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Features of Thymus Gland Structure in Children Immune System Dependence on Thymus

Korjavov Sherali Oblakulovich, Kuvandikov Golib Berdirasulovich, Kiyamov Bakhtiyor Ergashevoich
Samarkan State Medical University, Samarkand, Uzbekistan

Abstract: A huge mystery of the biology of medicine (primarily immunology) and in particular pediatrics is the thymus gland (thymus). This is despite the fact that he paid the closest attention of researchers for 4 or more centuries. Only in the 20th century did the attitude of scientists to the organ as a generator and regulator of immune responses, a participant in the production of many populations of immunocompetent cells, and so on, be determined. Thymus and is currently seen as a derivative of the immune system and, to a greater extent, as its central organ. Infectious diseases, systemic autoimmune diseases, oncology, the problem of tissue incompatibility determine the life expectancy of a person and therefore the scientific interest in the topic of studying the functions of the immune system and its central organ-thymus gland is clear. The difficulty of studying lies in the huge number of integral connections of the thymus gland with other components of the immune system, neuroendocrine, hematopoietic and connective tissue, organs (and cells) providing barrier function, etc. To isolate functions directly concerning the thymus from this continuum is a high-tech task of extreme complexity. The interest of pediatricians in this area of knowledge is associated with a certain understanding of human ontogenesis from birth to old age, where the thymus plays a major role in the antenatal and early postnatal period. The task of this review, if possible, to isolate and focus on some, in our opinion, "white spots" of an ambiguous assessment of the functions attributed to the thymus gland, its structures and cellular pulp.

Keywords: thymus; children; involution of the thymus gland; thymus morphology.

Relevance. From the perspective of the modern overview, the thymus is the central organ of the immune system, which mainly determines cellular and humoral immunity. Thymic factors are involved in the differentiation of thymocytes, which in turn provide antiviral, antifungal, antitumor, antitransplant, antituberculosis and other types of immunity. The powerful cooperation of thymocytes through intermediary T cells with B lymphocytes also provides adequate humoral (through antibodies) immunity. The entire huge population of lymphocytes is inserted and interacts (through receptors, cytokines) with the histocompatibility and microbiome system, with phagocytic mononuclear and complement systems, with cellular formations of barrier organs (skin, mucous membranes, etc.), endocrine and nervous systems, ultimately forming an organically functioning powerful continuum that provides control over the persistence of the internal environment and which is commonly called the body's immune system. Failure or breakdown of one of the main links of immunity (including the thymus) should affect the functioning of the entire continuum (to a greater or lesser extent) and this, first of all, should be manifested by weak anti-infectious protection (including against opportunistic infections), the risk of systemic, oncological diseases, tuberculosis, etc. In addition to the fact

that the thymus is an organ of the immune system, it is the iron of internal secretion, and during intrauterine development it finds itself in reciprocal relationships with the processes of formation of the hypothalamus, endocrine and lymphoid organs, and subsequently, throughout life, through the interaction of the thymic-lymphatic, hematopoietic and neuroendocrine systems, the microbiome is involved in maintaining homeostasis (adaptation) of the organism [1]. Despite the fact that the term "thymus" has been known since the time of ancient medicine (Claudius Galen quite often mentioned it in his works, linking it to the emergence of a number of diseases), and the history of a relatively intensive study of the organ is about 400 years old, the thymus gland (VV) to date remains a "gland - a mystery," the structural and functional features of which at different age periods have not yet been studied [1]

The literature available for study describes several variants of the origin of the name of the organ. The anatomical shape of the thymus in the form of a fork gave it the name "thymus gland." Another equally common name for the gland - the thymus - is also related to its shape and comes from the word "thyme" - a leaf of thyme that it apparently resembled to ancient anatomists. It is possible that the name of the organ is also associated with the Greek word "thymos" - soul [1, 2]. It should be noted that in foreign literature the name "thymus" has become more widespread; both names of the organ are allowed by domestic scientists. One of the main immunological functions of the thymus was discovered in 1961, when immunologist Jacques F.A.P. Miller showed that a thymectomy performed on mice immediately after birth made them highly susceptible to infections and caused their premature death. He also observed marked lymphopenia in the blood, spleen and lymph nodes of these mice. These animals also could not reject a foreign skin graft, which was an integral sign of an immune response at the time. Miller concluded that thymus is the organ responsible for the development of immuno-competent cells that make up the specific cell population of thymus-dependent (T) lymphocytes [3].

