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Diagnostic Feature of Neuronspecific Enolasis in Undependent Children with Perinatal CNS Treatment.

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Abstract To assess the activity of neuron-specific enolase in premature infants with perinatal CNS damage, depending on gestational age. The level of NSE on average was 86.8 ± 9.7 ng / ml - in newborns of group 1, 64.3 ± 9.0 ng / ml - in newborns of group 2, 56.2 ± 7.3 ng / ml - in children of group 3. The average level of this indicator on the 4th day of life in healthy full-term infants was at the level of 8.8 ± 1.9 ng / ml ($p < 0.01$). From the second week of life, the NSE level was 64.5 ng / ml; 38.4 ng / ml; 26.3 ng / ml; 6.2 ng / ml, respectively. By the end of the early neonatal period, a statistically significant high concentration of serum NSE was recorded in newborns of all examined groups, which confirmed the neurological pathology in these children. Our results allow us to conclude that a pronounced positive relationship between the level of neurospecific markers and the severity of hypoxic damage to the central nervous system at birth persists throughout the neonatal and postneonatal period.

Keywords: premature infants, extremely low body weight, very low body weight, neurospecific enolase, hypoxic-ischemic encephalopathy.

Introduction. Clinical examination of newborns, especially those born prematurely, in the first hours, days and months of life does not always reveal a clear and distinct picture of a neurological defect. This is due to insufficient maturity and differentiation of the central nervous system of premature infants, when a limited set of responses is determined with different in nature and localization of pathological processes in the nervous system; their uniformity and generalization do not allow the clinician to judge the severity and localization of cerebral injuries [1,2,3]. The search for early markers of brain damage is currently underway. For predicting and early detection of neurological complications, some markers, neurospecific proteins, determined in blood serum, have recently begun to be used. Among the known neuron-specific proteins, the most studied and adequately characterizing the proper membrane functions of the blood-brain barrier (BBB) is neuron-specific enolase (NSE), which is currently used to diagnose acute conditions characterized by cerebral ischemia and cerebral hypoxia, as well as to study the pathogenesis of neurological diseases occurring with impaired BBB function [4,5,6]. Damage to neurons, incl. against the background of hypoxic ischemic lesions of the central nervous system, leads to the release of this antigen into the peripheral bloodstream [7,8]. From damaged cells, they enter the extracellular environment, which makes it possible to

determine the depth and intensity of structural and functional disorders of biomembranes in the central nervous system with their increase [9,10,11]. An important advantage of the immunochemical determination of the NSE level in a biological fluid in comparison with other diagnostic methods is its high sensitivity and accuracy. Diagnostically significant changes in the level of NSB in plasma are detected much earlier than clinical manifestations. The quantitative determination of this protein in blood serum provides valuable information on the severity of neuronal damage and violations of the integrity of the blood-brain barrier, which characterizes the degree of postischemic brain damage and makes it possible to consider this enzyme as a biological marker of damage to the nervous system. Determination of neurospecific antigens is advisable to use in order to monitor the course of diseases of the central nervous system and predict their outcomes in various brain injuries, in particular, in perinatal hypoxic-ischemic lesions of the central nervous system [11,12]. In this regard, pathological changes in neurochemical aspects allow to more accurately determine the prognosis of morphological changes in the brain, which is a priority in neonatological practice.

Purpose of the study - to evaluate the activity of neuron-specific enolase in premature infants with perinatal CNS damage depending on gestational age.

Materials and methods

The study was carried out in the department of nursing premature newborns of the Republican Specialized Scientific and Practical Medical Center of Pediatrics. To achieve this goal, 69 newborns with perinatal CNS lesions were examined. The gestational age of newborns varied from 29 to 36 weeks, the birth weight, depending on the gestational age, ranged from 800-2300 grams. Analyzing the gestational age of newborns, we found that 24.6% of children were born at a gestational age of 28-30 weeks; 31-34 weeks - 40.6% of children; 35-36 weeks - 34.8% of children. On the basis of gestational age and birth weight, children are divided into 3 groups:

Group 1 - 17 newborns with a gestational age of 29.4 ± 0.12 weeks, with extremely low body weight (ELBW), which averaged 855.5 ± 15.8 g, body length - 37.3 ± 2, 5 cm.

