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PATHOMORPHOLOGY OF LYMPHATIC NODES DURING NEONATAL SEPSIS

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Abstract

Background. Morphofunctional state of newborn immunity organs, in particular lymph nodes, during sepsis has not been well-studied so far. This research was dedicated to study the morphological and morphometric features of the lymph nodes of infants who died in the neonatal period because of sepsis.

Methodology. The research materials were samples of paratracheal and mesenteric lymph nodes which were taken from 42 neonatal infants’ autopsy specimens. Morphological, histochemical and morphometric methods were used to study lymph node samples obtained from different localizations. Morphometric analysis was applied to evaluate the lymph node diameter, cortex (B-zone) width, paracortical T-zone as well as the medullary layer and also to determine the paracortical zone/cortex and cortex/medullary layer ratio or the coefficient.

Results. The neonatal sepsis in the newborns is accompanied by intrauterine-acquired and secondary immunodeficiencies. It was revealed that in intrauterine-acquired immunodeficiency, the main morphological and functional zones of the peripheral organs of immunogenesis are shown to be immature and hypoplastic due to underpopulation of lymphocytes. Depending on the disruption level of the humoral or cell-mediated immune system, lack of lymphocyte activation in light reproduction centers as well as corresponding structural and functional zones depletion of lymph nodes occur in secondary immunodeficiencies. They are followed by zone replacement with reticular and connective tissue.

Conclusions. In intrauterine sepsis, there was the lag in the main morphologic formation which is functional zones of the lymph nodes, in postnatal sepsis on the background of the
secondary immunodeficiency that the devastation of the corresponding structural and functional zones of the lymph nodes was observed according to the damage of the cellular or humoral immunity.

**Keywords:** sepsis, immunodeficiency, lymph node, neonatal period, lymphoid follicles, paracortical zone, T-dependent zone, B-dependent zone.

**INTRODUCTION**

Children face the highest risk of dying in their first month of life at an average global rate of 18 deaths per 1,000 live births in 2018. Globally, 2.5 million children died in the first month of life in 2018, which means that approximately 7,000 neonatal deaths every day most of which are close to 75% dying, with one third dying on the first day [1]. Despite widespread concerted international efforts, neonatal infections continue to be the leading cause of death under 28 days of age. Improving global access to health care along with ongoing sanitation can significantly reduce neonatal mortality. However, despite optimal medical care, neonatal infections remain common even in developed countries, especially in premature low birth weight babies [2]. Sepsis can be difficult to diagnose in newborns, and it often leads to death if timely treatment is not given. In clinical practice, treatment is also complicated by the insufficient sensitivity of bacterial cultures and the lack of accurate diagnostic markers that go beyond the measurement of blood counts or other laboratory tests, such as C-reactive protein [3]. Antibiotic treatment is also increasingly complicated by the emergence of bacterial resistance, which has become a real problem in several nurseries throughout Central Asia [4]. The complex nature of these problems requires an interdisciplinary effort by the scientific community to improve our understanding of the immunological causes of sepsis in newborns at a mechanistic level to improve diagnostic tools and therapeutic interventions [5].

Sepsis is a non-cyclic infectious process, which is usually based on the non-adequate system inflammatory response of an immunocompromised body to the bacterial component. Usually the infection is conditionally pathogenic, which leads to generalized damage of the vascular endothelium, persistent microcirculation disorders, hemostatic disorders along with compulsory compensated or
decompensated disseminated intravascular coagulation (DIC) syndrome and further proceeding with multiple organ failure [6]. Sepsis is an extremely difficult issue that neonatologists face because it is most frequent in neonatal period, which is because of the insufficiency of non-specific barrier mechanisms of both the mucous membranes and immune system at the time of birth and due to the low reserve capacities during the formation of the biocenosis, which causes the system imbalance, the lack of control over the release of cytokines and other mediators, since the act of birth itself leads to hypercytokinemia [7]. The physiological features of the immune status of newborns, regarded as a temporary biologically feasible immunodeficiency state (IDS) associated with the period of intrauterine life, labor stress and a transition period from the conditions of intrauterine development to the non-uterine one [8].