Involution of a timus and his functions in ontogenesis. Today the embryogenesis and anatomic location of a timus are to some extent studied. Laying of a timus comes by the end of the first month of pre-natal development from III and IV couples of branchiate pockets. By the time of the birth he is the largest and only in an organism completely structurally and functionally created lymphoid body. The critical period of pre-natal formation of Thymus are 7-12 weeks, during this period there is a formation of the main structures of body. The morphogenesis of a timus approaches a closing stage by 17th week of pre-natal development; from 21st week тимус it is distinctly visualized by results of a sonografiya [6] and, at last, by 24th week full is a function of a timopoez. From 21st on the 36th week of a gestation monthly the thymus increases by 1.7-1.9 times; since 37th week, rates e è growth slow down (increase happens no more than by 1.3 times). It is necessary to emphasize that at newborn healthy children тимус it is completely created, well functions and it is completely active, regardless of activity of this body at their mothers [7]. Goitrous gland of the newborn makes 0.5% of body weight (these are 10-15 grams) while a spleen – 11 grams, and heart – 24 grams. There is an opinion that at newborn children the dispersions e è can reach values from 3.2 g to 20.0 g [8]. Authors of the publications devoted to pathoanatomical research Thymus note that the mass of a timus of the newborn averages 4.8 g, at the age of 1 month – 5.9 g, in 2 months – 7.9 g, in 6 months – 9.4 g, in 1 year – 10.8 g, in 2 years – 9.9 g [2]. According to some researchers-morphologists, the largest growth тимус is observed within the first year of life of the child, and the maximum mass of body concerning body weight is noted in 2-4 years. The absolute maximum mass of a timus (25.0-40.0) is observed in the puberty period then there is a reduction of body, and the Thymus ferruterous fabric is replaced fat [1, 2]. The size and mass of Thymus are changeable, strongly vary within the same age group, and undergo age changes [6, 9]. The Thymus form can be listovidny (68.8%), cylindrical (9.6%), pyramidal (cone-shaped) (7.2%), is more rare bean-shaped, oval, or uncertain [10]. In some cases authors point to existence of communication between the Thymus form and pathology; for example, the cylindrical form is often observed at mature age, or at children at chronically proceeding diseases, sepsis, purulent

pleurisy, a hypotrophy 2-3 degrees. Assume that uneven speed, the variable direction of growth of vessels is created by prerequisites to variability of growth of a parenchyma of a timus, as is the cornerstone of his morphological feature at different children in population [11]. The highest products of T-lymphocytes remain up to two years. These years there are primary contacts with infectious agents and long-living T-cages of memory which live more than 20 years are formed and reproduce themselves. Further, receipt of new pathogens becomes more rare event in this connection the contents by an organism of the whole timus becomes inexpedient and тимус 3% a year of truly timichesky fabric are exposed to age involution with a speed ~. The pool of mature peripheral T-lymphocytes created with big power expenses (in the subsequent migrating from a timus in fabric) includes rather long-living cages capable to answer with clonal expansion (proliferation) a meeting with antigen. Therefore age involution of a timus doesn't lead to catastrophic decrease in immunity. Besides, the immune system has some compensatory opportunities of replacement of separate functions of missing T-lymphocytes [12]. From the functional point of view тимус it is possible to subdivide into two compartments: parenchyma and to Strom. The cellular structure of a parenchyma is presented: T-lymphocytes, dendritny cages, macrophages and V-cages, that is cages of a haemo poetic row. Cellular structure of a stroma: dendritny cells, macrophages, cells of an endothelium, fibroblasta and timichesky epithelial cells (TEC) [13]. In general, Strom represents the organized three-dimensional network causing the structure of all body which promotes implementation of processes of maturing and a differentiation of T-lymphocytes. Indispensability of energy industry at differentiation of T-cages is confirmed by the fact that any genetic mutations in these cages cause immunodeficiency and violations of autoimmune character. According to modern representations, in segments of a parenchyma of a timus distinguish 4 structurally functional zones [14]:

