



## THYMOGENIC IMMUNOCORRECTION OF CHILDREN WITH CONGENITAL HEART DEFECTS

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### Introduction

The prevalence of congenital heart defects CHD at birth was 6.7 per 1,000 live births, with two cases out of five being severe. Immune status indicators were studied in children who were referred to surgical correction of CHD without thymectomy or with thymectomy of varying degrees of completeness. It was found that changes in the normal emigration of T cells from the thymus, in particular under the influence of thymectomy, significantly affect the number of T and B lymphocytes in the blood.

Immunomodulatory therapy in children has some features associated primarily with the greater reactivity of the immune system in comparison with the immune system of adults.

**Keywords:** CHD (Congenital heart defects), immune, thymus, thymectomy, surgical, immune response, T-killers, TNF- $\alpha$ , CD cells, Thymogen, immune correction, ventricular septal defect (VSD)

### Objectives

To evaluate the effectiveness of immune correction with the use of the drug “Thymogen” in children with congenital heart diseases (CHD)

### Characteristics of Patients and Research Methods

Blood immunological parameters were studied in 30 children with ventricular septal defect (VSD) before surgery, 12 children after 1 month of immunotherapy before surgical correction of CHD, 3 months after surgical correction (7 patients), and 6 months after surgical correction of VSD (11 patients).

Recommended to enter Thymogen locally, intranasally (in the nose) once a day for children from 1 to 6 years of age 25 mkg (1 dose in one nasal passage), from 7 to 14 years of age 50 mkg (1 dose in each nasal passage). The course of treatment was 10 days.



## Results and Discussion

For complex therapy with the inclusion of Thymogen there was a significant increase in T-lymphocyte counts in children with BPH 3 and 6 months after surgical correction of CHD on the background of immunotherapy to  $34.2,2 \pm 1.0\%$  and  $37.0,0 \pm 2.4\%$ , respectively, concerning the group before treatment ( $p < 0,05$ ). The relative content of CD4+ lymphocytes tended to significantly normalize after 1 month of immunotherapy before surgery and 3 months after surgery. Application Thymogen therapy contributed to a decrease in the number of CD20+ cells 3 months after surgical correction of VSD. Analysis of the results of studying the concentration of immunoglobulins showed a tendency to increase IgA 1 month after immunotherapy before surgical correction and gradual normalization of the level 3 and 6 months after surgical correction of VSD.

## Conclusion

Thus, enabling Thymogenicity to basic therapy in children with CHD helps restore many of the studied parameters of cellular and humoral immunity. Against the background of regular use Thymogen 3 months after surgical correction of sick children with ventricular septal defect, the suppressed function of neutrophil phagocytes increases, and the level of circulating immune complexes normalizes. [13,14,23]

The prevalence of CHD at birth was 6.7 per 1,000 live births, with two cases out of five being severe [2,22,24]. In recent years, the number of cases of detection of severe lesions has significantly increased. This has increased the burden on resources that are already limited in middle-income countries. Therefore, a strategic and comprehensive program of pediatric and congenital heart disease surgery is needed [4,21,25].

Immune status indicators were studied in children who were shown to undergo surgical correction of CHD without thymectomy or with thymectomy of varying degrees of completeness. It was found that changes in the normal emigration of T cells from the thymus, in particular under the influence of thymectomy, significantly affect the number of T and B lymphocytes in the blood. It can affect the state of immunological functions. At the same time, it is significant that such an effect can be a consequence of not only complete but also partial thymectomy, i.e., the surgical intervention that accompanies operations for CHD in children [1].



The mechanisms that regulate the constancy of the internal environment (homeostasis) are a complex set of neurohumoral processes that allow the body to maintain viability and stability in the environment. At the same time, the stability of the internal environment is closely related to the level of biological protection of the body[3,5,16].

Among the various regulatory structures of the body, the immune system occupies a special place in its complexity and versatility. Most of the effector and auxiliary functions of immune system cells are performed with the participation of special endogenous structures of intra-systemic hormones and mediators[6,7,10].

The results of many years of research show that dipeptides, without having any specific specificity, can restore disorders in the immune system. That is why these drugs were classified as thymomimetics.

Immunomodulatory therapy in children has some features associated primarily with the greater reactivity of the immune system in comparison with the immune system of adults[8,13,14]. This determines the application strategy of Thymogen in the complex treatment of infectious and inflammatory diseases.

