

Characteristics and significance of risk factors in the development of hematological syndromes in children

Características y significado de los factores de riesgo en el desarrollo de síndromes hematológicos en niños

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Abstract

In order to identify the causes of the development of diseases of the blood system and hematopoietic apparatus in children at the early stages of their formation, the risk factors for the development of hematological abnormalities in children of 1378 children living in Russia were studied. For this, the results of anamnesis and laboratory diagnostic methods of research were used. The data of peripheral blood, iron metabolism, biochemical analysis and bone marrow hematopoiesis were taken into account. The results of the study made it possible to identify risk factors for the development of hematological abnormalities in children. It was determined that persistent hematological abnormalities in children can form against the background of congenital inferiority or intrauterine damage to the hematopoietic system, caused by the influence of unfavorable factors at the ante and postnatal stages of development, alimentary disorders, immaturity and failure of the immunohematological system. Hematological deviations arising in response to the action of endo - and exogenous factors can be considered as adaptive transformations of peripheral blood parameters, reflecting the general reaction of the hematopoietic system. Taking into account risk factors makes it possible to form children into risk groups for the occurrence of hematological syndromes in the early stages of development, to timely diagnose and treat them.

Key words: iron deficiency anemia, leukopenia, iron deficiency, children, risk factors.

Resumen

Para identificar las causas del desarrollo de enfermedades del sistema sanguíneo y del aparato hematopoyético en niños en las primeras etapas de su formación, se estudiaron los factores de riesgo para el desarrollo de anomalías hematológicas en niños de 1378 niños que viven en Rusia. Para esto, se utilizaron los resultados de la anamnesis y los métodos de investigación de diagnóstico de laboratorio. Se tuvieron en cuenta los datos de sangre periférica, metabolismo del hierro, análisis bioquímico y hematopoyesis de la médula ósea. Los resultados del estudio permitieron identificar factores de riesgo para el desarrollo de anomalías hematológicas en los niños. Se determinó que las anomalías hematológicas persistentes en los niños pueden formarse en el contexto de inferioridad congénita o daño intrauterino al sistema hematopoyético, causado por la influencia de factores desfavorables en las etapas ante y posnatal del desarrollo, trastornos alimentarios, inmadurez y falla del sistema inmunohematológico. Las desviaciones hematológicas que surgen en respuesta a la acción de factores endógenos y exógenos se pueden considerar como transformaciones adaptativas de los parámetros sanguíneos periféricos, lo que refleja la reacción general del sistema hematopoyético. Tener en cuenta los factores de riesgo permite agrupar a los niños en grupos de riesgo para la aparición de síndromes hematológicos en las primeras etapas del desarrollo, para diagnosticarlos y tratarlos a tiempo.

Palabras clave: anemia ferropénica, leucopenia, ferropenia, niños, factores de riesgo.

In recent decades, there has been an increase in the frequency of hematological abnormalities among the pediatric population^{18,31,38}. The most studied among them are iron deficiency anemia (IDA), which is widespread in many regions of the world^{14,39,40}. It was found that anemia is most often detected in pregnant women and children^{9,12,15}. Thus, anemia is diagnosed in 88% of pregnant women living in India, in 50% and 40%, respectively, in Africa and Latin America. In childhood, anemia in these regions averages 40-50%, reaching 100% in some areas^{6,11,38}. In industrially developed countries, iron deficiency anemia is diagnosed in 20.1% of children under 4 years of age and in 5.9% of children under 14 years old, in Russia, iron deficiency anemia is detected in 6-40% of the child population and its frequency prevails among children of early and adolescence^{5,9,12,19}.

The development of hematological syndromes in children may be associated with functional inferiority of the bone marrow as a result of the myelotoxic action of endo- and exogenous factors, physical, chemical and biological agents, radiation, drugs, or be a consequence of genetic defects in myelopoiesis, viral and bacterial infections^{17,20,26,28}.

Interest in the study of hematological abnormalities is increasing due to the fact that some authors consider them as precursors of pre-leukemic changes that increase the risk of their leukemic transformation^{16,17,34}. A number of studies have shown that the stage of pre-leukemia does not have characteristic clinical symptoms, the onset of leukemia occurs under the "mask" of an acute respiratory or other infection^{7,10,29}, which complicates the diagnosis of leukemia in the early stages of development^{8,22,23}. In this regard, the role of prenatal diagnostics of such transformations in the hematopoietic system increases, especially in persons with a burdened oncohematological history. At the same time, the greatest emphasis is given to taking into account risk factors that contribute to the onset of the formation of transient hematological changes that are capable of subsequently, in conditions of prolonged unfavorable myeloid aggression, to the progression of the pathological process.

To date, there is information about the relationship between the debut and the nature of the initial period of acute lymphoblastic leukemia with the constitutional type of the child³, various forms of leukemia, myelodysplastic syndrome - with the unfavorable socio-economic status of the family, chromosomal abnormalities, Down syndrome, immunodeficiency, Fanconi anemia, Shwachman's syndrome, and others^{2,7,24,27}.

