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# HYPOXIC BRAIN DAMAGE IN PREMATURE INFANTS (MORPHOLOGICAL STUDY)

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**ABSTRACT** — The aim of the study was to investigate the morphological signs of hypoxic damage to the central nervous system (CNS) in premature infants.
Material and methods: The autopsy reports of 20 premature infants were analyzed. The mean gestational age was 25.9±3.7 weeks, median birth weight was 650 [535;940] grams, and height was 32.6±5.4 cm. We analyzed clinical assessment of the infant's condition at birth, the course of the neonatal period, blood gases and acid-base status, the mode and parameters of mechanical lung ventilation, as well as the oxygenation index (OI) and oxygen saturation index (OSI). Macroscopic and histological signs of damage to various brain structures were studied during pathological anatomical examination. Cortex, parietal subcortex, hippocampus, striatum, cerebellum, foci of hemorrhage were examined.
Results: The main causes of mortality in premature infants were severe asphyxia and its sequelae such as combined ischemic and hemorrhagic brain and spinal cord damage (45%). Severe hypoxia was confirmed by laboratory investigations. Critical lactate and acid-base blood values corresponding to decompensated lactate acidosis were registered in newborns including hyperlactatemia up to 9±3.6 mmol/l, pH 7.01±0.21, BE (-12.3) [-30; -7.9] mmol/l. The OI and OSI, indicating severity of hypoxia, were significantly elevated with their medians being 13.7[9.6;19.8] and 31.8[9.6;16.2], respectively. All infants had central nervous system lesions of varying severity with the underlying morphological immaturity. Pericellular and perivascular cerebral edema, unilateral or bilateral subcortical and subependymal hemorrhages, intraventricular hemorrhages of various degrees, up to tamponade and blood leakage into the cisterna magna, and cerebral leukomalacia were the most frequent findings. In all patients, altered neuronal shape and size as well as hyperchromic nuclei were revealed in the subcortical zone. Changes in all cell structures (cytoplasm, nuclei, and nucleoli), as well as satellitosis and neuronophagy, were characteristic.
Conclusion: Polymorphic morphological changes were observed in the brain structures of premature infants who died as a result of perinatal hypoxia. Along with signs of morphological immaturity, irreversible changes in cortical and subcortical neurons were found. The magnitude of changes is associated with the severity of perinatal hypoxia and decompensated lactate acidosis.

**KEYWORDS** — newborn, lactic acidosis, perinatal hypoxia, brain, subependymal hemorrhage, intraventricular hemorrhage.

## INTRODUCTION

Perinatal brain damage in newborns is one of the leading causes of morbidity and mortality, and even in a surviving infant it can result in severe motor and cognitive impairment, as well as disability in various life periods [1–5]. Perinatal hypoxia, especially in premature infants, plays a leading role in these conditions [6, 7, 8, 9]. Severely premature infants born at 22–32 weeks' gestation are at high risk of brain damage, leading to death or various central nervous system (CNS) abnormalities. Morphogenesis and angiogenesis are active during these gestational periods, and brain regions have unique anatomical characteristics corresponding to a particular gestational age [10, 11, 12]. Premature birth can dramatically change the trajectory of brain development. Premature infants born before 27 weeks of gestation demonstrate a massive decrease in cortical and subcortical volumes, brainstem volume reduction, an increase in cerebrospinal fluid volume, and loss of cortical gray matter [13]. Ball G. et al. found that severely premature infants have reduced volumes of the thalamus, hippocampus, orbitofrontal lobe, posterior cingulate cortex, and impaired development of such brain areas as the thalamocortical system [14]. Any adverse exposure can disrupt physiological organ development, cerebral circulation, and vascular system integrity. Low cerebral blood flow and fluctuations in systemic blood flow combined with impaired cerebral autoregulation can cause damage to anatomical brain structures accompanied by hemorrhages in premature infants [12, 15].

The microcirculatory system is responsible for the transport of oxygen and nutrients, which aids the physiological development of the brain structures. However, in a premature infant born at 30–33 weeks' gestation, the formation of the structural components of the microvasculature is not yet complete. The major abnormalities of early neonatal period resulting in various CNS lesions are low vascular density of the microcirculatory system and non-uniform caliber of arterioles

and venules, which significantly worsens intracerebral circulation and increases the risk of complications. At the end of the neonatal period, when the angiogenesis is still in progress, the hemodynamic imbalance persists due to the dysregulation of capillary blood flow and functioning arteriolo-venular shunts [16].

