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Research Article

The Differential Diagnosis of Iron Deficiency Anemia in Children with Somatic Pathology in Outpatient Practice

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Abstract

The study aimed to identify the clinical and laboratory diagnostic features of iron deficiency anemia in children with somatic pathology in outpatient practice. The study involved 160 children residing in Russia. The medical history, objective status of the children, and results of laboratory diagnostic tests were analyzed. Parameters of ferrokinetics including serum iron parameters, total serum iron binding capacity, transferrin saturation coefficient with iron, ferritin, and soluble transferrin receptors were used to evaluate peripheral blood and biochemical parameters. The study results showed that iron deficiency anemias in children with somatic pathology are characterized by normochromic and normocytic features, mild or moderate severity, dependence on the degree of inflammation, and stability of ferritin and soluble transferrin receptors. The leading clinical symptoms were non-specific signs of iron deficiency anemia, which were hidden under the "mask" of lesions of internal organs. These symptoms related to adaptive transformations of peripheral blood parameters reflecting the general reaction of the hematopoiesis system to infectious or non-infectious aggressions. The identified clinical and hematological characteristics were most pronounced in the group of children with inflammatory diseases. At the same time, true iron deficiency anemia was characterized by the absence of clinical and laboratory markers of inflammation, low ferritin levels, and an increased value of soluble transferrin receptors. The diagnosis of such hematological changes can serve as an early diagnostic criterion for predicting persistent transformations in the hematopoietic and iron exchange system and can help prevent complicated course of somatic pathology in children. In this regard, traditional methods for diagnosing anemic syndrome in children with somatic pathology can be used for wide application in outpatient pediatric practice.

Keywords: Anemia; Iron metabolism; Iron deficiency; Inflammation; children.

Introduction

Iron-Deficiency Anemia (IDA) in childhood has specific features of formation and development [1,7,24,31]. Currently, according to the experts of the World Health Organization, up to 600 million children worldwide suffer from anemia, half of which are iron-deficiency anemia [33]. Their frequency is predominant among young and adolescent children [8,10,14,19]. The development of iron-deficiency anemia in children may be associated with the influence of unfavorable ante- and postnatal factors. Iron metabolism disorders may be the result of toxic effects of endo- and exogenous agents or may be a consequence of dietary disorders, viral and bacterial infections [3,8,13,17]. Interest in the study of iron-deficiency anemia in children is increasing since numerous internal organ disorders are accompanied by the development of anemia symptoms, increasing the risk of iron metabolism disorders [9,17]. Currently, the role of anemia accompanying somatic diseases of various origins is increasing, and they begin to occupy a high proportion among all types of anemia in childhood [1,3,16,31]. Klochkova-Abelyants S.A., Surzhikova G.S. (2019), Sahin V.T., Madzhanova E.R., Kryukov E.V., and others (2018), Anushenko A.O., Potapov A.S., Tsimbalova E.G., Gordeeva O.B. (2016) note the peculiarities of the formation of etiopathogenetic mechanisms of the anemic syndrome in infectious-inflammatory, autoimmune, and other pathological processes [3,13,17]. According to Aliyeva A.M. et al. (2017), Blindar V.N., Zubrikhina G.N., Matveeva I.I. (2016), Nairz M. et al. (2016), Wang M. (2016), iron metabolism disorders in children, as characterized by the state of ferrokinetics and the peculiarities of the formation of anemic syndrome in

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infectious diseases, determine the inadequacy of the immune system, leading to a tendency of children to frequent respiratory infections [1,7,27,31].

Anemic syndrome accompanying somatic diseases is often the cause of transient changes in the blood-forming system and the onset of iron-deficiency anemia, in which case it may present itself under the guise of internal organ diseases. This complicates the timely diagnosis of anemia in the early stages of its development, leading to the ineffectiveness of disease therapy on an outpatient basis. Therefore, the role of timely outpatient diagnosis of early stages of iron metabolism disorders in patients with iron-deficiency anemia increases, and their somatic burden should be considered, which, under conditions of prolonged unfavorable aggression, can provoke the progression of the pathological process.

The issues of diagnosing anemia of chronic inflammation are extremely relevant, especially in pediatric practice. The emergence of new data on the pathogenesis of anemia developing against the background of chronic diseases contributes to the development of modern diagnostic systems and the improvement of approaches to therapy. Therefore, timely clinical and laboratory diagnosis of iron-deficiency anemia in children with somatic pathology on an outpatient basis can be an important source of information about the state and causes of iron metabolism disorders, assess their relationship with internal organ diseases, assess the probability of an unfavorable course of diseases in the future, and increase the effectiveness of therapeutic and preventive measures.

Objective

To assess the features of clinical and laboratory diagnosis of iron-deficiency anemia in children with somatic pathology in an outpatient setting.

Materials and Methods

Evaluation of clinical and hematological signs of iron-deficiency anemia was carried out among 100 children with comorbidities of various etiologies living in the territory of the Republic of Bashkortostan, Russia. Among them, there were 48 boys (48%) and 52 girls (52%). The mean age of the children was 8.7 ± 1.57 years (ranging from 1 to 17 years). The comparative group consisted of 30 children with iron-deficiency anemia without somatic pathology (15 boys and 15 girls), with a mean age of 7.43 ± 1.61 years (ranging from 1 to 17 years). The control group included 30 children (16 boys, 14 girls) with a mean age of 7.76 ± 3.80 years (ranging from 1 to 17 years).

The research plan involved clinical and laboratory examination of patients, considering their complaints, medical, and personal history. The diagnosis of iron-deficiency anemia was based on the analysis of clinical symptoms and laboratory indicators. The number of erythrocytes and hemoglobin content per liter of blood, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), and Red blood cell Distribution Width (RDW) were determined using an automated analyzer ("Beckman Coulter" LH750, USA; Sysmex KX-21 MEK-6410K, Japan); the concentrations of Serum Iron (SI) and Serum ferritin (SF), Total Iron-Binding Capacity of Serum (TIBC), Transferrin Saturation Coefficient (TSC), and Soluble Transferrin Receptor (sTfR) were studied on the Architect C8000 using the "Abbott Diagnostics" kit. The criteria for diagnosing iron-deficiency anemia were hemoglobin concentration levels in children determined according to the World Health Organization's guidelines [Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011].