The main point of the septic process is considered to be the inability of the body to destroy microbes, associated primarily with IDS [9]. The latter may be seen as a background component, i.e. available in the body before the onset of the infectious process, and also as a natural occurrence of it as a result of action of pathogens and their toxins, and the therapy. It has already been mentioned that sepsis usually occurs in children with some background illness states, which, as a rule, is accompanied by IDS [10]. The Systemic inflammatory response syndrome (SIRS) of any genesis is caused by the combination of secondary IDS [11]. Hereditary and acquired (as a result of intrauterine viral infections such as herpes, cytomegalovirus, etc.) immunodeficiencies are all considered to be the factors of high risk for sepsis occurrence [12]. At the same time the immunity suppression and specific immunological tolerance with an excessive number of microbes in the blood can occur – or a critical mass formation [13].

In an immunodeficiency state, the characteristic changes primarily occur in the organs of the lymphoid system, such as in central (thymus, bone marrow) and peripheral (spleen, lymph nodes) tissues [14]. According to some research results [15, 16] morphologically all deviations in the structure of the thymus and peripheral organs of immunogenesis, which go beyond changes during accidental
transformation (AT) and age-related involution processes are the indicators of immunodeficiency. Simultaneously, there is no data on typical morphological rearrangements developing in the lymph nodes in immunodeficiency states, especially in prenatal immunodeficiency states [17].

In this article we have studied the features of morphological and morphometric changes in the lymph nodes in neonatal sepsis on the background of newborn immunodeficiency which is acquired in utero- and postnatal periods as well as the ones who died from neonatal sepsis.

MATERIAL AND METHODS

The objects of our research were paratracheal and mesenteric lymph nodes which have been taken during the autopsy of 42 newborn babies who died in the neonatal period from sepsis and who were diagnosed with intrauterine and postnatal immunodeficiencies after death according to morphological studies of the thymus. From children autopsy the cases with neonatal sepsis series were picked up by clinical laboratory parameters and by morphological studies of thymus. It is known that sepsis is clinically manifested with the following main signs: the body temperature is usually higher than 38°C or lower than 36°C; the heartbeat rate is over 90 per minute in adults, the breath rate is more than 20 per minute in adults; leukocyte count is more than 12 000/μl or appearance of over 10% of non mature forms.

18 out of 42 cases of them were diagnosed with neonatal sepsis and in other cases the late neonatal sepsis were identified. In the early neonatal sepsis the lymph nodes such as paratracheal and mesenterial were enlarged slightly. However, their sizes were equal in measure with the soft consistency. In cases of early neonatal sepsis during the thymus investigation, 7 cases had intrauterine acquired pathology, in 3 cases had primary pathology and in 8 cases were the immune system disruption at the perinatal period. Investigation of late-onset neonatal sepsis showed that the histological structure of the thymus experienced an accidental transformation of the tissue of different levels in 17 cases and it was up
to the 4th level of acquired thymus atrophy seen in some cases. For the histological investigation the paratracheal and mesenteric lymph nodes were worked up by common known methods. Pieces of the lymph nodes were fixed by 10% neutral formalin for a 72-hour period of time. After the wash in flowing water the dehydration in alcohols of increasing concentration and chloroform was carried out and it was poured into paraffin. Histological sections were made by a sledge microtome 5-7 microns thick were stained with hematoxylin eosin, RNA and DNA. A morphometric study of the lymph nodes was carried out using an eyepiece micrometer with a measurement of the thickness of the structural elements, and the mean values, arithmetic and mean squared errors of the indicators were calculated.

The lymph nodes were processed according to the standard methods during histological examination. Histological sections were stained with hematoxylin eosin and colored to divide the RNA and DNA. During the morphometry: the diameter of the lymph node, the width of the cortex (B-zone), the paracortical T-dependent zone and the medullary layer, were studied and their ratio or the coefficient of the paracortical zone/cortex and cortex/medullary layer was calculated. For a comparative study of the morphometric parameters of the lymph nodes during immunodeficiencies as a control group and as a normal reference it was taken from the lymph nodes of children who died from respiratory distress syndrome.

**Statistical analysis**

The obtained digital data were processed by the method of variation statistics with the calculation of Fisher-Student's criteria. The significant differences were considered to be reliable meeting the characteristics of p <0.05.

