



## The Thymus Gland (Thymus) Aspects in Children (Review of Literature)

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**Abstract:** The thymus gland (thymus) is a huge mystery of biology, medicine (primarily immunology) and, in particular, pediatrics. Despite the fact that it has been calling attention of researchers for over 4 centuries. Only in the 20th century, the attitude of scientists to the organ as to a generator and regulator of immune reactions, a participant in the production and differentiation of many populations of immunocompetent cells, and so on, was determined. The thymus is now regarded 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 to the functions of the immune system and its central organ - the thymus gland is understandable. The key challenge of the study is in the huge number of integral connections of the thymus gland with other components of the immune system, microbiome, neuroendocrine, hematopoietic and connective tissues, organs (and cells) providing barrier function, etc. To isolate functions directly related to 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 periods. The purpose of this review, as far as possible, is to isolate and focus on some, in our opinion, «white spots» of an ambiguous assessment of morphological transformations and functions attributed to the thymus gland, its structures and cell pool.

**Key words:** thymus; children; thymic involution; thymic morphology

**Relevance.** The enlargement of the thyroid gland in children was quite often diagnosed by doctors based on the results of radiography of the chest organs, and the degree of this increase is using the calculation of the cardiothymic-thoracic index (KTTI). J. Gewolb et al. is the ratio of the width of the cardiothymic shadow at the bifurcation site of the trachea to the transverse diameter of the chest at the level of the diaphragm dome [1]. KTTI, equal to 0.23-0.26, corresponded to normal dimensions of LV; 0.33-0.37 - thymomegaly (TM) of I degree; 0.37-0.42 - grade II thymomegaly; KTTI is more than 0.42 - thymomegaly of III degree [2, 31]. But this method of evaluating the morphometric parameters of the HV did not quite suit doctors due to the radiation load, the lack of a three-dimensional measurement of the organ, the lack of the ability to monitor the dynamics of the organ length. In the literature there is information on the detection of hyperplasia (thymomegaly) of the thymus gland during computed tomography (CT) of mediastenia [3]. The disadvantage of CT is the presence of a high radiation load, which limits its use in pediatric practice [3-5]. A number of publications are devoted to the diagnosis of VG volumetric formations by CT: thymus [6-8], thymolipus [9, 10], VG cysts [5, 11], aberrant thymus [10, 12]. And this method, according to the authors, is leading in the diagnosis of the listed variants of thymus pathology [13].

There are also publications on the use of magnetic resonance imaging (MRI). This method is not invasive, allows you to obtain a three-dimensional image character, does not give a beam load, therefore, it can be repeatedly used in dynamic observation. Imaging in MRI allows you to obtain an almost anatomical image of HV, with a well-differentiated tissue of HV and surrounding fiber. Researchers note that MRI data are more reliable than in CT scans [14, 15]. Detailed characteristics of HV according to MRI are developed normally and in various pathological conditions, including in children [14-16]. The only limitation of widespread use in child practice is the need to use anesthesia to stop the motor activity of the child at the time of the procedure.

In the literature of recent years there are quite a lot of reports on the use of ultrasound of the thymus gland in pediatric practice, the authors of which, as advantages of this method, note its high effectiveness, safety for the patient, lack of contraindications for research, the possibility of dynamic observation of the structure and size of the thymus, including in newborns [17, 18]. Echographic criteria for evaluating the thymus are linear parameters (length, width, anterior-posterior size), on the basis of which it is possible to calculate the mass, volume of the organ, and after birth the thymic index [19]. The great advantage of sonography over radiography is the ability of the patient to determine the "decrease" in thymus dimensions, which can correspond to hypoplasia and atrophic changes of the organ in the IV-V stages of the so-called accidental involution [20, 21].

The national manual for the radiation diagnosis of thoracic organs (including the thymus gland) defines indications for ultrasound: unclear allergic manifestations; preparation for operations or vaccinations; atypically high child weight; severe diseases suffered and/or their atypical course; radiologically detected dilation of mediastinum shadow; cases of sudden death syndrome in childhood among the child's relatives [22].

In domestic and foreign literature there are few publications devoted to the problem of normative parameters of ultrasound assessment of thymus state in children [9, 13, 21, 23, 24]. The existing difference in the sonometric parameters of the thymus in different regions, but in groups of the same age, most likely arises due to territorial, ethnic, and environmental characteristics, variability of bacterial and viral flora, living conditions and other factors affecting the child's body. However, some work now provides an idea of the regional regulatory size of VW according to age [21, 25, 26, 31, 32]. However, the generally accepted reference population values for the above-mentioned thymus parameters (mass, volume) in children are not established, which significantly complicates the process of designating TM, hypoplasia, atrophy as phenomena that go beyond the norm. Probably, for this

reason, at the moment ultrasound examination of HV is not included in the standard of examination of healthy children [27, 33].

