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PROSPECTS FOR THE DIAGNOSIS AND TREATMENT OF VARIOUS TYPES OF ANEMIA IN CHILDREN

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Annotation*: Data from the World Health Organization (WHO) indicate that anemia requires close attention, as the issues of diagnosis and the possibilities of modern therapy are still poorly understood. Despite the fact that any variants of anemia can occur in childhood, anemia associated with a lack of substances (in particular iron) necessary for normal hematopoiesis still occupies a central place. At the same time, some clinical forms of anemia develop as a result of various influences and have a complex pathogenesis, such as anemia of chronic diseases. In the presence of anemia, the child's growth slows down, its harmonious development is disrupted, intercurrent diseases develop more often, foci of chronic infection are formed, and the course of other pathological processes is aggravated. Deep tissue and organ changes in anemic syndrome lead to the development of hypoxia and disorders of cellular metabolism. Timely diagnosis, replacement of iron deficiency, treatment of anemia itself and concomitant diseases contribute to full recovery. Due to the widespread introduction of modern hematological analyzers that allow taking into account various red blood cell indices, as well as the introduction of new laboratory indicators of iron metabolism, the possibilities of differential diagnosis of anemia have significantly expanded.*

Keywords: *anemia, children, treatment.*

An urgent problem remains the search for available laboratory methods that allow for differential diagnosis of anemic conditions.

Anemia is a pathological condition accompanied by a drop in the level of hemoglobin and/or red blood cells per unit volume of blood. In children's practice, it is possible to use R. Sills regulatory data [1] or WHO criteria that characterize anemia as a decrease in hemoglobin levels of less than 110 g / l in children from 6 months to 6 years, less than 115 g / l in children from 6 to 11 years, and less than 120 g / l in children over 12 years of age and adults. In most of the classifications recognized in the medical world, the basis is the mechanism of development of the disease, which divides anemia into three main groups: post-hemorrhagic; hemolytic and due to a violation of the formation of red blood cells and hemoglobin. Anemia in chronic diseases in childhood, anemia of chronic diseases (AHD) is the second most common disease. Anemia of chronic diseases develops in patients with infections, inflammation, and neoplasia and lasts for more than two months. At the same time, there is a decrease in the production of red blood cells and a violation of iron reutilization. As a result of inflammatory reactions in the child, pro-inflammatory cytokines are activated, which in turn can cause inhibition of erythron, which leads to inadequate iron metabolism and the formation of hemoglobin, which is synthesized along the carbonate-dependent chain. As a result, hemoglobin that is not resistant to hypoxia is formed, which quickly breaks down [15].

There are four main mechanisms underlying the pathogenesis of AHD: 1) violation of iron metabolism; 2) suppression of erythropoiesis; 3) inadequate production of erythropoietin; 4) hemolytic process. As a result of impaired iron reutilization from macrophages, there is a failure

