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ORIGINAL ARTICLE

Neuroimmunological features in premature infants with perinatal infections

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ABSTRACT.

Background: The purpose of this study was to examine the neurological status, taking into account the neuroimmunological indicators (neuron-specific enolase (NSE), interleukin-1β (IL-1β), Interleukin-6 (IL-6) in the serum of neonates with perinatal infections. **Methods:** We conducted a complex clinical, laboratory and instrumental examination of 433 infants with perinatal infections with a gestation period of 27-37 weeks. Determination of the level of NSE, IL-1β, IL-6 was performed with the standard method of the immune-enzyme analysis. Hypoxic ischemic, hemorrhagic, infectious lesions of the central nervous system (CNS) were more common in newborns with concomitant infection and sepsis. High levels of NSE, IL-6, IL-1β in the serum of the examined newborns reflect a combined, deeper character of the CNS damage. **Conclusion:** A good diagnostic value of neuroimmunological indicators in the blood serum of newborns with perinatal infections makes it possible to use them as a marker for assessing the severity of the CNS lesions.

Keywords: *perinatal infections, preterm infants, neuron-specific enolase, cytokines.*

Perinatal infection is one of the important and complex medical problems of modern neonatology and leading cause of morbidity and mortality among newborns [1,2]. Intrauterine infections are chronic in 80% of cases and are cause of death of 61.8% of premature newborns and 49.7% of term newborns [3].

Despite the significant improvment in understanding of mechanisms leading to development of perinatal infections in newborns, they continue to be one of the main causes of severe neurological injury at birth [4,5]. The intrinsic difficulty of newborn assessment makes it requirement to employ wide range of noninvasie diagnostic methods, including ultrasonography of brain, as well as laboratory tests, including testing for neuronspecific proteins (NSP), enabling to objectively determine and assess the degree of structural changes that can also be secondary to infection of CNS. It is well known that neuronspecific enolase (NSE) is considered as one of the most specific markers of neuron damange. It is used as an indicator of degree of neuron injury and overall changes in permeability of blood-brain (hematoencephalic) barrier [6].

The important pathogenetic role that neuroinflammation plays in CNS disorders,

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makes it possible to use the level of proinflammatory cytokines as indicators for determination of the severity of CNS injury [7-10]. According to the available research, the high levels of proinflammatory cytokines in hypoxic-ischemic encephalopathy is not only an indicator of severity of brain injury in newborns, but is an additional noxious factor [5,11].

Therefore, research into the dynamics of neurospecific proteins, immuncytokines, determination of their diagnostic and prognostic value in perinatal CNS disorders among newborns with perinatal infections is of paramount interest.

Objective of research: determine the neurological state of newborns with perinatal infections in relation with neuroimmunological indicators including neurospecific enolase, IL-1β, and IL- 6.

Materials and research methods: Research team conducted clinical and laboratory evaluation of 433 premature newborns with gestational age ranging from 27 to 37 weeks with perinatal infections admitted to the departments of diseases of premature newborns, anesthesiology, reanimathology and intensive care of Scientific-research Institute of Pediatrics after K.Y.Faradjova during period of 2012–2017.

Based on the results of comprehensive evaluation and ethiology of the disease, the newborns with infections were divided into 3 groups:

I qroup: 220 newborns with intrauterine CMV infection;

II qroup: 118 newborns with mixed infection;

There was 85 newborns with CMV and HSV-2, 8 newborns with CMV and toxoplasmosis, 25 newborns had CMV and bacterial infection (neonatal sepsis). Bacteriological examination of the blood revealed 50 children (52,6±5,1%) with *Staphylococcus aureus*, 18 (18,9±4,0%) — with *Streptococcus spp*., 11 (11,6±3,3%) — with *Klebsiella spp*., 15 (12,3±3,0%) — with *Escherichia coli*. All pathogens were present in concentrations of 105–107 colonyforming units per 1 ml. Newborn weight ranged from 800 grams to 2500 grams and averaged as 2035,9±27,8. Among children included in the study, there were 246 (56,8%) boys, and 187(43,2%) girls. Gestational age varied from 27 to 37 weeks and averaged as 33,9±0,1. Among them, there were 222(51,3±2,4%) children of 37-35 gestational age, 127(29,3±2,2%) children of 34-32 gestational age, 127(29,3±2,2%) – of 31-29 gestational age, 17(3,9±0,9%) – of 28-27 gestational age. The age of pregnant women varied from 17 to 43 years old and averaged 22,6±2,0 years old. There were 277(64,0±2,3%) prima gravida and 156 (36,1±2,3%) with more than one pregnancy. The control group included 33 relatively healthy newborns without intrauterina infections. Gestational age of newborns in control group ranged from 30 to 37 weeks and averaged 34,8±0,2 weeks. The weight of newborns varied between 2000 and 3170 grams and averaged 2259,1±38,7 grams. There were 5 (15,2%) boys and 28(84,8%) girls in the healthy group. The height of children varied from 39 sm to 52 sm, averaging 46,2±0,6 sm; the head circumference ranged from 28 to 36 sm and averaged 31,6±0,3 sm; chest circumference ranged from 26 to 34 sm averaging 30,0±0,3 sm.

