LABORATORY PROGNOSTIC MARKERS OF ANEMIA IN PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS

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Abstract. *Anemia initiated by juvenile rheumatoid arthritis (JRA) has its own specific pathogenesis. Thanks to the results of our research, we can come to the main conclusion that the development of anemia in children with JRA is characterized by both qualitative and quantitative changes in red blood cells, and gross violations of the protein transport function for the absorption of iron in the child's body.*

Keywords*: JRA, anemia, ferritin, erythropoietin, ferroportin.*

Relevance of the problem. Anemia is one of the most common extra-articular manifestations in patients suffering from rheumatoid arthritis (RA), with a reported prevalence ranging from 15 to 60%. It is well known that anemia in JRA is associated with higher disease activity, worse outcome parameters, and increased mortality. The opinion of most researchers agrees that anemia of chronic disease (ACD) most often prevails in patients with RA, with the combination of ACD and IDA in second place, with the overall prevalence of anemia ranging from 30 to 70% [8]. Others have suggested that in groups of patients with well-controlled disease, IDA may be more common. In studies conducted in the UK in 2011, more IDA was detected in patients with RA than ACD [4]. Regardless of the type of anemia, according to the consensus of researchers, treatment of anemia should begin with treatment of the underlying disease [6,7,8,11]. Systemic-onset juvenile chronic arthritis (JCA) is associated with high circulating levels of interleukin-6 (IL-6) and is often complicated by severe microcytic anemia, the pathogenesis of which is unclear [2].

-induced cytokines and the master regulator of iron homeostasis, hepcidin, block intestinal iron absorption and cause iron retention in reticuloendothelial cells, leading to iron-limited erythropoiesis [3]. In addition, shortened erythrocyte half-life, suppressed erythropoietin response to anemia, and inhibition of erythroid cell differentiation by inflammatory mediators further contri bute to disease-specific IS. Studies have confirmed that patients with active JRA often have low hemoglobin (Hb) levels due to inflammation and/or iron deficiency [1]. In the absence of inflammation, serum ferritin, as an indicator of total body iron stores, is the most useful parameter for differentiating ACD from IDA [5]. However, in acute and chronic inflammatory diseases, high serum concentrations ferritin are the result of increased secretion by iron-containing macrophages. In addition, serum ferritin is an acute phase protein that is induced by inflammatory mediators [9]. Thus, in inflammatory conditions, ferritin loses its diagnostic value as an indicator of total iron stores in the body.

Several biomarkers have been studied for their ability to detect iron deficiency in the presence of inflammation. Among them, soluble transferrin receptor (sTfR) is the biomarker that is most commonly used in clinical practice. [10]. Among several markers studied for their ability to detect true iron deficiency in inflammatory conditions, sTfR is the most commonly used biomarker in clinical practice and is thought to be independent of inflammation [10]. Despite the

huge amount of research in this direction, today the question of the pathogenesis and course of anemia in patients with juvenile rheumatoid arthritis remains open.

Purpose of the study. To study laboratory prognostic markers of anemia in patients with juvenile rheumatoid arthritis.

Materials and methods. 129 patients with JRA aged 3 to 18 years were examined. The duration of the disease ranged from 3 months to 8 years. The duration of the disease ranged from 3 months to 8 years. All patients were divided into two groups: a main group of 99 children diagnosed with JRA and with anemic syndrome and a comparison group of 30 children diagnosed with JRA without signs of anemia. In addition to traditional clinical and laboratory studies, a blood test was performed for rheumatoid factor, C - reactive protein, erythropoietin, ferroportin, ferritin, serum iron, hemoglobin equivalent in reticulocytes RET-He, IL 6, radiography of joints. The activity of the JRA was assessed based on a clinical examination, the nature of the articular syndrome and the JADAS 10 index. The functional activity of patients was assessed according to the Steinbrocker criteria.

Results and discussion. Of the 129 JRA patients examined, 99 (76.7%) were diagnosed with anemia. According to the criteria for diagnosing anemia and its severity, based on the hemoglobin concentration, all patients were divided into groups with mild - 63.6% and moderate - 36.4% severity. There were no patients with severe profound anemia with hemoglobin less than 60 g/l. Among the examined patients, 36 were diagnosed with a moderate degree of anemia and 63 with a mild degree of the disease. 47 boys and 52 girls (Figure 1).

