELOPMENT OF CONGENITAL HEART DEFECTS // Siberian Medical Journal, 2016, Volume 31, No. 2 - pp. 63-66
9. Shabaldin A.V., Sinitskaya A.V., Shmulevich S.A. THE ROLE OF CYTOKINE GENES AND Toll-LIKE RECEPTORS IN THE PATHOGENESIS OF CONGENITAL HEART DEFECTS // Medical Immunology 2022, vol. 24, No. 3, pp. 605-616
10. Alenezi A M, Albawardi N M, Ali A, et al. The epidemiology of congenital heart diseases in Saudi Arabia: a systematic review. J Pub Health Epidemiol. 2015;7(7):232–240. doi: 10.5897/JPHE2015.0723
11. Asim A, Agarwal S, Panigrahi I. Frequency of congenital heart defects in indian children with down syndrome. Austin J Genet Genomic Res.2016;3(1):1-3
12. Baggen VJM, van den Bosch AE, van Kimmenade RR, et al. Red cell distribution width in adults with congenital heart disease: A worldwide available and low-cost predictor of cardiovascular events. Int J Cardiol. 2018; 260:60–65. doi: 10.1016/J.IJCARD.2018.02.118. [PubMed] [CrossRef] [Google Scholar]
13. Bhardwaj R, Rai SK, Yadav AK, et al. Epidemiology of congenital heart disease in India. Congenit Heart Dis. 2015;10(5):437–446. doi: 10.1111/chd.12220
14. Chiang PJ, Hsu JF, Tsai MH, Lien R, Chiang MC, Huang HR, et al.. The impact of patent ductus arteriosus in neonates with late onset sepsis: a retrospective matched-case control

study. Pediatr Neonatol. (2012) 53:309–14. 10.1016/j.pedneo.2012.07.006 [PubMed] [CrossRef] [Google Scholar]

15. Davey BT, Elder RW, Cloutier MM, Bennett N, Lee JH, Wang Z, et al.. T-cell receptor excision circles in newborns with congenital heart disease. J Pediatr. (2019) 213:96–102.e2. 10.1016/j.jpeds.2019.05.061 [PubMed] [CrossRef] [Google Scholar]
16. Groot HE, Ali LA, Iwan C, Horst V, Schurer RAJ, van der Werf HW, et al.., Plasma interleukin 6 levels are associated with cardiac function after ST-elevation myocardial infarction. Clin Res Cardiol. (2019) 108:612–21. 10.1007/s00392-018-1387-z [PMC free article] [PubMed] [CrossRef] [Google Scholar]
17. Hartman J, Frishman WH. Inflammation Inflammation and atherosclerosis: a review of the role of interleukin-6 in the development of atherosclerosis and the potential for targeted drug therapy. Cardiology Rev. (2014) 22:147–51. 10.1097/CRD.0000000000000021 [PubMed] [CrossRef] [Google Scholar].
18. Huang R, Zhu L, Guo H, Wang L, Zhang J, Li W, et al.. Cellular immunity profile in children with congenital heart disease and bronchopneumonia: evaluation of lymphocyte subsets and regulatory T cells. Cent Eur J Immunol. (2014) 39:488–92. 10.5114/ceji.2014.47734 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
19. Molecular mechanisms of congenital heart disease /H. Jingbin et al. //Cardiovasc. Pathol. – 2009
20. Mozaffarian D, Benjamin EJ, Go AS, et al. heart disease and Stroke Statistics-2016 Update: a report from the American Heart Association. Circulation. 2016;133(4): e38–360. doi: 10.1161/CIR.0000000000000350
21. Opotowsky AR, Valente AM, Alshawabkeh L, et al. Congenital heart disease Prospective cohort study of C-reactive protein as a predictor of clinical events in adults with congenital heart disease : results of the Boston adult congenital heart disease biobank. Eur Heart J. 2018; 39:3253–3261. doi: 10.1093/eurheartj/ehy362. [PMC free article] [PubMed] [CrossRef] [Google Scholar].
22. Outcome of infants with hypoplastic left heart syndrome who undergo atrial septostomy before heart transplantation /M.A. Kuhn, R.L. Larsen, N.F. Mulla et al. //Am. J. Cardiol. – 2000. – V. 85. – P. 124127.
23. Park Myung, H. Pediatric cardiology for practitioners. 4th ed. /H. Park Myung. – USA, 2002. – P. 93109, 165173.
24. Paul W.E. Fundamental Immunology. – New York: Lippincott-Raven, 1999. – P. 121-127.