The statistical analysis of the research results was performed using SPSS 16.0 (Statistical Package for the Social Sciences, "Biostat", Version 4.03). The significance of differences was determined using the Student's t-test, and significance (p) was calculated. The difference between two compared values was considered significant if $p<0.05$. The Kolmogorov-Smirnov test was used to check the hypothesis of the "normality" of the feature distribution in the compared groups.

Results

The study results showed that iron-deficiency anemia is detected in somatic diseases of inflammatory and non-inflammatory origin. Inflammatory conditions (upper or lower respiratory tract diseases, gastritis, enterocolitis, urinary tract infections, cystitis, etc.) were diagnosed in 55 (55%) of children, and non-inflammatory conditions (organ developmental abnormalities, eating disorders, vegetative dystonia, thyroid and reproductive gland dysfunction, diabetes, etc.) were diagnosed in 45 (45%).

Differences in the intensity of clinical manifestations of iron-deficiency anemia in children depending on the etiology of somatic pathology were identified in the study. Specific and non-specific signs of anemia were detected in all cases, but their frequency and severity depended on the severity of the disease ($p=0.0044$). Among the clinical features of iron-deficiency anemia, a sideropenic syndrome was identified, which is caused by a deficiency of iron in tissues and is characterized by a variety of clinical symptoms associated with metabolic disorders due to the dysfunction of iron-containing enzymes. This syndrome is manifested by dystrophic changes in the skin and its appendages, atrophy of mucous membranes, distortion of taste and smell, and muscle hypotonia.

In cases of combination of iron-deficiency anemia with accompanying pathology, most children demonstrate pronounced anemic syndrome, manifested by pallor of the skin and mucous membranes, decreased appetite, physical and mental fatigue, dizziness, ringing in the ears, muffled tones of the heart, and the presence of a systolic murmur. They were also more often presented with symptoms of intoxication, tachycardia, dyspepsia, vegetoneurosis (30% vs. 8% respectively; $p=0.024$), and asthenia symptoms (46.7% vs. 24%; $p=0.064$).

The risk of increasing the severity of iron-deficiency state was established in the presence of lesions of internal organs of various etiology. This dependence was found to be more pronounced in children with respiratory organ diseases (OR=7.36; S=0.38; $P<0.05$) and inflammatory diseases of the kidneys and urinary system (OR=6.89; S=0.75; $P<0.05$), and least pronounced in non-inflammatory diseases with involvement of the endocrine and nervous systems (OR=0.36; S=0.46; $P<0.05$) with a diagnostic coefficient of 5.7 and 7.8, respectively, and a feature informativity of 0.70 and 1.09, respectively.

Analysis of hematological parameters showed a decrease in hemoglobin, erythrocyte, MCV, MCH, MCHC, and RDW levels in patients with anemia of all groups, regardless of the etiology of the disease. However, specific laboratory signs of iron metabolism disorders were detected in patients, allowing to differentiate true iron deficiency from iron-deficiency anemia developing against the background of accompanying somatic

diseases of different origins. Biochemical tests of ferrokinetics were assessed by determining the serum levels of serum iron, TIBC, transferrin saturation, serum ferritin, and sTfR. Peripheral blood parameters in children with iron-deficiency anemia in the presence or absence of somatic pathology and depending on its etiology were characterized by the same direction of changes, although the reasons for their development were caused by different factors of inflammatory and non-inflammatory origin (Table 1).

A decrease in hemoglobin levels (85.3±1.78 g/L, p<0.001), erythrocytes (3.7±0.18x10^12/L, p<0.001), MCV (59.0±2.92 femtoliters, p<0.001), MCH (7.65±0.74 picograms, p<0.05), MCHC (27.35±0.69 g/L, p<0.001), RDW (20.51±1.34%, p<0.001), and an increase in the number of reticulocytes (1.91±0.11%, p<0.05) were found in children without somatic pathology. All patients showed signs of microcytic (anisocytosis, microcytosis) and hypochromic (color index less than 0.85) anemia.

In children with somatic pathology, changes in blood parameters with anemia were moderately expressed (92.00±0.96 g/L, p<0.001; 3.83±0.11x10^12/L, p<0.001; 65.0±0.93 femtoliters, p<0.001; 19.5±0.41 picograms, p<0.05; 29.6±0.49 g/L, p<0.001; 25.0±0.52%, p<0.001 respectively, and 1.7±0.11%, p<0.05 respectively). At the same time, mainly normochromic erythrocytes of usual form and size were detected.

The study results showed differences in changes in peripheral blood parameters in children depending on the etiology of internal organ damage (Table 2). Hemoglobin levels in children with inflammatory diseases were equal to 88.55±1.31 g/L (p<0.001), erythrocytes - 3.37±0.09x10^12/L (p<0.05), while in non-inflammatory diseases - 90.67±0.5 g/L (p<0.05) and 3.56±0.071x10^12/L (p<0.001), respectively.

The study of these peripheral blood parameters and iron metabolism in children with true iron-deficiency anemia revealed their dependence on the severity of the disease (Table 2). A decrease in hemoglobin levels was noted to be 94.5±1.78 g/L in mild anemia, 80.0±0.96 g/L in moderate anemia, and 58.0±1.26 g/L in severe anemia (in healthy individuals - 127.50±1.71 g/L; p=0.000001; p=0.000001; p=0.000001 respectively). The number of erythrocytes was equal to 3.98±0.18 x 10^12/L in mild anemia, 3.76±0.13 x 10^12/L in severe anemia, and 3.83±0.11 x 10^12/L in moderate anemia (in healthy individuals – 4.75±0.06 x 10^12/L; p=0.28; p=0.22; p=0.37 respectively). The MCV indicator was equal to 65.00±2.92 fL in mild anemia, 59.00±0.93 fL in moderate anemia, and 54.90±1.07 fL in severe anemia (in healthy individuals – 81.16±0.62 fL; p=0.05; p=0.003; p=0.01 respectively). The level of MCH is reduced in mild (18.65±0.74 picograms), moderate (17.5±0.41 picograms), and severe (15.90±0.45 picograms) anemia (in healthy individuals – 27.95±0.24 picograms, p=0.09; p=0.0003; p=0.0004 respectively). MCHC is reduced in mild anemia to 29.35±0.69 g/dL, in moderate anemia - to 27.60±0.49 g/dL, and in severe anemia – to 26.10±0.31 g/dL (in healthy individuals - 34.10±0.15 g/dL; p=0.04; p=0.0001; p=0.0004 respectively). A reliably high increase in RDW was found in mild anemia to 20.51±1.34%, moderate anemia – to 20.00±0.52%, and severe anemia – to 21.4±0.61% (in healthy individuals – 13.40±0.16%; p=0.20; p=0.39; p=0.13 respectively). The number of reticulocytes was increased in severe (1.9±0.10%) and moderate (1.80±0.11%) anemia, as well as in mild (1.75±0.11%) anemia (in healthy individuals - 1.45±0.14%; p=0.5; p=0.35; p=0.80 respectively) (Table 2).