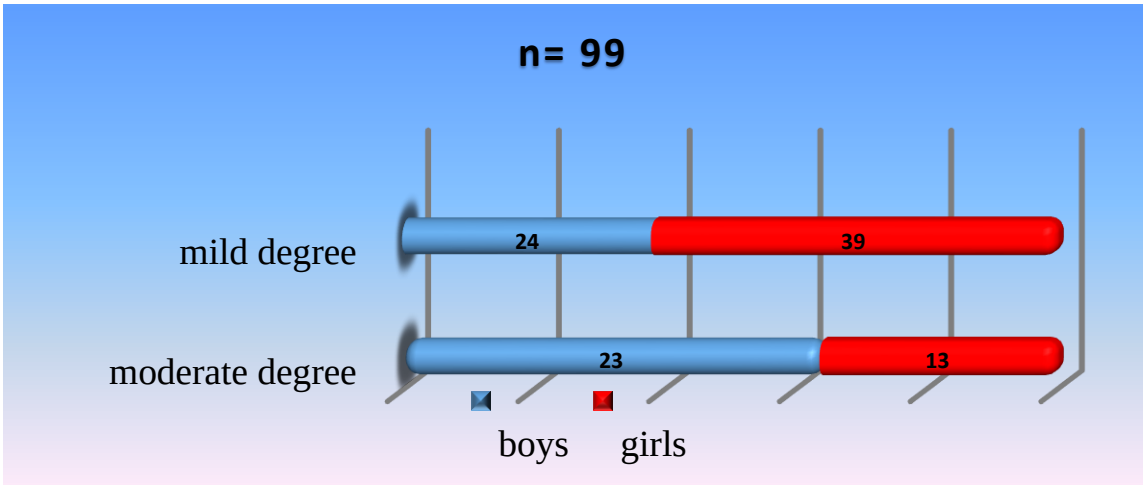

Figure 1. Distribution of JRA patients with anemia by severity

In patients with JRA there is a tendency to decrease the content of red blood cells, which also corresponds to the directly proportional severity of the level of hemoglobin in the blood, thus it can be discussed that there is a direct correlation between these parameters. A strong positive correlation was revealed between the hemoglobin concentration and the number of red blood cells ($r = 0.66$) and the color index ($r = 0.69$).

The erythrocyte indices studied during the work make it possible to assess not only the size of erythrocytes but also the quantitative content of hemoglobin in them. They also characterize the cell itself, and not their number, as a result of which these indicators are relatively stable parameters.

Analysis of mean corpuscular volume (MCV), erythrocyte hemoglobin content (MCH), and mean erythrocyte hemoglobin concentration (MCHC) and RET-Hb (reticulocyte hemoglobin equivalent) are presented in Table 1.

Table 1.

Features of the morphological characteristics of erythrocytes in sick children with JRA

Index	Group comparisons n =30	Lightweight degree anemia n= 63	Moderate degree anemia n= 36
MCV, (80-97 fl)	84.2±0.88	76.5±0.9***	73.9 ± 0.4***
MCH, (30-35pg)	29.3±0.39	24.1 ±0.5***	21.1±0.6 ***^^^
MCHC, (315-350g/l)	350.2±3.56	280.4±3.4***	250.2± 2.2 ***^^^
RDW, (11-16%)	11.1±0.3 7	16.5±0.32*	18.3±0.14** *
RET-H b , (0-99pg)	28.0± 0.4 5	24.6 ± 0.34***	21.6 ± 0.24 ***^^^

Note: * - p <0.05, ** - p <0.01, *** - p <0.001 - significance of differences in indicators with the comparison group;. ^^^ - p<0.001 - significance of differences within the main groups

Thus, from the table it can be noted that almost all the studied indicators of the morphological characteristics of erythrocytes differed significantly both with the comparison group and among themselves, with the exception of the MCV and RDW parameters - only in relation to the comparison group.

MSV – corresponds to microcytic anemia in patients with mild and moderate degrees of anemia (p<0.001, p<0.001). The data indicate reliably low values, respectively.

Anisocytosis index RBC RDW also showed a trend towards increasing anisocytosis with increasing degree of anemia. In patients with a moderate degree, it was 18.3±0.14%, which was significantly different from the control group, where anisocytosis was not observed (p<0.001) and the rate was 11.1±0.3%, in the group of patients with In mild anemia, anisocytosis was 16.5±0.32%, which was already responsible for the appearance of a large number of different forms of erythrocytes (p<0.05).

When studying EPO in relation to the degree of anemia, a decrease in EPO content in the group of patients with moderate anemia can be observed. Upon detailed study, it becomes clear that EPO decreases due to the activation of IL6, an inflammatory cytokine that blocks EPO. Thus, it can be debated that there is a cytokine-mediated decrease in the concentration of EPO in the blood serum. And the development of anemia is accompanied by its own etiopathogenesis, which is not typical for known anemias.

Next, we studied transport proteins depending on the degree of anemia. By studying the indicator of transport protein function, we discovered patterns that helped reveal the pathogenesis of the development of anemia in children with JRA, as well as what happens to the proteins responsible for the transfer of iron molecules immediately after absorption. Ferritin as an acute-phase indicator increased in patients in groups 1 and 2 to 104.6 ± 39.4 and 212.7 ± 14.8 ng / ml, however, it did not in any way reflect the state of iron depot in the body (p<0.00) in all comparison groups and among themselves, ie The greater the clinical manifestations of juvenile rheumatoid

arthritis, the higher ferritin became. Ferroportin in patients with mild anemia was 0.21 ± 0.04 ng / ml, which indicates its decrease, but with an increase in the degree of anemia, it began to decrease significantly p< 0.001 and in the group with moderate anemia it was 0.16 ± 0.01 ng/ ml. Based on this, we can conclude that the more ferritin increases, ferroportin decreases in direct proportion to it. Another transport protein, transferrin, had a high degree of confidence in its increase in the blood, which means the body's compensatory work to increase the uptake of iron molecules, so in patients with mild anemia it was 290.3 ± 21.1 mg/dl, while in in the comparison group it was 230.6±15.7 mg/dl (p<0.001). In patients who developed moderate anemia, transferrin was 315.7 ± 10.4 mg/dl, a high level of significance (p< 0.001) between both study groups.

Conclusions. Thus, laboratory prognostic markers of anemia in patients with juvenile rheumatoid arthritis is the determination of erythropoietin, a soluble transferrin receptor ferritin, transferrin and IL 6. Based on the results of our studies, we can come to the conclusion that The development of anemia in children with JRA is characterized by both qualitative and quantitative changes in red blood cells and gross disturbances of the protein transport function for the absorption of iron in the child's body.

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