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Diagnostics of septic myocardial dysfunction in neonates

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Neonatal sepsis (NS) continues to be the one of the major problems in neonatal practice. This is due to the variability of clinical manifestations and, in part, the lack of available diagnostic markers that are significantly associated with mortality as a result of neonatal sepsis.

The purpose — to study the role of paraclinical markers of myocardial dysfunction in neonates with sepsis.

Materials and methods. To achieve this goal, 87 newborns (the main group) with manifestations of a generalized infectious-inflammatory process were under our observation. The control group included 30 newborns, in which infectious and inflammatory diseases were refuted. Examination and treatment of patients with NS was carried out in accordance with modern international guidelines and recommendations.

Results and discussion. Based on a comprehensive clinical and paraclinical examination of neonates of the main group, it was found that 25 (28.7%) newborns suffered from early sepsis, respectively, the remaining 62 (71.3%) patients had late NS. According to the severity of the condition, 76 (87.4%) children of the main group included in the study required intensive care, which was provided in the neonatal intensive care unit. The average value of procalcitonin in the main observation group was 2.53±0.33 ng/ml, respectively, in the control group — 0.24±0.04 ng/ml ($p<0.05$). The mean values of creatine phosphokinase, MB fraction and troponin I in the main observation group were 58.44±2.39 U/l and 0.33±0.05 ng/ml, respectively, in the control group — 41.74±2.45 U/l and 0.04±0.01 ng/ml ($p<0.05$).

Conclusions. Generalized infectious-inflammatory process in neonates is accompanied by increased activity of cardiotropic biochemical markers.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Local Ethics Committee of the institution mentioned in the work. Informed consent of the children's parents was obtained for the research.

No conflict of interests was declared by the authors.

Keywords: neonate, neonatal sepsis, septic myocardial dysfunction.

До питання діагностики септичної міокардіальної дисфункції в новонароджених

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Неонатальний сепсис (НС) й надалі залишається однією з основних проблем у неонатальній практиці. Це зумовлено варіабельністю клінічних проявів та частково браком доступних діагностичних маркерів, достовірно пов'язаних зі смертністю внаслідок НС.

Мета — вивчити роль окремих параклінічних маркерів міокардіальної дисфункції в новонароджених із сепсисом.

Матеріали та методи. Для реалізації поставленої мети під спостереженням перебувало 87 новонароджених (основна група) із проявами генералізованого інфекційно-запального процесу. До групи контролю увійшло 30 новонароджених, в яких інфекційно-запальні захворювання спростовані. Обстеження та лікування хворих на НС здійснювали відповідно до сучасних міжнародних настанов і рекомендацій.

Результати. На підставі комплексного клінічно-параклінічного обстеження новонароджених основної групи встановлено, що на ранній сепсис страждали 25 (28,7%) новонароджених, відповідно в решти 62 (71,3%) пацієнтів мав місце пізній НС. Відповідно до тяжкості стану, 76 (87,4%) дітей основної групи потребували проведення інтенсивної терапії, яку надавали у відділенні інтенсивної терапії новонароджених. Середнє значення прокальцитоніну в основній групі спостереження становило 2,53±0,33 нг/мл, у контрольній групі — 0,24±0,04 нг/мл ($p<0,05$). Середнє значення креатинфосфокінази, фракції МВ та тропоніну І в основній групі спостереження становило 58,44±2,39 Од/л та 0,33±0,05 нг/мл, у контрольній групі — відповідно 41,74±2,45 Од/л та 0,04±0,01 нг/мл ($p<0,05$).

Висновки. Генералізований інфекційно-запальний процес у новонароджених супроводжується підвищенням активності кардіотропних біохімічних маркерів.

Дослідження проведено відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом установи, зазначеної в роботі. Дослідження виконано за інформованої згоди батьків дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: новонароджений, неонатальний сепсис, септична міокардіальна дисфункція.

Introduction

Modern definition of neonatal sepsis (NS) suggests signs of life-threatening multiorgan dysfunction caused by generalized infectious-inflammatory process and, above all, inadequate response and invasion of pathogens [25]. At the same time, constellation scales confirm the existence of life-threatening dysfunctional insufficiency of individual organs and organ systems, as well as the degree of its severity [23].