The study revealed changes in iron metabolism parameters in patients with iron-deficiency anemia without somatic pathology and their dependence on the severity of the disease (Table 2). A significant decrease in SI to 5.2±1.13 µmol/L (p<0.001) and SF to 10.3±2.96 µg/L (p<0.001) was found, as well as a decrease in TS to 5.9±1.74% (p<0.001) and an increase in TIBC) to 85.3±1.0 µmol/L (p<0.001). A decrease in SI level was observed from 3.5±0.85 µmol/L in mild anemia to 2.7±0.37 µmol/L in moderate anemia and 2.5±0.31 µmol/L in severe anemia (in healthy individuals - 18.85±0.65 µmol/L; p<0.20; p<0.05; p<0.37 respectively). TIBC was significantly increased to 78.7±1.09 µmol/L in mild anemia, 82.6±2.4 µmol/L in moderate anemia, and 85.02±1.5 µmol/L in severe anemia (in healthy individuals – 51.2±1.8 µmol/L; p<0.001; p<0.001; p<0.05); TS was decreased from 12.6±1.2% in mild anemia to 4.7±3.0% in severe anemia (in healthy individuals – 23.5±1.7%; p<0.001; p<0.05 respectively).

Patients with iron-deficiency anemia and comorbid somatic pathology showed less pronounced changes in iron metabolism parameters. Thus, a decrease in serum iron to 8.02±0.86 µmol/L (p<0.001) and serum ferritin to 13.5±1.63 µg/L (p<0.001) was noted, as well as a decrease in transferrin saturation to 12.2±1.29% (p<0.001) and an increase in total iron-binding capacity to 71.24±1.91 µmol/L (p<0.001). Serum Ferritin (SF) levels are an indicator of iron stores in the body. SF

Table 1: Peripheral blood parameters in children with iron-deficiency anemia.

№	Indicators	Children with IDA without somatic pathology	Children with IDA with somatic pathology	Healthy children
1	Erythrocytes, 10^{12}/L	3,7±0,18 **	3,83±0,11 **	4,75±0,06
2	Hemoglobin, g/L	85,3±1,78 **	92,00±0,96 **	127,5±1,71
3	MCV, femtoliter	59,0±2,92 **	65,0±0,93 **	81,5±0,62
4	MCH, picogram	7,65±0,74 *	19,5±0,41 *	27,95±0,24
5	MCHC, g/L	27,35±0,69 **	29,6±0,49 **	34,1±0,15
6	RDW, %	20,51±1,34 **	25,0±0,52 **	39,4±0,67
7	Reticulocytes, %	1,91±0,11 *	1,7±0,11 *	1,45±0,14
8	Leucocytes, 10^9/L	5,61±0,80 *	7,1±0,51	8,37±0,37

** - statistical significance of differences in indicators compared to data from healthy children, p<0.001
* - statistical significance of differences in indicators compared to data from healthy children, p<0.05.

Table 2: Peripheral blood and iron metabolism parameters in children depending on the severity of iron-deficiency anemia.

№	Indicators	Patients with mild anemia	Patients with moderate anemia	Patients with severe anemia	Healthy patients	P_1	P_2	P_3
1	Erythrocytes, 10^{12}/L	3,98±0,18	3,83±0,11	3,76±0,13	4,75±0,06	0,28	0,22	0,37
2	Hemoglobin, g/L	94,5±1,78	80,00±0,96	58,00±1,26	127,5±1,71	0,000001	0,000001	0,000001
3	MCV, femtoliter	65,0±2,92	59,0±0,93	54,9±1,07	81,5±0,62	0,05	0,003	0,01
4	MCH, picogram	18,65±0,74	17,5±0,41	15,90±0,45	27,95±0,24	0,09	0,0003	0,0004
5	MCHC, g/L	29,35±0,69	27,6±0,49	26,1±0,31	34,1±0,15	0,04	0,0001	0,0004
6	RDW, %	20,51±1,34	22,0±0,52	21,4±0,61	39,4±0,67	0,20	0,39	0,13
7	Reticulocytes, %	1,75±0,11	1,8±0,11	1,9±0,10	1,45±0,14	0,50	0,35	0,80
8	Leucocytes, 10^9/L	5,61±0,80	7,1±0,51	7,1±0,41	8,37±0,37	0,19	0,16	0,70
9	Thrombocytes, 10^9/L	330,5±31,82	422,0±31,11	327,0±21,63	318,5±16,64	0,02	0,84	0,02
10	Serum iron, µmol/L	3,5±0,85	2,7±0,37	2,5±0,31	18,85±0,65	0,20	0,05	0,37
11	Ferritin, mcg/L	10,5±0,42	10,0±0,17	10,0±0,30	39,9±1,63	0,04	0,06	0,79
12	TIBC, µmol/L,	78,7±1,09	82,60±2,4	85,02±1,5	51,2±1,8	0,001	0,001	0,05
13	KHT, %	12,6 ±1,2	7,4±2,1	4,7±3,0	23,5±1,7	0,01	0,03	0,05
14	sTfR, mcg/ml	3,5±0,30	4,2±0,04	5,2±0,03	1,9±0,02	0,06	0,02	0,09

