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# NEONATAL DYNAMICS OF NEURON-SPECIFIC ENOLASE IN NEWBORNS WITH POSTHYPOXIC ENCEPHALOPATHY

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The purpose of the study was to determine the informativeness of neuron specific enolase in prediction of the course of posthypoxic encephalopathy in newborns. 68 newborns with posthypoxic encephalopathy were included in the study (main groups): group I – 41 premature children (28–36 weeks of gestation), divided into 2 subgroups: subgroup IA (n=19; 28–31 weeks of gestation), subgroup IB (n=22; 32–36 weeks of gestation); group II – 27 full-term children (37–40 weeks of gestation). The control group consisted of 29 children without perinatal asphyxia. Neurosonography and determination of neuron specific enolase in blood serum were performed in dynamics of neonatal period. According to results, compared to the control group, the concentration of neuron specific enolase was higher in children with perinatal asphyxia, the highest level was noted in group IB. The levels of neuron specific enolase in the dynamics of the early neonatal period (days 1–3; 5–7) was twice as high in newborns of subgroups with structural changes of the brain, compared to subgroup without structural changes on neurosonography. Thus, it is obvious, that neuron specific enolase can be used in practice to predict the course of posthypoxic encephalopathy.

**Key words**: perinatal asphyxia, newborns, neuron specific proteins, neurosonography, neonatal brain damages

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## НЕОНАТАЛЬНА ДИНАМІКА НЕЙРОН-СПЕЦИФІЧНОЇ ЕНОЛАЗИ У НОВОНАРОДЖЕНИХ З ПОСТГІПОКСІЧНОЮ ЕНЦЕФАЛОПАТІЄЮ

Метою дослідження було визначити інформативність нейронспецифічної енолази у прогнозуванні перебігу постгіпоксичної енцефалопатії у новонароджених. До дослідження включено 68 новонароджених з постгіпоксичною енцефалопатією (основні групи): I група – 41 недоношена дитина (28–36 тижнів гестації), поділених на 2 підгрупи: підгрупа IA (n=19; 28–31 тижнів гестації), підгрупа IB (n = 22; 32–36 тижнів гестації); II група – 27 доношених дітей (37–40 тижнів гестації). Контрольну групу становили 29 дітей без перинатальної асфіксії. Нейросонографію та визначення нейрон-специфічної енолази в сироватці крові проводили в динаміці неонатального періоду. Згідно з отриманими результатами, порівняно з контрольною групою, концентрація нейрон-специфічної енолази була вищою у дітей з перинатальною асфіксією, найвищий рівень відзначений у групі IB. Рівні нейрон-спеціфічної енолази в динаміці раннього неонатального періоду (1–3 доба; 5–7 доба) були вдвічі вище у новонароджених підгруп зі структурними змінами головного мозку порівняно з підгрупою без структурних змін за даними нейросонографії. Отже, очевидно, що нейрон-специфічна енолаза може бути використана на практиці для прогнозування перебігу постгіпоксичної енцефалопатії.

**Ключові слова:** перинатальна асфіксія, нейрон-специфічні білки, нейросонографія, неонатальні ушкодження мозку

Four million infants experience perinatal asphyxia (PA), leading to hypoxic-ischaemic encephalopathy (HIE), each year. HIE is one of the most common contributors to early neonatal mortality [7].

The incidence of moderate to severe HIE is 1–3 per 1,000 live births in high-income countries. Hypoxic-ischaemic brain damage is a complex process that represents an evolving cascade of harmful events [8]. As a result of fundamental research, it was determined that nerve cells-neurons are more sensitive to hypoxia than cells of other organs. Chronic hypoxia is the main damaging factor of the complex pathochemical processes occurring in neurons during the intrauterine period and is manifested by various types of damage in the brain [1].

Along with the metabolic changes (acidosis) that develop as a result of an increase in the concentration of lactic acid against the background of hypoxia, there are morphological changes in nerve cells – swelling of the nuclei of neuroblasts, edema in interstitial areas, etc. is happening. As a result of these changes, venous stasis, hemorrhagic infarction and diapedesis hemorrhage develop, and primary brain blood circulation disorder occurs, resulting in the destruction of the matrix, which is the main substance, and the death of neurons of the cortical and subcortical nuclei; the retardation of the differentiation of neuroblasts and the formation of the vascular network of the brain causes secondary cerebral blood circulation disorders [9].