Another issue is the presence of the germinal matrix in premature infants, which can become the main source of intraventricular hemorrhage (IVH) of varying severity if exposed to negative factors [17, 18]. Such features of germinal matrix as vascular network fragility, paucity of pericytes, insufficient fibronectin in basal lamina, promote disruption of its integrity and hemorrhages. Hypoxia and ischemia, hypercapnia, acidosis, pneumothorax, respiratory distress syndrome (RDS) of the neonate, sepsis, hemostasis disorders directly affect the anatomical structures of the germinal matrix. The impact of these adverse factors enhances the cerebral blood flow fluctuations, thus contributing to IVH development [19, 20]. There is a linear correlation between the frequency of this complication and gestational age: the smaller the gestational age, the higher the risk of hemorrhage. At the same time, IVH grade 1–2, ligation of hemodynamically significant patent ductus arteriosus, and lung diseases can contribute to delayed brain development in preterm infants in the postnatal period [13].

The aim of the study was to examine the morphology of hypoxic brain injury in premature infants.

## MATERIAL AND METHODS

This prospective study was approved by the Independent Ethics Committee of the Clinical Research Center of Immanuel Kant Baltic Federal University and was performed at the Children's Kaliningrad Regional Hospital (Protocol 14, dated October 27, 2020). The sample included 20 premature infants who died between March 2019 and December 2020. Pathologic and histologic examination protocols were analyzed. The mean gestational age of the children was 25.9±3.7 weeks, median birth weight was 650 [535; 940] grams, and height was 32.6±5.4 cm. In the sample, 17 (85%) newborns had extremely low birth weight (ELBW). Severe asphyxia was detected at birth in 19 (95%) newborns, with a median Apgar score of 2 [1.0; 3.0] points at minute 1, and 4 [2.0; 5.0] points at minute 5. At birth, the newborns received basic or advanced life support in accordance with neonatal resuscitation guidelines [21].

The following parameters were studied:

1. Clinical assessment of a newborn, which includes Apgar score at 1 and 5 minutes postpartum.
2. Clinical evaluation of the neonatal period.
3. Blood gases, the acid-base balance and lactate levels in arterialized blood using a Gem Premier 3000 analyzer (USA).
4. Brain pathology after its extraction during autopsy and dissection according to Buyalsky-Flexig technique including examination of the surface, areas of suspected malacia, infarcts, cysts, hemorrhages, malformations. The dura and pia mater, ventricles, vascular plexuses were also examined, and evidence of hydrocephalus was assessed. After examination, frontal sections of the cerebral hemispheres according to the Fischer technique were made and the samples from the following areas were taken for analysis: cortex, parietal subcortical tissue, hippocampus, striatum, cerebellum, and hemorrhage zones. After labeling the material in plastic cassettes, the routine preparation was performed, followed by placement into Histomix homogenized mixture and preparation of paraffin-embedded blocks. Histological sections were stained with hematoxylin and eosin, as well as according to Nissl. Histological examination was performed using a Nikon Eclipse 55i microscope.

Statistical analysis was performed using Statistica 10 (USA) software. Arithmetic mean (M) and standard deviation (SD) were calculated for normally distributed data. Median (Me) and interquartile range (Q1; Q3) were determined for quantitative characteristics with non-normal distribution. The character of distribution was tested using Shapiro-Wilk test.

## RESULTS

### *A review of the causes of fatal outcomes and laboratory criteria for severe perinatal hypoxia*

The major causes of death in 9 (45%) premature infants were severe asphyxia and its consequences such as combined ischemic-hemorrhagic brain and spinal cord injury, the other included neonatal ARDS and bronchopulmonary dysplasia in 6 (30%), congenital infections in 3 (15%), birth trauma in 2 (10%) cases. At birth, newborns had clinical signs of severe perinatal asphyxia such as very low Apgar score and acute respiratory failure. Clinically diagnosed severe hypoxia was confirmed by laboratory tests. Critical lactate and acid-base blood values, corresponding to decompensated lactic acidosis, such as hyperlactatemia (9±3.6 mmol/l), abnormal pH (7.01±0.21), and BE ((-12.3) [-30.0; -7.9] mmol/l) were revealed. The neonatal period was extremely unfavorable, the measures taken did not stabilize or improve the neonates' condition. In all cases progressive deterioration resulting in death was observed. Fifteen (75%) newborns died in the early neonatal period, with a median life expectancy of 18 [11.0; 36.0] hours, and in 20 (25%) cases

the disease duration ranged from 10 to 90 days, with a median life expectancy of 19 [10.0; 28.0] days.

Brain pathomorphology in the preterm infants

The pathological examination revealed that all children had brain damage of varying severity with gestational age-specific morphological immaturity. Pathological changes in the brain structures depended on the duration of antenatal hypoxia and acid-base disorders, respiratory distress syndrome of the newborn, life expectancy and had a complex character. Pericellular and perivascular cerebral edema, unilateral or bilateral subcortical (Fig. 1), subependymal hemorrhages, intraventricular hemorrhages of various degrees, including tamponade and blood leakage into the cerebellar-medullary cistern, cerebral leukomalacia were recorded in all cases.