All children received comprehensive dynamic clinical examination, laboratory evaluation, biochemical and bacteriological tests of blood, urine and stool (per indications). Verification of ethiological diagnosis was made by immunoenzyme analysis on Sirio (Italy)

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laboratory equipment with use of reactants of Nova-Lisa firm (Germany) through testing for specific IgM, IgG type antibodies against CMV, HSV-1 and HSV-2. The detection of infectious agents by PCR in biological fluid samples (blood, saliva, urine) were also performed for confirmation of congenital infection.

Determination of neurospecific enolase (NSE), IL-1β, IL-6 was performed using standart method of solidphase («sandvich» variant) of immunoenzyme analysis by using the diagnostic test systems by «Vektor-Best» (Novosibirsk, RF) on ElisysUnoHuman analyser (Germany).

Statistical analysis of the obtained results were completed per modern requirements and included one-way analysis of variance by Kruskall-Wallis, correlational using ρ-Spirman, discriminative analysis using "Cut of Point", dispersion analysis using ANOVA and ROC-analysis. We used EXCEL-2010 and SPSS-20 to conduct statistical data analysis.

Results and discussion:

The research included the analysis of patient records, prenatal and intranatal risk factors, as well as prevalence of pathogens causing perinatal infection among observed children. The impact of maternal, fetal and newborn-related factors to the development of perinatal infections, the one way analysis of variance based on non-parametric criteria by Kurskall-Wallis test for determinational ofthe prevalence of these factors among the studied groups was performed. The differences between the compared parameters were statistically significant with $p<0,05$.

Following the analysis of health status and details of somatic anamnesis of mothers of premature babies with perinatal infections, we found that 253(58,4±2,4%) had extragenital pathologies which was higher than among mothers of healthy babies ($\chi^2=19,3$; $F=15,2$; $p<0,001$). Analysis of obstetric anamnesis demonstrated that majority of mothers of premature babies with perinatal infections (205 (47,3±2,4%)) had gynecological diseases ($\chi^2=23,2$; $F=18,9$; $p<0,001$). Among mothers with complicated obstetrical anamnesis there was statistically significant prevalence of stillbirthes ($\chi^2=19,2$; $p<0,001$; $F=1,46$;$p=0,225$) comparing with medical abortions ($\chi^2=2,3$; $p=0,511$), with prenatal fetal death ($\chi^2=4,6$; $p=0,198$). As the comorbidities complicating the pregnancy, the gestosis of second half of pregnancy was found in 151(34,9±2,3%) cases ($\chi^2=39,4$; $p<0,001$; $F=3,71$; $p=0,012$), pregnacy termination concern – among 104(24,0±2,1%) cases ($\chi^2=46,7$; $p<0,001$ $F=1,4$; $p=0,241$) and anemia was found among 301 (69,5±2,2%) cases ($\chi^2=50,9$; $p<0,001$ $F=1,01$; $p=0,36$).

Complicated labour and delivery, surgical delivery and number of mothers with infections were statistically significant.

Syndrom of CNS depression was found to be most prevalent neurological diagnosis that was reported equally in all three groups, including control group. It is important to indicate that analysis of main neurological syndromes of neonatal period revealed that seizures were noted among 32 (27,1±4,1%) premature newborns with mixed infection and among 24(25,3±4,5%) with sepsis. Tonic-clonic seizures were most prevalent in these groups. Seizures were found among 28 (12,7±2,2%) children with CMV infection. Our research also demonstrated that hypertensive syndrom 32 (27,1±4,1%) is more prevalent among premature newborns.

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Although the syndrome of autonomous-visceral disorders was found in all three groups of newborns, however it was statistically more prevalent in the group with bacterial infection 23(24,2±4,4%).