in the turnover and use of iron, so often iron therapy is ineffective. It is justified only in the case of concomitant iron deficiency. The parenteral method of drug administration is also excluded, since iron accumulates in macrophages and its entry into the bone marrow is difficult [16]. Inhibition of erythropoiesis is associated with the action of inhibitors and the presence of cytokines that suppress the action of erythropoietin (EPO). Hemolysis of red blood cells can be caused by the formation of microthrombi in latent disseminated intravascular coagulation (DIC), probably caused by macrophage procoagulants. There is also damage to the red blood cell membrane by products of lipid peroxidation. As a result, not only the ability of red blood cells to recover from deformity decreases, but also their life expectancy (up to 80-90 days). Great importance is attached today to hepcidin, a protein that regulates iron metabolism, consisting of 25 amino acids and 4 disulfide bonds synthesized in the liver. Hepcidin was named for its bactericidal properties [17]. Hepcidin production in the liver depends on the body's iron stores, endogenous EPO activity, and inflammatory activity. If there is a lack of iron, the level of hepcidin should decrease in order to release iron from the depot into circulation through ferroportin, which is a molecular target of hepcidin and is expressed by macrophages, hepatocytes, enterocytes, and placental cells [18, 19]. The release of iron from the cell is blocked by the binding of hepcidin to ferroportin, which is absorbed into the cytoplasm and destroyed by the cell's lysosomes. Macrophages overloaded with iron, which are often found in chronic inflammation, also interact with the hepcidin–ferroportin complex. As a result of the blockade of ferroportin, the release of iron from macrophages is hindered. In anemia and hypoxia, there is a decrease in the expression of the hepcidin gene, which leads to an increase in iron uptake from both macrophages and the intestine. In the works of various scientists, the dominant effect of hepcidin on the occurrence of iron deficiency in AHD has been proved: after an increase in the level of interleukin (IL) 6, the level of hepcidin increases and the level of iron in serum decreases, while the level of serum ferritin increases. The concentration of transferrin tends to decrease in the acute phase period, so in order to exclude a false interpretation of the dynamics of ferritin and transferrin concentrations, it is necessary to study the dynamics of other indicators. The most sensitive and specific is IL 6. On the other hand, EPO is a regulator of hepcidin levels. In experiments on mice, it was shown that the introduction of exogenous EPO reduces the production of hepcidin . The use of modern genetic engineering technologies using transgenic mouse lines has shown that hepcidin it is a negative regulator of iron uptake in the small intestine and iron release from macrophages [2]. It can also block the transport of iron through the placenta and the release of iron from macrophages. Hypoxia increases the expression of hypoxia-induced factor (HIF-1), which controls the expression of the EPO gene, thereby being involved in iron metabolism. Suppression of hepcidin synthesis is observed in iron deficiency, for example y, in transgenic mice. In IDA, hepcidin production decreases, andiron outflow from the cell to plasma increases [3]. The reduction in iron levels induced by IL-6 andhepcidin occurs within a few hours. IL increases the secretion of hepcidin in the liver, and it blocks the release of iron from macrophages. This leads to iron retention in macrophages of the reticuloendothelial system (RES), which causes inadequate erythropoiesis with sufficient iron reserves in the body. Iron content decreases in reticulocytes, which can serve as an additional indicatorfor assessing the level of iron in the body [4]. In anemia and hypoxia, low oxygenation of the blood with oxygen induces the production of eitropoietin in the kidneys. An increase in the level of EPO contributes to an increase in the erythropoietic activity of the bone marrow, as well as increased mobilization of iron from the depot. Cytokines and cells of the reticuloendothelial system induce changes in iron metabolism, proliferation of erythroid precursors, and production of erythropoietin. However, limiting the functional availability of iron and reducing the biological activity of erythropoietin lead to a decrease in erythropoiesis and the development of anemia [6].

