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NEURON-SPECIFIC ENOLASE AND BRAIN-DERIVED NEUROTROPHIC FACTOR LEVELS IN UMBILICAL CORD BLOOD IN FULL-TERM NEWBORNS WITH INTRAUTERINE GROWTH RETARDATION

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▪ Neuron-specific enolase (NSE) and brain-derived neurotrophic factor (BDNF) levels in umbilical cord blood in full-term newborns with asymmetrical intrauterine growth retardation resulted from chronic placental insufficiency have been studied. Not only a 2.0–2.5-fold increase in the blood NSE level, but also a reduction in BDNF levels were observed, indicating brain damage combined with the lack of adequate compensatory capabilities. With an increase in the duration of intrauterine fetal development under conditions of chronic hypoxia, the degree of damage to neuronal structures increases. This article discusses the mechanisms of the revealed changes, as well as the diagnostic and prognostic significance of the use of biochemical markers.

▪ **Keywords:** newborn; intrauterine growth retardation; neuron-specific enolase; brain-derived neurotrophic factor.

СОДЕРЖАНИЕ НЕЙРОНСПЕЦИФИЧЕСКОЙ ЕНОЛАЗЫ И МОЗГОВОГО НЕЙРОТРОФИЧЕСКОГО ФАКТОРА В ПУПОВИННОЙ КРОВИ ДОНОШЕННЫХ НОВОРОЖДЕННЫХ С ЗАДЕРЖКОЙ ВНУТРИУТРОБНОГО РАЗВИТИЯ

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▪ Изучено содержание нейронспецифической енолазы (NSE) и нейротрофического фактора роста (BDNF) в пуповинной крови доношенных новорожденных, имеющих асимметричную форму задержки внутриутробного развития в результате осложнения беременности хронической плацентарной недостаточностью. Установлено не только повышение в 2,0–2,5 раза содержания в крови NSE, но и снижение уровня BDNF, что указывает на наличие повреждения мозга в сочетании с отсутствием адекватных компенсаторных возможностей. С увеличением продолжительности внутриутробного развития плода в условиях хронической гипоксии степень повреждения нейрональных структур возрастает. В статье обсуждаются механизмы выявленных нарушений, диагностическое и прогностическое значение использования биохимических маркеров в клинической практике.

▪ **Ключевые слова:** новорожденный; задержка внутриутробного развития; нейронспецифическая енолаза; нейротрофический фактор роста.

Over the recent years, there has been an increase in the number of newborns with intrauterine growth retardation (IUGR), which is characterized by not only high perinatal morbidity and mortality, but also significant deviations of neuropsychic development in subsequent years of life [1–4]. It is known that under conditions of chronic hypoxia with placental insufficiency, the genetic

program for the development of all functional systems of the fetal organism is disturbed, which complicates postnatal adaptation and programs the risk of adverse effects [5–9]. In addition, significant structural and functional changes at the cellular level contribute to the occurrence of profound disorders in brain homeostasis, the production and metabolism of neurotransmitters, neuromodulators, and neurohormones [10–13]. In this regard, researchers pay special attention to the diagnostic and prognostic significance of biochemical markers of neuronal damage in fetuses and newborns [14–17]. Such markers include neurotrophins and neurospecific proteins that have essential roles in brain development. One of the markers of neuronal damage is neuron-specific enolase (NSE). NSE is localized in the cytosol of neurons and endocrine cells and is found in the blood when being destroyed.

An increase in the level of NSE in premature infants with a history of asphyxiation or cytomegalovirus infection was an unfavorable prognostic factor for further psychomotor development [18]. Perinatal mortality, necrotizing enterocolitis, the need for intubation, and artificial pulmonary ventilation in premature infants (24–34 weeks old) with IUGR can be predicted by determining the NSE level in umbilical blood immediately at birth [19]. However, a successful prognosis requires determining not only the presence and degree of damage but also the possibility of compensatory mechanisms that occur in response to changes in the brain after hypoxia and contribute to the restoration of impaired functions. Brain-derived neurotrophic factor (BDNF) has attracted the special attention of researchers because it is involved in the differentiation, development, and preservation of brain neurons, including sensory neurons, cholinergic, and dopaminergic neurons of the forebrain and substantia nigra, as well as neurons of the hippocampus and substantia nigra [20]. It has a neurotrophic effect under adverse conditions such as cerebral ischemia, hypoglycemia, and neurotoxicity. BDNF also stimulates and controls the growth of new neurons from neural stem cells, is involved in both the suppression of apoptosis and the restoration of functions of hypoxia-damaged neurons [15, 16, 21, 22]. In the brain, BDNF mRNA, and the protein itself were found in the hippocampus, thalamus, hypothalamus, cerebellum, neocortex pyramidal cells, and spinal cord [20]. Experimental studies have shown that in newborns, its level in the cerebral cortex correlates with that in blood serum [23]. Therefore, the determination of NSE and BDNF in umbilical cord blood enables one not only to detect the presence of damage, but also to evaluate the compensatory possibilities of remodeling the neural structures of the neonatal brain simultaneously, and to predict the consequences of adverse effects during antenatal life. It has been revealed that in full-term infants, the level of neurotrophins in umbilical cord blood is higher than in premature infants, and depends mainly on the presence of perinatal pathology [24–26]. Moreover, data in the literature on the content of NSE and BDNF in umbilical cord blood in both ill and healthy full-term newborns are contradictory, since the authors combined children with different perinatal pathologies into one group and did not take into account the method of their birth [26–28].