concentration measurements in patients demonstrated depletion of iron stores in true iron deficiency anemia not associated with somatic pathology. The decrease in SF levels in true anemia (10.3±2.96 µg/L; p<0.001) was more significant compared to SF levels in children with anemia and comorbid somatic pathology (13.5±1.63 µg/L; p<0.001). This is also indicated by the decrease in SF levels in mild anemia (10.5±0.42 µg/L), moderate (10.0±0.17 µg/L), and severe (10.0±0.30 µg/L), which differed reliably from the values in healthy patients (39.90±1.63 µg/L, p=0.04; p=0.06; p=0.79 respectively). The reliable criterion for the diagnosis of anemia of various etiologies is the determination of the level of sTfR, which allows to assess of erythropoiesis and differential diagnosis of anemia of inflammatory and non-inflammatory origin. An increase in sTfR levels up to 4.3±0.8 mg/mL (p<0.001) was characteristic of true iron-deficiency anemia associated with iron-deficient erythropoiesis, which is not typical for anemia developed due to the suppression of erythropoiesis by proinflammatory cytokines in comorbid conditions (1.9±0.02 mg/mL; p<0.001). Therefore, the study found an increase in sTfR levels in anemia without comorbid conditions, in contrast to levels in children with comorbid conditions (p<0.001). The lack of changes in sTfR concentration in anemia in children with somatic diseases is an advantage compared to the determination of SF concentration.

In true iron-deficiency anemia, a correlation was found between changes in sTfR levels and disease severity. Thus, in mild iron-deficiency anemia, the sTfR level was 3.5±0.30 µg/mL, in moderate anemia – 4.2±0.04 µg/mL, and in severe anemia – 5.2±0.03 µg/mL (in healthy individuals 1.9±0.02 µg/mL; p=0.06; p=0.02; p=0.09 respectively). Determining the sTfR level significantly improves the criterion for diagnosing iron deficiency anemia and functional iron deficiency in the presence of somatic diseases. sTfR level measurement is particularly valuable in cases of organ damage where evaluation of iron stores by SF levels is uninformative due to paradoxical ferritin elevation caused by disturbances in iron utilization and storage mechanisms.

Thus, iron-deficiency anemia in children with comorbid somatic pathology of different origins is characterized by less pronounced decrease in red blood cell indices and iron metabolism compared to anemia without organ damage, which is characterized by exhaustion of all iron reserves. In anemia with comorbid pathology, there is no pronounced iron-deficiency component, the reserve fund of iron, the content of serum ferritin, soluble transferrin receptor levels are minimally affected; normochromic erythrocytes of normal size and shape are detected against the background of a moderate decrease in hemoglobin, serum iron, transferrin saturation percentage and an increase in the number of reticulocytes and TIBC. The identified clinical-hematological status is typically characteristic of the functional stage of iron-deficiency anemia with a redistributive genesis due to impaired mobilization of iron from the depot, despite its normal stores in the body. Moreover, the greatest susceptibility to such changes was found in the group of children with anemia accompanied by somatic pathology of inflammatory genesis. Therefore, studies of the clinical-hematological status, taking into account the genesis of pathological processes that determine the destabilization of iron metabolism processes in the early stages of development of anemic syndrome in children with somatic pathology, can be used for their early diagnosis, treatment, and prevention in outpatient conditions.

Discussion

It is known that infectious-inflammatory diseases in children often lead to the development of anemic syndrome with manifestations identical to those of iron-deficiency anemia [13,27,35]. Wang M. (2016) differentiates between different types of anemia developing in children with various diseases, including true iron-deficiency anemia [30]. Works by Beckett A.C. et al. (2016) and Maeva I.V. et al. (2016) indicate the development of anemia in children infected with Helicobacter pylori [23,16]. The study by Moya-Alvarez V., Bodeau-Livinec F., Cot M. (2016) determined the relationship between the development

of iron deficiency and malaria [26]. Beltrame A.P. et al. (2016) assert the significance of iron-deficiency anemia formation in children with caries [23]. Timely differential diagnosis of such anemias can have a decisive prognostic value in the development of accompanying pathology in childhood.

Currently, the pathogenesis of anemia in chronic diseases involves processes of immune-mediated autoimmune activation of T-cell and monocyte regulation, producing cytokines that suppress the differentiation processes of erythroid precursor cells, erythropoietin production, etc. [1,8,35]. Aliyeva A.M. et al. (2017), Zubrikhina G.N., Blindar' V.N., Matveeva I.I. (2014) elaborate on different mechanisms of anemia development, disturbances in iron metabolism, the action of erythropoiesis inhibitors, leading to the development of functional iron deficiency associated with impairment of iron mobilization from the depot [1,37].

A comparative assessment of clinical and laboratory data in children with iron-deficiency anemia against the background of somatic pathology of various origins showed the presence of similar tendencies in the disturbance of iron metabolism at different stages of their formation. A reliable burden of changes in laboratory parameters was found depending on the nature of the etiopathogenesis of the pathological process. These changes concerned the indicators of erythrocyte, transport, and reserve iron reserves. Moreover, the presence of concomitant pathology was found to be an unfavorable factor for the initial manifestations of iron metabolism disorders, and over time it increased the likelihood of developing a true iron-deficiency condition. At the initial stage, due to insufficient release of iron from the depot to meet the increased needs of the bone marrow in the process of forming new erythrocytes, signs of anemia syndrome characteristic of functional iron deficiency were detected. The study showed that at this stage, patients had nonspecific symptoms of anemia, which may be characteristic of internal organ damage. At the same time, the values of MCV, MCH, MCHC, RDW were statistically significantly lower in true IDA than in IDA against the background of somatic pathology, unlike in healthy individuals ($p<0.001$). However, if in IDA the decrease in indicators was associated with low iron reserves in the depot, then in anemia against the background of somatic pathology, it was due to a violation of iron release from the depot into the blood.

The combination of signs of anemia syndrome and sideropenia, developing due to a decrease in the content of deposited iron in the absence of signs of inflammation, indicates the development of true iron deficiency in patients. Thus, in children without somatic pathology, a decrease in hemoglobin content ($p<0.001$), erythrocytes ($p<0.001$), MCV ($p<0.001$), MCH ($p<0.05$), MCHC ($p<0.001$), RDW ($p<0.001$) and an increase in the number of reticulocytes ($p<0.05$) were established. Characteristic signs of microcytic (anisocytosis, microcytosis), hypochromic (color index less than 0.85) anemia were present, confirming the iron deficiency nature of the disease.