Group 2 - 28 premature infants with a gestation period of 32.3 ± 0.2 weeks, with very low body weight (VLBW) - 1508.5 ± 45.47 g, body length - 42.9 ± 1.2 cm;

Group 3 - 24 premature infants with a gestational age of 35.5 ± 0.9 weeks, with a low birth weight (LBW) at birth - 2116.0 ± 15.7 g, body length -48.3 ± 1.0 cm ;

The control group consisted of 30 practically healthy full-term newborns with a gestational age of 38.9 ± 4.6 weeks, with a birth weight of 3120 ± 156.6 g, a body length of 52.4 ± 4.2 cm. The severity of the condition of newborns in the early neonatal period was due to both individual maladjustment syndromes and their combinations: all children had manifestations of perinatal hypoxic-ischemic lesions of the central nervous system of varying severity. The diagnosis of HIE was made on the basis of a set of anamnestic data (features of the course of pregnancy and childbirth, intrauterine state of the fetus, benefits in childbirth, drug therapy for the mother during pregnancy and childbirth, assessment of the infant's condition on the Apgar scale at birth) and analysis of the dynamics of clinical symptoms in the child [5]. NSE levels in blood were determined by ELISA using standard test systems

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"Fujirebio" (Sweden). In all the studied groups, the dynamics of the NSE level was studied depending on the gestational age and the degree of DIE. Static processing of the obtained results was carried out using the applied programs of mathematical and statistical analysis Microsoft ExelVersion 7.0.

Results.

In order to identify risk factors for the development of critical conditions in newborns and their outcomes, as well as to determine the significance of the identified factors in the prevention of cerebral injuries, an analysis of the obstetric and gynecological anamnesis of mothers, the characteristics of their pregnancy and childbirth was carried out. The risk factor meant any features of the course of pregnancy and childbirth, leading to an increase in the likelihood of developing perinatal lesions of the central nervous system. The history of pregnancy was assessed taking into account the possible impact of the mother on the fetus of adverse factors.

In the structure of extra genital pathology in mothers of newborns of all groups, moderate and severe anemia (from 34.3% to 53.3%) and diseases of the cardiovascular system (from 30.2% to 40.0%) were most common. This indicates that anemia and cardiovascular diseases have a significant share of the risk of developing perinatal fetal damage. Exacerbation of chronic pyelonephritis was observed on average in 22.0% of women. A burdened obstetric history was more common in groups 1 and 2, including previous children with low birth weight, miscarriages, prematurity, and newborn asphyxia. In mothers of groups 1 and 2 and 3, in 43.5%, 33.3%, 29.5% cases, respectively, preeclampsia of varying severity and the

Group	1-3 points Apgar	4-6 points Apgar	>6 points Apgar	Total
1 group	10 (58,8%) $P_1<0,05$	7 (41,2%) $P_1>0,05$		17
2 group	11 (39,2%) $P_2<0,05$	13 (46,4%) $P_2>0,05$	4 (14,3%) $P_2>0,05$	28
3 group	8(33,3%)	11 (45,8%)	5 (20,8%)	24

Table 1. Birth Weight and Apgar Score in Newborns

Note: P1 - reliability of indicators of children of group 1 relative to indicators of children of group 3; P2 - reliability of the indicators of children of the 2nd group relative to the indicators of children of the 3rd group;

threat of miscarriage were observed.

When analyzing the early neonatal period, it was revealed that 36.3% and 44.4% of children were born in severe and extremely serious conditions (4-6

and 1-3 points), respectively. Newborns with an Apgar score at the fifth minute of less than 5 points required primary resuscitation care and transfer to mechanical ventilation due to severe respiratory failure.

To assess the degree of damage to the central nervous system, along with standard clinical and instrumental examination methods, we determined the level of NSE in the blood serum of newborns. An important advantage of the immunochemical determination of the NSE level in a biological fluid in comparison with other diagnostic methods is its high sensitivity, accuracy, and a small amount of the test material. By its level, one can judge about disturbances of the general integrity of the blood-brain barrier, which characterizes the degree of post-hypoxic brain damage.