This work aimed to study the content of NSE and BDNF in the umbilical cord blood of full-term infants with IUGR because of pregnancy complications of chronic placental insufficiency, and to compare the data obtained with those in healthy newborns, taking into account the gestational age and method of birth.

Materials and research methods

Seventy-one full-term newborns were examined. Group 1 (study group) consisted of 18 pediatric patients whose prenatal development proceeded under hypoxia with complications of pregnancy by chronic placental insufficiency, which was confirmed by the results of histological examination of the placenta (subcompensated hypoplastic form). All newborns had an asymmetric IUGR; five pediatric patients had a failure to gain weight of less than 10% (degree II), and 13 pediatric patients had a failure to gain weight of less than 3% (degree III). There was also a delay of 2–4 weeks in the formation of tonic and reflex reactions compared with normal by the said gestational age. The pediatric patients' body weight was 2520 ± 135.6 g, and the height was 47.6 ± 0.9 cm. The Apgar score was 7–8 points. Subgroups were made depending on the method of delivery, namely seven infants were born through vaginal delivery (Ia) and 11 infants (Ib) were born through cesarean section indicated because of the lack of effect from the treatment of severe gestational toxicosis and chronic placental insufficiency, and impaired hemodynamics in the fetus of degree II.

The control group (II) consisted of 53 pediatric patients, 31 of whom (subgroup IIa) were born through vaginal delivery, and 22 (subgroup IIb) were born through an elective cesarean section, the indication of which was the presence of a scar

on the uterus after previous surgeries. Mothers of pediatric patients were healthy; the pregnancy was not accompanied by complications. The body weight was 3440.2 ± 123.4 g, and the height was 51.7 ± 0.4 cm. The Apgar score was 8–9 points.

Tables by Amiel-Tisson (1974) and Dargassies (1974) were used to assess compliance with a gestational age of postural, passive and active tone, and reflex reactions. A neurosonographic (NSG) examination was performed in all pediatric patients with IUGR.

The study included newborns from mothers with obesity, pre-gestational or gestational diabetes mellitus, with multifetal pregnancies, with a history of acute asphyxiation, transient tachypnea, and infection.

The content of NSE and BDNF was determined in blood serum from the umbilical cord vein of the newborn, which was sampled immediately after birth. The blood was centrifuged for 8 minutes at 3500 rpm to obtain the serum. The resulting serum in a volume of 100–300 μl was frozen and stored at a temperature of -20°C for no more than two months. When determining the amount of NSE, we used the CanAg NSE EIA test system based on the solid-phase non-competitive enzyme-linked immunosorbent assay (Elisa). The amount of BDNF was calculated using the Human BDNF Quantikine Elisa test system, which is based on a quantitative enzyme-linked immunosorbent assay of the sandwich type. In both cases, the optical density was measured on an enzyme-linked immunosorbent analyzer BioTek EL-808 at a wavelength of 450 nm. The concentration of NSE in the samples was determined by the calibration curve and expressed in μg/L, and the amount of BDNF was expressed in pg/ml. Statistical processing of the material was performed using the standard application software Statistica v.6 and a personal computer IP 166 MMX. Descriptive statistics methods included arithmetic mean (M), mean root square deviation (σ), and mean error (m). The significance of differences between the average values of the parameters was determined using the Mann–Whitney U-test. The critical confidence level of the statistical null hypothesis was taken equal to 0.05.

Study results and discussion

The study results are presented in Table 1, which shows that the NSE content in umbilical cord blood in pediatric patients with IUGR is significantly higher than that in healthy newborns with different methods of delivery. Moreover, in pediatric patients with IUGR, like in healthy children, higher rates are observed in those born through vaginal delivery than in those born through cesarean section. At the same time, the content of BDNF is significantly lower than normal for all methods of birth, but, like in healthy ones, it is higher in those born through vaginal delivery than in those born through cesarean section.

