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PARTICULAR PARACLINICAL INDICES IN NEWBORN SEPSIS PATIENTS WHOSE PARENTS CONSTANTLY LIVED IN DIFFERENT ENVIRONMENTAL CONDITIONS

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Abstract

Xenobiotics can have a variety of effects on the human body, and especially on the course of intrauterine development. Numerous researchers point out that it is the nature of the environment that can negatively affect the course of certain diseases in both children and adults. Neonatal sepsis is one of the most serious diseases in neonatology practice. And, in our opinion, the topic of the influence of adverse environmental factors on the features of sepsis in newborns depending on the ecological situation of their parents' habitats is unclarified.

The research aims at the particular paraclinical indices in children with neonatal sepsis whose parents constantly lived in different environmental conditions.

Material and methods. To study the aim, a comprehensive survey of 260 newborns who suffered from neonatal sepsis in 2016-2018 was conducted. The groups have been formed based on the complex evaluation of the prolonged influence of the anthropogenic pollution of air, water and soil on the body of parents of newborns in the parts of the region.

The ecological risk coefficient (ERC) has been proposed concerning the environmental situation in the regional centers. Thus, the first clinical group (the main group) included neonatal sepsis patients whose parents permanently lived in parts with an ERC of 2.0 or more and with unfavorable environmental characteristics of the regional center. The second group (comparison) was formed by newborns with sepsis, whose parents permanently lived in areas with a low risk of adverse effects of these environmental factors on their body (ERC<2.0).

Results and discussion. The content of interleukins-6, -8.-10, C-reactive protein, presepsin and procalcitonin in the blood serum of patients with neonatal sepsis showed the activity of the systemic inflammatory response of the body to an infectious agent. It should be noted that high serum levels of interleukin-10, which has an anti-inflammatory effect, was more often registered in patients of the I clinical group. Thus, the blood content of this interleukin 35.0 pg/ml occurred in the newborn of the main group in 23.7% of cases, and in children of the comparison group – in 18.1% of observations. Along with a clearer identification of high levels of anti-inflammatory interleukin-10 in patients of the I group, a significant decrease in serum concentrations of immunoglobulins of classes A, G, M was observed in these newborns.

Conclusions. The decrease in the level of the above serum immunoglobulins is probably due to the immunosuppressive effect of xenobiotics on the fetus, whose mother was under the conditions of long-term action of xenobiotics. This, in turn, reduces the resistance of the newborn body to infection and contributes to a more severe course of the infectious process. Probably, the more severe manifestations of neonatal sepsis in newborns of the I clinical group are partly due to a combination of decreased immunoglobulin synthesis and increased interleukin-10 production.

Keywords: neonatal sepsis; presepsin; immunoglobulins; contamination.

According to the decision of the World Health Organization, prevention, diagnosis and classic management of sepsis are recognized as a priority task of public health in the coming decades due to its high morbidity and mortality [1-2]. The frequency of sepsis, the nature of its course and the consequences of the disease are influenced by numerous factors, in particular, the environmental situation in the places where parents of sick children live. Adverse environmental influences, especially during sensitive periods of intrauterine fetal development, can cause structural, metabolic and genetic changes that increase the susceptibility to infectious diseases after birth [3, 4]. Immunotoxicity of xenobiotics leads to damage to the functional state of innate and adaptive immunity, and a violation of the balance

between activation and suppression leads to hypersensitivity reactions [5]. The risk of pathogenic effect of adverse environmental factors is increased by the features of toxicokinetics, changes in the functional state of the placenta and the metabolism of xenobiotics under environmental load, where they act as predisposition factors [6]. Numerous studies are aimed at adults [7,8], but there are practically no studies concerning children, so such studies are topical and promising.

The aim of the study is to investigate the particular paraclinical indices in children with neonatal sepsis whose parents constantly lived in different environmental conditions.

Material and methods. To study the aim, a comprehensive survey of 260 newborns who suffered from neonatal sepsis in 2016-2018 was conducted. Examination of patients was carried out in neonatal departments of the Municipal Medical Institution "Regional Children's Hospital" in Chernivtsi, as well as the corresponding departments of Khmelnytskyi.

The entry criteria were:

- informed consent of parents to conduct research;
- the presence of the diagnostic criteria for sepsis in a child;
- neonatal period of life;
- permanent residence of parents in places with a certain amount of environmental load on the body of environmental factors;
- the first day of the disease and intensive treatment in the neonatal intensive care unit.