The study found that in children with somatic pathology and anemia, changes in hemoglobin content ($p<0.001$), erythrocytes ($p<0.001$), MCV ($p<0.001$), MCH ($p<0.05$), MCHC ($p<0.001$), RDW ($p<0.001$) and an increase in the number of reticulocytes ($p<0.05$) were moderately expressed and mostly revealed normochromic red blood cells of regular forms and sizes. Indeed, according to Blindar, V.N., Zubrikhina, G.N., and Matveeva, I.I. (2016), anemia in chronic diseases at the initial stage is normocytic normochromic with a normal content of reticulocytes, but with progression, it transforms into normocytic hypochromic anemia, which ends up with the development of microcytic hypochromic anemia, in which, however, MCV is not less than 72 fL [7].

The iron-deficiency nature of changes in peripheral blood parameters in children with accompanying pathology and anemia can be etiopathogenetically associated with various mechanisms. The research results showed differences in changes in peripheral blood parameters in children depending on the etiology of internal organ damage (Table 2). At the same time, changes in hemoglobin content ($p<0.001$) and erythrocytes ($p<0.05$) in children with inflammatory diseases were more pronounced than in non-inflammatory diseases ($p<0.05$ and $p<0.001$ respectively). Such changes, due to individual reasons specific to a particular pathological process, are characteristic and unrelated to true iron deficiency. The confirmation of this was the results of the analysis of the obtained blood parameters, which showed that in iron-deficient anemia in children without somatic pathology, all iron reserves are affected, which is reflected both in the peripheral blood parameters and in all indicators of iron metabolism. For anemia in the presence of somatic pathology, similar but less pronounced changes in blood parameters of transient nature are detected, which are not associated with iron metabolism disorders and are characteristic of functional iron deficiency state. The study results may indicate the unfavorable effect of accompanying pathological processes on iron metabolism and hematopoiesis, which leads to the development of anemia in children. Moreover, hematological changes in anemia in children with internal organ damage are non-specific in nature and depend on the etiopathogenesis of the diseases, reflecting the general reaction of the hematopoietic system to the effect of the infectious agent in inflammatory diseases. Anushenko et al. (2016), Alieva et al. (2017), Zubrikhina et al. (2014), and Dignass et al. (2015) suggest that such manifestations may be due to mechanisms such as suppression of erythropoiesis by activating erythropoiesis inhibitors, the action of cytostatics, shortening of the lifespan of red blood cells due to intravascular or autoimmune hemolysis, increased consumption of iron by non-erythroid cells, disruption of iron release from macrophage reserves, and others [1,3,24].

The study revealed a high frequency of inflammatory somatic pathology, which allowed to identify them as leading prognostic factors increasing the risk of anemia. It was found that iron deficiency anemia is more often accompanied by the development of focal infection of the nasopharynx, respiratory tract pathology, and less often by lesions of other organs and systems ($p<0.001$). Confirmation of this is the higher frequency of respiratory tract infections (OR=7.36; S=0.38; $p<0.05$), kidney and urinary system (OR=6.89; S=0.75; $P<0.05$) of inflammatory genesis in children with anemia. This is also evidenced by studies by Orynbasarova K.K., Dzhaksybaeva I.S., Ismailova D.B. (2018), noting the detection of anemia in 42.8% ($p<0.01$) of cases in patients with cytomegalovirus infection [16]. In addition, considering the results of the work by Afanasyev B.V., Zubarovskaya L.S. (2018), it is important to remember that the prolonged period of dyspoiesis in such children may develop against the background of transient changes in the bone marrow, which complicates the course of pathological processes [4]. The stage of functional changes in the hematopoietic and iron metabolism systems is clarified in the works of Zubrikhina G.N., Blindar V.N., Matveeva I.I. (2014). Therefore, studies on accounting for the genesis of the pathological process that determines the destabilization of hematopoietic and iron metabolism processes

in anemia in children with somatic pathology can be used for timely diagnosis and prevention.

However, in most cases, anemia in diseases of different etiologies of internal organs is a combination of iron deficiency and anemia of chronic diseases [3,6,9,12]. Studies show that the presence of a mixed variant of anemia can be suspected with normal or moderately elevated levels of serum ferritin (16-100 ng/ml) and the detection of clinical and laboratory signs of inflammation [12,17,30].

It should be noted that the results of the study allowed to identify a decrease in the level of serum iron and saturation of transferrin with it in anemia of any etiology. However, the mechanisms of their development were different. Usually, in case of iron deficiency, anemia develops due to an absolute deficiency of iron in all stores, whereas in anemia accompanied by somatic pathology, there is no significant reduction in the iron reserve, but only the inability to utilize it from the reticuloendothelial system. The study found that the serum iron content in patients of all groups was below the reference intervals, but the greatest decrease in serum iron was observed in true anemia and anemia accompanying inflammatory somatic pathology. The changes in the serum iron level were correlated with low KHT levels in all patients, despite differences in the underlying causes. The investigated parameters in children in both groups were decreased and statistically significantly different from the levels in healthy children ($p<0.001$).

Currently, various modern methods of research are used in the diagnosis or differential diagnosis of anemia [7,30,36,37]. Among them, the determination of hepcidin concentration in the blood serum as a regulator of iron metabolism, inhibiting its absorption in the small intestine, and releasing it from macrophages and hepatocytes [2,20,32,36], may be significant. According to the authors, hepcidin interacts with transferrin receptor-1 on the surface of hepatocytes, blocks iron release from macrophages by binding to ferroportin, leading to disruption of iron transport, and hyperproduction of this protein during inflammation contributes to the development of anemia [2,21,32,36]. In order to differentiate functional and absolute iron deficiency, various methods are proposed by Zakharova I.N. et al. (2015), Mast A.E., Blinder M.A., Dietzen D.J. (2008), Pande S., Ranjan R., Kratasyuk V.A. (2019), including the study of reticulocyte indices, hemoglobin content in reticulocytes, which is the most sensitive marker of iron deficiency at an early stage of the disease, unlike MCV, MCH, and MCHC, which reflect changes in erythropoiesis at later stages [11,25,28]. Several works indicate the possibility of using the study of cytokine concentrations in the differential diagnosis of anemia of chronic diseases, which can induce changes in iron metabolism, proliferation of erythroid precursors, and erythropoietin production. Inflammatory cytokines such as IL-1, IL-6, and TNF-alpha can have inhibitory effects on erythroid precursors and disrupt iron metabolism, leading to the suppression of erythropoiesis [1,9,31]. However, most of these methods are not available for outpatient practice due to their complexity and financial constraint. Therefore, already known traditional and equally important methods for studying iron metabolism are more commonly used for the differential diagnosis of anemia.