Anemia in AHD worsens as the disease increases. Dysregulation of iron metabolism is a pathophysiological sign of AHD with increased iron consumption and retention by RES cells. This leads to the shutdown of iron from metabolism in the RES depot, followed by a restriction of the suitability of iron for red blood cell progenitor cells and iron-restrictive erythropoiesis. The normal functioning of the erythron system is due to sufficient production of EPO by the kidneys, a functioning bone marrow sprout, and adequate supply of iron to the bone marrow [7]. A defect in one of these components leads to anemia. In experiments on mice that were injected with pro-inflammatory cytokines-IL 1 and tumor necrosis factor (TNF) - a decrease in serum iron was observed and anemia developed. This combination was one of the conditions for cytokines to induce the synthesis of ferritin — the main protein associated with iron storage in macrophages and hepatocytes. Advances in genetics confirm that in hemochromatosis type 1-3, there is a mutation in the gene that regulates the expression of hepcidin, and iron overload occurs when there is a deficiency of hepcidin. As a result, increased iron reabsorption in the duodenum occurs, whilethe iron output of their macrophages increases [8, 9]. A mutation in the HAMP hepcidin gene was also detected, which disrupts its structure and leads to a gradual loss of its biological activity. This is more common in juvenile hemochromatosis type 2b. These children develop early cirrhosis of the liver, hypogonadism, and cardiomyopathy and endocrine disorders. A mutation in the TMPRSS6 gene creates an excess of hepcidin, disrupts iron absorption and release from macrophages, decreases serum iron levels, and develops anemia resistant to iron therapy. The mutant USF-2 gene encodes an enzyme — type II transmembrane serine protease, which is a negative regulator of hepcidin transcription, as a result of which anemia is also refractory to iron preparations. Anemia in chronic kidney disease has some features of AHD, however, changes in iron metabolism occur due to a decrease in the production of erythropoietin due to a decrease in the mass of the functioning renal parenchyma. In addition, the development of anemia can be caused by a reduction in the life expectancy of red blood cells from 120 to 70-80 days, as well as blood loss, inhibition of erythropoiesis as a result of acidosis, chronic inflammation, lack of free iron in the body and nutritional deficiency. Anemia can develop even in the early stages of a decrease in the functional activity of the kidneys. Erythropoietin is a central regulator of erythropoiesis proliferation. EPO is a glycosylated polypeptide consisting of 165 amino acid residues with a molecular weight of 34 kDa. Glycosylation increases the stability of the molecule in the blood, but does not affect the metabolic activity. EPO expression is inversely proportional to tissue ischemia and hemoglobin levels, and there is a semi-logarithmic relationship between the erythropoietin response and the degree of anemia [5]. There are observations indicating that EPO responses in AHD are notadequate to the degree of anemia [15]. Correction of anemia in the treatment of the underlying disease is very important for eliminating tissue hypoxia. In kidney diseases, the use of recombinant erythropoietin is justified, and pathogenetic treatment is carried out with steroids. Erythropoietin competes with its precursors, increases the expression of transferrin receptors, and they become sensitive to iron. The determination of defective EPO products is based on an incongruously low concentration of serum EPO relative to the patient's hematocrit or hemoglobin value compared to" reference " patients with the same hematocrit or hemoglobin value. Patients with IDA or hemolytic anemia can be taken as a" standard". In the presence of a normal EPO-forming apparatus in the kidneys, the concentration of erythropoietin should increase exponentially with the decrease in hematocrit or hemoglobin. Clinical syndromes with inadequate EPO production for anemia are diverse. They can be divided into 2 groups depending on damaged or normal kidney function. The first group includes anemia in chronic renal failure (CRF), the second — anemia in malignant neoplasms. Until recently, it was believed that the main function of EPO is the induction of erythropoiesis; however, numerous data indicate that EPO also acts on non-erythroid organs and

tissues, including the central nervous system, heart, and kidneys [16]. The mechanisms of action of EPO on these organs include neuroprotective, trophic, anti-apoptotic, anti-inflammatory and antioxidant effects, as well as angiogenesis. Under hypoxic conditions, EPO expression may increase in some non-hematopoietic cells. Cellular tissues. EPO receptors are found on erythroid cells, as well as receptorson the neuroglia and retina of the eye [3].

Conclusion. In case of anemia, it is necessary to study reticulocytic and erythrocytic parameters to assess the activity of erythropoiesis and clarify the genesis. Indicators of iron metabolism (trasnferrin, ferritin, soluble transferrin receptor) and markers of inflammation (C-reactive protein, IL 6), as well as the level of hepcidin and erythropoietin, play an important role. Evaluation of the entire complex of laboratory tests that reflect iron metabolism and inflammatory changes in the body is necessary for differential diagnosis and further treatment of various types of anemia in childhood. New data on the pathophysiological mechanisms of iron metabolism disorders, its imbalance and deficiency, leading to a decrease in the proliferation of erythroid precursors, contribute to improving the therapeutic strategy in the treatment of anemia and chronic diseases. The basis of this approach is the treatment of the underlying disease with the addition of rf-EPO and / or iron. Further study of new methods of diagnosis and treatment of various types of anemia in children is promising.

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