Thymogen has a regulating effect on the reactions of cellular and humoral immunity and nonspecific resistance of the body. Stimulates regeneration processes in case of their suppression. Improves the course of cellular metabolism processes. Increases the expression of differentiation receptors on lymphocytes, normalizes the number of T-helper cells, cytotoxic T-lymphocytes, and their ratio in patients with various immunodeficiency conditions. The drug quickly enters the systemic circulation after its intranasal administration. Alpha-glutamyl-tryptophan sodium under the influence of peptidases is broken down into L-glutamic acid and L-tryptophan, which are involved in peptide synthesis in the body[9,26].

## **Objectives**

To evaluate the effectiveness of immune correction with the use of the drug “Thymogen” in children with congenital heart diseases (CHD)

## **Characteristics of Patients and Research Methods**

A clinical and laboratory examination of 30 children with CHD was performed. The control group consisted of 30 healthy children. The exclusion criteria were



immunological and endocrine diseases, congenital heart defects with chromosomal diseases.

To determine the main populations of human lymphocytes, we used monoclonal antibodies of the LT series developed at the Institute of Immunology of the Ministry of Health of the Russian Federation, NPC Sorbent (Moscow) by indirect rosette formation.

The content of immunoglobulins was determined by the Manchini radial immunodiffusion method Manchini using monospecific sera against immunoglobulins G, A and M produced by the Moscow Institute of Microbiology and Epidemiology. N. F. Gamalei.

The phagocytic activity of leukocytes was determined by the Kudryavtseva method. Melamine-formaldehyde latex with a diameter of 1.5 microns (Research Institute of Biological Instrumentation, Moscow) was used in the study.

To determine cytokines, we used test systems developed in GovSRI OCHB (St. Petersburg) and produced by the company "Cytokine". The ELISA kit uses "sandwich" - a variant of solid-phase enzyme-linked immunosorbent assay using horseradish peroxidase as an indicator enzyme.

Statistical processing of the obtained results was carried out by methods of variational statistics using the Statistica for Windows application software package. Digital data was processed on an IBMPC personal computer using Microsoft Excell-97 application program memory. The data were considered reliable if  $t \geq 2$  and  $P < 0.05$ .

Blood immunological parameters were studied in 30 children with ventricular septal defect (VSD) before surgery, 12 children after 1 month of immunotherapy before surgical correction of CHD, 3 months after surgical correction (7 patients), and 6 months after surgical correction of VSD (11 patients).

Recommended to enter Thymogen topically, intranasally (in the nose) once a day for children from 1 to 6 years of age 25 mkg (1 dose in one nasal passage), from 7 to 14 years of age 50 mkg (1 dose in each nasal passage). The course of treatment was 10 days. Repeat course of Thymogen was performed no earlier than in 1 month, only 3 courses.

1st course Thymogen is prescribed for a 10-day cycle before surgery, the 2nd course when the patient goes to the doctor after surgery, the 3rd course 1 month after the 2nd course.

## Results and Discussion

IN 30 pediatric patients with BPH included in complex therapy with Thymogen, along with clinical improvement, revealed pronounced positive changes in the immunological parameters of the blood.

For complex therapy with the inclusion of Thymogen there was a significant increase in T-lymphocyte counts in children with VSD 3 and 6 months after surgical correction of CHD on the background of immunotherapy to  $34.2,2 \pm 1.0\%$  and  $37.0,0 \pm 2.4\%$ , respectively, about the group before treatment ( $p < 0,05$ ).

Table 1. Dynamics of cellular immunity parameters in children with CHD (VSD) under the influence of the drug of Thymogen ( $m \pm m$ )

Indicator	Before immunotherapy n=30	After 1 month of immunotherapy before surgery n=12	3 months after surgery n=7	6 months after surgery surgery n=11
White blood cells, abs.	8700±32,5	8900±30	7880±32,0*	7780±28,0*
Lymphocytes, %	28,2±2,8	32,0,0±1,6	34,2,2±1,0*	37,0,0±2,4*
Lymphocytes, abs.	2232±28	2560±21	2842±18	3360±22*
WithD4+, %	21,3±2,1	32,2±1,1	41,3±1,1	44,7±1,1*
CD4+, abs	1178±11,2	1290±11,2*	1432±10,0	1330±11,0*
CD8+, %	22,3±1,6	21,3±1,1	20,3±of 1.1	to 21.2±1,0
CD8+, abs	378 ± 21,0	368 ± 16,0	372 ± 17,0	366 ± 13,0
CD4/ CD8	0,95±0,8	1,5±0,9	2,0±0,7	2,1±0,7