In this regard, the study of risk factors for the formation and risk factors for an unfavorable course of hemocytopenia is an important source of information about the state of hematological status and determining the likelihood of an unfavorable prognosis of cytopenic transformations.

Purpose of the study:

To study the data of the anamnesis and establish the risk factors for the development of hematological abnormalities in children.

To study the anamnesis data, the study included 1378 children of both sexes, aged from birth to 17 years old, living in the Republic of Bashkortostan, Russia. The conclusion of the Expert Council on Biomedical Ethics in Clinical Disciplines of the Bashkir State Medical University was obtained for the research, based on the informed consent of the research participants. Among the studied patients with iron deficiency anemia were 129 (9.36%), including boys - 56 (43.41%), girls - 73 (56.59%); children with leukopenia - 798 (57.91%), of which boys - 442 (55.39%), girls - 356 (44.61%) and patients with iron deficiency anemia, combined with leukopenia in the peripheral blood - 451 (32, 73%), of which boys - 201 (44.57%), girls - 250 (55.43%). Children aged from birth to 3 years amounted to 175 (12.70%), from 4 to 6 years 208 (15.09%), from 7 to 14 years 870 (63.14%), from 15 to 17 years 125 (9.07%). For the control group, 76 healthy children of similar age were selected, the hematological parameters of which were within the range of age fluctuations.

The research program included the collection of anamnesis data, determination of risk factors for the disease, examination of children and laboratory control to establish the diagnosis of iron deficiency anemia and leukopenia.

The history of the life of children revealed the presence of adverse factors affecting the state of health of the child, starting from the antenatal stage, family history, medical and social living conditions. To diagnose hematological abnormalities, the general condition and clinical status of children were assessed when they went to a hospital or polyclinic, medical records and laboratory results were studied. In all children, the indicators of a general blood test performed on an automatic analyzer (Unicel DxH 800, "Beckman Coulter", USA) were studied, the concentration of hemoglobin, the number of erythrocytes, hematocrit, erythrocyte indices (average erythrocyte volume, the width of distribution of erythrocytes by volume), reticulocytes and hemoglobin content in reticulocytes. Determined the concentration of serum iron and ferritin, the total iron-binding capacity of serum. Transferrin iron saturation coefficient

(%) is calculated by the formula: $\text{TS} = \frac{\text{TSF}}{\text{TIBC}} \times 100\%$. The criterion for the diagnosis of leukopenia was the content of leukocytes below $5.9 \cdot 10^9 / \text{L}$, IDA - the concentration of hemoglobin in children depending on age in accordance with the WHO recommendations [Haemoglobin concentrations for the diagnosis of anemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011].

For statistical processing of the research results, the graphical and static packages Microsoft Excel and Foxgraph, Statistica 6.0 for Windows were used. The results at $p < 0.05$ were considered reliable, which is generally recognized in medical research. When choosing criteria for comparing group means, the distribution normality was checked using the Kolmogorov - Smirnov test. When comparing group averages, for which the Kolmogorov-Smirnov test confirmed the normal distribution, the student's t test was used. When comparing group averages, the normality of distribution of which was rejected, a nonpara-

metric criterion was used - the Mann-Whitney test. The comparison of the frequencies of a binary feature in two unrelated groups was carried out by analyzing 2x2 tables using an original computer program.

The significance of risk factors for the formation of hematological deviations was assessed by the frequency of occurrence of factors (absolute risk, %) and by calculating the mean values % of the relative chance (OR, conventional units). The odds ratio (OR) = $(A / B) / (C / D)$ was determined, where A is the frequency of a symptom in the sample of patients, B is the frequency of patients without a sign, C is the frequency of a sign in the control, D is the frequency in the control sample without a sign.... The indicators were considered reliable with a confidence interval (CI) greater than or less than one. If the CI is more than one, the OR is statistically significantly higher in the group corresponding to the first row of the four-field table and there is an increase in OR. If the CI is less than one, the OR is statistically significantly lower in the group corresponding to the first row of the four-field table and there is a decrease in OR.

Results

The results of studying the anamnesis of the life of children made it possible to establish that the significant risk factors for the development of hematological abnormalities in children were separate medical - biological and social - hygienic factors (Tables 1, 2). In young children, the most noticeable were a burdened obstetric and gynecological history, an unfavorable course of the ante - and postnatal periods (Table 1.2). Studies have shown an increase in the likelihood of developing hematological disorders in children born after an unfavorable course of pregnancy in 1297 mothers (94.12%, $p < 0.05$, OR = 4.13). Among children with anemia, they were 121 (93.80%; $p < 0.001$) patients, with leukopenia - 753 (94.36%; $p < 0.001$) and with anemia combined with leukopenia - 423 (93.79%; $p < 0.001$).