Studies have shown that the content of NSE in pediatric patients with IUGR increases significantly with an increase in gestational age, whereas in healthy children, it does not change significantly (Fig. 1). As for the content of BDNF in sick pediatric patients, it remains at the same level for 37–39 weeks in the prenatal period, whereas in healthy children, it reaches its maximum values by week 39 (Fig. 2).

When comparing the data obtained with the clinical condition of pediatric patients, a particularly low BDNF content was recorded in newborns with a severe form of IUGR and born through cesarean section because of hemodynamic disorders in the fetus, which served as an indication for an emergency delivery at a term of 37 weeks.

An analysis of the ratio between the content of NSE and BDNF in the umbilical cord blood of newborns showed a direct correlation between their changes in healthy children ($r = 0.37$; $p < 0.05$), and

Table 1 / Таблица 1

NSE and BDNF levels in umbilical cord blood in neonates in Groups I and II
Содержание NSE и BDNF в пуповинной крови новорожденных I и II групп

Parameter	Groups				Significance of difference between groups			
	I (n = 18)		II (n = 53)		p_1 (Ia–IIa)	p_2 (Iб–IIб)	p_3 (Ia–Iб)	p_4 (IIa–IIб)
	Ia (n = 7)	Iб (n = 11)	IIa (n = 31)	IIб (n = 22)				
NSE (μg/l)	32,0 ± 4,8	20,1 ± 3,3	14,2 ± 1,0	9,4 ± 0,6	< 0,05	< 0,05	< 0,05	< 0,05
BDNF (pg/ml)	452,9 ± 60,9	332,9 ± 36,8	946,5 ± 41,8	545,8 ± 27,9	< 0,05	< 0,05	< 0,05	< 0,05

N o t e . N S E —neuron-specific enolase; BDNF—brain-derived neurotrophic factor.

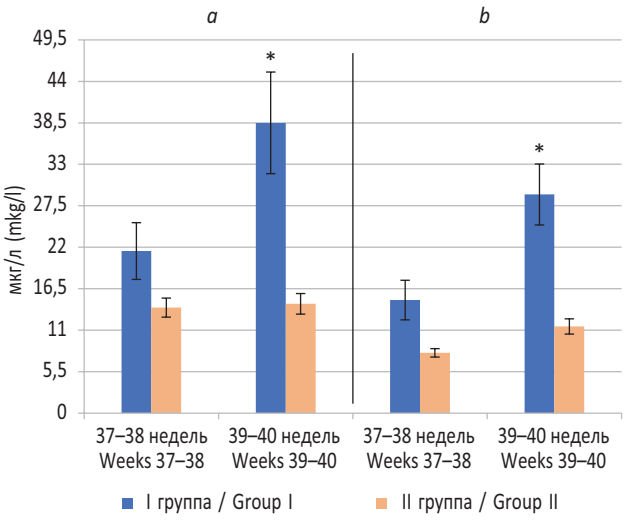

Fig. 1. NSE levels in umbilical cord blood in neonates, depending on gestational age (indicator in infants born: *a* — naturally; *b* — using a cesarean section). * $p < 0.05$ compared to weeks 37–38 in Group I

Рис. 1. Содержание нейронспецифической енолазы (NSE) в пуповинной крови новорожденных в зависимости от гестационного возраста: *a* — показатель у детей, родившихся естественным путем; *b* — показатель у детей, родившихся с помощью операции кесарева сечения. * достоверность различий содержания NSE ($p < 0,05$) у детей I группы

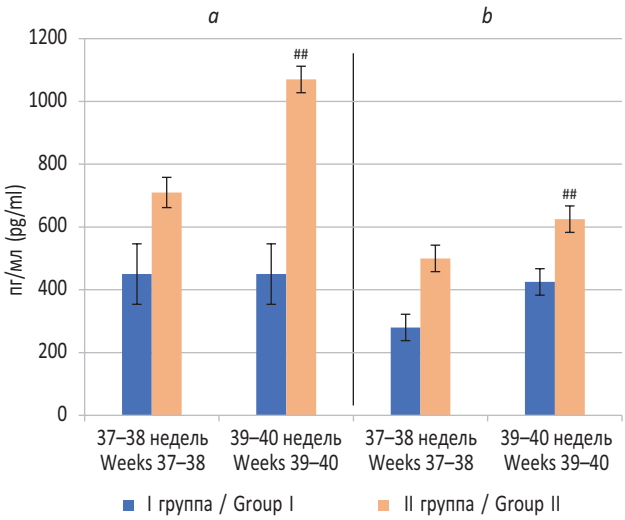

Fig. 2. BDNF levels in umbilical cord blood in neonates, depending on gestational age (indicator in infants born: *a* — naturally; *b* — using a cesarean section). ## $p < 0.05$ compared to weeks 37–38 in Group II

Рис. 2. Содеражние нейротрофического фактора роста (BDNF) в пуповинной крови новорожденных в зависимости от гестационного возраста: *a* — показатель у детей, родившихся естественным путем; *b* — показатель у детей, родившихся с помощью операции кесарева сечения. ## достоверность различий содержания BDNF ($p < 0,05$) у детей II группы

its absence in pediatric patients with a history of chronic hypoxia.

