

Summary Morphological Structure of the Thymus in Newborns with Congenital Cytomegalovirus Infection

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Abstract: The aim of the work was to study the morphological structure of the thymus gland in 36 full-term newborns who died at the 2-5 day of life. The main group included 16 newborns who were diagnosed with intrauterine cytomegalovirus infection by the serological method and polymerase chain reaction. Cerebral ischemia of moderate and severe degree, subarachnoid and periventricular hemorrhages, as well as markers of local and generalized forms of congenital infection were revealed in children of this group. The comparison group was represented by 20 newborns with antenatal ontogenesis, uncomplicated by acute respiratory and herpes-virus infections, moderate and severe somatic and obstetric pathology in their mothers during pregnancy. The cause of their death was birth trauma, intranatal and postnatal hypoxia. In the description of the neonatal thymus, attention was paid to the following features: the general plan of the structure; structural changes in the capsule of the gland; the structure of the cortical and brain matter; violation of loose fibrous connective tissue and blood vessels of the organ. It was found out that the structure of the thymus gland in the main group was different from that in the comparison group, especially a predominance of neonates with increase and decrease in the organ mass. With the growth of the mass of the thymus there was frequently revealed sub capsular hemorrhage; the sharpness of borders decreased or completely disappeared between cortical and medullary substance; the areas of crust delymphatisation, Hassall's corpuscles filled with detritus were often identified. The edema of the interlobular loose fibrous connective tissue increased, the endothelial edema and its desquamation in the lumen of blood vessels were noted. Lymphocyte clusters in the interlobular connective tissue were clearly visualized. In the case of a decrease in the body mass, small lobules, excessive formation of collagen fibers in the interlobular connective tissue, the loss of lymphocytes in the cortical substance and small Hassal's bodies were more often recorded. Stimulation of thymus growth may be associated with the direct cytodestructive effect of the virus and intrauterine stress, leading to a drop in cortisol content. In the inhibition of immunopoesis growth, prolonged antenatal antigenic stimulation, higher level of cortisol against progressing alterative processes in glandulocyte of the cortex of suprarenal glands of the fetus play an important role.

Key words: thymus gland, full-term newborns, congenital cytomegalovirus infection.

Relevance. The thymus gland in newborns takes an active part in the formation of their immunological resistance [1, 3, 4]. Despite the known role of herpesvirus infection in thymus morphology impairment [2], the nature of its structural changes in intrauterine cytomegalovirus infection (CMVI) has not yet been established.

The purpose of the work was to study the morphological structure of the thymus gland in newborns with congenital CMVI.

Research materials and methods. The morphological structure of the thymus gland in 36 dead full-term newborns under various conditions of intrauterine development was studied. The main group consisted of 16 newborns with moderate to severe cerebral ischemia, hypertension-hydrocephalic syndrome, pseudocysts of the vascular plexus, subependymal and subarachnoid hemorrhages, monocytosis, vesiculosis, pneumonia, hepatitis and meningoencephalitis. The development of antenatal viral aggression occurred against the background of chronic subcompensated placental insufficiency and inflammation in the provisional organ (funiculitis, chorioamnionitis, deciduitis). The comparison group was presented by 20 newborns with antenatal ontogenesis, uncomplicated acute respiratory and herpesvirus infections, moderate to severe somatic and obstetric pathology in their mothers during pregnancy. The cause of their death was birth trauma, intranatal and postnatal hypoxia. All children in the study groups died on day 2-5 after birth.

Verification of congenital viral infection was carried out by detecting IgM antibodies to CMV, quadruple the growth of IgG antibody titers to CMV in mother-newborn couples, as well as a DNA pathogen in cord blood, nasopharyngeal aspirate and cerebrospinal fluid. During autopsy, thymus sections were taken, which were fixed in 10% neutral formalin, dehydrated in alcohols and poured into paraffin. The general structure of the organ was studied on histological sections with a thickness of 5-7 μm , after staining with hematoxylin Bemer-eosin. Van Gison color was used to detect collagen fibers. When comparing the frequency of the alternative feature distribution, Fisher's exact test was used ($r < 0.05$).

Study results and discussion.

The morphological picture of the thymus gland in the dead of the main group differed from that in the comparison group by more pronounced alterative and dyscirculatory changes. In children with antenatal cytomegaly infected with the virus, an increase in organ weight, small lobules, hemorrhages under the organ capsule, significant edema-dystrophic changes in the intercostal moat of fibrous connective tissue, as well as coedies of the neat-tissue scaffold of blood vessels were statistically significantly more often ($r < 0.05$) (Table 1, Fig.). The frequency ($r < 0.05$) of visualization of pronounced full blood, edema of endotheliocytes, as well as desquamation of endothelial cells into the vascular lumen increased. Only newborns of the main group were found to have a thymus of less than 6 grams (Table 1).