The non-entry criteria were:

- the presence of congenital malformations in newborns;
- suspicion or presence of primary immunodeficiency in the child and inborn errors of metabolism;
- significant changes in the principles of treatment of neonatal sepsis;
- the presence of technical issues that did not allow a comprehensive examination of newborns.

Diagnosis and treatment of neonatal sepsis were carried out according to the recommendations of leading neonatologists in Ukraine, taking into account international recommendations [9, 10]. The groups have been formed based on the complex evaluation of the prolonged influence of the anthropogenic pollution of air, water and soil on the body of parents of newborns in the parts of the region. The ecological risk coefficient (ERC) has been proposed concerning the environmental situation in the regional centers. Thus, the first clinical group (the main group) included neonatal sepsis patients whose parents permanently

lived in parts with an ERC of 2.0 or more and with unfavorable environmental characteristics of the regional center. This clinical group will be further defined as the "main group". The second group (comparison) was formed by newborns with sepsis, whose parents permanently lived in areas with a low risk of adverse effects of these environmental factors on their body (ERC<2.0). This clinical group will be designated as a "comparison group".

Assessment of the environmental situation in the places where parents live was carried out following the methodological recommendations [11].

Complex anthropo-technogenic load on the environment, taking into account the bioavailability of pollutants in soil, water and air in certain areas of the region by the value of the proposed environmental risk coefficient (ERC) was determined by the formula:

$$ERC = \frac{soil + 2 * water + 3 * air}{3}$$

where the amount of pollution of the components was defined as the ratio of local and regional indicators, that is, the ratio of pollution in a particular area to the average value for all districts of the region. The coefficients before the terms conditionally showed the bioavailability of the load on the body of pollutants of soil, water and air. Taking into account these coefficients and following the methodological recommendations [11], the value of ERC less than 2.0 was regarded as an index of a favorable environmental situation, and ECR 2.0 or more indicated the risk of adverse effects of environmental factors on the body. The source of data on soil, water and air pollution in Chernivtsi and Khmelnytskyi regions was the data provided in the materials by the State Statistics Service [12].

Table 1 - Clinical characteristics of patients

Clinical Groups	Number of patients	Frequency of cases, (%)			
		Sex		Maturity	
		Boys	Girls	Mature	Prematurely born
I (Main)	141	84 (59%)	57(41%)	24 (17%)	117 (83%)
II (Comparison)	119	64(54%)	36(56%)	31 (26%)	88 (74%)
P		>0.05	>0.05	>0.05	>0.05

Thus, a large proportion of the general sample of children who suffered from sepsis in the neonatal period was represented by patients whose parents lived in places with adverse environmental conditions. Taking into account the fact that the comparative general clinical

characteristics of the comparison groups did not reveal significant differences, we can assume that the clinical groups were formed correctly.

The study was conducted prospectively using the "experience-control" method in parallel groups using a simple random sample. The design of the non-randomized controlled examination provided for the identification of clinical, laboratory, and instrumental features in children with neonatal sepsis, whose parents constantly lived in places with different environmental and hygienic characteristics. A comprehensive examination of patients with neonatal sepsis was performed on the 1st day of the disease, which was determined by the day of diagnosis and the beginning of intensive care, as well as on the 3rd and 7th days of treatment.

Immunological studies were conducted in the laboratory of MMI "Regional Children's Clinical Hospital" in Chernivtsi by the enzyme-linked immunosorbent assay on the device "Stat Fax 303/Plus" (USA):

- the content of immunoglobulins A, G, M in blood serum (g/l) using the test systems of Ltd. "GRANUM" (Kharkiv, Ukraine);
- the concentration of interleukins -6,-8,-10 (pg/ml) in blood serum using a set of reagents "Interleukin-6 ELISA-BEST", "Interleukin-8 ELISA-BEST", " Interleukin-10 ELISA-BEST»;
- the content of C-reactive protein in blood serum (mg/l) using reagents "SRP ELISA-BEST highly sensitive" (RF);
- determination of serum presepsin (Human sCD14, ng/ml) using a reagent: Hycult Biotech NK 320, Netherlands.

The obtained research results were analyzed using the computer package "Statistica 6" Stat Soft and Excel XP for Windows on a personal computer using parametric and nonparametric calculation methods.

The results of research and discussion. The identification of certain features of the disease manifestations (namely, more severe in the main group) in the comparison groups during a physical examination of the patients with neonatal sepsis suggested the presence of changes in the detailed blood tests. Table 2 shows the indices of red blood cells in the examined patients on the 1st day of the disease.