The clinical manifestation of posthypoxic encephalopathy of different nature is characterized by relatively identical symptoms and is mainly determined by the size of the lesion and its morphological structure, the intensity of hemodynamic disturbances, the level of ischemic and hemorrhagic changes, as well as atrophy and gliosis. In addition, the clinical course of posthypoxic perinatal encephalopathies is influenced by a number of other factors – somatic and gynecological diseases of the mother, duration of chronic hypoxia, gestational age, intrauterine growth retardation, etc. defines [2, 5, 11].

Determining the factors that play an important role in the pathogenesis of posthypoxic encephalopathies, assessing their risk level for the development of the child, both intrauterine and postnatal, lays the groundwork for the development of early diagnostic and prognostic criteria for these pathologies [14]. lthough modern neuroimaging methods allow detection of perinatal pathologies and evaluation of structural changes in the brain during these pathologies, metabolic, biochemical and immunological changes occurring in neurons cannot be detected with these methods. Therefore, there is a need to use more informative biomarkers to assess neuronal changes during posthypoxic perinatal encephalopathy. It has been suggested that various biomarkers may be useful to predicting outcomes of neonatal HIE, but none of these have been established in clinical settings [8]. Currently, it has been established that neuron specific proteins (NSP) play an important role in the prevention of various types of neuronal damage (hypoxic, ischemic, hemorrhagic, metabolic, degenerative). These proteins are directly involved in autoregulatory processes, in the formation of autoimmune complexes. They have also been used for protein profiling of cerebrospinal fluid (CSF) from preterm infants [3].

Studies have confirmed that in posthypoxic encephalopathy, the permeability of the blood-brain barrier (BBB) increases and neuron specific proteins readily enter the blood. Among the neuron specific proteins in modern clinical neurology, including perinatology and neonatology, neuron specific enolase (NSE) is considered a highly specific predictor of various types of brain damage. NSE, as an intracellular enzyme of brain neurons, performs a number of important functions - autoregulatory, immune, mediator, receptor, etc. [6].

Determining the concentration of NSE in the blood serum during brain tissue damage of various nature allows to determine the level of BBB permeability disturbance and the severity of the pathological process. All mentioned dictates the importance of studying NSE for early diagnosis and prediction of course of posthypoxic encephalopathies in newborns.

**The purpose** of the study was to determine the clinical significance and informativeness of neuron specific enolase in the early diagnosis and prediction of the course of posthypoxic encephalopathy in newborns.

**Materials and methods.** Research work was carried out in 2014–2016 at the Educational-Surgical Clinic of the Azerbaijan Medical University and the K. Ya. Farajev Research Institute of Pediatrics.

68 newborns with hypoxic encephalopathy who had perinatal asphyxia were included in the study (main group). All examined children were divided into 2 groups: group I included 41 children born prematurely (28–36 weeks of gestation), group II included 27 children born on time (37–40 weeks of gestation). In turn, children in I group were divided into 2 subgroups depending on gestational age: subgroup IA included 19 children born at 28–31 weeks of gestation, and subgroup IB included 22 children born at 32–36 weeks of gestation. The control group consists of 29 children whose gestational age and body mass correspond to the main groups.

The degree of severity of morphofunctional damage of brain tissue in posthypoxic encephalopathy is clinically evaluated according to the Sarnat score [10]. The grade (stage) 1 injury was evaluated as 1–13 points, the grade 2 injury as 14–26 points, and the grade 3 injury as 27–39 points.

To determine the level of NSE in blood serum, a solid-phase immunoenzymatic test method was used; a test based on this assay has a sensitivity of 1 μg/L for NSE.

Descriptive statistical methods (mean, standard error, frequency, percentage, minimum and maximum) were used while evaluating the study data. A Mann-Whitney U–test was used for comparisons between two groups of non-normally distributed quantitative variables. Qualitative analysis was carried out by using the $\chi^2$ criterion (Pearson's correlation coefficient). Statistical significance was accepted as $p<0.05$.