Sequential organ failure assessment (SOFA), a system for quantitative assessment of organ dysfunction, recommended according to the materials of the Third International Consensus on Sepsis and Septic Shock [25], did not meet the requirements of neonatology and needed to be adapted [18]. The Neonatal SOFA Constellation System (nSOFA) was developed to meet the need for a consensus definition of neonatal sepsis [31]. It should be noted, in particular, that cardiac dysfunction associated with neonatal sepsis is not as well studied as in older patients [2,7], but it is believed that cardiac dysfunction caused by sepsis occurs more often in newborns and older children than in adult patients [30].

Although overall neonatal survival rates have improved [34], sepsis remains an important factor associated with long-term morbidity and mortality, especially in the preterm infants [1,5,22,26]. Despite the fact that estimates of the global burden of NS differ significantly according to various sources, it is still believed that sepsis in the neonatal period leads to the annual loss of about 1.4 million children [11,24]. Thus, late sepsis, which occurs after 72 hours of life, affects from 20% to 30% of extremely premature infants and is accompanied by 15% mortality [8,10,12,27–29].

Despite numerous efforts to improve methods of diagnostics and treatment, the progress achieved in the fight against NS should be recognized as rather modest, which is partly due to the lack of available diagnostic markers that are significantly associated with mortality due to NS [4,14,32].

Unfortunately, the sepsis diagnostic clinic in newborns has some difficulties. The first manifestations of the disease are often nonspecific and can be easily confused with the manifestations of noninfectious diseases. Thus, this leads to variability of the criteria used to diagnose NS [13]. It should be noted that sepsis-mediated myocardial dysfunction is one of the most common components of multiorgan mismatch in the severe sepsis and the septic shock [15]. Myocardial dysfunction in NS is the one of the important risk factors for the growth of neonatal mortality, and its correction today seems to be quite limited both in terms of diagnostics and treatment. To date, several factors contributing to cardiomyocyte damage in NS have been identified, including increased regulation of innate immunity receptors in the heart itself, cytokine circulation, changes in nitric oxide synthesis, impaired calcium homeostasis, and oxidative stress [9,16,17].

Thus, today the issue of searching for modern screening methods that can be used to verify the possible development of septic myocardial dysfunction in newborns remains relevant.

The purpose — to study the role of paraclinical markers of myocardial dysfunction in neonates with sepsis.

Materials and methods

To achieve this goal on the basis of Neonatal Intensive Care Unit (NICU), the Department of Neonatal Pathology (DNP) and Care Unit for Premature Babies in Chernivtsi Regional Children's Clinical Hospital under our observation there were 87 newborns (the main group) with manifestations of the generalized infectious-inflammatory process. With the informed consent of parents, the control group included 30 newborns of the neonatal units of Regional Children's Clinical Hospital (RCCH) who were of the same age (up to 28 days) and in whom infectious and inflammatory diseases were refuted, and the predominant nosological forms were hypoxic-ischemic encephalopathy, hyperbilirubinemia (due to indirect fraction), breastfeeding disorders, etc. Investigated newborns of the main group were divided into two subgroups, depending on the necessary of treatment inotropic support. Thus, 36 (41.4%) newborns received inotropic support because of hemodynamic instability, and these children were included in 1st subgroup. The 2nd subgroup consisted of the remaining 51 (58.6%) patients who did not have clinical symptoms of sepsis-associated cardiovascular disorders.

Criteria for inclusion in the main group were: age 0–28 days of extrauterine life, the presence of factors predisposing to infectious-inflammatory process by the mother and/or newborn, taking into account specific propensity factors, the presence of one or more loci of infection, the development of clinical manifestations of organ dysfunction, associated with the infectious and inflammatory process.

The exclusion criteria were: other pathological conditions of the neonatal period, accompanied by multiple organ dysfunction, as well as conge-

Table 1

General characteristics of comparison groups

Indicator			Main group (n=87)	Control group (n=30)
Gestational age, weeks		M±m	35.3±0.39	37.9±0.48*
Body weight at birth, g		M±m	2561.2±102.37	3077.3±134.52*
Body length at birth, cm		M±m	47.3±0.72	51.1±0.77*
Sex	male	abs. (%)	53 (60.9)	18 (60.0)
	female	abs. (%)	34 (39.1)	12 (40.0)
Birth by caesarean section		abs. (%)	37(42.5)	8 (26.7)

Note: * — difference between the main group and the control group, p<0.05.

nital heart defects and cardiomyopathy of another (non-infectious) origin. The general characteristics of the comparison groups are given in table 1.