1. the subcapsular zone in which pre-T lymphocytes with a non-lymphoid element of the thymus are likely to occur, as well as the proliferation of T lymphocytes and the first stage of their maturation.
2. The internal cortical zone, where direct contact is made with macrophages and epithelium, which, with the help of antigens of the first and second classes of the HLA system, as well as under the action of thymic hormones and interleukins, affect the next stage of T cell maturation and the emergence of autotolerance.
3. The medullary zone, in which for the most part already mature T lymphocytes are located and, probably, their antigen-independent development occurs upon contact with intermediate and epithelial cells, as well as under the influence of thymic hormones and interleukins. It is from this zone that mature T cells migrate from the organ to the periphery.
4. Intracolular perivascular spaces, along which T-cells move, and in the cortical matter these spaces are also part of the hematothymic barrier, which also includes epithelial cells with a basement membrane, pericytes and vascular endothelium [2]. The main working cell of the immune system is the lymphocyte. The lymphocyte comes from a stem hematopoietic polypotent cell. Its marker is CD34.

Early precursors of T lymphocytes migrate from the bone marrow to the thymus, but, thanks to the hematothymic barrier, no more than 5% of cells achieve their goal. Lymphocytes entering the cortical layer of the thymus are called thymocytes.

The decisive event in the development of T-lymphocytes is the formation of an antigen-recognizing receptor, which can occur under the conditions of the thymic microenvironment. Thymic microenvironment refers to the presence of a pool of cells in the environment of which T-lymphocytes differentiate under the action of biologically active substances released by them [15]. It is epithelial cells that create a microenvironment in the thymus that determines the development of T lymphocytes [11]. For example, reticular epitheliocytes are a source of signals that cause the formation of receptors for antigens and the separation of T-lymphocytes into subpopulations of CD4 + (T-helper), CD8 + (T-cytotoxic), etc.

It is known that various stages of proliferation, separation, metabolic and functional activity of thymus cells are controlled by various biologically active substances (BAS). Thymus produces a large number of BAS (up to 40 species), divided into cytokines (interferon gamma, interleukins, tumor necrosis factor, granulocyte colony stimulating factor, etc., which act as endocrines) and thymic hormones (thymosin, thymic humoral and thymic tenth factor, thymulin, thymopoietin and thymostimulin, etc.). It should be noted that the biological role of hormonal substances of the thymus has not yet been finally established. They are known to have an effect not only on lymphopoiesis, but also on calcium and phosphorus metabolism, glucose exchange and utilization, muscle tone, growth and puberty, have analgesic effects, affect pigment metabolism. By participating in the differentiation of T lymphocytes, they also form optimal tolerance to their own antigens. The number of B lymphocytes in the thymus is about 1% and varies little further before birth [12]. The matured autotolerant T lymphocytes leave the thymus through the intradolar perivascular spaces, and the autoaggressive lymphocytes are eliminated [13]. Leaving the thymus, T lymphocytes migrate to the thymus-dependent zones of the peripheral organs of the immune system, where they acquire the ability to specifically activate. As already mentioned, under the influence of stromal elements, lymphocytes become able to respond to microenvironment stimuli, i.e. to thymic factors, and synthesize specific markers of T lymphocytes [20]. Peripheral T cells are divided into various subpopulations (T helper - Th CD4, T killer - CD8, etc.). In general, to date, more than 10 types of T cells are already isolated, and in the future it is necessary to find even greater diversity of them. However, in any case, it should be remembered that different classes of T cells recognize different receptor molecules. Using modern methods of biochemical, serological and molecular genetic analysis of cloned T-cell populations, it is possible to identify differences between these receptor molecules (CD - abbreviated Cluster differentiation) [12]. On a surface of T-cages it is obviously possible to find, for example, the following CDs: CD2 – is found on all mature peripheral T-lymphocytes, takes part in process of nonspecific activation of T-cages; CD3 – is a specific signal for activation of a mature T-cage (at this CD3 participates in signal transmission in a cage); CD4 – is inherent in the T-lymphocytes which are functionally characterized as helper and inductors; at contact of T-lymphocytes with an antigenprezentiruyushchy cage CD4 acts as the specific place of binding of determinants of proteinaceous molecules of the Ministry of Taxes and Tax Collection of class II; CD25 – expressirutsya on the activated T-lymphocytes [12]. Cages with markers of CD4 and CD8 form so-called effector group of T-lymphocytes which is directly responsible for the cellular immune answer. The role of CD4, Th1 ("inflammatory T-cages"), in this cooperation comes down to activation of macrophages, synthesis of IFN-y, IL-2 which stimulate proliferation and a differentiation of CD8 cages and NK cages. The essence of work of CD8 consists in recognition of the antigens presented on the Ministry of Taxes and Tax Collection of the I class from the activators (viruses, mycobacteria, etc.) breeding intracellularly. Recognition of an infitsirovannoykletka happens on change of a molecule of the Ministry of Taxes and Tax Collection of the I class then CD8 lymphocytes by means of a limfotoksin cause increase in permeability of a membrane of a cage target, her osmotic swelling, an exit from her intracellular contents (lysis), thereby causing death [15]. In peripheral department of the immune system the TRACK are present mainly at the T-cages which were recently emigrating from a timus (NTE or RTE – Recent thymic emigrants) which didn't manage to share after an exit from a thymus; that is, on naive timichesky T-lymphocytes with superficial molecule CD31. Contents the TRACK in peripheral T-lymphocytes reflects intensity of two processes – emigrations of T-cages from a timus and the level of proliferative processes in the periphery. As for lack of intensive anti-gene stimulation the level of proliferation of T-cages on the periphery varies poorly, contents the TRACK (including and CD 31) it is possible to consider mainly as indicator T-limfopoeticheskoy of function of a timus [14]. The methods applicable for assessment of function of a timus in models on animals (introduction of fluorescent dyes in тимус in Vivo with the subsequent definition of their concentration in blood, application of gene-modified cages), can't be used for this purpose at the person. Definition the TRACK is the only approach which is suitable for a research of T-cages both at animals, and at the person [18]. Identification the