**Results of the study and their discussion.** According to the Sarnat score, central nervous system (CNS) injuries were grade 3 in 11 (26.8 %) prematurely born children, grade 2 in 20 (48.9 %) children (moderately severe–23.4±0.4 points), 10 (24.4 %) children were evaluated as grade 1 (mild–9.6±0.5 points). When comparing with the II group, the children of the I group, especially the IA subgroup children, mostly did not scream after birth and when it was weakly noticeable ($p<0.01$); also, spontaneous motor activity ($\chi^2=5.64$; $p<0.05$) and communicative ability ($\chi^2=4.89$; $p<0.05$) were observed slower in children of subgroup IA than in subgroup IB ($p<0.01$), cranial innervation disorder did not differ between subgroups ($p>0.05$). In full-term children group: in 18.5 % of children grade 3 injuries, in 37.0 % – grade 2, and in 44.4 % – grade 1 injuries were noted.

Most children with severe or moderate perinatal asphyxia have areflexia or hyporeflexia, amyotonia or hypomyotonia. These changes were mostly symmetrical. Asymmetry of muscle tone was noted in 1 child with periventricular hemorrhage (subgroup IA), muscle dystonia – in 2 children with transient hyperechogenicity (II group). Supported and automatic stepping, Galant and Perez reflexes are

delayed. Babinski's reflex was relatively stable, and disappeared in more severe patients. Compared to I group, muscle tone and reflex activity were more prominent in children of II group (p<0.01), periosteal reflexes were more delayed in group IA, and delay of Perez reflex was more delayed in children of group IB compared to II group.Table 1 shows changes in the dynamics of the neonatal period depending on the gestational age of the concentration of NSE in the blood serum of newborns with perinatal asphyxia and posthypoxic encephalopathy.

Table 1

**Dynamics of the concentration of NSE in the blood (µg/l) depending on the gestational age in newborns with posthypoxic encephalopathy(M±m; min-max)**

| Days of life | group I | | group II | Control group |
|---|---|---|---|---|
| | IA, n=19 | IB=22 | n=27 | n=29 |
| 1-3 | 13.6±1.4$^{xx}$ (4.4–26.5) | 22.8±3.2$^{xx}$ (5.8–36.0) | 24.6±3.4$^{xx}$ (9.4–38.6) | 1.59±0.05 (0.3–2.6) |
| 5-7 | 12.1±1.2$^{xx}$ (3.2–28.0) | 20.2±2.4$^{xx}$ (6.4–34.0) | 22.4±3.0$^{xx}$ (80.2–32.0) | 1.76±0.06 (0.9–26) |
| 21-28 | 6.1±0.8$^{x}$ (2.0–18.2) | 18.8±2.1$^{xx}$ (4.2–28.4) | 16.4±2.2$^{xx}$ (3.9–24.0) | 1.82±0.05 (0.6–2.5) |

Note: P-Statistical sinificance of indices compared to the control group: $^{x}$–p<0,05; $^{xx}$–p<0,01.

The level of NSE in the blood serum of newborns who experienced perinatal asphyxia differed in various gestational age groups. Compared to the control group, the concentration of NSE was higher in all groups and subgroups, and a higher level was noted in IB group – premature babies with a gestational age of 37–40 weeks (24.6±3.4 mg/ml). In this group of children, the high level determined on days 1–3, gradually decreased in the dynamics of the early neonatal period and the end of the neonatal period was equal to 16.4±2.2 mg/ml (p<0.01). Changes in the same direction were noted in both subgroups of group I. The concentration of NSE in the early (days 1–3) and late periods (days 21–28) of the neonatal period differed between all groups, a significant difference of more than 2 times decrease was noted in subgroup IA (p<0.01).

The dynamics of NSE depending on the nature of the structural changes of the brain in newborns of different gestational ages who have experienced perinatal asphyxia and posthypoxic encephalopathy was showed on Table 2.

Table 2

**The dynamics of concentration of NSE in blood (µg/l) depending on the nature of structural changes in newborns with posthypoxic encephalopathy (M±m; min-max)**