**The purpose of the study.** Analysis of the literary volume of enlargement of the thyroid gland in children based on the results of radiography of the chest organs, and the degree of this increase by calculating the cardiothymic-thoracic index (KTTI). J. Gewolb et al. is the ratio of the width of the cardiothymic shadow at the bifurcation site of the trachea to the transverse diameter of the chest at the level of the diaphragm dome.

**Literary scientific analysis.** The interest of researchers and practitioners (pediatricians, endocrinologists, immunologists, pulmonologists) is primarily due to the significant prevalence of thymomegaly syndrome (TM) in the children's population and its connection with excess respiratory morbidity. Mainly due to the high variability in the size of HV, in the work of domestic and foreign researchers there is no unambiguous assessment of its bipolar transformations. There is a certain problem in terminology. The following definitions are used in the medical literature to indicate an increase in HF in children: thymomegaly (TM), thymus hyperplasia, true thymus hyperplasia, thymus ricochet hyperplasia, thymus hypertrophy, persistent thymomegaly, accidental involution (AI), thymus enlargement syndrome (SUWJ) In some sources, there is the use of such definitions as: "large thymus," "small thymus" and "thymus of average magnitude," along with the concepts of "thymomegaly" and "hypoplasia of thymus" [13, 27, 33]. In the domestic literature of recent years, the term "timomegaly," "acidental involution" is more often used, in the English-language - the concept of "thymus hyperplasia," "acute thymus involution," "thymus atrophy" [26. 14. 8-16] is more common.

The term "timomegaly," by which morphologists understand an increase in the volume and mass of the thymus above the age limits while maintaining normal histoarchitectonics of the organ, was proposed in 1970 by prof. I.E. Ivanovskaya [11, 12]. Beginning in 1970, this term began to be widely used by both morphologists and clinicians. Often, the authors point out that TM is accompanied by a decrease in the function of HV, which determines the dysfunctional quality of life of these children [1, 27, 24, 25]. Timomegalia was divided into congenital (primary) and acquired (secondary) [52]. The detection of TM in stillborn and children of the first months of life suggested the existing innate nature of the process [26, 27]. Various adverse intrauterine effects, both in the first trimester of pregnancy and during fetogenesis [13, 22, 28], were noted as etiological factors influencing such transformation of Tm. Great importance was given to the factor of intrauterine infection [20, 24, 30]. It is noted that the assumed congenital TM is accompanied by a decrease in hormone secretion against the background of dysfunction of the neuro-endocrine system, hyperplasia of lymphoid tissue, disruption of metabolic processes in combination with congenital abnormalities in the development of various organs and systems [20, 22, 24]. Kuzmenko L.G. considers congenital TM as a variant of fetodysplasia, malformation [20]. Loginova N.P. also describes the close association of congenital heart defects with morphological changes in the thymus and its reduced activity in the production of timulin and T-lymphocytes with CD3 + differentiation clusters. The author also notes a direct correlation between the complexity of the defect, the level of timopoiesis and the increment of timulin, which are significantly lower than in healthy children [25].

A number of published works assume the hereditary nature of thymomegaly [2, 3]. There are analytical data [10, 15, 16-18] from outpatient maps, medical histories that describe some features of the history and constitution of children with congenital SUVH and TM, as well as risk factors and markers for their intrauterine formation, for example, such as: an aggravated family history of autoimmune and oncological diseases, the presence of chronic nasopharyngeal pathology in blood relatives [20. 29]; birth by caesarean section [10, 19]; high maternal disease rates such as anemia (62.4%), pyelonephritis (28.2%), obesity (34%), iodine deficiency conditions (37%), TORCH

syndrome (46%) [18, 20, 30]; presence of chronic hypoxia in the fetus in the antenatal period, birth trauma [10, 20, 29].

According to T.V. Matkovskaya, there is a direct relationship between the age of parents and the development of TM in their children [24, 27].

It is believed that the acquired TM is based on primary or secondary hypocorticism, which develops under the influence of various pathological conditions and diseases (addison disease, injuries, inflammatory lesions of the adrenal cortex or its destruction in massive hemorrhages and tumor process, hypothalamic syndromes in vasculitis, progressive, often occlusive hydrocephaly, tumors At the same time, immunodeficiency syndrome is noted, similar to that in congenital TM [22].