When examining the anamnesis, it was found that 1132 (82.15%; $p < 0.001$, OR = 1.58) pregnant women had complications during childbirth, and 1217 (88.32%; $p < 0.001$) women had a burdened obstetric history (Table. 12). Moreover, this percentage was the highest in the group of children with leukopenia, in second place was the group of children with anemia combined with leukopenia and lower in the group of children with anemia (711 - 89.09%; $p < 0.001$ and 398 - 88.25%; $p < 0.001$ versus 108 - 83.72%; $p < 0.001$).

The chance of developing hematological abnormalities in children increased in the presence of extragenital pathology in 84.11% of mothers ($p < 0.001$, OR = 5.82), during childbirth from the third and more pregnancies - in 38.67% ($p < 0.05$; OR = 1.35) children. Diseases of the neonatal period were found in one third of children, prematurity in 12.7% ($p < 0.05$) of cases. IDA in the first year of life was diagnosed in 38.48% of children, leukopenia - in 33.31%.

The study of the alimentary factor and the identification of alimentary disorders were important in the diagnosis of abnormal-

ities in the child's health (Tables 1, 2). It is known that a diet with a low or low bioavailability of iron, insufficient content of basic food ingredients, vitamins, minerals and deficiencies of other micronutrients can cause the development of pathological conditions, especially in children from families with low socioeconomic status. The study found that 272 (19.74%; $p < 0.05$, OR = 3.33) children of the first year of life were on early artificial feeding or feeding with unadapted milk formulas. Most of the schoolchildren had irregular monotonous meals with an unbalanced diet and a low content of meat products. The predominance of flour, dairy and sweet foods in the diet was found in 589 (42.74%, $p < 0.001$, OR = 2.29) schoolchildren and only in 23.76% ($p < 0.05$) children in the control group. Of these, a rare intake of vegetables and fruits was noted in 41.24% ($p < 0.05$) of children, an irregular intake of meat products - in 35.92% ($p < 0.05$) of patients. A significant risk factor for the development of iron deficiency anemia in 27.89% of adolescent children was insufficient intake of iron from food with a vegetarian diet versus 7.14% ($p < 0.05$) in the control.

Among the postnatal factors, the importance of various pathological conditions, including frequent acute and chronic diseases, was revealed, which indicated a decrease in the function of the body's defense systems and increased the risk of developing immunohematological disorders that determine the failure of bone marrow hematopoiesis (Tables 1, 2). Against the background of violations of the daily regimen and food intake, this could cause an increased morbidity in children. Significance of violations of the daily regimen was noted in 1042 (75.62%; $p < 0.05$) patients. Deviations in physical and neuropsychic development were found in 862 (62.55%; $p < 0.05$) children, of whom 79 (61.24%; $p < 0.05$) patients with anemia, 484 with leukopenia (60.65%; $p < 0.05$) and children with anemia combined with leukopenia - 299 (66.30%; $p < 0.05$).

In the first year of life, 61 (47.29%; $p < 0.001$) children from the group of children with anemia, 352 (44.11%; $p < 0.001$) children with leukopenia, and 209 (46.34%; $p < 0.001$) children from the group of children with anemia in combination with leukopenia (Tables 1, 2). Moreover, in 12.92% of patients, the formation of deviations proceeded against the background of allergies ($p < 0.05$; OR = 2.43).

678 (49.20%; $p < 0.001$; OR = 14.08) children over one year of age had frequent respiratory diseases (Table 1.2). Of these, in the group of children with anemia, there were 53 (41.09%; $p < 0.001$) children, in the group of children with leukopenia - 412 (51.63%; $p < 0.001$) and in the group of children with anemia combined with leukopenia - 213 (47.23%; $p < 0.001$).

Diseases of various organs and systems were found in 657 (47.68%; $p < 0.001$) children with hematological abnormalities (Tables 1, 2). The largest number of such patients was found in the group of children with anemia in combination with leukopenia and anemia than in the group of children with leukopenia (243 - 53.88%; $p < 0.001$ and 66 - 51.16; $p < 0.001$ versus 348 - 43, 61%; $p < 0.001$, respectively). The lesion of the digestive system was accompanied by the development of hematological disorders and was diagnosed in 454 (32.95%; $p < 0.001$; OR = 3.56) patients, which increased the chance of the formation

of the latter (Tables 1, 2). Among them, diseases of the digestive system were more often detected in the group of children with leukopenia and in children with anemia in combination with leukopenia than in patients with anemia (257 - 32.21%; $p < 0.001$ and 154 - 34.15; $p < 0.001$ versus 43 - 33.33%; $p < 0.001$, respectively).

Studies have shown the presence of chronic blood loss (nosebleeds, prolonged and heavy menstruation in adolescent girls) in 16.67% ($p < 0.05$) girls and 7.12% ($p < 0.05$) boys, which is higher than in the control (7.51% and 3.11%; $p < 0.05$; respectively).