The data from Table 2 and the presented figures indicate that in the thymus gland in the dead of the main group more often than in the comparison group ($r < 0.05$) there was a decrease in the clarity of the boundaries and the absence of a border between the cortical and cerebral matter, delymphatization sites (Fig. 4), Gassal small bodies (Fig. 5), as well as their degenerative forms, in the central part of which eosinophilic masses, destroyed cell nuclei and calcium salts were found (Fig. 6).

Only children infected with CMV in utero showed hemorrhages into the cavity of Gassal's bodies. A common morphological finding was the accumulation of lymphocytes in the capsule (Fig. 1) and inter-protein connective tissue (Fig. 3), as well as an increase in collagen fibers in loose fibrous connective tissue between the thymus lobules (Fig. 2).

With a thymus mass of more than 14 grams under the organ capsule, small hemorrhages were often detected, the boundaries between the cortical and cerebral matter were erased or absent, the number of lymphoid elements decreased, the frequency of their destructive changes increased, Gassal bodies were found, in the central part of which fragments of nuclei and calcium salt were determined, edema of connective tissue and pronounced fullness. The intra-organ veins and arteries were dominated by large endotheliocytes, as well as desquamation of endothelial cells into the lumen of blood vessels. Small lobes, an abundance of collagen fibers in the interlobular loose fibrous connective tissue and accumulation of lymphocytes, a decrease in the number of lymphocytes in the cortical matter, as well as small Gassal bodies were clearly visualized in the thymus gland weighing less than 6 grams.

Note: hereinafter RF is the degree of reliability of the difference between groups

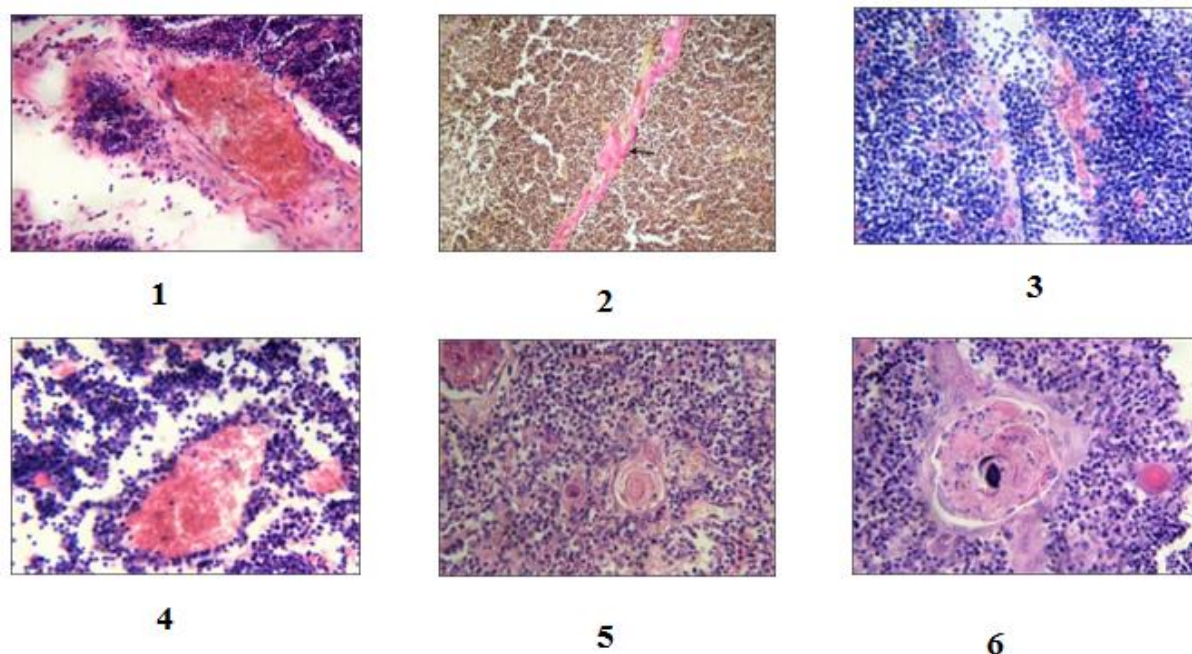


Figure 1-6. Thymus gland of a newborn with congenital CMVI, 5 days. IgM to CMV, DNA + to CMV. Hematoxylin Bemera-eosin coloration. Coloring 10. Lens 40.

1. Against the background of full blood vessels and hemorrhage in the gland capsule, large accumulations of lymphocytes are detected.
2. In the interlobular loose fibrous connective tissue, an excessive amount of collagen fibers is detected (van Gison color).
3. Removal of lymphocytes into the interlobular loose connective tissue against the background of vascular fullness.
4. Against the background of areas of delymphatization, pronounced full blood and vasodilation, focal hemorrhages occur.
5. In cortical matter, cells with a rounded, large hyperchromic nucleus surrounded by the rim of the eosinophilic cytoplasm are determined among lymphocytes and single Gassal bodies.
6. In the cerebral matter, small Gassal bodies with homogeneous eosinophilic contents are detected, as well as large Gassal bodies with destructive-altered cells and calcification.