**RESULTS AND DISCUSSION**

This research results showed that the majority of newborns and neonates who died from sepsis were untenable immunologically. Intrauterine-acquired
immunodeficiency is based on immaturity, hypoplasia, dysplasia, thymic dysgenesis, hypoplasia of the main morphofunctional T- and B-dependent zones in other lymph organs, as well as a decrease in passive immunity transferred from the mother’s body. In these cases morphological manifestations of an immunodeficiency state such as a variety of hypoplastic, dysplastic and degenerative changes were revealed in the lymph nodes. In some cases, the lymph nodes were immature or on the path of normal development, and they were represented by dilated sinuses filled with edematous fluid without lymphocytes (Fig.1), the cortex of nodes occurred with small accumulations of lymphoid cells in the perivenular zone but has taken place without lymphoid follicles formation. In other cases, layers orientation of the lymph nodes were disturbed, the sinuses captured almost the entire tissue of the node, between which single lymphocytes were contained in the pulp cords, forming follicle-like foci surrounded by reticular cells.

Reticular epithelium of the lymphatic nodes are completely depleted during congenital thymic hypoplasia. The medullary layer occupied a significant part of the node, the sinuses were widened and empty, the pulp cords were thickened unevenly due to histiocytosis and reticulosis. The cortex and paracortical zone were absent, instead of them there was a narrow layer consisting of reticular cells and a small number of lymphocytes (Fig. 2). In some cases, it was noted that the atrophy of the lymph node reaches deep depletion, when the medullary layer pulp cords of the sinuses thicken due to histiocytosis and sclerosis (Fig. 3); the vascular walls and perivascular zones were also shown to be sclerotic.

Results of the morphometric study showed that in babies of the control group, the diameter of lymph nodes averaged 2058±154 µm. This number decreased when neonatal sepsis was accompanied by intrauterine damage of the lymphoid organs and reached 1284±118 µm. Normally, if the width of the cortical layer of the lymph node is 598±47 µm, then during the neonatal sepsis amid the intrauterine immunodeficiency it is significantly reduced (287±31 µm). The paracortical zone is also smaller compared to its normal range (314±38 µm). The
increase in the paracortical zone/cortex coefficient (1.09±0.04) was noted, compared to the normal ranges (0.73±0.09) (table).

In late neonatal period sepsis the influence of various pathogens, both viral and bacterial infections were seen on the background of the secondary immune system failure, diseases associated with eating disorders, metabolism and prolonged use of hormones and cytostatic drugs. Pathomorphologically, secondary immunodeficiencies were manifested on their IV-V phases of the accidental transformation acquired by thymus atrophy. We revealed the structurally functional zone devastation, their replacement with reticular and connective tissue, as well as the lack of activation of lymphocytes and light centers of reproduction in the peripheral organs of immunogenesis.

On the background of secondary immunodeficiencies with insufficient cellular immunity, we noted the T-dependent zone hypoplasia in the peripheral organs during neonatal sepsis. The paracortical zone was not determined in the lymph nodes, the cortex was also represented by hyperplastic lymphoid follicles with a wide reproduction center, consisting of hypertrophied reticular cells and lymphoblasts (Fig. 4). The lymphocytes form a loose shaft Around the lymphoid follicles. Medullary sinuses and pulp cords are filled with plasma cells. Immunodeficiencies accompanied by hypoplasia of the B-dependent zones were also accompanied by intrinsic morphological changes in the lymph nodes: the cortical layer was wide due to the paracortical zone, which occupies a large area and was represented by hyperplastic vessels, around which the reticular cells and lymphocytes penetrate the cortex and the medullary layer. The cortex was atrophied, represented by the remnants of lymphoid follicles, consisting mainly of reticular cells and lymphoblasts. Lymphocytes dominated over the plasma cells in the pulp cords and sinuses.
Morphometric indicators of lymph nodes with the development of immunodeficiencies during neonatal sepsis, (µm).

<table>
<thead>
<tr>
<th>Indicators</th>
<th>The control</th>
<th>Intrauterine immunodeficiency</th>
<th>Postnatal Immunodeficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lympth node diameter</td>
<td>2058±154</td>
<td>1284±118</td>
<td>1751±133</td>
</tr>
<tr>
<td>Cortex width</td>
<td>598±47</td>
<td>287±31 *</td>
<td>711±64</td>
</tr>
<tr>
<td>Width of the paracortical zone</td>
<td>434±38</td>
<td>314±27 *</td>
<td>93±19</td>
</tr>
<tr>
<td>The width of the medullary layer</td>
<td>1026±87</td>
<td>683±53 *</td>
<td>947±77</td>
</tr>
<tr>
<td>Paracortical zone/cortex coefficient</td>
<td>0.73±0.09</td>
<td>1.09±0.04 *</td>
<td>0.13±0.02</td>
</tr>
<tr>
<td>Cortex / medulla coefficient</td>
<td>0.58±0.05</td>
<td>0.42±0.02 *</td>
<td>0.75±0.08</td>
</tr>
</tbody>
</table>

* - P = 0.01 - significance of differences compared with the control group,
** - P = 0.001 - significance of differences compared with the previous group.