The issue of whether an increase in HV is a variant of the norm for young children or a pathology is still under discussion [17, 22, 29, 31].

Krasnoperova K.E. [13] considered the increase in Timus in young children under various non-infectious influences as a manifestation of adaptation syndrome with changes in metabolic processes and dysfunction of the immunogenesis system. Other authors also considered the increase in HV physiological, in the process of the same active adaptation of the children's organism, but now to the non-sterile conditions of the outside world [12, 14, 15]. Bruhm E.B. considers the radiologically detectable increase of Timus in young children also as a normal physiological state, due to the peculiarities of the structure of VJ [16].

There is also the opposite view that TM is a pathological condition accompanied by immunodeficiency and impairment of neuro-endocrine system function [14, 17-22]. In this case, TM was attributed to the number of heterogeneous states in which an increase in HV could be both the result of accidental involution (direct disruption of Tm function) and the result of secondary changes in this organ associated with other diseases (for example, thymus cyst) [23]. In some sources, the reasons for the increase in HV and its stage (for example, I-III) were discussed within the framework of accidental involution, which was considered from the position of G. Selier's theory. [8, 9, 10].

Erofeeva L.M. believes that an increase in HV occurs when the weight of the organ exceeds the age norm: in the absence of viral-bacterial infection - by 50% or more; on the first day of viral and bacterial diseases - 100% or more; for infectious-inflammatory diseases with prolonged flow, after resuscitation or steroid treatment - by 5% or more [83].

It should be noted that the information about the prevalence of thymomegaly in childhood is quite mixed. On radiographs of the chest organs of children, thymomegaly was detected with a frequency of 8.1% [3] to 80-85% [18, 19]. According to sectional data, the frequency of increased HV was recorded among stillborn fetuses of 28-42 weeks in 36% cases, and in 16% - among children who died in the first year of life; in those who died between the ages of 1 and 5, this percentage is significantly reduced to 0.2% [12, 17, 20]. According to A.V. Tyazhka, TM occurs in 12.8% of young children [22]; according to Yu.P. Tkachenko - 29.9%); S.G. Huseynova - 37.1% [21]. In the work of Z.I. Esmurzieva et al. it was shown that according to the results of thymus ultrasound, the incidence of thymomegaly of different severity in full-term newborns reaches 21.5%. The frequency of occurrence of grade III thymomegaly in the population, according to the author, does not exceed 4%, and HV hypoplasia of grade III is not more than 2% [28, 33]. In boys, thymomegaly occurs 2-2.5 times more often than in girls [11, 13, 18]. There are data on spontaneous regression of HV sizes by 3-5 years of age in 98% of children [23, 32].

Evidence of influence on transformation of thymus of adverse environmental factors and nature of child feeding is given [22-24].



Many authors note that certain constitutional features are characteristic of children with TM: gentle pale skin, pastosity, plentiful growth of hair on the head, good development of a hypodermic and fat layer, poor development of muscles, decrease in turgor of fabrics, increase in the cross sizes of a body, flattening of a facial skull and nose bridge, shortening of a neck and thorax, lengthening of shins, forearms and feet [11, 15, 16, 30]. According to L.G. Kuzmenko et al., signs of different degrees of diesembriogenesis are observed in 90% of children with timomegaly [15, 20]. Other authors note higher rates of growth and body weight in these children [15, 22, 28, 29], the presence of microanomalies and malformations with a incidence rate of 23.1% to 80.9% [5, 6, 7, 8]. Among the stigmas, diastasis of the direct abdominal muscles, Gothic palate, hip dysplasia, umbilical and inguinal-scrotum hernias [8] are most often noted, among developmental defects - congenital defects of the heart and main vessels [10, 17, 19, 20], defects in the development of the endocrine system, multiple non-chromosomal abnormalities, biochemical defects [17, 18, 21, 22]).

Children with TM may develop symptoms of compression of mediastinal organs in the form of dry cough, noisy breathing, swelling of cervical veins [24]; lymphoid apparatus hyperplasia [24, 27, 28, 30], increased number of leukocytes and lymphocytes in peripheral blood [21, 23, 24, 25], impaired adrenal function and hypothalamic-pituitary-adrenal system [3, 4, 7, 8, 10, 12, 16]. There are works in the domestic literature, the authors of which statistically significantly more often reveal signs of secondary adrenal insufficiency with a decrease in the level of ACTH, 11-OKS and cortisol in children with TM [4, 8, 10, 17]. There is evidence of more frequent cases of hypoplasia and atrophy of the adrenal cortex in this category of children [4, 17], signs of hypofunction of the thyroid [4, 7, 9, 10, 18] and genital glands [14, 19]. There are presented works with recording of decrease of thymic hormones level in blood serum of children with TM and impaired function of endocrine organs [14, 15, 18, 19, 20-23]. All the above facts did not rule out the development of polyglandular insufficiency syndrome in children with similar transformation of VJ to one degree or another [17, 18, 19, 20].