Identified intergroup differences were considered regular, which reflected the correctness of the formation of comparison groups, but they were not associated with risk factors for the development of NS.

Examination and treatment of patients with NS was carried out in accordance with modern international guidelines and recommendations [20,21]. All newborns, in addition to clinical examination, on the basis of the biochemical laboratory of Chernivtsi Regional Children's Clinical Hospital using a biochemical analyzer HTI BioChem FC-200 (USA) and reagents "Cormay" (Poland), biochemical determination of markers of ischemic myocardial lesions in blood serum was performed: lactate dehydrogenase activity (LDH, norm 225–450 U/l), creatine phosphokinase, MB fraction (MB-CPK, norm 24 U/l). The content of troponin I in the blood serum was determined by immunochemiluminescent analysis in the educational and scientific laboratory of BSMU (Maglumi IAA analyzer (CLIA), manufactured by Shenzhen New IBECo, PRC; reagents manufactured by SNIBE Co., Ltd, PRC, norm up to 0.10 ng/ml) and procalcitonin (analyzer Maglumi IAA (CLIA), manufactured by Shenzhen New IBECo, PRC; reagents manufactured by SNIBE Co., Ltd, PRC, norm up to 0.50 ng/ml).

The study was conducted with the informed consent of the patient's parents and was performed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee (protocol No.7 dated April 19, 2018) for all children who participated in the study. Statistical processing of the results of the study was carried out using the methods of variation statistics with the calculation of the arithmetic mean (M) and the standard error of the mean (m). Clinical and epidemiological risk indicators were assessed by calculating the ratio of chances of an event (OR) and relative risk (RR), taking into account their 95% confidence intervals (95% CI), as well as indicators of specificity, sensitivity, prognostic value, likelihood ratio and attributable risk (AR). Statistical processing of actual data was performed using the program StatSoft Statistica v 6.0., with a known number of observations (n). The critical level of significance of "P" in testing statistical hypotheses in this study was considered at $p<0.05$.

Results and discussion

During the study, the diagnosis of NS was made on the basis of a comprehensive clinical and paraclinical examination of newborns, in particular, 25 (28.7%) newborns suffered from early sepsis, respectively, the remaining 62 (71.3%) had late neonatal sepsis. According to the severity of the condition, 76 (87.4%) children of the main group included in the study required intensive care, which was provided in the neonatal intensive care unit. It should be noted that 24 (27.6%) newborns of the main group needed inotropic support, which lasted 3.08±0.41 days at the stage of maternity hospitals. In addition, 25 (28.7%) newborns required inotropic drugs for 5.25±0.97 days in NICU of RCCH ($p<0.05$). The average therapeutic dose of dobutamine was initially 6.13±0.52 μg/kg/min, and in the neonatal intensive care unit — 6.87±0.81 μg/kg/min ($p>0.05$), which reflected the severity disorders of the cardiovascular system in this cohort of newborns with neonatal sepsis. Regarding the control group, it was noted that in 3 (10%) cases the general condition after birth was assessed as severe, however, in none of the cases neonates required inotropic support.

Thus, the issue of searching for preclinical markers of cardiovascular damage that would allow timely suspicion of this complication of NS remains relevant. So, all children on admission to the neonatal intensive care unit underwent routine laboratory tests. The main indicators of the complete blood count (CBC), absolute neutrophil count (ANC), leukocyte intoxication index (LII) and nuclear intoxication index (NII) according to G.D. Dashtayantsom were taken into account. Indicators of the complete blood count at hospitaliza-

Table 2

Some indicators of the complete blood count at hospitalization in newborns of comparison groups

Indicators	Main group (n=87)	Control group (n=30)	p
Blood leukocytes ($\times10^9$/l), ±m	20.09±1.25	13.41±0.79	p<0.05
Band neutrophils (%), ±m	18.0±0.94	8.33±1.09	p<0.05
ANC, ($\times10^9$/л), ±m	14.08±1.07	6.51±0.62	p<0.05
LII, ±m	2.59±0.47	0.42±0.06	p<0.05
NII, ±m	0.61±0.06	0.41±0.04	p<0.05
Thrombocytes, G/l, ±m	255.28±16.28	291.44±12.62	p>0.05

Notes: ANC — absolute neutrophil count; LII — leukocyte intoxication index; NII — nuclear intoxication index.