The analysis of clinical data showed that clinical condition of newborns at birth as well as during the next days of life remained severe and very severe. Therefore it is extremely difficult to define the neurological syndromes of CNS injury. The severity of general clinical condition along with morphological and functional immaturity secondary to premature birth conceal neurological syndromes. This highlights the importance of complete and comprehensive evaluation with the goal of early differential diagnosis of CNS disorders and development of treatment strategies.

Analysis of neurosonographic data demonstrated that percentage of intracerebral bleeding was higher in the group of premature newborns with CMV infection and sepsis (table 1). It was revealed that premature newborns with intrauterine infections had concomittant CNS lesion such as intraventricular hemorrhages, which was partly attributed to hypoxia, partly to the injurious impact of toxins on the vascular wall leading to the increased permeability and in anatomically "weak spots" (periventricular zones) also causing the damage to vasculature and development of hemorrages.

Hemodynamic changes of infectious origin were equally reported in all groups of premature newborns: 34(15,5±2,4%); 20(16,9±3,5%); 18(18,9±4,0%). Analysis of neurosonography demonstrated that ventriculitis occured more often among newborns with CMV and sepsis, while the meningitis – among children with mixed and bacterial infection.

Although ventriculomegaliy (enlargement of horns of lateral ventricules) of various severity, including hydrocephalus, was equally diagnosed among newborns with infection, however it occured more often in II group 30 (25,4±4,6%) and III groups 22 (23,4±4,4%). These findings represent very severe pathological processes (intracranial hemorrhages, intrauterine infections of the brain among premature newborns with low birth weight.

Pathological neurosonographic signs (calcifications, cysts, mineralising vasculopathy) were reported less among evaluated premature newborns in groups I and II than among term newborns. Thus, calcifications in group I were reported among 13(7,3±2,0%) term newborns and 9(4,1±2,0%) of prematurely born babies, in group II it was respectively 9(4,1±2,6%) and 14(11,9±3,0%). Mineralising vasculopathy occured more often in the group of premature newborns with mixed infection.

Evaluation of children with intrauterine infections showed that 14 premature newborns with defects of brain development had other developmental defects, 2 children (0,9±0,6%) had CMV infection, 11 (0,8±0,8%) had mixed infection and 2 (0,9±0,6%) newborns had sepsis.

Table 1.

Sonographic signs of cerebral pathology in premature newborns with perinatal infection. (see Annex)

Hypoxic ischemic, hemorrhagic, infectious lesion of CNS occured more often in newborns with mixed infection and sepsis. Concentrations of NSE in the plasma of children were determined on 5-7th day of life in the acute phase of disease upon admission to the ward and

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again on 25-28th day of life (upon completion of neonatal period). The level of NSE in the plasma of healthy premature newborns was 6,0±0,8 ng/L, while in premature babies with CMV infection it was 3.4 times higher averaging 20,3±1,3 ng/L. Our research showed 4.9 fold increase in the levels of NSE in the late neonatal period compared with early neonatal period (29,6±2,5 ng/L and 20,7±1,8 ng/L respectively) in premature newborns with mixed infection. The levels of NSE was 3.4 fold higher in prematurely born babies with sepsis in comparison with control group (p<0,001). In early neonatal period the level of NSE ranged between 7,9 and 31 ng/L, averaging 20,3±1,9 ng/L. Monitoring of NSE level demonstrated constantly higher levels averaging 18,0±1,5 ng/L, and it did not normalize by the ned of neonatal period.

The characteristics of cytokine status in newborns with perinatal infection was studied using criteria of Kruskel-Wallis and revealed the statistically significant increase in level of pro-inflammatory cytokines in comparison with that of control group: IL-6 – 5.4 fold increase (χ^2=33,9; p<0,001), IL-1β – 5.5 fold increase (χ^2=27,0; p<0,001),

Highest level of IL-1β was demonstrated in premature babies with CMV and bacterial infections, while premature babies with mixed and bacterial infections had highest level of IL-6.

Table 2.
Neuroimmunological indicators of blood in premature newborns with perinatal infections. (see Annex)

While analysing the levels of NSE in premature babies, we defined the area under curve ROC, standart error, defined upper and lower limits of CI 95% as well as asymptomatic levels (CI). According to the levels of NSE the area under curve was S=0,971±0,022 (95%CI: 0,928-1,000; p<0,001), IL-1β in premature babies - S=0,990±0,012 (95% CI: 0,966-1,00; p<0,001), IL-6 - S=1,000±0,000 (95% CI: 1,000-1,000; p<0,001).