Table 1. Biomedical and socio-hygienic risk factors for the development of hematological abnormalities in children

Indicators	IDA		Leukopenia		IDA with leukopenia	
	absolute number	relative number	absolute number	relative number	absolute number	relative number
1	2	3	4	5	6	7
Burdened obstetric history	108	83,72 **	711	89,09 **	398	88,25 **
Pathological course pregnancy	121	93,80 **	753	94,36 **	423	93,79 **
Deviations in the state of health of children in the first year of life	61	47,29 **	352	44,11 **	209	46,34 **
Frequent acute respiratory infections	53	41,09 **	412	51,63 **	213	47,23 **
Chronic diseases of the digestive system	43	33,33 **	257	32,21 **	154	34,15 **
Diseases of other organs	66	51,16 **	348	43,61 **	243	53,88 **
Developmental deviations	79	61,24 *	484	60,65 *	299	66,30 *
Professional harmfulness:						
- mothers	18	13,95 *	96	12,03 *	78	17,29 *
- father	86	66,67	514	64,41	303	67,18
Chronic diseases:						
mothers	46	35,66 *	194	24,31 *	185	41,02 *
father	25	19,38	148	18,55	108	23,95
Unsatisfactory living conditions	37	28,68 **	218	27,32 **	187	41,46 **
Single-parent family	21	16,28	98	12,28	90	19,96
Unfavorable psychological microclimate in the family	11	8,53	57	7,14	38	8,43

* $p < 0.05$; ** < 0.001 - reliability of differences in risk factors between sick and healthy children.

Artificial feeding	30	23,26 *	145	18,17 *	97	21,51 *
Social status:						
mothers:						
- working	57	44,19	388	48,62	261	57,87
- employee	64	49,61	370	46,37	176	39,03
- others	8	6,20 *	40	5,01 *	14	3,10 *
father:						
- worker	84	65,12	504	63,16	315	69,84
- employee	39	30,23	251	31,45	115	25,50
- others	6	4,65	43	5,39	21	4,66
The nature of work:						
mothers:						
- mental	33	25,58	149	18,67	85	18,84
- physical	58	44,96	388	48,63	261	57,88
- mixed	38	29,18 *	261	32,70 *	105	23,28 *
father:						
- mental	23	17,83	139	17,42	74	16,41
- physical	84	65,12	504	63,16	315	69,84
- mixed	22	17,07	155	19,42	62	13,75

Analysis of medical and social anamnesis data showed that 442 (32.08%; $p < 0.001$) children lived in unsatisfactory living conditions, of which the majority turned out to be children suffering from anemia in combination with leukopenia, to a lesser extent children with anemia and leukopenia (187 - 41.46%; $p < 0.001$ versus 37 - 28.68%; $p < 0.001$ and 218 - 27.32%; $p < 0.001$, respectively). It was found that 209 (15.17%) patients lived in single-parent families, the number of which prevailed in the groups of people with anemia combined with leukopenia and people with anemia than in the groups of people with leukopenia (90 - 19.96%; and 21 - 16.28% versus 98 - 12.28% respectively). 386 (28.01%; $p < 0.001$) families with children had low material wealth and 106 (7.69%) children lived in an unfavorable psychological microclimate and asocial behavior of their parents (Tables 1, 2). Their number also prevailed in the groups of persons with anemia and anemia in combination with leukopenia than in the groups of persons with leukopenia (11 - 8.53% and 38 - 8.43% versus 57 - 7.14%, respectively). In terms of social status, among the parents of children, workers predominated, among whom there were 706 mothers (51.23%; $p < 0.05$; OR = 1.10) and 903 fathers (65.53%; $p < 0.05$). By the nature of their work, mothers and fathers were more likely to engage in physical labor (707 - 51.31%; $p < 0.05$ and 903 - 65.53%; $p < 0.05$, respectively).

The study established the presence of occupational hazards in 192 (13.93%; $p < 0.05$) mothers, among whom there were more persons from the group with anemia in combination with leukopenia than among persons with anemia and leukopenia (78 - 17.29%; $p < 0.05$ versus 18 - 13.95%; $p < 0.05$ and 96 - 12.03%; $p < 0.05$). 178 (12.92%; $p < 0.001$, OR = 9.75) children with hematological abnormalities were born to mothers with bad habits (smoking and drinking alcohol).

It was found that 425 (30.84%; $p < 0.05$; OR = 2.30) children with hematological abnormalities had their mothers suffering from chronic diseases of various organs and systems (Tables 1, 2). Of these, the largest percentage of patients was in the group of children with anemia combined with leukopenia and anemia, rather than in children with leukopenia (185 - 41.02%; $p < 0.05$ and 46 - 35.66%; $p < 0.05$ versus 194 - 24.31%; $p < 0.05$). Chronic diseases were found in the fathers of children in 20.39% of cases ($p < 0.05$). Allergic diseases were diagnosed in 10.59% of mothers and 12.92% of fathers of children ($p < 0.05$). Iron deficiency anemia was diagnosed in 1282 (93.03%; $p < 0.001$; OR = 2.60) mothers and in 13.78% ($p < 0.05$) fathers of patients (Tables 1, 2).