These data suggest that the average values of erythropoiesis in peripheral blood in children of the comparison groups did not differ significantly. However, it is worth noting that cases of an increase in the average volume of red blood cells of more than 115 fl. were observed in patients of the I group (77.8%) more often than in children of the II group

(22.2%). At the same time, a decrease in the hemoglobin content in the red blood cell mass below 150 g/l was observed in 55.6% of cases in the main group and 33.3% of observations (P<0.05) in the comparison group. On the following day of observation, the indices of erythropoiesis in peripheral blood did not differ significantly.

Table 2 - Indices of peripheral blood erythrocytes in the examined newborns on the 1st day of the disease

Clinical groups	Number of patients	Hemoglobin (g/l)	Erythrocytes (10^{12}/l)	Mean Corpuscular Volume, (fl)	Mean hemoglobin content in the red blood cell mass, (g/l)
I	141	141	162,2±2,8	4,8±0,08	110,7±2,1
II	119	119	166,1±3,3	5,0±0,09	103,7±4,2
P		>0.05	>0.05	>0.05	>0.05

Table 3 shows the indices of peripheral blood leukogram in children of the comparison groups.

Table 3 - Leukocyte formula in the examined children on the 1st day of the disease

Clinical groups	Number of patients	Leukocytes, 109	Neutrophils (%)		HI≥0.5*	Lymphocytes, (%)
			Band neutrophil	Segmented neutrophil		
I	141	15,8±0,7	14,2±0,7	39,2±1,2	0,45±0,03	39,0±1,3
II	119	16,1±0,7	14,4±0,9	43,0±1,5	0,42±0,04	34,4±1,56
P		>0,05	>0,05	>0,05	>0,05	<0,05

Note * - neutrophil index

Despite the absence of significant differences in the content of white blood cells and neutrophil granulocytes in the peripheral blood of children of the comparison groups, a qualitative analysis of these indices allowed us to establish certain features. Thus, the content of leukocytes in peripheral blood less than 5.0 G/l was observed in the I group in 2.2% of patients, and in the II group – 0.8% of observations (P<0.05). The relative content of segmented neutrophils more than 50.0% was more often observed in patients of the II group (39.1%) than in patients of the main group (28.1%, P<0.05).

On the 3rd day of treatment, there were no significant differences in the relative content of leukocytes and neutrophil granulocytes in peripheral blood compared to the 1st day of the disease in the comparison groups. The relative content of lymphocytes in patients did

not differ significantly compared to the 1st day, as well as in the comparison groups. Thus, the relative content of lymphocytes in newborns of the main group was 35.1±1.27%, and in the comparison group – 37.3±1.5% (P>0.05). Qualitative analysis of the content of lymphocytes in peripheral blood on the 3rd day of treatment of sepsis patients in the comparison groups did not establish significant differences.

On the 7th day of treatment, the content of white blood cells in the blood of patients of the I group was 16.1±0,76 G/l (P1:7>0.05), band neutrophils – 10.4±0.86% (P1:7>0.05), segmented neutrophil granulocytes – 37.8±1.21% (P1:7>0.05), lymphocytes – 42.4±1.45% (P1:7>0.05), neutrophil index - 0.32±0.04 (P1:7<0.05). Indices of leukogram in children of the comparison group did not differ significantly from the leukogram of patients of the main group and were respectively 15.2±0.67 G/l, 10.6±1.07%, 36.9±1.36%, 43.3±1.7% (P1:7<0.05).

There were no cases of leukopenia in the examined children on the 3rd and 7th days of treatment. The neutrophil index on the 7th day of treatment was 0.32±0,04 in group I (P1:7<0.05), and 0.35±0,05 in group II (P1:7>0.05).

The average platelet content in children of the main group on the 1st day of the disease was 212.4± 10,0 G/l, on the 3rd day - 223.1±10,57 G/l and the 7th day – 207.2±11.37 G/l (P3:7<0.05). In the comparison group in these terms of treatment of patients, the content of platelets in the peripheral blood of children was 220.3±11.2 G/l, 220.7±11.9 G/l and 251.4±14.7 G/l (P1.3:7<0.05), respectively. On the 7th day of treatment for sepsis, the content of blood plates in patients of the comparison group was significantly higher concerning patients of the main group (P<0.05). It should be noted that the platelet content of less than 100 G/l on the 1st day was observed in 15.5±3.0% of cases in newborns of the main group, and on the 7th day - in 26.2±3.7% of cases (P<0.05). In the comparison group, such a decrease in platelet content was not identified. Thus, on the 1st day of sepsis treatment, the platelet content in the blood of these patients <100 G/l was observed in 19.8±3.6% of cases, and on the 7th day - in 17.9±3.5% of cases (P>0.05).