Table 3

Activity of biochemical markers of cardiovascular system damage in newborns of comparison groups

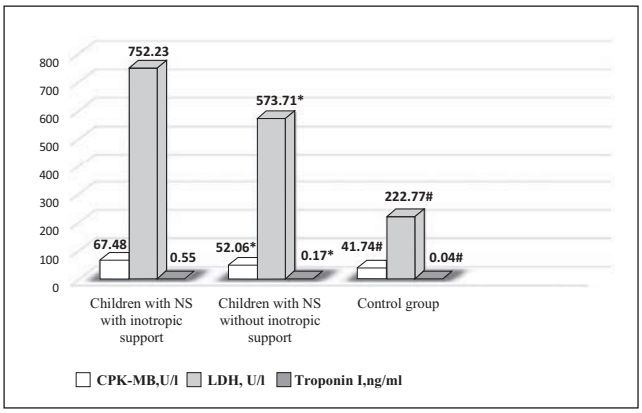
Indicators	Main group (n=87)	Control group (n=30)	p
CPK-MB, U/l, ±m	58.44±2.39	41.74±2.45	p<0.05
LDH, U/l, ±m	647.59±30.94	222.77±21.85	p<0.05
Troponin I, ng/ml, ±m	0.33±0.05	0.04±0.01	p<0.05

Notes: CPK-MB — creatine phosphokinase, MB fraction; LDH — lactate dehydrogenase.

tion in children of research groups are given in table 2.

Thus, the assessment of hemogram indicators, leukocyte indices in newborns with NS reflected the inflammatory response of the body. Along with a significant increase in the number of band neutrophils, the analysis showed that the content of leukocytes in peripheral blood more than 20.0 G/l was observed in the main group in 36 (41.4%) of patients, and in the control group — 1 (3.3%) of observations (p<0.05). Despite the lack of significant differences in absolute platelet count among newborn comparison groups, it was found that thrombocytopenia less than 100.0 G/l was observed in the main group in 13 (14.9%) of patients, and in the comparison group such a decrease in platelet count was not observed. Significant excess of the reference values of procalcitonin levels in all blood serum samples of the examined newborns confirms its importance for the verification of the infectious process in newborns [13]. Thus, the average value of procalcitonin in the main observation group was 2.53±0.33 ng/ml, respectively, in the control group — 0.24±0.04 ng/ml (p<0.05).

It should be noted that due to the lack of clear diagnostic criteria in the sources of the research of the cardiovascular system damage in NS, there



Notes: * — comparison between subgroups of children with NA with the need for inotropic support and without inotropic support, p<0.05; # — comparison between a subgroup of children with NA with the need for inotropic support and without inotropic support with the control group, in all cases p<0.05; CPK-MB — creatine phosphokinase, MB fraction; LDH — lactate dehydrogenase.

Fig. 1. Distribution of the mean serum activity indicators of cardiospesific markers among newborns with NS

are significant difficulties in assessing the cardiac syndrome in newborns. Today, significant markers of cardiomyocyte death, which may indicate the involvement of the myocardium in the infectious-inflammatory process, are increased activity of blood MB-CPK, LDH and cardiac troponin I (cTn I) [6]. According to the statements in the reference resources used in the research, in newborns under the influence of the trigger factor there is an activation of the lipid peroxidation system and a decrease in antioxidant protection, which does not cope with the neutralization of reactive oxygen species that are formed. This leads to severe secondary damage to cell membranes, including cardiomyocytes, which contributes to the persistence of the pathological process and complicates the prognosis. Thus, it is shown that pathological disorders in the lipid peroxidation system persist during the first year of life, which explains the duration of preservation of CPK-MB activity and cTn I content at a high level [33].

Table 3 shows the the activity characteristics of cardiospecific enzymes in the blood serum of the examined newborns of the comparison groups.

The analysis of troponin levels and activity of the above cardiospecific enzymes in patients of the main group depending on the need of children for inotropic support during treatment requires special attention. Figure 1 shows an analysis of the frequency distribution of the mean values of the serum activity of cardiospecific markers in patients with and without inotropic support, as well as similar markers in the comparison group.