The clinical picture of the early neonatal period in the first group was marked by a syndrome of cerebral oppression in 11 (64.7%) newborns manifested in the form of hyporeflexia, decreased muscle tone and a weak reaction to an external stimulus, in 4 (23.5%) there was a syndrome of cerebral excitation, characterized by spontaneous Moreau reflex and tremor of arms and legs, in 2 (11.8%) - convulsive syndrome. In children of the second group, the syndrome of cerebral oppression was observed in 19 (67.8%) newborns, in 6 (20%) - the syndrome of cerebral excitement, in 3 (10.7%) - the syndrome of vegetative-visceral disorders. Analysis of the neurological status of the infants of the third group showed that deviations in 30% of newborns (changes in muscle tone, decreased motor activity) were of a transient nature.

A comparative study of blood serum parameters based on the NSE content revealed the presence of significant differences between the groups of newborns, depending on the gestational age and the degree of damage to the central nervous system. In the initial determination of the NSE in children of the studied groups, the dependence of the indicator on gestational age was noted: the lower the gestational age, the higher the NSE indices, which may indicate the dependence of the BBB permeability on the degree of maturity of the structures forming it. This fact testifies in favor of the fact that in premature infants with the same lesion factors and the same severity of the condition, expressed in the Apgar score, the BBB resistance is reduced due to the morphofunctional immaturity of its structures, as well as the death of some neurons in the damaged areas (apoptosis) is expressed in more than full-term.

An increased level of NSE was noted on the 4th day of life in 94% of cases in children of all groups when compared with the norm and averaged 86.8 ± 9.7 ng / ml - in newborns of group 1, 64.3 ± 9.0 ng / ml - in newborns of group 2, 56.2 ± 7.3 ng / ml - in children of group 3. The average level of this indicator on the 4th day of life in healthy full-term infants was at the level of 8.8 ± 1.9 ng / ml ($p < 0.01$).

Analyzing the dynamics of the content of this enzyme, we revealed that from the second week of life in deeply premature newborns of group 1, the NSE indicator tends to decrease, but remains increased compared to the indicators of children of groups 2 and 3, and significantly

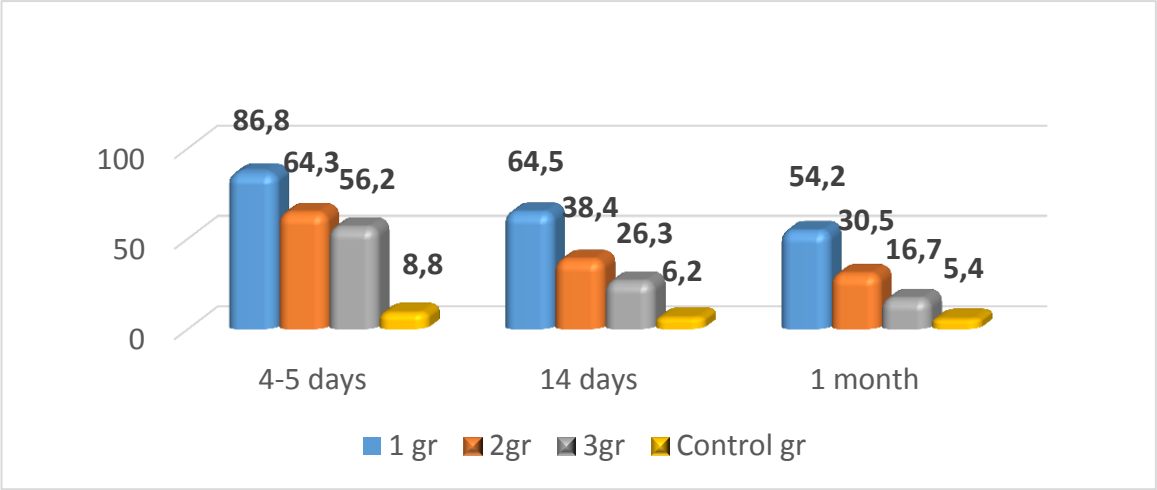

Figure 1. The content of neuron-specific enolase in the examined newborns (ng / ml)