Thus, in full-term newborns with II–III degree IUGR, the blood levels of NSE was not only increased by 2–2.5 times, but a low level of neurotrophic factor BDNF was also determined. The data obtained indicate the presence of brain damage in combination with the lack of adequate compensatory capabilities. Therefore, the degree of damage to neuronal structures increases with an increase in the duration of embryofetal development under conditions of chronic hypoxia.

Single reports in the literature indicate the importance of determining the NSE level as a marker of the degree of brain damage in pediatric patients with IUGR, in combination with other concomitant perinatal pathologies (intrauterine infection, sepsis, birth injury, asphyxiation at birth, and others). Moreover, newborns differed in gestational age and method of delivery [16, 18]. At the same time, we previously established a significant effect of the act of delivery on the dynamics of the NSE and BDNF content in the umbilical cord blood of healthy full-term infants [29], which was subsequently demonstrated by other authors [27]. In this study, this pattern was also confirmed in pediatric patients with IUGR. It should be emphasized that the pediatric patients examined had no perinatal pathology, except for IUGR, and their clinical condition was satisfactory, although there was a delay in the formation of tonic and reflex reactions at weeks 2–4.

Moreover, those who had a delay in week 4 had higher NSE values (1.5–2 times more; 20.0 μg/L), and they were born by cesarean section because of the appearance of signs of disability according to Doppler velocimetry. Mazariko et al. [30] also found a correlation between unfavorable Doppler velocimetry indices a week before the birth of fetuses with IUGR and the increased content of NSE in their umbilical cord blood. In addition, the higher the NSE was in pediatric patients at birth, the more pronounced was the delay in their psychomotor development at the age of two years. According to the authors, this indicates a high prognostic value of this biochemical marker [31]. Other researchers have also confirmed the relationship between the severity of structural changes in the neurosonography, electroencephalogram, and the NSE content in the blood of newborns with a history of asphyxiation and cerebral ischemia [32–35].

It should be noted that we previously revealed a delay in psychomotor development in the first year of life in pediatric patients who had an asymmetric

IUGR and delay in the formation of tonic, reflex reactions, and cyclical sleep organization [2, 10]. Thus, the increased NSE content in umbilical cord blood can serve as evidence of cerebral ischemia during the prenatal period of the child's life, the further development of which will depend to some extent on the presence of compensatory abilities, in particular, the content of BDNF and, possibly, other neurotrophic factors. Our results indicate that in pediatric patients with a history of chronic hypoxia and those born through cesarean section at a term of 37 weeks, this possibility is significantly limited since with a high content of NSE in umbilical cord blood, the BDNF level was 2.5–3 times lower than normal. The data available in the literature show that the content of BDNF in umbilical cord blood is increased in newborns with a history of acute hypoxia, but is reduced with moderate or severe cerebral ischemia [24, 34, 36, 37]. According to experimental studies, during fetal development under conditions of chronic hypoxia, BDNF levels are significantly reduced in the hippocampus and cerebellum, which can lead to impaired development of nerve cells, the proliferation of dendrites, and synaptic contacts in these structures [11, 38]. Oxidative stress and oxidative modification of proteins in chronic placental insufficiency disrupt the production of synaptic proteins, the activity of enzymes, in particular, TrkB phospholipase, which inhibits the participation of BDNF in neuronal brain development [39–41]. The endogenous production of nitric oxide, which increases under hypoxic conditions, suppresses the secretion of BDNF in hippocampal neurons [42]. Under conditions of prenatal stress, which is noted in chronic intrauterine hypoxia, the DNA methylation of the brain neurotrophic factor changes, resulting in a decrease in BDNF production in the brain. Consequently, the level of BDNF in the blood decreases, which is a marker of an unfavorable prognosis of neuropsychic pathology in the child's later life [43–45].

Experimental and clinical evidence has accumulated on the role of antenatal damage to the genetic program of morphofunctional development of brain structures in the emergence of cognitive disorders, autism, aggressive behavior, and schizophrenia in offspring [3, 9, 13, 46–48]. The data obtained indicate the need to determine NSE and BDNF in infants with IUGR for an objective assessment of the severity of damage to brain structures and the timely implementation of the necessary amount of therapy to prevent adverse effects.

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