Table 2. Comparative OR indicators in children with hematological abnormalities

Risk factors	Frequency of signs		OSH
	Absolute number	Relative number	
Pathological course of pregnancy	1297	94,12 *	3,85
Complicated labor	1132	82,15 **	1,58
Extragenital pathology	1159	84,11 **	5,82
Third or more pregnancy	533	38,68 *	1,35
Artificial feeding	272	19,74 *	3,33
Unbalanced diet	589	42,74 **	2,29
Frequent acute respiratory infections	678	49,20 **	14,08
Repeated bronchitis, pneumonia	242	17,56 *	5,24
Diseases of the digestive system	454	32,95 **	3,56
Allergic diseases	383	27,79 *	2,43
Rickets	103	7,47 *	2,16
Mother's waiting	1282	93,03 **	2,60
Chronic diseases in the mother	425	30,84 **	2,30
Social status mothers - working	706	51,23 *	1,10
Occupational hazards in the mother	192	13,93 *	120,81
Bad habits of the mother	178	12,92 **	9,75

* $p < 0.05$; ** < 0.001 - reliability of differences in risk factors between sick and healthy children.

Analysis of the medical and social history revealed the importance of social burden factors in increasing the chance of developing deviations in the child's health (from $p < 0.05$ to $p < 0.001$ with OR = 120.82). The OR indicator had a significant value in the unfavorable course of pregnancy in 94.12% of children ($p < 0.05$; OR = 4.13), complicated childbirth - in 82.15% ($p < 0.001$; OR = 1.58), with extragenital pathology - in 84.11% ($p < 0.001$; OR = 5.82), with the third or more pregnancy - in 38.67% ($p < 0.05$; OR = 1.35).

The probability of the formation of hematological abnormalities was higher in 93.03% of children born to mothers with iron deficiency anemia ($p < 0.001$; OR = 2.60) and in 30.84% of women with chronic diseases ($p < 0.05$; OR = 2, thirty).

The chance of developing hematological changes increased in children with concomitant abnormalities. The incidence of anemia and leukopenia was higher in children prone to recurrent acute diseases and in patients with foci of chronic infections (Tables 1, 2). This turned out to be typical for 49.20% of frequently ill children ($p < 0.001$; OR = 14.08), for 78.08% ($p < 0.001$) of patients with foci of chronic infection, for 32.95% of patients with chronic diseases of the digestive system. ($p < 0.001$; OR = 3.56), for 27.79% of patients with allergies ($p < 0.05$; OR = 2.43) and 7.5% of children with rickets ($p < 0.05$, OR = 2.16).

Studies have shown higher OR of the development of hemocytopenia with early transfer to artificial feeding in 19.74% of infants ($p < 0.05$; OR = 3.33) and those on an unbalanced diet and having alimentary disorders in 42.74% of children older age ($p < 0.001$, OR = 2.29).

The OR was revealed in 32.08% ($p < 0.001$) of patients living in unsatisfactory material and living conditions, in 28.01% ($p < 0.001$) - with low material wealth, in 51.23% ($p < 0, 05$; OR

= 1.10) of patients whose mothers were engaged in physical labor, in 13.93% ($p < 0.05$; OR = 120.81) children whose mothers were exposed to various occupational harmful factors and in 12.92% ($p < 0.001$; OR = 9.75) children whose mothers had bad habits.

The results of the study reliably indicate the unfavorable consequences of various medical and social factors on the health of the child, increasing the risk of developing hematological abnormalities in children. The chance of developing such deviations in children increased due to the immaturity and high vulnerability of the immune systems, blood and hematopoiesis, low disinfection ability, low reactivity to the total adverse effect of damaging factors.

Thus, the analysis of anamnestic data made it possible to identify the main risk factors for the development of hematological abnormalities in children. Among them, endo - and exogenous factors were identified, including ante - and postnatal and medico-social factors, which turned out to be significantly significant in the formation of hematological abnormalities, which allows them to be attributed to risk factors for the development of anemia and leukopenia at various stages of their development.

Discussion

The results of the study showed that in children with hematological syndromes, various unfavorable factors are revealed, which are present long before the child is born. A significant multifactorial ante -, peri - and postnatal burden was found, accompanying the formation of hematopoietic dysfunction in children with hematological syndromes. The most significant of them at different stages of the child's development have been identified. Thus, among antenatal and intrapartum causes, the main ones were extragenital pathology, unfavorable course of pregnancy, complicated childbirth, chronic diseases of pregnant women, including IDA, which determine the onset of the formation of hematopoietic disorders during intrauterine development. This is evidenced by the formation of iron deficiency anemia and leukopenia in more than a third of children in the first year of life. The likelihood of the formation of iron deficiency anemia in children increased in the presence of late childbirth in women (over the age of 30), third or more pregnancies.