Thus, markers of decreased hemoglobin synthesis were more often detected in the peripheral blood in newborns of the main group than in the comparison group on the 1st day of the disease. Indices of the blood leukocyte formula showed the inflammatory response of the body without significant inter-group differences. Cases of thrombocytopenia in newborns of the main group increased by the 7th day of sepsis treatment.

Fig. 1 shows the content of the studied interleukins (Il) in the blood serum of newborns of the comparison groups on the 1st day of sepsis treatment.

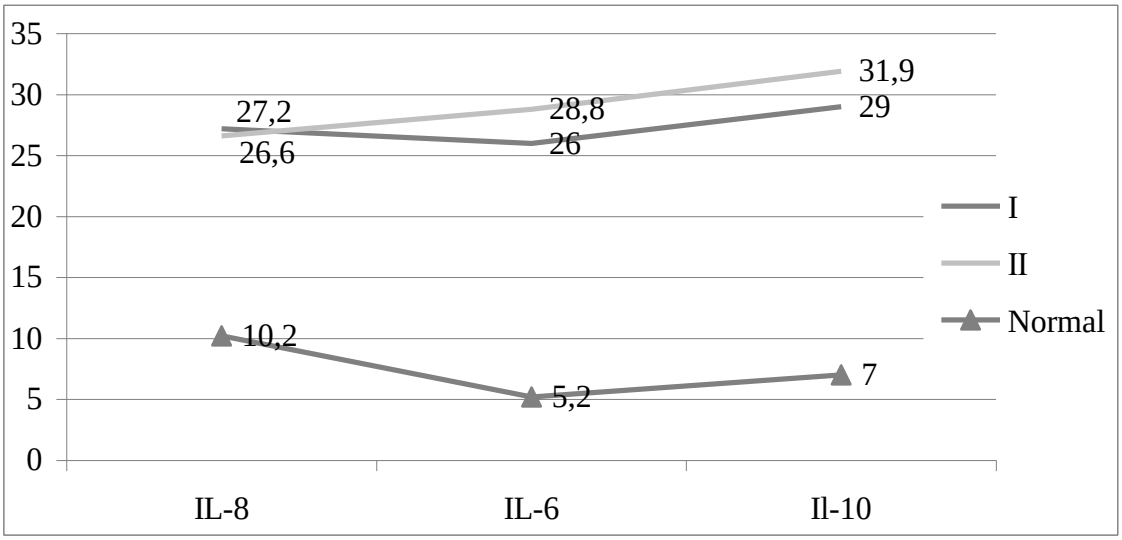


Fig. 1 - Diagram. The content of interleukins (pg/ml) in the blood serum of newborns of the comparison groups on the 1st day of the disease

These data give reason to believe that the average content of interleukins-6, -8, -10 in the blood serum of patients of comparison groups on the 1st day of the disease did not differ significantly. The blood content of interleukin-6 and interleukin-8 more than 40.0 pg/ml was detected in 20.1±3.4% and 18.0±3.5% of cases in the main group and 25.9±3.6% (P>0.05) and 20.7±3.7% (P>0.05) of cases in the comparison group. The content of the mentioned interleukins in the blood less than 10.0 pg/ml was observed in 31.6±3.9% and 46.0±4.2% of children of the main group and 30.0±4.2% and 42.2±4.5% of the II group (P>0.05). The concentration of interleukin-10 at the level of 35.0 pg/ml or more was observed in 23.7±3.5% of patients of group I and 18.1±3.5% of newborns of the II group (P>0.05). The interleukin-10 content of less than 7.0 pg/ml was identified in 29.5±3.8% of cases in the main group and 38.8±4.5% of cases in the comparison group (P>0.05).

It should be noted that the ratio of intreleukin-6 to interleukin-10, which is a specific indicator of neonatal sepsis in children of the comparison groups, was the same and made 0.9.