TRACK is carried out by means of the polymerase chain reaction (PCR) which is the most reliable and rather widely used method of assessment of a functional condition of a timus of the person now. Life term the TRACK is estimated in 3.8 years [16] that it is important to consider at interpretation of results [13]. After NTE exit from a timus and their "delivery" to peripheral bodies of the immune system there is a division of naive timichesky T-lymphocytes to CD31 phenotype for accumulation of a cellular pool during what they lose TREC and, along with it, on these cages the superficial molecule CD31 [3] ceases to expressirovatsya. That is, from the category of "naive" T-lymphocytes they pass into group of "mature". It should be noted that due to reorganization of the T-cellular receptor there is a formation of immunological tolerance. Thus, definition of naive T-lymphocytes with superficial molecule CD31 by efficiency is brought closer or is even equivalent to definition of TREC – for assessment of a produktivnoysposobnost of Thymus[19]. CD45RA + cages are necessary for the adequate answer of the immune system at a meeting with new antigen as at infection of an organism or surgical intervention it is necessary to have for formation of T-cages of memory based CD4+CD45RA+CD45R0–, and emergence upon their surface of molecules CD45R0 instead of an isoform of CD45RA [7]. Steroid hormones in general, and glucocorticoid hormones in particular, make impact on lymphoid fabric, and the type of effect depends on a dose of hormone and a stage of a differentiation of cages. The same hormone in different doses can cause both apoptosis, and proliferation of timotsit. After the termination of a puberty there is a continuous decrease in mass of a timus approximately by 3% annually [19]. Fatty tissue replaces lymphoid, generally in the field of the connecting capsule and септ. In general, age involution of a timus is connected with decrease in number of predecessors from marrow, with death of cages of a stroma, with change of a hormonal background, even with concentration of cytokines and growth factors in a timus, not to mention efficiency of a rearanzhirovka of the T-cellular receptor, but still more concrete mechanisms causing age involution aren't defined yet. However, dazhepr of obviously expressed atrophy тимус nevertheless performs the function and supports a differentiation of T-cages [10]. Apparently, age involution is quantitative, but not high-quality process as there are data on full proliferation of timotsit and a rearanzhirovka of TcR in the aging timus. Besides, from the histologic point of view the residual zones of a cortex and a medulla look normal and remain immunocompetent and also the role of a timus in resumption of a peripheral pool of T-lymphocytes after antiretroviral therapy, chemotherapy and transplantation of haematopoietic stem cells at adults is noted [8]. The so-called aktsidentalny involution (AI) of a timus which, according to many authors, can represent morphological reorganization of body in response to any stressorny influences is of great interest to a research. For example, O.I. Ismoilov et al. [5] connect the stereotypic response of Thymus to various adverse, extremely strong impacts on an organism with the aktsidentalny involution (AI) (diseases, injuries, intoxication, hunger, cooling, etc.) [16]. These causes of development of AI can be extremely diverse. Besides above specified, it and malignant tumors, metabolic disorders in an organism [14]. Cases of development of AI Thymus after a splenektomiya are noted [12].