To determine the prognostic value of NSE based on coordinates of ROC, we defined the cut-of-points that reflects the point when total values of sensitivity and specificity reaches the maximum level. The optimal cut-of-point of NSE in prematurely born babies was 11 pg/ml. At this point the sensitivity was equal (Se) 85,3±6,1% and specificity (Sp) - 90,0±9,5%. Optimal cut-of-point forIL-1β was 3,5 pg/ml. At this point, the sensitivity (Se) is equal to 97,1±2,9%, specificity (Sp) - 90,0±9,5%; while for IL -6 ≥ 4 – Se = 100,0%, Sp = 90,0±+9,5%.

Table 3.
«Cut-of-points» for NSE, IL-1β, IL-6 in premature newborns with perinatal infections.

	NSE ≥ 11	**IL-1β>3,5**	**IL-6>4**
Sensitivity – true (+) results Se	85,3±6,1	97,1±2,9	100,0±90,0
Specificity – true (-) results Sp	90,0±9,5	90,0±9,5	90,0±9,5
Predictive value (+) results pPV	96,7±3,3	97,1±2,9	97,1±2,8
Predictive value (-) results nPV	64,3±12,8	90,0±9,5	100,0±0,0
Likelihood ratio (+) results LR+	8,53 good	97,1 good	10,00 good
Likelihood ratio (-) results LR-	0,16 good	0,03 excellent	0,00 excellent
Overal diagnostic value of the test DK	86,4±5,2	95,5±3,1	97,7±2,2

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Overal diagnostic value of the NSE test was 86,4±5,2%, of IL-1β - 95,5±3,1%, of IL-6 - 97,7±2,2%. This confirms their overall good diagnostic efficiency.

Further we used one factor dispersion analysis ANOVA (Analysis of variance) and determined that weight of factor for values of NSE≥11 was 84,8(95% CI:86,3-83,3; p<0,001), for IL-1β>3,5 weight of factor was 313,1 (95% CI:333,8-292,4; p<0,05), for IL-6>4,0 weight of factor was 695,5% (95% CI 753,2-637,7; p<0,001),

In premature newborns with perinatal infections we used correlational analysis by ρ-Spirmen and determined several associations between the lesions of CNS, NSE and other parameters defining the severity of the disease. The level of NSE was found to be in direct average correlation with anemia of prematurity which was defined by lower than normal Hb (ρ_s=0,508, p=0,001) and erythrocytes (ρ_s=0,355, p=0,27). Level of NSE is dependant from hyperproduction of IL -1β (ρ_s=,584,p<0,001), IL-6 (ρ_s=,450,p=0,001). Correlational analysis demonstrated the direct average association between CNS lesion (ρ_s=,501, p<0,001) and weak association with infections of CNS (ρ_s=,353,p=0,019).

The premature birth of children with perinatal lesion of CNS was associated with complicated antenatal period, including: gynecological diseases (ρ_S=0,101, p=0,30), anemia of pregnancy (ρ_S=0,116,p=0,030), extragenital pathologies (ρ_S=0,131,p=0,005). Hypoxic injury of CNS was negatively associated with the antropometric parameters at birth. These babies had smaller birth weight (ρ_S=-0,098, p=0,035), height (ρ_S=-0,119, p=0,013), Apgar score at 1st minute (ρ_S=-0,485, p<0,001) and 5th minute (ρ_S=-0,440, p<0,001), hemoglobin level (ρ_S=-0,174, p<0,001) and RBC count (ρ_S=-0,156, p<0,001). Direct correlation was identified between CNS lesion and elevate level of bilirubin уровня билирубина (ρ_S=0,256, p<0,001), IL-1β(ρ_s=,579,p<0,001), IL-6(ρ_s=,547,p=0,003), IL-18(ρ_s=,514,p<0,001), TNF-α (ρ_s=,363,p=0,016).

The clinical data analysis showed that perinatal infections were more often associated with neurological disorders that included hypoxic-ischemic, hypoxic-hemorrhagic lesions and CNS infections. Identified correlation between the levels of NSE and cytokines demonstrates the ongoing acute systemic inflammatory reaction to the infectious agent amid the severe CNS injury.

Conclusion: We used comprehensive approach including clinical, echo and doppler study, immunological studies in newborns with perinatal infections to provide for timely prognostic evaluation of severity of CNS damage. It seems that higher levels of NSE, IL-6, IL-1β in the plasma of newborns with infectious and inflammatory diseases reflect the concomittant, more severe lesion of CNS as the result of hypoxia, intoxication and inflammation. Thus, the good diagnostic value of neuroimmunological indicators found in plasma of newborns with perinatal infections enables to use them as markers of damange to blood-brain barrier, provide for timely prognostic evaluation, define the severity of CNS injury and commence early treatment.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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ETHICAL APPROVAL

No ethical approval was required as this was a clinical case.