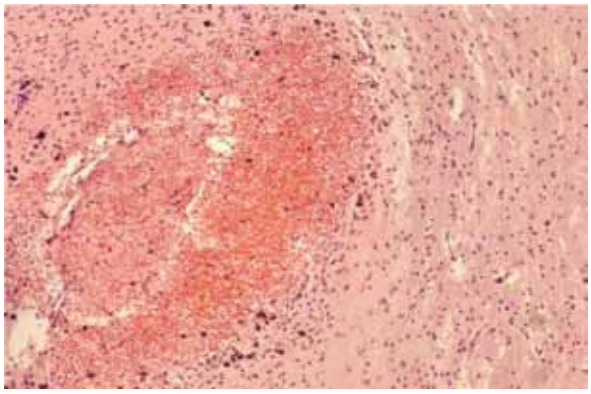

***Fig. 1.*** *Subcortical hemorrhage in a newborn with gestational age of 36 weeks. Hematoxylin and eosin staining. ×200*

Histological examination revealed immature neurons in all cortical layers represented by rounded, small cells with hyperchromatic nuclei and a narrow cytoplasmic rim in preterm infants born at 22–29 weeks' gestation with ELBW (Fig. 2). The most hyperchromatic nuclei were located predominantly in the second cortical neuronal layer. As gestational age increased up to 30–33 weeks, larger differentiated neurons with distinct cytoplasm appeared in layers 3 and 5 of the cortex; pyramidal neurons also occurred.

In all cases, differentiated neurons were visualized in the subcortical area, however, along with the larger ones, clusters of smaller round-shaped neurons with hyperchromatic nuclei were found. Nucleoli were detected in some of the neurons. In this zone, neuronal nucleoli were larger and intensely stained. In some nuclei chromatin was located peripherally as small granules. The karyoplasm in these nuclei was lightly stained. Nuclei and nucleoli were located peripherally: the former were found near the outer membrane

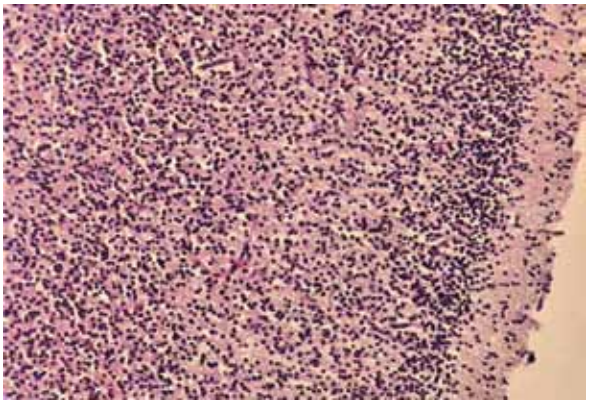

***Fig. 2.*** *Small rounded cortical neurons at gestational age of 29 weeks. Hematoxylin and eosin staining. ×200*

of neurons, the latter lost their central location in the nucleus and were localized near the its membrane. In some neurons, nuclei were not stained, which indicated kariolysis. Clusters of intensely stained neurons, the so-called *dark* neurons, many of which deformed with irregular contours, were detected (Fig. 3). In addition, satellitosis and neuronophagy were observed. The neuronal alterations were registered both in the cerebral cortex and subcortical structures.

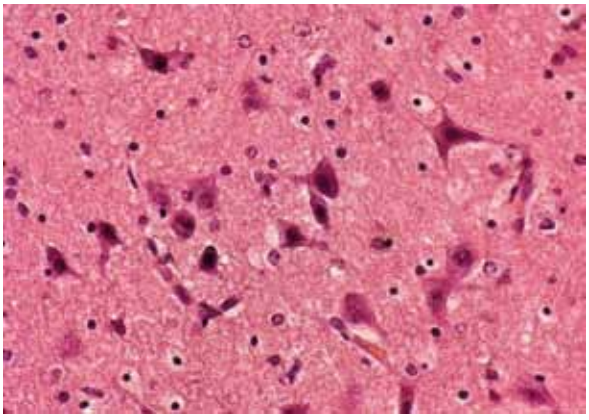

***Fig. 3.*** *Subcortical neurons, dark neurons, pericellular and pericapillary edema at gestational age of 33 weeks. Hematoxylin and eosin staining. ×400*

Nissl staining revealed non-uniform dye uptake among various neurons: the *dark* ones had more intensive stain accumulation, the others were lightly stained or had chromatolysis with Nissl dye dispersion. Many neurons demonstrated stained cytoplasmic periphery with pale perinuclear region (Fig. 4).

