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A Modern View on Clinical and Experimental Studies on the Effect of Thymectomy on the Immune System: A Review

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Abstract The article provides an analysis of the results of studies of domestic and foreign researchers on the study of complete and partial thymectomy on the parameters of the immune system in sick children and laboratory animals, the results of experimental studies on the effect of thymectomy on other organs and systems of the body of experimental animals.

Keywords Thymus, Thymectomy, Immune system, Clinical and experimental studies, Experimental animals

1. Introduction

The thymus is the central organ of the immune system in humans and other mammals. The place of this organ is great in the activity of the immune system and its regulation; proliferation and differentiation of T-lymphocytes, which are one of the main immunocompetent cells, takes place here [3,22,29].

It has been established that in a number of diseases it is necessary to perform thymectomy to save the life of patients [31], there are scientific works of a clinical and experimental nature on the study of the immune system after partial and complete thymectomy in different age categories in patients and laboratory animals [19,24,34]. However, they are rare, they do not cover the entire immune system, the degree and direction of changes in this system, the prediction of quantitative changes in immunocompetent cells in the experiment.

It was found that in the thymus, whose mass reaches 37-40 g by the mature age, maturation and subsequent differentiation of T-lymphocytes and the formation of central tolerance occur [1,15].

Studies have established that the thymus consists of lobes covered with a capsule, consisting of connective tissue. Flat partitions extending from the capsule inside the thymus divide the tissue into lobules 1-2 mm in size, and the lobule itself is a structural unit of the thymus. On the periphery of the lobule is the bulk of the thymus lymphocytes - the cortical zone, towards the center the concentration of lymphocytes is less - the brain zone. Precursor cells that came with the blood flow from the bone marrow are localized on the periphery of the thymus lobule and actively divide, forming many small lymphocytes. As they mature, lymphocytes enter the medulla, from where mature T cells enter small venous vessels and are carried with the bloodstream throughout the body [8,14].

The human thymus is laid at the beginning of the second month of development in embryos from two sources: the ectoderm and endoderm of the ventral walls of the third pharyngeal pockets and slits in the form of two separate rudiments, there are three periods of thymus growth: 1-period - in the middle of the second month, which is associated with ingrowth of blood vessels into the thymus and the colonization of the epithelial anlage of the organ by cells of the lymphoid series, 2-period - at the end of the 3rd month, which is associated with the completion of organogenesis, 3-period - 6-8 months of development, which corresponds to the active growth of the fetus [18,26,29].

The thymus reaches its maximum size by puberty. By this time, its mass reaches an average of 37.5 g, at the age of 16-20 the thymus mass decreases to an average of 25.5 g, and at 21-35 years to 22.3 g, at 50-90 years it decreases to 13 .4 g. The lymphoid tissue of the thymus does not disappear even in old age (75-90 years), remaining in the form of separate islands separated by adipose tissue [13,26].

During early childhood, the thymus consists of lobules of various sizes, separated by layers of connective tissue. There are more macrophages in the medulla. Intralobular septa are clearly expressed, in the thickness of which full-blooded blood vessels lie, Hassall's bodies are noted. In older people, in contrast to the period of early childhood, the epithelial stroma is largely replaced by adipose tissue, and the number of lymphocytes in the thymus decreases. Studies have shown that during this period, the thymus lobules are reduced to narrow strands and bands, the vascular network is represented by large arteries and veins [1,30].

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The lower third of the cervical and upper third of the thoracic regions of the right and left lobes become the largest in terms of their size and intensively developing; the end of the study period becomes closer to the sternum. The authors found that the structural features of the cervical and thoracic parts of the human thymus lobes in the prenatal period of ontogenesis should be taken into account during its screening study [5].

2. Materials and Methods

The highest production of T-lymphocytes persists up to two years of age. During these years, primary contacts with various microorganisms occur and long-lived memory T-cells are formed, which live for more than 20 years and reproduce themselves. In the future, the intake of new antigens becomes more rare, therefore, the maintenance of the whole thymus by the body becomes inappropriate and the thymus undergoes age-related involution at a rate of 3% per year of true thymic tissue. The created pool of mature peripheral T-lymphocytes, subsequently migrating from the thymus to the tissues, includes relatively long-lived cells capable of responding by clonal proliferation to an encounter with an antigen. Therefore, the age-related involution of the thymus does not lead to a noticeable decrease in the activity of the immune system. In addition, the immune system has compensatory capabilities to replace certain functions of T-lymphocytes [22].