The results of the study may indicate the unfavorable influence of the revealed factors on the state of hematopoiesis of the fetus and the newborn, causing the development of hemocytopenia in young children. According to research by I.B. Alakaeva I.B. et al. (2009) hematological changes in newborns with perinatal infections are non-specific and reflect the general reaction of the hematopoietic system to the effect of an infectious agent. As the child grows, the nature of hematological changes and cytopenic reactions are diagnosed in children older than 1 month¹. Of the medical and biological antenatal and intrapartum causes, the main ones were placental insufficiency, maternal bleeding, prematurity, multiple births, diseases of pregnant women, including anemia.

As a result of the study, a high frequency of the presence of an infectious factor in patients was revealed, which made it possible to identify them as the leading prognostic factors that increase the risk of a complicated course of hemocytopenia. This was stated on the basis of diagnostics in children with hematological syndromes of frequent respiratory diseases ($p < 0.001$; OR = 14.08), foci of chronic infection ($p < 0.001$), including chronic diseases of the digestive system ($p < 0.001$; OR = 3, 56), infectious-allergic burden ($p < 0.05$; OR = 2.43), the presence of background deviations ($p < 0.05$, OR = 2.16). The importance of infectious processes, accompanied by a decrease in the immune reserves of the child's body in hematological syndromes, is evidenced by the author's works of I.B. Alakaeva. et al. (2009), Rumiyanseva A.G. et al. (2015), Husain E.H. et al. (2012). The studies of Inoue S., Wolfe LC., Windle M.L., Crouch G.D., Jones G. (2017) provide information on the differential diagnosis of autoimmune and chronic benign neutropenia³⁰. Neutropenia in these patients is classified as idiopathic, but in most cases its immune mechanism is implied. Thus, the research of S.I. Ilchenko, E.S. Korenyuk, A.A. Fialkovskaya. (2018) described a clinical mask of cyclic neutropenia in the form of severe chronic bronchopulmonary disease in a child⁷.

This is also evidenced by the work of Mary Territo, MD, David Geffen (2018), which shows that patients with neutropenia are more likely to develop such lesions of an infectious origin as furunculosis, pneumonia, stomatitis, gingivitis, paraproctitis, colitis, sinusitis, paronychia, otitis media, etc. others³². The authors note that the infectious process can be accompanied by neutropenia as a result of impaired cell production, immune destruction, or more rapid depletion of neutrophil reserves. In this case, neutropenia can cause the development of bacterial and fungal infections. In viral diseases, neutropenia develops from the first days of the disease and lasts up to 8 days. Transient neutropenia may result from the redistribution of neutrophils from the circulatory bed to the marginal pool, due to viral particles or endotoxins in the blood³².

Among the causes of acute (transient) neutropenia Newburger P.E. (2016) also considers infections - viral (cytomegalovirus, Epstein-Barr viruses, human immunodeficiency virus, influenza, parvovirus b19), bacterial (Anaplasma Bruzella, Eherihia, paratyphoid, M. tuberculosis, tularemia, typhoid), protozoal (Plasmodium species)³⁴.

Husain E. H., Mullah-Ali A., Al-Sharidah S. et al. (2012) also point to a frequent association of transient, or acute, isolated neutropenia with viral infections²⁹.

The research results of K.K. Orynbasarova, I.S. Dzhaksybaeva, D.B. Ismailova (2018) note that hematological changes in cytomegalovirus infection in 58.3% are accompanied by cytopenic syndromes¹¹. Thus, anemia is diagnosed in patients in 42.8% ($p < 0.01$) cases, thrombocytopenia - in 11% ($p < 0.05$), neutropenia - in 11% ($p < 0.05$); monocytosis - in 11.5% ($p < 0.05$). The authors noted that among the risk factors for the development of hematological syndromes, the leading place is taken by cytomegalovirus infection¹¹.

A number of scientific studies have described hemocytopenia under the action of hepatitis B, C, D, E viruses, parvovirus B19,

influenza viruses, the action of pathogens of rickettsial infections, typhoid, paratyphoid, yersiniosis, tularemia, brucellosis, tuberculosis, toxoplasmosis, etc.^{13,20,29}

Chesnokova N.P., Nevvazhai T.A., Ponukalina E.V. et al. (2015) determine the possibility of developing neutropenia in inflammatory diseases, shock, collapse, neurotic conditions, etc.¹⁷. As a result of the study, the authors clearly established the inhibition of bone marrow hematopoiesis in viral, protozoal and bacterial infections (typhoid fever, scarlet fever, viral hepatitis, infectious mononucleosis, measles, rubella and influenza)¹⁷.

According to Mourot-Cottet R., Maloisel F., Severac F. et al. (2016) the causative agents of infection in neutropenia are gram-positive cocci in 18% of cases; in 12% - gram-negative bacilli; in 3% of cases - other microorganisms³³.