Note: \* Values are significant for the pre-treatment group ( $p < 0,05$ )

The relative content of CD4+ lymphocytes tended to significantly normalize after 1 month of immunotherapy before surgery and 3 months after surgery to  $32.2 \pm 1.1\%$  and  $41.3 \pm 1.1\%$ , as well as 6 months after surgical correction of CHD to  $44.7 \pm 1.1\%$  compared to the group before treatment ( $p < 0,05$ ). (Figure 1.)

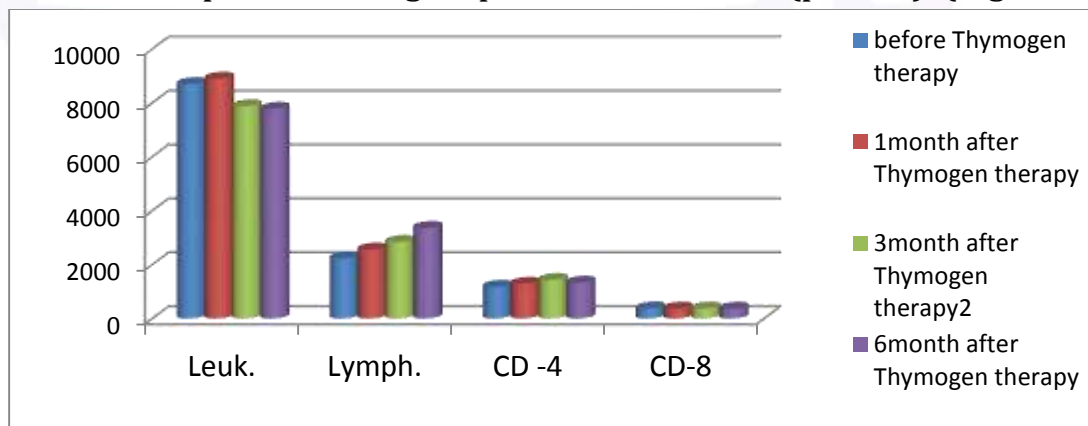


Figure 1. Dynamic results of immunotherapy

In the dynamics of immunotherapy in patients with VSD, some unreliable fluctuations in CD8- lymphocyte/suppressor parameters were observed, with a

gradual normalization of the CD4/CD8 ratio 3 months after surgical treatment. (Table 1)

The number of B-lymphocytes gradually changed in the dynamics of immunotherapy ( $p < 0.05$ ) (Fig.2)

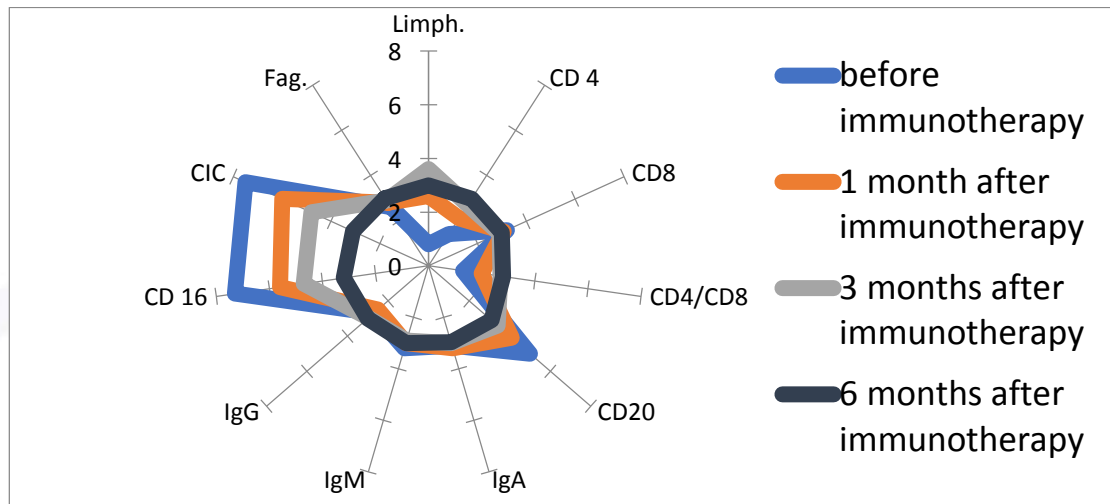


Figure 2. Dynamics of T and B-cell immunity parameters in children with CHD (VSD) after immunotherapy with Thymogen