As follows from the above data, cases of high activity of cardiospecific enzymes occurred in the group of newborns with NS who needed inotropes in the treatment process, which indicated a deeper damage to cardiomyocytes. Based on this, it can be assumed that an increase in these markers is associated with a high risk of developing septic myocardial dysfunction and can be considered risk criteria for the presence of this complication in a cohort of newborns with sepsis. Distribution of activity indicators of cardiospecific markers and troponin levels in patients with and without

Table 4

Distribution of indicators of cardiospecific marker activity among neonates with sepsis depending on reference values and averages

Indicator	A subgroup of neonates with NS on inotropic support, 1st subgroup (n=36)	A subgroup of neonates with NS without inotropic support, 2nd subgroup (n=51)	Control group (n=30)	p
Frequency of cases is above average				
CPK-MB >54.16 U/l	25 (69.4%)	23 (45.1%)	6 (20%)	p1st:2nd <0.05 p1st,2nd:c<0.05
LDH >541.38 U/l	26 (72.2%)	28 (54.9%)	—	p>0.05
Troponin I >0.27 ng/ml	24 (66.7%)	5 (9.8%)	—	p<0.05
Frequency of cases is above the normative values				
CPK-MB >24 U/l	36 (100%)	48 (94.1%)	27 (90%)	p1st:2nd >0.05, p1st,2nd:c>0.05
LDH >450 U/l	33 (91.7%)	35 (68.6%)	—	p<0.05
Troponin I >0.1 ng/ml	36 (100%)	11 (21.6%)	—	p<0.05

Notes: CPK-MB — creatine phosphokinase, MB fraction; LDH — lactate dehydrogenase.

Table 5

Diagnostic value of troponin I in the detection of cardiac dysfunction in NS

Indicators	Diagnostic value, % (95%CI)				Likelihood Ratio	
	sensibility	specificity	Predictive value		positive result	negative result
			positive result	negative result		
Troponin I >0.27 ng/ml	68.7 (58.6-77.6)	90.9 (83.4-95.7)	88.3 (78.9-94.5)	74.4 (65.7-81.8)	7.55	0.34

inotropic support was analyzed, using the specified normative values and average indicators as the distribution point in the total cohort of examined newborns (Table 4).

Analysis of these indicators in the control group showed that the frequency of exceedances of CPK-MB >54.16 U/l was observed in 20% of cases, while exceeding the level of LDH and troponin I above the average in this group did not occur. Analyzing these indicators in accordance with the reference values, it was found that the activity of LDH and troponin I did not go beyond their limits in any case and only in 90% of newborns the level of CPK-MB exceeded 24 U/l. Increased CPK-MB activity can probably be associated with perinatal hypoxia, cardiotoxic effects of indirect bilirubin in neonates of the control group [3,19].

In such a way, taking into account the above data, the prognostic indicators of the risk of developing septic myocardial dysfunction in newborns with sepsis were studied based on the assessment of troponin I activity in blood serum. Thus, in relation to representatives of the subgroup of newborns with NS who did not require inotropic support, in the comparison group with a level of troponin I in the blood serum >0.27 ng/ml, the risk of administration of vasopressor drugs is respectively: OR — 21.92 (95% CI 9, 83–48.8), RR — 3.44 (95% CI 1.83–6.49), AR — 0.63. Using this paraclinical marker for diagnostic purposes in relation to cardiac dysfunction in neonatal sepsis, its diagnostic value has been measured, shown in Table 5.

The relative risk of developing septic myocardial dysfunction with the need for inotropic support in terms of CPK-MB activity >54.16 U/l was 1.7 (95% CI 1.3–2.2), the odds ratio was 2.8 (95% CI 1.54–4.9), and the attributable risk is 0.24.

Conclusions

Generalized infectious-inflammatory process in newborns is accompanied by increased activity of cardiotropic biochemical markers.

If there is a level of troponin I >0.27 ng/ml in the blood serum, the risk of developing septic myocardial dysfunction in newborns, which is manifested by the need for inotropic support, is 21.92 (95% CI 9.83–48.8) with sensitivity 68.7% of this test.

Prospects for further research: timeliness of diagnostics of myocardial disorders in newborns with sepsis is one of the prerequisites for rational therapy aimed at eliminating these disorders and preventing further complications.

No conflict of interests was declared by the authors.

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