Pathological processes associated with inflammation are characterized by an increase in serum ferritin levels, as an acute phase protein, accompanied by an increase in levels of acute phase plasma proteins, haptoglobin, and CRP. The study has shown that iron deficiency anemia in children accompanying internal organ damage is characterized by a relatively moderate decrease in the iron reserve (ferritin level of 13.5±1.63 μg/L; $p<0.001$), while true iron deficiency anemia is characterized by a more pronounced decrease in this indicator (ferritin level of 10.3±2.96 μg/L; $p<0.001$). Iron deficiency anemia in children without comorbid somatic pathology is caused by a disturbance in iron metabolism at all stages, primarily due to its deficiency associated with insufficient intake of the micronutrient or impaired absorption or increased losses. However, moderately reduced values of serum ferritin do not exclude iron deficiency because ferritin is not only a marker of iron stores but also reflects the activation of mononuclear phagocyte system cells during various infectious, immune, and other pathological processes. This is confirmed by moderately reduced levels (ferritin levels of more than 12 μg/L) that combine with comorbid somatic pathology of various origins and low levels of hemoglobin. According to the WHO (2015), depletion of tissue iron stores and iron deficiency can be determined when serum ferritin levels are below 12 μg/L, which confirms the presence of iron deficiency anemia [33]. If its concentration is above this threshold, other causes of anemia should be ruled out. The obtained results confirm the significant role of serum ferritin as a marker of iron stores and inflammation in iron deficiency anemia with comorbid somatic pathology. True iron deficiency anemia is characterized by a significant decrease in iron content in all pools. Blindar V.N., Zubrikhina G.N., Matveeva I.I. (2016), Vasilieva E.V., Aslanyan K.S., Piskunova S.G. (2017), Zubrikhina G.N., Blindar V.N., Matveeva I.I. (2014) discuss the diagnosis of anemic syndrome and note the dual role of serum ferritin in determining the genesis of the disease [7,8,37]. However, Skikne B., Punnonen K., Caldron P., et al. (2011) established signs of anemia of chronic disease in 52% of patients with serum ferritin levels below 30 ng/mL. In groups with normal (>30 ng/mL) and high (>100 ng/mL) serum ferritin levels, iron deficiency was detected in 67% and 25% of patients, respectively [29]. Other studies have shown that a serum ferritin level of less than 100 ng/mL can be considered indicative of iron deficiency in these patients, while a level above 100 ng/mL indicates the absence of deficiency [26]. Therefore, in the presence of concomitant iron deficiency, the ferritin indicator decreases, but it is never as low as in true iron deficiency anemia.

Thus, the results of the study indicate that among the statistically significant diagnostic factors of anemia, the determination of iron reserves is crucial. This is confirmed by the marked decrease in serum ferritin levels in iron deficiency anemia that is not associated with somatic pathology, indicating primary disturbances in iron exchange pools, leading to the development of iron-deficiency anemia.

In addition, the study also found that a reliable criterion for the differential diagnosis of iron deficiency anemia may be the determination of soluble receptor levels for transferrin. Yoon et al. (2015) and Turgeon O'Brien et al. (2016) investigated this parameter for the differential diagnosis of iron deficiency anemia in the presence of inflammation [30,34]. The authors found that in the presence of inflammation, depletion of iron reserves and iron-deficient erythropoiesis was detected in half of the children, while in the absence of an inflammatory process, it was observed in one-third of patients ($p<0.0001$) [30,34].

Unlike ferritin, the concentration of soluble transferrin receptors increases in iron deficiency and does not change significantly in somatic diseases. Determination of sTfR concentration significantly increases the accuracy of the laboratory diagnosis

of iron deficiency in patients of different categories [34]. It is believed that sTfR is one of the markers of iron deficiency, the concentration of which is not dependent on the presence of concomitant inflammation and increases in response to iron deficiency. This allows for more accurate differential diagnosis of iron deficiency anemia and anemia of chronic disease. The level of ferritin reflects only iron reserves in the depot, while the sTfR level can indicate the bioavailability of iron for the body. Additionally, the sTfR level can help assess iron metabolism at the stages of reserve formation, transportation, and disposal [30,34].

The evaluation of soluble transferrin receptor levels in children with IDA has revealed an increase in this parameter that depends on the severity of anemia in cases without concomitant somatic pathology. This fact can be used in diagnostic searches or differential diagnosis of anemias. The study has shown that the increase in the parameter in anemia patients without internal organ involvement is due to the iron-deficient character of erythropoiesis, while the absence of changes or a decrease in the parameter in somatic diseases may be linked to the suppression of its synthesis by pro-inflammatory cytokines, the synthesis of which is enhanced in organ damage of inflammatory genesis.

Thus, the study results have shown that children with concurrent somatic pathology in iron-deficient anemia have reduced red blood cell parameters. Moreover, the hemoglobin level can be reduced in the early stages of the disease and is related to short-term hemolysis when macrophages remove aging erythrocytes from the blood (iron redistribution). As a result, the development of an inflammatory process in the affected organ continues to inhibit erythropoiesis, leading to a decrease in serum iron, an increase in transferrin saturation, and a moderate decrease in iron stores due to a low sTfR level. Considering the informativeness of these diagnostic factors in the presence of initial signs of anemia will allow for an increased detection of patients at the primary visit to a pediatrician and reduce the occurrence of anemic syndrome in children with internal organ diseases. In addition, the diagnosis of iron-deficient states in children with somatic diseases will help prevent the transformation of transient disturbances in the hematopoietic system into stable hematocytopenia. At the same time, timely verification of the causes of iron-deficient anemia that develops against the background of somatic pathology will improve diagnosis and increase the effectiveness of disease therapy, thus improving the child's quality of life.