| Groups | | Days of life | | |
|---|---|---|---|---|
| | | days 1–3 | days 5–7 | days 21–28 |
| IA n=19 | Str Ch (–) | 9.2±0.8$^{xx}$ (4.4–14.2) | 8.1±0.6$^{x}$ (3.2–13.4) | 3.8±0.2$^{x}$ (2.0–10.1) |
| | Str Ch (+) | 18.6±0.9$^{xx}$ (8.1–26.5) | 16.8±0.8$^{xx}$ (5.6–22.0) | 7.5±0.4$^{xx}$ (5.0–18,2) |
| IB n=22 | Str Ch (–) | 12.4±1.8$^{xx}$ (6.8–21.0) | 10.4±1.4$^{x}$ (6.4–20) | 8.6±0.5$^{xx}$ (4.2–16.0) |
| | Str Ch (+) | 24.6±1.9$^{xx}$ (10.6–36.0) | 22.0±1.6$^{xx}$ (12.1–34.0) | 20.4±1.4$^{xx}$ (10.8–28.4) |
| II n=27 | Str Ch (–) | 14.4±1.6$^{xx}$ (9.4–24.2) | 12.2±1.4$^{x}$ (8.2–22.1) | 8.6±0.8$^{x}$ (3.9–13.2) |
| | Str Ch (+) | 28.8±1.8$^{xx}$ (16.0–38,6) | 24.4±1.6$^{xx}$ (12.4–32) | 18.0±1.0$^{xx}$ (9.4–24.0) |
| Conrol group | | 15.9±0.05 (0.3–2.4) | 1.76±0.06 (0.9–2.6) | 1.82±0.05 (0.6–2.5) |

Note: Str Ch (–) without structural changes- Str Ch (+) with structural changes- Statistical sinificance compared control group: x-p<0.05; xx-p<0.01.

The concentration of NSE in the dynamics of the early neonatal period (days 1–3; 5–7) was twice as high in newborns of subgroups Str Ch (+), where structural changes of the brain were detected in the neurosonographic examination, compared to subgroup Str Ch (–), where structural changes were not detected. The observed difference continued until the end of the neonatal period (days 21–28).

Depending on the nature of the pathological process, the highest level of NSE concentration was noted on the days 1-3 of the child's life in all subgroups, regardless of gestational age. The decrease in the concentration of NSE in the dynamics of the neonatal period was observed with the stabilization of the general clinical condition, the normalization of cardiorespiratory functions and the recovery process in hemo- and liquor dynamics.

The level of NSE in the blood serum was analyzed depending on the nature of the damage – ischemic or hemorrhagic - in children whose structural changes of the CNS were detected in neurosonography. It was determined that the level of NSE in newborns with intraventricular hemorrhage gradually decreased in the dynamics of the neonatal period (days 1–3; 5–7; 21–29); a more pronounced decrease was noted in group IA (28–31 weeks of gestation) premature births. In contrast to hemorrhagic injuries, the level of NSE in children with ischemic injuries did not undergo significant changes in the dynamics of the neonatal period; In group IA, the level of NSE remained high in the early neonatal period.

Thus, our study demonstrated that there are significant relationships between levels of NSE in serum the course of posthypoxic encephalopathies in newborns. The dynamics of NSE concentration depends on various factors incudes gestaional age, nature of hipoxic brain damage, etc.

The similar results were showed by Peng H, et al (2014). The authors revealed that serum NSE levels in neonates of the full-term group and two preterm groups gradually decreased with increasing birth age ($P<0.01$). The early preterm group had significantly higher serum NSE levels than the full-term group on postnatal days 1, 3, and 7 ($P<0.01$) [13]. But, in contrast to our work, in that study influence of HIE and various brain damages (hemorrhagic, ischemic) were not evaluated.

It is known that as a result of perinatal asphyxia, the permeability of the cell membrane increases, the destruction of neuronal and glial cells accelerates due to necrosis and (or) apoptosis, the structural integrity of the BBB is disturbed [14]. Ischemic damage of brain tissue depends on the degree of its trophic supply. Apparently, the concentration of NSE in the group of premature babies (obtained by us) remains at a high level and persists in dynamics, which is associated with the morphofunctional immaturity of the brain and active proliferation of microglia. In premature infants with perinatal asphyxia, due to unsatisfactory antenatal factors, the active differentiation of neurons and astrocytes is delayed, their membrane is damaged, and as a result, the transfer of NSE, an endoplasmic neuron specific protein, into the bloodstream is accelerated [9].

According to Pei XM, et al, dynamic monitoring of serum NSE levels may be helpful for the early diagnosis of HIE and the assessment of brain injury repair in newborns with HIE. The authors recommended also assess erythropoietin due to high informativeness of this parameter in evaluation of repair of neurons and glial cells. The limitation of our study was using only NSE as a potential predictor [12].