Table-1. Condition of cortical and cerebral substances of the thymus gland in dead full-term newborns with congenital CMVI (number of cases, abs.).

Indicators	Study groups		RF
	Comparisons (n=20)	Basic (n=16)	
Reduced definition of the boundaries between cortical and cerebral matter	2	9	<0,05
No boundary between cortical and cerebral matter	1	7	>0,05
Pronounced delymphatization of cortical matter	1	8	<0,05
Small Gassal bodies	1	9	<0,05
Large Gassal bodies	5	6	>0,05
Degenerative forms of Gassal's bodies	2	10	<0,05
Gassalle body hemorrhages	-	4	-
Minor cortical hemorrhages	3	7	>0,05

It has been shown that intrauterine stress, including due to chronic subcompensated placental insufficiency, is accompanied by an increase in cortisol levels in cord blood [5, 10], as well as the development of thymomegaly with accidental gland transformation [3].

Exacerbation of CMVI in mothers during pregnancy may induce activation of the systemic inflammatory response in their offspring. Thus, with generalized infection (sepsis) in newborns, accidental involution of the thymus gland is often diagnosed, which is manifested by the picture of the "starry sky," as a result of apoptosis and loss of lymphocytes in the cortical layer of the gland, an increase in Gassal bodies, among which there are morphological forms with disorganization, necrotic changes and calcification. A long course of intrauterine infection is accompanied by a decrease in the content of lymphocytes in the cortical matter and the area of the lobules, condensation and degenerative changes in Gassal's bodies [6].

Thus, in the pathogenesis of the disorder of the structural and functional state of the thymus gland, an important role is played by the activation of systemic inflammation and the development of placentitis in their mothers during pregnancy [7, 9]. cytotoxic and toxic effects of virus DNA on steroidogenesis in adrenal cortical glandulocytes [2], antigenic stimulation [3], as well as dyscirculatory processes in the brain and damage to the diencephalic region, involved in the regulation of hormone synthesis in the cortex of the suprarenal glands [8]. It is known that the most intense thymus gland growth is observed in the intrauterine fetus at 22-24 weeks of gestation [1]. Therefore, congenital CMVI can not only stimulate thymus gland growth, but also inhibit its development against the background of direct contact of pathogens with epithelial and connective tissue elements of the immunopoiesis organ, higher cortisol, endotoxemia and cytokinemia [5, 7, 8].

The above morphological changes of the thymus in full-term patients with congenital CMVI can reduce their immunological resistance and adaptation responses in postnatal ontogenesis.

Conclusions. In dead full-term newborns with congenital CMVI, compared with children of the same age of the comparison group, an increase in thymus mass is more often observed. Only against the background of this antenatal viral aggression are newborns with a small body mass of immunopoiesis. The peculiarities of thymus gland growth in newborns may be due to a different degree of severity of the cytotoxic effect of the pathogen, violation of steroidogenesis and "breakdown" of the main links of regulation of the system "fetal adrenal cortex - thymus."

In the thymus gland, in full-term newborns with congenital CMVI, in contrast to the immunopoiesis organ in children with ontogenesis uncomplicated by acute infectious diseases and exacerbation of chronic somatic diseases in their mothers during gestation, edema and increased crimp of collagen fibers of inter-ring loose connective tissue, pronounced full blood, edema endotheliocytes and their desquamation into the lumen of blood vessels. This allows us to argue about the violation of the metabolic-trophic function of connective tissue and blood vessels, which complicates the process of delivering metabolites to thymocytes, complicates the process of regulating their growth and differentiation, as well as intercellular cooperation.

When thymus weight decreases in antenatal cytomegaly of full-term newborns infected with the virus, in comparison with that in children of the comparison group, the number of small lobes, excessive collagen formation and accumulation of lymphocytes in the inter-ring loose fibrous connective tissue, the number of small single Gassal bodies in the cortical matter increases. In the restructuring of the morphological structure of the gland, it seems that a direct and prolonged mediated negative effect of the causative agent of infection on the formation of its cortical and cerebral matter plays an important role.

Increased thymus mass in full-term newborns with congenital CMVI, in comparison with the organ of immunopoiesis of children of the same gestation period, in the antenatal ontogenesis of which there are no viral infections, moderate and severe somatic and obstetric pathology in their mothers during pregnancy, accompanied by small hemorrhages under the organ capsule, a

decrease in clarity or disappearance of the boundaries between the cortical and cerebral matter, the appearance of delymphatization sites, the predominance of destructive forms of Gassal bodies, alterative changes in thymocytes, edema, full blood and pathological changes in the endothelial lining of blood vessels. Disorders of the structural organization of the thymus can be explained by the progressive depression of steroidogenesis in the fetal adrenal glands as a result of frequent thinning of the cortex and the appearance of adenomatous-like structures in it - markers of lower hormonal activity.

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