Due to the topography of the thymus, in congenital heart defects, thymectomy is performed to improve visualization of the structures of the heart. Removal of the thymus during the neonatal period is critical for the formation of the T-cell link of the immune system in the postnatal period. The immune system is a system of adaptation of the child to various environmental factors. The functioning of the immune system also depends on the quality of organogenesis of these organs [12,32].

High surgical activity leads to an increase in children who underwent thymectomy. The immunosuppressive effect of cardiac surgery is reasonably associated with surgical trauma, general anesthesia, cardiopulmonary bypass, blood loss, the effect of antibiotics, hormones, and non-steroidal anti-inflammatory drugs on the immune system [21]. In this regard, thymectomy can lead to various disorders of the functioning of the immune system.

There are works that describe changes in the immune status in children after thymectomy performed during a cardiac operation. It has been shown that the removal of the thymus in the first three months of a child's life leads to a decrease in the number and activity of T-cells. It has been proven that a decrease in the number of T cells occurs during the first year after thymectomy. At the same time, after thymectomy, an increase in T cell proliferation is recorded, which indicates their activation [24,28,35].

The first fundamental experimental work on the study of the function of the thymus was the experience of the English pathologist Miller (1961) and a group of American researchers (Good, 1962), which showed that thymectomy performed on mice immediately after birth makes them susceptible to infections and causes their premature death. The researchers observed marked lymphopenia in the blood, spleen, and lymph nodes of these mice. These animals could not reject the foreign skin graft, which was a sign of the body's immune response [36].

The results of animal studies leave no doubt that the thymus has a formative influence on the development of the entire lymphoid system. Animals subjected to removal of the thymus in the neonatal period are characterized by signs of Wasting syndrome (wasting syndrome), characterized by growth retardation, dystrophic changes in the skin. In addition, removal of the thymus in newborn rodents impairs the formation of lymphoid tissue [31,32].

Thymectomy, regardless of its completeness, causes a decrease in the content of lymphocytes carrying TREC (T-cell receptor excisions circles). A change in the normal mode of T-cell migration from the thymus during thymectomy affects the number of T-lymphocytes in the peripheral blood, which may be one of the reasons for the greater number of complications in thymectomy children. The TREC level is considered as an indicator of the functional activity of the thymus - to produce T-lymphocytes [37].

Analysis of immunological parameters in sick children from 6 months to 3 years, from 3 to 7 years, from 7 to 12 years and older than 12 years, taking into account the degree of thymectomy, revealed a number of unidirectional changes in general, regardless of age and degree of thymectomy. First of all, it is necessary to note the decrease in the relative content of CD3+-, CD4+-lymphocytes and the absolute number of CD3+-cells in patients. Similarly, there was a decrease in the phagocytic activity of neutrophils in children of older age groups and in the content of IgA in children aged 0 to 3 years. In most children, an increase in the level of circulating immune complexes was observed [15,16,31,32].

Loginova N.P. et al. [16] published the results of studies on the role of risk factors in the formation of congenital heart defects (CHD) in children and their clinical parameters after radical correction of the defect revealed a deviation in the subpopulation composition of T-lymphocytes. The earlier the radical correction of CHD (thymectomy) was carried out at an earlier age, the smaller the subpopulation of T-helpers with the CD4+CD45RA+CD31+ phenotype in the peripheral blood. After thymectomy, first of all, it neutralizes the role of thymic hormonal factors and contributes to the cessation of proliferation and release of T-helpers from the thymus to the periphery.

Comparative analysis included patients who had total or subtotal (less than 90%) thymectomy during surgical treatment of congenital heart disease. The authors noted a decrease in CD3+ lymphocytes [4,7]. The maximum immunological changes in patients operated on for congenital heart disease were noted even after partial thymectomy in the immediate postoperative period. Patients with total thymectomy showed a significant decrease in

CD4+- and CD8+-cells.