Morphometric studies of the lymph nodes showed a slight decrease of their diameter in both types of immunological instability. In case of cellular immunity insufficiency, the paracortical zone (93±19µm) is significantly reduced with the expansion of the cortex (711±64µm) (table). Medullary zone was also wide enough (947±77µm). In the case of humoral immunity insufficiency, the cortex was hardly determined, lymphoid follicles were very small, and consisted of the remnants of reticular cells and lymphocytes, the cortex width was 37±7 µm. Paracortical zone (457±44 µm) enlargement was marked. The medullary layer (1149±91 µm) was also expanded due to the thickening of the pulp cords and the enlargement of the duct sinuses. In this case, the paracortical zone/cortex coefficient was significantly increased (5.25±1.05) which is 7 times more than normative ranges.

Thus, morphometric changes in the lymph nodes depending on the damage they cause to individual morphofunctional zones showed that each of the immunodeficiency forms had reliable histometric data, which served as evidence of hypoplasia of a particular zone in peripheral lymphoid organs.

It can be noted that in neonatal sepsis, on the background of intrauterine acquired immunodeficiency, the main morphological and functional zones of the peripheral organs of immunogenesis are found to be immature and hypoplastic due...
to the under population of lymphocytes. Our data are consistent with the indications of some authors [18] that, in newborns there is immunological failure and they die in the neonatal period from sepsis caused by flora or opportunistic processes. On the background of secondary immunodeficiencies during neonatal sepsis, depending on the damage to the cellular or humoral immunity, changes occur in the form of depletion of the corresponding structural and functional zones of the lymph nodes, their replacement by reticular and connective tissue, as well as the absence of activation of lymphocytes and light reproduction centers.

CONCLUSION
2. Neonatal sepsis on the background of intrauterine-acquired immunodeficiency occurs with main morphological and functional zones of the peripheral organs of immunogenesis (including lymph nodes) that which are revealed to be immature, hypoplastic due to the underpopulation of lymphocytes.
3. During neonatal sepsis on the background of the secondary immunodeficiency, which is acquired in early postnatal period, there are changes in the lymph nodes related to the damage caused to cellular or humoral immunity in a corresponding depletion of structural and functional zones, and its substitution into the reticular connective tissue, and the lack of activation of lymphocytes and bright centers of reproduction.

REFERENCES

Fig. 1. Lymph node with early neonatal sepsis on the background of intrauterine acquired immunodeficiency. Hypoplasia of the cortical layer, expansion of the medullary sinuses. Coloration with: hematoxylin and eosin. X: c.10. v.20

Fig. 2. The lymph node view in neonatal sepsis on the background of congenital thymus reticuloepithelial hypoplasia. The cortex and paracortical zones are absent, the pulp cords are sclerotic with single lymphocytes. Coloration with: hematoxylin and eosin. X: c. 10. v.20.

Fig. 3. Late neonatal sepsis with deep depletion of the lymph node with histiocytosis and sclerosis of the medullary and cortical layers in congenital thymic hypoplasia. Coloration with: hematoxylin and eosin. X: c. 10. vol.20.

Fig. 4. Late neonatal sepsis, the lymph node in secondary view in secondary immunodeficiency, deficient in cellular immunity. Hypertrophy of the lymphoid follicle with a wide bright center. Coloration with: hematoxylin and eosin. X: c. 10. vol.20.
**Fig. 5.** Violation of the histotopography of the lymph node due to edema, loosening and septic inflammation. Coloration with: hematoxylin and eosin. X: c. 10. vol.10.

**Fig. 6.** Proliferation of macrophages and histiocytes in the germinal center. Coloration with: hematoxylin and eosin. X: c. 10. vol.40.

**Fig. 7.** Sclerosis of trabeculae and histiocytic sinus lymphadenitis. Coloration with: hematoxylin and eosin. X: c. 10. vol.20.

**Fig. 8.** The subcapsular sinus is filled with histiocytes, macrophages and lymphocytes. Coloration with: hematoxylin and eosin. X: c. 10. vol.40.