Graham EM, et al noted that recently here are numerous reports about blood biomarkers for evaluation of perinatal encephalopathy. However, brain-based biomarkers differ in their ability to predict short-term in-hospital outcomes and long-term neurologic deficits [4]. Our study confirmed that NSE has high predictive ability due to specific dynamics depends on nature of hypoxic brain damage.

## Conclusions

1. Compared to the control group, the concentration of NSE was higher in children with PA, the highest level was noted in group IB – premature children with a gestational age of 37–40 weeks (24.6±3.4 mg/ml).

2. The concentration of NSE in the early (days 1–3) and late periods (days 21–28) of the neonatal period differed between all groups of children with PA, a significant difference of more than 2 times decrease was noted in subgroup IA ($p<0.01$).

3. The levels of NSE in the dynamics of the early neonatal period (days 1–3; 5–7) were twice as high in newborns of subgroups with structural changes of the brain compared to subgroups without structural changes in neuro sonography.

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## RESULTS OF A MORPHOLOGICAL STUDY OF THE THYROID GLAND IN PATIENTS WITH AUTOIMMUNE THYROIDITIS

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The purpose of the study was to conduct a morphological analysis of autoimmune changes in the thyroid gland in patients with autoimmune thyroiditis who received various treatment methods. The work is based on 481 patients' treatment results, including surgical and diagnostic material. Using data from fine-needle aspiration puncture biopsy and cytological examination of punctate samples, the nature of cytological changes in the thyroid gland was assessed. The diffuse-nodular form of autoimmune thyroiditis is characterized in most patients by an autoimmune process with goiter changes manifested by nodular and multinodular encapsulated formations. Outside of goiter changes, atrophic and sclerotic changes in the parenchyma and stroma of the gland, lymphoplasmacytic infiltration and oxyphilic cell transformation of the follicular epithelium are detected. Smaller transitional forms of B cells are observed in the foci of oxiphilic cell transformation. In the diffuse-pseudonodular form of autoimmune thyroiditis, the described changes persist in most patients but with less frequency (54.7–68 %).

**Key words:** autoimmune thyroiditis, cytological changes, fine-needle aspiration biopsy

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## РЕЗУЛЬТАТИ МОРФОЛОГІЧНОГО ДОСЛІДЖЕННЯ ЩИТОВИДНОЇ ЗАЛІЗИ У ХВОРИХ НА АУТОІМУННИЙ ТИРЕОЇДИТ

Метою дослідження було проведення морфологічного дослідження аутоімунних змін щитовидної залози у хворих на аутоімунний тиреоїдит, які отримували різні види методів лікування. Робота ґрунтується на вивченні результатів лікування 481 хворого. Досліджено операційний та діагностичний матеріал, отриманий від пацієнтів із різними формами аутоімунного тиреоїдиту. На підставі даних тонкоголкової аспіраційної біопсії та цитологічного дослідження пунктати (за системою Bethesda) проведено оцінку характеру цитологічних змін щитовидної залози у хворих, які перенесли різні методи лікування. Вузлова форма аутоімунного тиреоїдиту у більшості хворих характеризується ознаками аутоімунного процесу у поєднанні із зобними змінами, які проявляються вузловими та багатовузловими інкапсульованими утвореннями. Мають переважно колоїдну будову. Поза зобними змінами виявляються атрофічні та склеротичні зміни паренхіми та строми залози, лімфоплазмоцитарна інфільтрація та оксифільноклітинна трансформація фолікулярного епітелію. У вогнищах окисифільноклітинної трансформації спостерігаються дрібніші перехідні форми В-клітин. При дифузно-хибновузловій формі аутоімунного тиреоїдиту описані зміни зберігаються у більшості пацієнтів, але зустрічаються вони з меншою частотою (від 54,7 до 68 %).

**Ключові слова:** аутоімунний тиреоїдит, цитологічні зміни, тонкоголкова аспіраційна біопсія.

According to the literature, the frequency of autoimmune thyroiditis (AIT) among all thyroid diseases is 25–35 %, ranking it second after diabetes among endocrinological diseases. Autoimmune thyroiditis primarily affects women aged 35–65 years [8, 13]. The issues of choosing a treatment method for patients with AIT are still far from a final decision. Despite reasonable indications for surgical treatment of nodular forms of AIT, the choice of treatment for patients with a diffuse form of the disease remains