exceeded the same indicator of the control group (p <0.001) by 9.8 times and in dynamics by 1 month of life decreased by 1.6 times compared with the early neonatal period. In children of group 2, this indicator significantly decreased and at the age of one month of life there was a decrease in the indicator by 2.1 times (p <0.001) compared with the early neonatal period. In premature newborns of the 3rd group, a decrease in the values of NSE by 1 month of life was recorded by 2.9 times, which may indicate a decrease in the destructive processes of neurons.

It was found that by the end of the early neonatal period in newborns of all examined groups a statistically significant high concentration of serum NSE was recorded, which confirmed the neurological pathology in these children.

Of undoubted interest is the study of the relationship between the index of neurospecific protein and the severity of CNS damage. The development of intracranial hemorrhages occurs, as a rule, due to pronounced hyperperfusion of cerebral vessels against the background of disruption of autoregulation of cerebral blood flow, which also contributes to the release of NSE into the systemic circulation. It was established that in children with severe IVH (grade 3-4) visualized with neurosonography, the values of serum NSE at the age of 5-7 and 14 days of life were significantly higher.

The NSE concentration is directly related to the degree of IVH. Patients of the study groups with grade 2 and 3 IVH had a higher content of NSE in the blood serum compared with children who, according to ultrasound examination, showed signs of grade 1 IVH.

The revealed changes indicate an increase in the content of NSE with deeper injuries in newborns, the depth and intensity of structural and functional disorders of brain cells, which is due to the consequences of the postponed hypoxia.

Table 2. The Content of Neurospecific Enolase in Premature Infants Depending on the Degree of IVH (ng / ml)

Group	**IVH 1 degree**	**IVH 2 degree**	**IVH 3 degree**	**Control group**
Premature newborns, n=69	24,8 ±2,4 ***	48,0± 3,4 ***	72,4± 5,4 ***	8,8 ±1,9

Note: *** - reliability of differences between indicators of children with IVH and the control group.

Discussion.

An increase in the content of NSE in the blood serum of deeply premature infants with hypoxic lesions of the central nervous system in the neonatal period is apparently due to destructive processes in neurons, which led to the development of vasogenic and cytotoxic cerebral edema, due to pronounced metabolic disorders, the triggering mechanism of which was hypoxia. One of the factors confirming these changes is the clinical picture of cerebral edema in this category of children (development of hypertensive-hydrocephalic, convulsive syndromes, coma) and indicators of instrumental research methods (development of periventricular edema, IVH). A delayed increase in the concentration of NSE after perinatal hypoxic-ischemic damage to the central nervous system may indicate a possible secondary damage to the cellular structures of the brain and impaired BBB permeability.

Our results allow us to conclude that a pronounced positive relationship between the level of neurospecific markers and the severity of hypoxic damage to the central nervous system at birth persists throughout the neonatal and postneonatal period. Thus, the highest NSE indices at 5-7 days of life and at 1 month were recorded in newborns with severe hypoxic lesions of the central nervous system in deeply premature newborns. This indicates that the NSE indices depend on the severity of hypoxic damage to the central nervous system. Our data indicate the presence of a violation of the permeability of the blood-brain barrier for NSE, which is a marker of neuronal damage, which continues for a long period after perinatal hypoxic-ischemic lesion of the central nervous system. This method can be used for additional verification of the severity of perinatal damage to the central nervous system, as well as as a criterion for assessing the effect of various methods of therapy in the post ischemic period, in particular, neuroprotective drugs.

Conclusion. Thus, the data obtained showed that a comprehensive determination of the NSE level in the blood serum of newborns with hypoxic CNS lesions could be used in clinical neonatology as an informative marker for assessing the severity of CNS damage in children with critical conditions. Pathological changes in the balance of neurospecific protein will make it possible to more accurately determine the prognosis of morphological changes in the brain; their study is a priority in neonatology.

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