Therefore, the development features of iron-deficiency in children with somatic pathologies of an inflammatory genesis can be determined by analyzing the integration of iron metabolism indicators. The assessment of the severity of these changes can reflect the severity of anemia and the activity of pathological processes in somatic diseases. Preservation or moderate changes in iron reserve indicators are more typical for anemia accompanying somatic pathology. Depletion of iron stores with low levels of serum ferritin indicates the presence of true iron deficiency anemia. When iron deficiency is combined with anemia and concomitant diseases, the significance of the ferritin level indicator is not high. A reliable criterion for differential diagnosis of such anemias is the determination of the level of soluble transferrin receptors in the blood. In IDA, this indicator significantly increases due to iron-deficient erythropoiesis. In anemia against the background of concomitant diseases, the level of soluble transferrin receptors decreases or remains unchanged due to the suppression of their synthesis by pro-inflammatory cytokines.

The study results showed that in IDA with concomitant somatic pathology, the concentration of hemoglobin has lower values in the early stages of the pathological process formation due to short-term hemolysis. Macrophages remove senescent erythrocytes from the blood (redistribution of iron in the body – increased consumption by macrophages). As the process becomes chronic, suppression of erythropoiesis is formed against the background of the development of an inflammatory process. Therefore, in case of chronic inflammation, the severity and nature of anemia are determined by the nature of the underlying disease. Anemia in inflammatory somatic diseases is characterized by a decrease in serum iron, transferrin saturation up to 10-20%, moderately decreased iron stores, and an TIBC increase on the background of low levels of soluble transferrin receptors.

Analysis of the literature data indicates many studies on the use of new promising markers for the diagnosis of anemia in pediatric practice [1,7,13,21]. However, such diagnostic tests are often unavailable in healthcare institutions, either due to their high cost, complexity, or lack of necessity since the use of traditional markers of iron metabolism is sufficient in the differential diagnosis of anemia at the outpatient level.

Thus, iron deficiency anemia in somatic pathology in children is characterized by non-specific symptoms of anemia and a slightly pronounced iron-deficient component. It has been noted that true IDA and IDA in children with concomitant diseases have different etiopathogenesis and require a differentiated approach to diagnosis. Anemia of any etiology was characterized by specific and non-specific symptoms of anemia, but the frequency and severity of these symptoms depended on the etiology and severity of the disease ($p=0.0044$). The increase in severity of iron deficiency was more pronounced in children with respiratory diseases (OR=7.36; S=0.38; $p<0.05$) and inflammatory diseases of the kidney and urinary system (OR=6.89; S=0.75; $p<0.05$), and less pronounced in non-inflammatory disorders in children with endocrine and nervous system disorders (OR=0,36; S=0,46; $p<0,05$), with a diagnostic coefficient of 5.7 and 7.8 respectively, and an informative value of the symptom of 0.70 and 1.09 respectively. It has been established that the development of anemic syndrome can be caused by deficient erythropoiesis and destabilization of iron metabolism, which is associated with impaired absorption and/or utilization of iron in true anemia, and with a decrease in erythrocyte production and a disorder in the recycling of iron from macrophages in anemia with concomitant diseases. Anemia in the presence of somatic diseases is characterized by a significant decrease in hemoglobin and erythrocyte levels, an increase in reticulocyte levels against the background of normochromic erythrocytes. In all children with IDA, an iron metabolism disorder was found in the form of a decrease in serum iron and KHT levels in combination with an increase in TIBC and increase in serum ferritin levels. Since depletion of iron stores is a stage in the formation of IDA, a decrease in ferritin levels is one of the significant signs of iron-deficient hypochromic anemia. In addition, as a protein of the acute phase, ferritin does not reflect iron stores in the body sufficiently specifically in the presence of an inflammatory process. Therefore, the decrease in ferritin levels in anemia in patients with somatic pathology was less pronounced. The absence of changes in the concentration of soluble transferrin receptor (sTfR) levels was found to be the most informative compared to

high levels in true IDA. The risk factors for an unfavorable prognosis of iron-deficiency anemia in the presence of comorbidities include respiratory, kidney, and urinary tract pathologies of inflammatory origin. The diagnostic and differential diagnostic methods for the anemic syndrome in children with various somatic diseases are available for practical use by pediatricians and can be employed in outpatient settings for comprehensive planning of preventive measures against anemia in the pediatric population.

Conclusion

Despite the frequency of foreign and domestic studies on the diagnosis of iron-deficient anemia associated with an inflammatory process, many aspects remain poorly understood. Currently, there are various interpretations of iron-deficient states that develop in chronic pathologies, and different methods for their diagnosis are proposed. Zubrikhina G.N., Blindar V.N., Matveeva I.I. (2016), Anushenko A.O. et al. (2016), Beltrame A.P. et al. (2016), Nairz M. et al. (2016), and Wang M. (2016) propose differentiating true iron deficiency anemia from anemia of inflammation [3,12,27,31]. Zarychanski R. and Houston D.S. (2008) consider anemia in chronic diseases as an adaptive response, not a pathological process [35].

For many years, such anemias have been diagnosed as fundamentally different conditions, but subsequent research has shown that the presence of functional iron deficiency does not necessarily exclude the presence of true iron-deficiency anemia. The criteria for diagnosing anemia of chronic diseases with absolute iron deficiency include a high level of soluble transferrin receptor, decreased transferrin saturation, increased transferrin levels, and decreased serum iron and ferritin levels. A decrease in the number of hypochromic erythrocytes and reticulocytes, a decrease in the mean hemoglobin content in erythrocytes, and a decrease in the mean cell volume of erythrocytes indicate iron deficiency. For true iron deficiency, a decrease in the number of iron-containing granules in erythroid precursor cells in the bone marrow and irregularities in the contours of erythropoiesis precursor cells are characteristic.

Research has shown that among comorbid somatic pathologies in children, respiratory and kidney diseases are more significant, which allows them to be classified as the most likely risk factors for the development of anemia. The results of the study have shown that anemia in chronic diseases has a complex multi-component genesis, based on disruptions in iron metabolism, proliferation and differentiation of erythropoiesis cells, and a decrease in the synthesis and biological activity of erythropoietin. Hematological indices and markers of iron metabolism are studied to diagnose such anemia. Reticulocyte parameters can be used to determine the cause of anemia and assess the state of erythropoiesis.