Cortical and subcortical capillaries were irregularly engorged, pericapillary edema and diapedetic

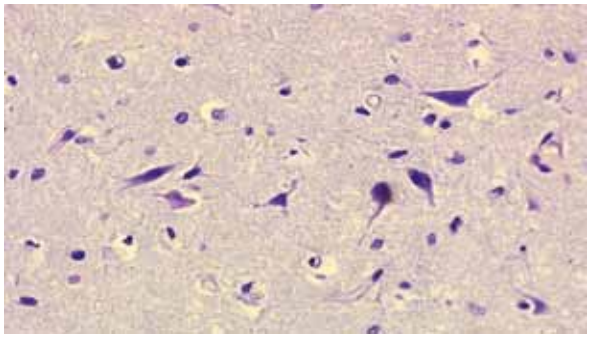

***Fig. 4.*** *Various intensity of neuronal staining at gestational age of 36 weeks. Nissl staining. ×400*

hemorrhages were evident. The pia mater was swollen with its vessels engorged. The vascular plexus was engorged, swollen, and vacuolar dystrophy of epithelial cells was observed (Fig. 5).

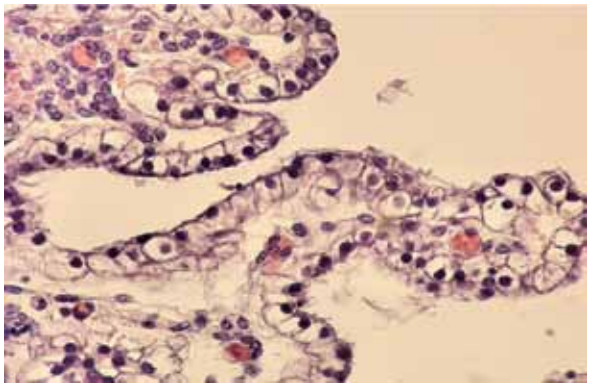

***Fig. 5.*** *Vacuolar dystrophy of vascular plexus epithelial cells at gestational age og 28 weeks. Hematoxylin and eosin staining. ×1000*

## DISCUSSION

Central nervous system development extends beyond the antenatal period far into the postnatal one. Any harmful exposure occurring during these periods can dramatically change the trajectory of brain development. One of the main factors negatively affecting this process is perinatal hypoxia, encompassing the antenatal, intrapartum and postnatal periods. The longer the antenatal hypoxia lasts, the more severe may be the hypoxic-ischemic injury to various parts of the brain in the fetus and the newborn [24, 25]. Severe antenatal hypoxia leads to neuronal death, which is associated with significant energy deficit and increased intracellular lactate production [26], directly affecting the increased levels of cytotoxic reactive oxygen species. This results in edema, swelling and necrosis of neurons [27, 28]. Hyperlactatemia found in children at birth is an important marker of severe hypoxia. It is associated with such morphological signs as pericellular and perivascular cerebral edema, intraventricular hemorrhages of various severity, cerebral leukomalacia.

At the same time, decompensated metabolic acidosis is another marker confirming the severity of perinatal hypoxia [29], which also leads to neuronal necrosis [4, 30]. Acidosis impairs neuronal activity by affecting pH-sensitive channels such as acid-sensing ion channel 1a (ASIC1a) [31, 32] and N-methyl-D-aspartate (NMDA) receptors [33].

In the case of preterm birth, the morphogenesis of CNS continues postnatally under special conditions, with a significantly increased risk of external factors impact. Ensuring the oxygenation of the developing brain in the postnatal period is the main therapeutic challenge in premature infants. Special attention should be focused on the study of cerebral blood flow variability, vasoreactivity and autoregulation, which differ dramatically in various periods of brain development [23]. Low cerebral blood flow and fluctuations in systemic hemodynamics combined with impaired cerebral autoregulation maintain hypoxia, which leads to varying damage to brain structures [15]. In preterm infants with gestational age less than 32 weeks, the periventricular white matter is the most sensitive to hypoxia, which can result in a specific type of damage, the so-called periventricular leukomalacia [34, 35].

As a result of long-term hypoxia and decompensated metabolic lactic acidosis, irreversible changes occur in the neurons of the cerebral cortex and subcortical structures. They affect all cell components including nucleus, nucleolus and cytoplasm.

## CONCLUSION

Morphological changes in the brain of premature infants who died as a result of perinatal hypoxia are polymorphic. Along with signs of morphological immaturity, irreversible changes in cortical and subcortical neurons can be detected. The magnitude of the alterations is associated with the severity of perinatal hypoxia and decompensated lactic acidosis.

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