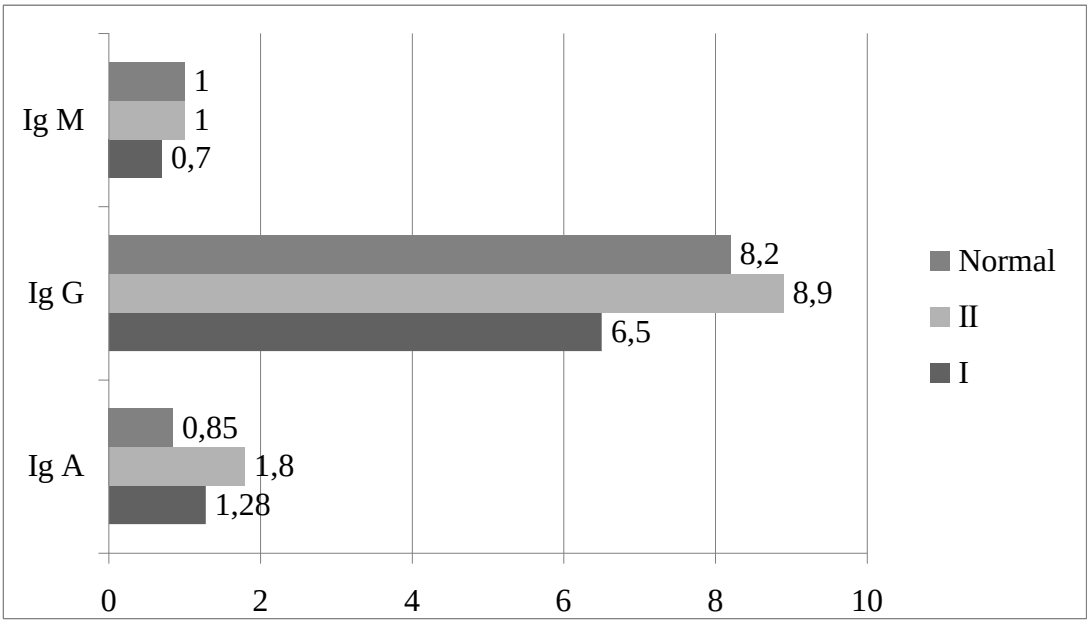
Table 4 shows the content of acute phase indices of inflammation (C-reactive protein, procalcitonin) and indices of activation of macrophage phagocytosis (presepsin) in the blood serum of patients of the comparison groups on the first day of the disease.

In newborns of the I clinical group, the serum content of reactive protein less than 10.0 mg/ml was observed in 32.4±3.9% of cases, and in the II group – in 25.0±3.9% of cases (P<0.05). Presepsin concentration of more than 900.0 pg/ml was found in 37.4±4.0% of children in the main group and 28.4±4.1% of patients in the comparison group (P<0.05).

Table 4 - The contents of the systemic inflammatory response and activation of phagocytes in blood serum of children of the comparison group

Clinical Groups	Number of patients	C-RP, mg/l	Presepsin, pg/ml	Number of patients	Procalcitonin, ng/ml
I	139	23,4±1,2	910,2±54,8	20	1,12±0,5
II	116	24,8±1,4	849,4±74,6	11	0,14±0,04
P		>0.05	>0.05		>0.05

Fig. 2 shows the average values of the content of immunoglobulins A, M, G (g\l) in the blood serum of children of the comparison groups on the 1st day of sepsis disease.



Note: * - P I: II <0.01

Fig. 2 - The content of immunoglobulins A, M, G (g/l) in the blood serum of children of the comparison groups on the 1st day of sepsis

Thus, in newborns of the main group, a significant decrease in the level of immunoglobulins A, M, G in the blood serum relative to patients of the comparison group was revealed. It was noted that in the newborns of the I group, the concentration of immunoglobulins A and M less than 1.0 g/l was observed in 64.9± 4.0% and 77.6±3.5% of cases, respectively, and the Ig G less than 5 g/l was determined in 49.2±4.2% of observations. In the comparison group, the above immunoglobulin content was detected in 38.4±4.4% (P<0.05) of patients, 64.2±4.4% (P<0.05), 27.7±4.1% (P<0.05) of children.

Conclusions. The decrease in the level of the above serum immunoglobulins is probably due to the immunosuppressive effect of xenobiotics on the fetus, whose mother was under the conditions of long-term action of xenobiotics. This, in turn, reduces the resistance of the newborn body to infection and contributes to a more severe course of the infectious process. Probably, the more severe manifestations of neonatal sepsis in newborns of the I clinical group are partly due to a combination of decreased immunoglobulin synthesis and increased interleukin-10 production.

The authors declare that they have no conflict of interest.

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