In the reviewed literature attention is paid to peculiarities of neuropsychiatric development of children with TM, which are characterized by immobility, delayed reactions, high tendon reflexes, rapid fatigue, reduction of internal inhibition processes [10, 18, 23, 27, 28]. So, for example, in the work of L.G. Kuzmenko et al. [30], when studying the features of the neuropsychiatric sphere in young children with thymomegaly (n = 90), it was found that among them schizoids (51%) and hypervisual (33%) predominate. The specific gravity of hypertimics is 10%, and healthy children - 6%.

The domestic pediatric literature is dominated by the view that TM is an immunodeficiency syndrome with a predominantly impaired T-cell unit [27, 29, 30], which shows a decrease in the level of functional activity of T-lymphocytes, a low level of thymic serum activity and functional activity of the B-cell unit of the immune system [1-9, 13-15]. Despite the high or normal content of B-lymphocytes, a decrease in the number of immunoglobulins of classes G and A was noted in serum in TM [3-8, 11-16]. The level of class M immunoglobulins can be both elevated [19] and normal [18,31]. There was an increase in the absorption capacity of neutrophils and macrophages with a decrease in their digestive ability [7, 8]. It is noticed that at children of early age with a timomegaliya all indicators of T-cellular immunity are significantly reduced: the maintenance of T-cages (CD3+), T-helperov (CD4+ of T-cages), cytotoxic T-lymphocytes (CD8+ of T-cages), regulatory T-cages (CD4+CD25hi) and also the activated T-lymphocytes (CD4+CD25lo and CD3+HLA-DR+). An increase in the severity of these changes was observed as the degree of thymomegaly progressed, and T-lymphopenia is associated with a decrease in the emigration of T cells from the thymus to the peripheral part of the immune system. Such changes, according to the authors, cause functional deficiency of the T-cell link of the immune system and can contribute to the manifestation of its insolvency, especially in conditions of increased burden by pathogens [12, 31].

Donetsk A.D. et al. [13] interpreted the detected reduction of TREC content in thymomegaly in children as evidence of weakening of thymus T-lymphopoietic function. A similar decrease in T-lymphocyte emigration due to impaired thymopoiesis led to a compensatory increase in homeostatic proliferation, which, in turn, distorted the structure of the peripheral T-lymphocyte population, which could lead to the development of autoimmune diseases in a distant period. In old age, the ability of thymus tissue to generate new naive T cells and combat new threats is practically absent, which makes a person open to infectious diseases, and vaccination is less effective [12, 13]. Thymomegaly and a frequently and/or long-term sick child. Lymphatic diathesis. The problem of a frequently ill child and the reactivity of his immune system requires some accentuation. This problem is far from unambiguous, it is more often based on socio-economic, environmental, biological and other factors. Traditionally, in the Russian Federation, increased respiratory morbidity is associated with a relatively insufficient immune protection of a child at a certain age period (from 1 month to 5 years). This is more true of organized childhood, where the problem is excessive infection.

At the same time, the proposal of Kuzmenko L. G. et al. [27,33] denote the transformation of the thymus by terms: megalothymus, microthymus, emphasizing, in a certain part, the functional nature of these changes (stress - overvoltage - exhaustion) and the complexity of predicting the further morphological evolution of the organ. But, since the morphology and functioning of any organ are dialectically inseparable, all these states (polar transformations) should negatively affect the administration of functions by iron by definition. This is often the case. It all depends on the depth and level of assessment of the morphological substrate and the functional state of the organ (integral or individual functions of it). And, of course, the time will come when a more accurate morphological assessment will be given to organometric transformations of HV (electron microscopy, immunohistochemistry, etc.) and a more accurate assessment of its specialized functions (identification of various biomarkers) [23,31].

We consider it advisable to designate at present the stages (degrees) of increase or decrease of morphometric parameters of VV, since these additions allow longitudinal observation, study, and, if necessary, correction of pathological conditions associated with VV depending on the depth (degree) of its transformation.

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