There is increasing attention being paid to studying the influence of hepcidin, pro-inflammatory cytokines on iron metabolism, and the development of this anemia [2,20,21,32]. These techniques are controversial in terms of their effectiveness and safety, but further research in this direction is necessary to develop unified algorithms for the diagnosis and treatment of such anemia. It is known that anemias associated with chronic diseases are normochromic and normocytic, of mild or moderate severity with a hemoglobin level often above 70 g/L. Furthermore, when the hemoglobin level falls below 70 g/L, it is necessary to search for other causes of erythrocyte loss or destruction.

The results of the study showed moderate changes in hemoglobin and erythrocyte levels, MCV, MCH, MCHC, and RDW indices, as well as an increase in the number of reticulocytes in children with somatic pathologies, despite the presence of normochromic erythrocytes of normal size and shape. Moreover, the levels of hemoglobin and erythrocytes were significantly lower in inflammatory diseases compared to non-inflammatory ones ($p<0.05$ and $p<0.001$, respectively). True iron deficiency anemia was confirmed by a combination of anemic syndrome and sideropenia caused by a decrease in the content of stored iron and significantly low levels of hemoglobin, erythrocytes, MCV, MCH, MCHC, and RDW, along with an increase in the number of reticulocytes in the background of microcytosis, anisocytosis, poikilocytosis, and hypochromia of erythrocytes.

Typically, the diagnosis of iron deficiency in such patients is based on the presence of a chronic disease, often of infectious-inflammatory, autoimmune, or neoplastic etiology. In such cases, the differential diagnosis of anemia is based on the assessment of iron metabolism, primarily on reserve iron stores or serum ferritin levels. The level of ferritin in patients with true iron deficiency anemia was lower than that in patients with anemia associated with somatic diseases. It is known that in anemia of chronic diseases, iron metabolism is disrupted due to the capture of freely circulating serum iron by reticuloendothelial cells, resulting in a decrease in its bioavailability to red blood cell precursor cells. Hepcidin, an acute-phase protein whose production is stimulated by interleukin-6 (IL-6) and lipopolysaccharides, plays a key role in the pathogenesis of such anemia. Binding to the iron transporter - ferroportin, hepcidin causes its degradation and reduces iron absorption in the duodenum [2,20,21,32].

Meanwhile, serum iron concentration and transferrin saturation were reduced both in true iron deficiency anemia and anemia associated with underlying diseases, which was not significant in differential diagnosis. The most important was the determination of an increase in the level of the soluble transferrin receptor in patients with true IDA and the smallest change in this indicator in patients with concomitant pathological processes causing increased immune or inflammatory activity and a decrease in iron absorption at different sites.

Along with disturbances in iron metabolism, deviations in the system of proliferation and differentiation of erythropoiesis cells can be found in patients with underlying diseases, which, in the absence of sufficient iron availability, can lead to the inhibition of erythroid precursor cell proliferation. It is known that various pathological processes caused by microbial invasion, autoimmune disorders, and malignant tumors activate CD3-T lymphocytes and macrophages, secreting cytokines (IFN-γ from T-cells, TNF-α, IL-1, and IL-6 from monocytes) that have a pro-apoptotic effect on erythropoiesis precursor cells, causing a decrease in the expression of erythropoietin receptors, its synthesis and activity [13,33].

In true iron deficiency anemia, an absolute iron deficiency develops, while anemia associated with other pathological processes is a multifactorial disease, although it is also accompanied by reduced serum iron and transferrin saturation levels. However, the levels of soluble transferrin receptor, which is a marker of iron stores in the body, differ. In true anemia, the indicator is significantly reduced, indicating a lack of iron reserves. However, evidence of depletion of tissue iron stores should be considered when the serum ferritin level is less than 12 μg/L (WHO, 2015), which is characteristic of true anemia [33]. The

study found that in anemia associated with somatic diseases, the ferritin level was higher than in patients with true anemia but lower than in healthy children.

Studies have found that true iron deficiency anemia often coexists with anemia of chronic diseases, although true anemia is characterized by microcytic anemia and tends to be more severe. With true IDA, transferrin saturation is reduced, but transferrin levels are increased, and when anemia is combined with chronic diseases, transferrin saturation is reduced primarily due to low iron levels in the blood. Research results confirm the increase in soluble transferrin receptor levels in true anemia, indicating a compensatory increase in the expression of transferrin receptors on cellular membranes under conditions of reduced iron stores. In patients with anemia of chronic diseases, the level of soluble transferrin receptors was significantly lower than the level of sTfR in patients with IDA, which indicated the independence of the indicator from the presence of inflammation and serves as a marker of increased erythropoiesis and iron levels in the body, which confirms the need for its use in the differential diagnosis of anemia.

Therefore, the course of iron deficiency states is largely determined by the nature and duration of the underlying somatic disease, which increases the risk of adverse transformation of anemia. Undoubtedly, the use of modern diagnostic methods is necessary for timely identification of irreversible factors associated with internal organ damage. At the same time, the role of studies of blood parameters and iron metabolism in the early stages of anemia, consistent analysis, and comprehensive assessment of etiopathogenetic factors of somatic diseases associated with anemia increases, which may allow the development of algorithms for their timely diagnosis and therapy of the disease.

Thus, the clinical and laboratory features of iron deficiency anemia in children with concomitant somatic pathology are characterized by a moderate degree of specific and nonspecific signs of anemia, more pronounced in children with respiratory, kidney, and urinary inflammatory diseases and to a lesser extent in diseases of the endocrine and nervous systems. Anemia is characterized by a normochromic and normocytic nature, mild to moderate severity, and dependence of disease severity on the activity of the inflammatory process, as well as the stability of ferritin and soluble transferrin receptor levels. The identified characteristics were most pronounced in the group of children with inflammatory diseases. At the same time, true iron deficiency was characterized by the absence of clinical and laboratory markers of inflammation, low ferritin levels, and increased levels of soluble transferrin receptors. Similar hematological deviations are characterized by the presence of nonspecific signs of iron deficiency anemia, hidden under the "mask" of other diseases and adaptive changes in peripheral blood indicators, reflecting the general reaction of the hematopoietic system to infectious or non-infectious aggression. The diagnosis of such hematological changes is available for outpatient care and can serve as an important preventive factor, allowing to timely identify the risk groups for the development of anemia in children with somatic pathology and improve the prognosis of hematological transformations.

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