CONSENT

Patient permission was obtained prior to writing this report.

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Table 1.

Sonographic signs of cerebral pathology in premature newborns with perinatal infection..

	I group (n=220)	II group (n=118)	III group (n=95)	χ^2 p_{ku}	F; p
Hemodynamic changes of ischemic nature:	133*** 52,0±3,8%	77*** 65,3±4,4%	57* 60,0±5,0%	χ^2=48,4 p<0,001	F=17,9 p<0,001
Disorders of brain circulation	89 40,5±3,3%	36 37,1±4,9%	29 30,5±4,7%		
Отек головного мозга	62 28,2±3,0%	13 13,4±3,5%	15 15,8±3,7%		
Cerebral ischemia of II-III degree	12 5,5±1,5%	1 1,0±1,0%	5 5,3±2,3%		
Periventricular leukomalacia	15 6,8±1,7%	2 2,1±1,4%	13 13,7±3,5%		
Hemodynamic changes of hemorrhagic nature:	58** 26,4±3,0%	57*** 48,3±4,6%	31** # 32,6±4,8%	χ^2=30,5 p<0,001	F=10,8 p<0,001
Perivetricular Bleeding (PVB) I grade	36 16,4±2,5%	34 28,8±4,2%	21 22,1±4,3%		
(PVB) II grade	16 7,3±1,8%	20 19,3±3,5%	8 8,4±2,8%		
(PVB) III grade	6 2,8±1,0%	3 2,5±1,4%	2 2,1±1,5%-		
Hemodynamic changes of infectious nature:	34 15,5±2,4%	20 16,9±3,5%	18^^^ # 18,9±4,0%	χ^2=7,1 p=0,069	F=2,4 p=0,068
Ventriculitis	33** 15,0±2,4%	16 13,6±3,2%	16 16,8±3,8%		
Meningitis	2 0,9±0,6%	4 3,4±1,7%	3 3,2±1,8%		
Calcifications	9 4,1±1,3%	14 11,9±3,0%	-		
Congential brain developmental defect	2 0,9±0,6%	11 0,8±0,8%	2 2,1±1,4%		
Periventricular cysts	16 7,3±1,8%	21 17,8±3,5%	1 1,7±3,6%		
Mineralising vasculopathy	12 5,5±1,5%	16 13,6±3,2%	2 2,1±1,4%-		

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Ventriculomegaly	45 20,5±2,6%	30 25,4±4,6%	22 23, 4±4,4%		

Notes:

1. Statistical power of difference with the control group: * – p<0,05; ** – p<0,01; *** – p<0,001.
2. CI 95% is given in the bracket (lower and upper limits). $\chi 2$; p_{ku} – results of one-way analysis of variance by Kruskal-Wallis
3. F; p– results of one factor dispersion analysis per Fisher.

Table 2.
Neuroimmunological indicators of blood in premature newborns with perinatal infections.

Indicators, пг/мл	**Control group**	**I group (n=14)**	**II group (n=9)**	**III group (n=21)**	**χ^2; p_{ku}**	**F; p**
IL-1β	2,8±0,2 (2,4 –3,2)	14,2±2,5 (8,8-19,5)	9,5±1,9 (5-13,9)	21,8±3,4 (14,2-29,3)	$\chi 2$=27,0; p <0,001	F =10,1; p <0,001
IL-6	3,4±0,1 (3,2 – 3,7)	12,7±1,6 (9,3-16,1)	16,1±2,0 (11,6-20,7)	28,2±2,2 (23,4-33,1)	$\chi 2$=34; p<0,001	F =35,6; p <0,001
NSE	6,0±0,8 (4 – 12)	20,3±1,3 (7-29)	29,6±2,5 (14-41)	20,3±1,9 (7,9-31)	$\chi 2$=20,3; p <0,001	F =9,1; p <0,001
NSE repeat testing	14,5±1,1 (8-21,2)	14,5±1,1 (8-21,2)	20,7±1,8 (12,8-32)	18,0±1,5 (9,9-23,5)	$\chi 2$=0,9; p <0,001	F =0,53; p= 0,006

Notes:
1.Statistical power of difference with the control group: * – p<0,05; ** – p<0,01; *** – p<0,001.
CI 95% is given in the bracket (lower and upper limits).
2. $\chi 2$; p_{ku} – results of one-way analysis of variance by Kruskal-Wallis
3.. F; p– results of one factor dispersion analysis per Fisher.

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