The thymus is sensitive to various external and internal influences. Violation of the structure and function under the influence of many stress factors can determine the defective state of the immune system as a whole, which is especially evident in childhood [15].

In the peripheral blood of children with CHD, the level of CD4+ and CD8+ lymphocytes is reduced, the subpopulation composition of T-lymphocytes is changed, and the balance of pro- and anti-inflammatory cytokines changes. Violation of immune processes is manifested by the suppression of all parts of the immune system, which can be not only the cause of infections, but also postoperative complications. It was found that the degree of immunosuppression in the postoperative period is more pronounced in children with CHD causing cyanosis of the mucous membranes and skin (blue type), while in children with CHD that do not cause cyanosis (white type), these changes are less pronounced [16].

Children with congenital heart disease have functional immaturity of the thymus by the time of birth, especially with complex heart defects. This fact is reflected in the proliferation and differentiation of thymocytes both in vivo and in vitro. After undergoing thymectomy for 3 years in this category of children, apoptosis of CD4+-, CD8+-lymphocytes increases, and the phagocytic properties of innate immunity cells also decrease. The obtained results on the assessment of the immune status reflect the insufficient activity of the immune system in children with CHD [28].

N.P. Loginova received attention-grabbing indicators. [15], where she showed that the level of thymulin in the blood of sick children correlated with the degree of complexity of CHD in them.

In addition to clinical and immunological studies on changes in the immune status during thymectomy in children, experimental studies were carried out on laboratory animals (outbred rats and mice, outbred rabbits) with complete and partial thymectomy.

Comparative characteristics of the structural features of the human thymus and white outbred rats in postnatal ontogenesis is of practical interest, since the data can be used to determine operational tactics during surgical interventions on the organs of the upper mediastinum in humans and be taken into account when modeling in experimental studies on white outbred rats. It has been established that the human thymus on the left is displaced somewhat posteriorly, while in rats the thymus lies parallel to the anterior chest wall. In humans, the lower pole of the right lobe of the thymus occupies a more caudal position, while in rats, on the contrary, the left lobe [18,19].

The human thymus consists of 2 lobes, they are tightly adjacent to each other. In the rat, 2 lobes of the thymus are also described (sometimes 1 or 3 lobes), it is stated that the thymus has 3 lobes in 21.8% of newborn white outbred rats, the additional lobe is reported only that it is always left and located caudal to the main lobe [20].

During the first month of postnatal life in the thymus of rats, the process of formation of new lobules slows down. After birth, both in the cortical substance and in the medulla, the number of small lymphocytes increases, while the number of medium lymphocytes and lymphoblasts decreases. The formation of the main structures of the thymus occurs in humans at the 17th week of intrauterine development, and in rats it continues in the postnatal period of ontogenesis [3].

It was established that as a result of experimental cold stress on the 7th, 21st and 30th days, there is a redistribution of the volume and cellular composition, various structural and functional zones, indicating a decrease in the functional activity of the thymus, an increase in the death of lymphocytes by the type of apoptosis, a decrease in mitotic activity and the accumulation of macrophages. in rats. The morphological and functional data of the 14th day of the experiment indicate the development of compensatory and adaptive changes in the thymus of rats to cold exposure, manifested in the form of activation of cell division in the cortex and cortico-medullary zone of this organ [6].

Tolstova E.M., Zaitseva O.V. [26] in their experimental studies proved that in the population of thymectomized experimental mice, immunodeficiency was accompanied by a complete absence of hair growth, a decrease in body weight and length, hypotrophic changes in organs and tissues, and a violation of the structure of the bones of the skeleton. Removal of the thymus in adult mice did not lead to the formation of secondary immunodeficiency, but the population of lymphocytes in the blood decreased.