Consequently, hematological disorders that develop under the influence of numerous adverse factors are accompanied by the development of focal infection of the nasopharynx, pathology of the respiratory tract, damage to various organs and systems ($p < 0.001$), causing a decrease in the body's defenses, which in turn increases the risk of immunohematological abnormalities and the risk of formation hemocytopenia. At the same time, taking into account the results of the works of B.V. Afanasyeva, L.S. Zubarovskaya (2018), it is important to remember that a long period of dyshemopoiesis in the bone marrow in the form of mono-, bi- and pancytopenia can be accompanied by clinical manifestations of myelodysplastic syndrome (MDS), which in children is more often secondary, developing on the previous background of transient changes in the bone marrow². Although hereditary genetic factors, congenital and acquired syndromes of bone marrow failure are of leading importance in etiology in children with MDS, immunological mechanisms play a significant role in the progression of the disease². In this regard, studies to identify risk factors in children with signs of ineffective hematopoiesis in the early stages of their development takes on a special role. In this case, the leading in the development of the initial stages of hematological syndromes can be the infectious-immune genesis of the pathological process, the timely registration of which can prevent unfavorable hematological progression and can be used to diagnose early transient hematological abnormalities.

According to the research results of Tayupova I.M. (2015) and N.B. Yudina, N.V. Brezhneva (2015) found that the development of iron deficiency anemia in pregnant women and chronic neutropenia in children, especially at an early age, may be associated with malnutrition^{14,20}. Studies indicate that severe protein deficiency, deficiency of vitamin B12, folic acid, etc., can determine the activity of myelopoiesis and cause the development of cytopenia, especially in patients from socially unadapted families^{14,20}.

The results of our own research also showed the importance of the factor of inappropriate nutrition in the formation of the pathology of the blood system in children. At the same time, early transfer to artificial feeding in children under one year of age ($p < 0.05$; OR = 3.33) and unbalanced nutrition in children over the age of one year ($p < 0.001$, OR = 2.29) ... This shows the statistical significance of such risk factors as alimentary disorders in

the development of abnormalities in the hematopoietic system in children ($p < 0.001$).

The significance of alimentary disorders in the development of cytopenic conditions is also indicated in other literature sources^{5,12,18,21}. In accordance with this, the main risk factors can be attributed to an unbalanced diet with a decrease in the use of meat products, a predominance of flour, milk, sweet diets, and rare consumption of vegetables and fruits^{6,9,14}. In the works of Zakharova I.N., Tarasova I.S., Chernova V.M., Machneva E.B. et al. (2015) found that $33.2 \pm 1.17\%$ of schoolchildren have irregular and monotonous meals ($p < 0.01$; RR 1.9). The authors found that a rare intake of vegetables and fruits contributes to the formation of iron deficiency in $45.0 \pm 2.01\%$ of children, meat products - in $35.9 \pm 1.53\%$ of patients⁵.

Along with this, Aigner E, Feldman A, Datz Ch. (2014) believe that the risk of developing iron deficiency anemia may be such a factor as obesity²¹. In the works of Pande S., Ranjan R., Kratsyuk V.A. (2019) also predicts the determination of body mass index as a biomarker of anemic syndrome³⁵.

In the works of Zakharova I.N., Tarasova I.S., Chernova V.M., Machneva E.B. et al. (2015) showed that asocial behavior of parents and low material income of the family, which determine the insufficient content of iron in the diet, contribute to the development of iron deficiency in $30.8 \pm 1.95\%$ - $45.4 \pm 2.11\%$ of patients⁵.

According to our own research, in fact, most of the identified risk factors for the development of hemocytopenia were more often manifested when raising children in families with low material income and low medical activity in the family, asocial, smoking parents. Among the statistically significant social risk factors for the development of early stages of hematological abnormalities in children, unsatisfactory living conditions, bad habits ($p < 0.001$; OR = 9.75) and unfavorable working conditions of the mother ($p < 0.05$; OR = 120, 81), tense psychological microclimate in the family and low social status of the family ($p < 0.05$; OR = 1.10).

Early identification of risk factors for hematological abnormalities in children is an important problem, since there is an opinion about the possibility of their pre-leukemic transformation. Confirmation of the justification of such statements are works devoted to the study of etiopathogenetic factors and their significance in the progression of hematological abnormalities with an outcome in oncohematological diseases^{2,3,4,37}. To date, it has been established that the stage of pre-leukemia is not characterized by special clinical symptoms and the onset of leukemia can acquire a "mask" of various diseases^{7,10,24}. So, Yu.V. Odinets et al. (2008) reveal various debut "masks" of acute leukemia in children; the works of I.I. Spichak, A.V. Gerasimova, E.V. Teplykh (2014) indicate that neutropenia is a natural accompaniment of the oncological process^{10,13}. Orynbasarova K.K., Dzhatsybaeva I.S., Ismailova D.B. (2018) provide a comparative description of hematological changes in children with cytomegalovirus infection¹¹. In the works of II Balasheva and LF Desyatova (2012) the significance of the constitutional factor in clinical polymorphism in children with acute lymphoblastic leukemia is shown³.