Application Thymogen therapy contributed to a decrease in the number of CD20+ cells in 3 months after surgical correction of DMC  $-23.4 \pm 1.3\%$ , occupying a significant significance with the group before immunotherapy  $-34.0 \pm 1.8\%$ .

Absolute values of CD20+ cells significantly changed over time, reaching a level of up to  $\pm 504.0-7.0$  in  $1 \mu\text{l}$  of blood 6 months after surgical correction of CHD (VSD) with the group before immunotherapy  $-841 \pm 11.0$  ( $p < 0,05$ ).

The study of the level of immunoglobulins of the main classes showed a positive effect Thymogen after 1 month of immunotherapy before surgical correction of VSD.

Levels M and IgG after complex treatment, they normalized in relation to the concentration of Ig M  $-123 \pm 1.0 \text{ mg}/\%$  compared to  $129 \pm 2.0 \text{ mg} / \%$  before immunotherapy ( $p < 0.01$ ), and in relation to the concentration of IgG  $-1012 \pm 3.5 \text{ mg} / \%$  vs  $1121 \pm 3.9 \text{ mg}\%$ .

Analysis of the results of studying the concentration of IgA showed its tendency to increase 1 month after immunotherapy before surgical correction and gradual normalization of the level 3 and 6 months after surgical correction of VSD,  $130.0 \pm 4.1$  and  $122.0 \pm 3.5 \text{ mg}/\%$ , respectively.

Increased CD16+ cell count in VSD after treatment with inclusion of Timogen has changed significantly. 6 months after surgical treatment, the concentration CD of



CD16<sup>+</sup> cells significantly decreased to the group before immunotherapy to  $12.1 \pm 2.0\%$  vs.  $27.6 \pm 2.1\%$ , and the absolute values decreased to  $192 \pm 7.0$  vs.  $224 \pm 9.0$  in  $1 \mu\text{l}$  of blood (Fig. 2).

Neutrophil phagocytic activity suppressed in children with VSD as a result of treatment Thymogen, increased 3 months after surgical correction and amounted to  $47.0 \pm 1.3\%$  vs.  $41.0 \pm 1.6\%$  before immunotherapy ( $p < 0.05$ ).

As a result of the treatment performed with the inclusion of Thymogen in children with VSD, the level of CIC significantly decreased ( $p < 0.01$ ).

Hence, enabling Thymogen integration into basic therapy in children with CHD helps restore many of the studied parameters of cellular and humoral immunity. As a result of complex therapy, including Thymogen integration into basic therapy in children with CHD after surgery was clinically uneventful. Immune correction performed during preoperative preparation, showed a tendency to normalize the total pool of T-lymphocytes, T-suppressors/cytotoxic lymphocytes, T-helpers/inducers, natural killer cells, and immunoglobulins G, A, and M.

In the postoperative period and 6 months after immune correction CD, the CD4-lymphocyte level increases by 2.0 times, the CD20-lymphocyte concentration decreases by 1.5 times, and the CD16-lymphocyte concentration decreases by 2.2 times. As a result of follow-up in the postoperative period, patients showed a decrease in ARVI episodes, normalization of blood rheology, and stabilization of cardiac hemodynamics, which excludes the long-term use of anticoagulants and diuretics.

## Conclusion

Thus, enabling Thymogen in basic therapy in children with CHD helps restore many of the studied parameters of cellular and humoral immunity. In children with CHD, the total pool of T-lymphocytes, T-suppressors/cytotoxic lymphocytes, T-helpers/inducers, natural killer cells, and G, A, and M immunoglobulins are normalized one month after treatment., A, M. Against the background of regular use Thymogen 3 months after surgical correction of sick children with ventricular septal defect suppressed function of neutrophil phagocytes increases; and the level of circulating immune complexes normalizes.



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