It has been experimentally proven that 25-30 days after neonatal thymectomy in mice, disturbances in the immune system are detected. The absence of thymus in mutant (nu/nu) mice and rats leads to impaired immuno-neuroendocrine regulation in offspring, manifested in changes in the structure and functions of the hypothalamus, pituitary gland, and peripheral endocrine glands. In the adenohypophysis, the number of basophilic cells decreases, the synthesis of growth hormone, prolactin, gonadotropins and thyroid-stimulating hormone is suppressed. The thyroid gland decreases in size, and the content of thyroid hormones also decreases. The mass of ovaries and testicles decreases, as well as the content of sex hormones, oogenesis and spermatogenesis are suppressed in experimental animals. The mass of the adrenal glands increases and the concentration of corticosteroids increases [9].

Zakharova L.A. [9] proved that the development and manifestation of endocrine imbalance depends on the timing of thymus removal. Thymectomy of male rats performed after birth caused a decrease in the mass of the adrenal glands, while that performed on the 3rd day after birth caused hypertrophy and hyperplasia of the adrenal glands. An increase in the mass of the adrenal glands in males is observed after 1.5 months, and in females after 3 months. after neonatal thymectomy. After 2-3 months. in male rats, the concentration of luteinizing hormone and prolactin decreases, and after 4-5 months. there is testicular atrophy, hypertrophy of β-cells of the pituitary gland, lymphoid infiltration in the pituitary gland, thyroid gland, prostate.

3. Result and Discussion

The results of a morphometric study of the spleen of male rats of reproductive age on days 7, 15, 30, 90, and 180 after removal of the thymus in the experiment indicate that the performed thymectomy causes immunomorphological reorganization in the spleen of animals [11].

Using models of passive and active avoidance and spatial memorization, it was demonstrated that the removal of the thymus in mice and rats reduces the level of their learning and conditioned reflexes. The revealed neuroendocrine changes and memory disorders are associated with disturbances in the interactions of cytokines with macrophages and lymphocytes controlled by the thymus [27].

Novoseletskaya A.V. [17] carried out experimental studies of an immuno-neuroendocrinological nature to study learning and memory disorders in thymectomy animals. It has been proven that this is associated with changes in the level of monoamines in the brain of rats. As a result, it can be expected that overcoming these learning and memory impairments in thymectomy animals can be based on the restoration of these neurochemical parameters. Demas G.E., Carlton E.D. came to the same conclusions. in their studies [33].

Other researchers [25] found that the conditions of thymectomy in the experiment were accompanied by a slowdown in the processes of both appositional and longitudinal growth of the lower jaw. This was manifested in the lagging of osteometric parameters from those of falsely thymectomy animals, and the severity of deviations depended on the age of the experimental animals. In thymectomized rats of immature age, a significant slowdown in the growth rate of overall dimensions and bone structures of the lower jaw is determined, which is determined from the 30th day of the experiment. These results obtained by the authors can be explained by the involution of the thymus, in addition, by the fact that under conditions of thymectomy, the aging processes of the body are also accelerated.

It was revealed that the signs of age-related involution of the thymus are a decrease in its relative mass, linear dimensions of the thymus, and a change in the histological structure. Typical age-related changes in the histology of the thymus are: changes in the size and shape of the lobules, a decrease in the cortical-cerebral index, an increase in the number of thymic bodies with a change in their morphology, an increase in the thickness of the capsule and septa, and septal lipomotosis [10,23,37].

Rats of the reproductive period and the period of senile changes are characterized by a combination of age-related and accidental involution of the organ, which is manifested by significant delymphatization of the morphofunctional zones of the thymic parenchyma [2].

Akhmedov A.T. [31,32] proved that thymectomy in the experiment led to an imbalance in changes in the immunological predictors of the rabbit organism, which led to an unfavorable prognosis of the outcome of the operation in the experiment. He was the first to develop a method for autoimplantation of the thymus in an experiment on rabbits and proved its clinical and immunological efficacy. It was found that during the first 9 weeks after autoimplantation of the thymus, there was a significant recovery in the content of CD3+-, CD4+- and CD8+ lymphocytes.

Thus, the analysis of the literature of domestic and foreign researchers on modern clinical and experimental studies on the effect of thymectomy on the parameters of the immune system showed that many studies are isolated, there is no comprehensive view of this problem, with the solution of immuno-microbiological problems. In this regard, the continuation of clinical and experimental studies on this topic are relevant and justified.

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