A number of studies have revealed a relationship between the unfavorable socio-economic status of the family, chromosomal abnormalities, Down's syndrome, Fanconi's anemia, immunodeficiency, Schwachman's syndrome, etc.^{24,25,36}.

However, the studies of K.S. Kaznacheeva (2011), Chesnokova N.P., Nevvazhai T.A., Ponukalina E.V. et al. (2015), Cherepanova V.V., Mikhailova Z.D., Mikhailova Yu.V., Sinkova V.V. (2019) indicate the complexity of solving the issues of early diagnosis of irreversible hematological transformations in children^{8,16,17}. At the same time, the role of a long-term combined effect of certain unfavorable factors on the hematopoietic system is not excluded, contributing to an unfavorable prognosis of pathological processes^{3,6,9,17}. The lack of accounting and verification of etiological risk factors, late diagnosis of the debut masks of such deviations, as well as an untimely comparative assessment of the informativeness of risk factors as etiological factors in the formation of hematopoietic disorders in the early stages of their formation, can cause the risk of recurrence of the manifestations of dyshemopoiesis. In this regard, the timely identification of etiopathogenetic risk factors for hematological syndromes in children will help.

Conclusion

The results of the study showed the presence of risk factors for the development of the disease in the examined children with hematological syndromes, which determine the early onset of their formation, which, with long-term existence, increases the likelihood of their progression. Among all the established reliably significant etiological mechanisms, endo - and exogenous factors were identified, including ante - and postnatal, medical and social, which actually underlie the formation of hematological abnormalities in children at different stages of growth and development. This allows us to attribute them to risk factors for the development of anemia and leukopenia. At the same time, the most significant among them were congenital inferiority and intrauterine damage to the hematopoietic system, caused by the influence of unfavorable factors on the health of a pregnant woman, aggravated by the pressure of adverse medical and social effects. In most cases, these are alimentary disorders, the failure of immunohematological mechanisms that contribute to an increased morbidity in children in the process of growth and development. In addition, in the aggregate, statistically significant risk factors for the development of hemocytopenia were more often manifested in the conditions of raising children in families with low material income and low medical activity in the family, asocial and smoking parents.

Consequently, the development of hematological syndromes in children may be associated with the myelotoxic effect of various endo - and exogenous factors. But interest in studying the problem is growing due to the fact that the course of hematological abnormalities is largely determined by the intensity and duration of the action of unfavorable factors, when the risk of an unfavorable prognosis is difficult to exclude. Evidence of the validity of this opinion is the research devoted to the identification of debut "masks" of acute leukemia in children, the beginning

of the formation of which is noted at the stage of transient deviations and then accompanying and oncological processes. Of course, for the timely identification of the risk of irreversibility of hematological transformations in children, it is important to know the risk factors for their development, the duration and intensity of their impact. At the same time, the importance of studies to determine the predisposing unfavorable risk factors for hematological syndromes at the early stages of formation increases. This can solve the issues of timely diagnosis, treatment and prevention, as well as improve the prognosis of hematological abnormalities associated with various deviations in the child's health, caused by various damaging agents, which will reduce the oncological interest of the problem.

The results obtained can be used as criteria for the diagnosis and prognosis of hemocytopenia. At the same time, oncological alertness is important in the study of anamnesis data, sequential analysis and a comprehensive assessment of the identified etiopathogenetic factors. Early diagnosis of oncohematological diseases in children is a difficult task due to the nonspecificity of the primary symptoms hidden under the "masks" of other diseases. The study of risk factors for the development of hematological syndromes at the initial stages of their formation will make it possible to develop algorithms for their timely diagnosis and therapy and prevent their unfavorable progression.

Thus, hematological abnormalities in children are formed under the influence of unfavorable ante - and postnatal factors, the intensity of which is determined by their multicomponent nature, immunohematological instability of the body, which increases the risk of hemocytopenia formation. Such early hematological abnormalities arising in response to the action of endo - and exogenous factors against the background of immaturity and failure of the child's body defense systems can be considered as adaptive transformations of peripheral blood indices of a non-specific nature, reflecting the general reaction of the hematopoietic system to infectious or non-infectious aggression. In turn, the diagnosis of such hematological changes can serve as an indicator of both the child's health status and an important diagnostic criterion for pre-leukemic and leukemic transformations of cytopenias. Identification of risk factors allows to form children into risk groups for the occurrence of hematological abnormalities, to timely carry out their diagnosis, treatment and prevention. The formation of a unified register of risk factors for hemocytopenia and the unification of children into risk groups for their development will contribute to the timely diagnosis and determination of individual tactics for managing patients, which will optimize the algorithms for diagnosing early hemocytopenia and prevent their further unfavorable transformation.

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