Conclusions. The value of cooling and a hypoxia are also ambiguous. For example, at newborns at sharp oxygen insufficiency of AI Thymus, as a rule, it wasn't observed. Authors S.M. Akhmedova and Sh.Zh. Teshayev note what at the congenital heart diseases which are followed by a hypoxia, AI either is absent, or isn't much expressed, being limited to initial stages [11]. But L. Kuzmenko's authors. And N.P. Loginova describe close connection between increase in the sizes of a timus and congenital defects [6]. Process of involution of Thymus at children is connected also with academic loads which, as a rule, work in the pressingovy mode of the unidirectional character, suppressing age dynamics of development of physiological systems, create critical conditions of tension of adaptation, disadaptation and development of a disease at school students. AI Thymus at children's age describe at infectious diseases, especially digestive tract, at heavy drain pneumonia, at meningoentsefalita, at sepsis, local nagnoitelny processes (phlegmons, osteomyelitis), malignant tumors, a kakheksiya of various genesis [2] more often. Follows from the above that the pathogenesis of AI Thymus is difficult and now up to the end it

isn't opened yet. Assume that it is more often is manifestation of an adaptation syndrome in response to stressful influence [14]. The leading value at the same time is allocated for reactive shifts in hypothalamo - hypophysial suprarenal to a system, the increasing quantity of glucocorticoids in blood, with decrease in development of Thymus of biologically active agents [2]. Process, as a rule, isn't unambiguous in all segments of Thymus, and a thicket corresponds to "degree of a maturity" of body by the time of emergence of a stressful factor [2]. In particular, V.B. Guzarevich et al. regard the fact of increase in a timus as result of compensatory reaction (i.e. option of norm and the natural phenomenon in response to influence of stressful factors), and in certain cases as the borderlines which are followed by morfofunktsionalny immaturity of bodies and systems [15]. In references, 5 stages of AI [10] are described. And, if the first three phases can be followed by increase in body (with consecutive increase in proliferation of Pre-t-lymphocytes [13], then their reduction due to increase in a pool of macrophages, increase in hypostasis and a polnokroviya of a stroma), then the subsequent 4th and 5th phases are characterized by his involution (reduction), violation of structure, cellular devastation, fibrosis and replacement with fatty tissue. As a rule, the 5th phase is irreversible [20]. According to this classification, it is difficult to carry the IV-V stage to "accidental, insignificant" the response of Thymus to an adverse effect of some stressor on an organism as this answer is fatal to body. And it semantic contradicts the definition of AI (from the Latin word "accedentis" – accident [11], or minor, insignificant [Wikipedia]). In these cases it is possible to assume existence of an atrophy or the previous, not distinguished dysplasia (various degree of expressiveness and as result of a fetopatiya) as the listed changes have irreversible character, are characterized by the phenomena of fibrosis of body and roughly break his main function – immunogenesis. I.e., there are still unknown an exact functional role of aktsidentalny involution and its probable outcome: whether it is natural reaction to a stressful situation in which the organism is put, or this manifestation of that fetopatiya, "inferiority" of a timus and his inability to react fully to a stressful precedent [6]. There are no accurate differentiations between IV and V stages of aktsidentalny involution and a true hypoplasia (dysplasia) or an atrophy of this body in literature and. There are no clear ideas and of a morphogenesis of various options of a timomegaliya [9]. Speaking of thymus atrophy, Haley et al. (2005), Ismoilov O.I. [9] imply the loss of the cell-viral gland, which is a physiological phenomenon and is well known in aging. They do not mention accidental involution, but believe that thymic atrophy occurs in many cases, such as psycho-emotional stress, malnutrition, infections and cancer treatment. Thymic atrophy may occur due to thymocyte apoptosis, thymic deterioration, loss of ETPs influx into the thymus, or combination of the above scenarios. The authors believe that these manifestations may occur both due to direct (e.g., effect of HIV infection on thymocytes) and indirect (e.g., increase in stress-induced glucocorticoids) effects on the thymus. In the first case, as in the following, there is no mention of accidental involution. For example, several experimental models and some studies in humans are known, where infections with pathogens lead to thymic atrophy.

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