WORLD JOURNAL OF ADVANCED SCIENTIFIC RESEARCH

Insight To The Disturbances Of Iron Metabolism

Nabiyev Abdusamat Utkurovich

Republican Specialized Scientific and Practical Medical Center of Pediatrics of Uzbekistan

Abstract. *Iron deficiency, as well as its excess, lead to serious disruption of these processes. Iron deficiency states are the reason for a decrease in working capacity, an increase in susceptibility to viral diseases, especially in children, and cause growth and development retardation. Iron overload and poisoning lead to the activation of processes that can cause cell death. In this regard, timely diagnosis of disorders of iron metabolism and subsequent monitoring of treatment require knowledge of not only pathophysiological mechanisms, but also methodological capabilities and correct interpretation of clinical and biochemical parameters of iron metabolism.*

Keywords: *iron deficiency anemia, hemochromatosis, hepcidin, hemosiderin, transferrin, ferritin.*

Iron is also found in a significant amount of enzymes involved in energy production (cytochromes), DNA biosynthesis and cell division, detoxification of endogenous decay products that neutralize reactive oxygen species (peroxidase, cytochrome oxidase, catalase). The role of iron-containing proteins (ferritin, transferrin) in the implementation of cellular immunity, regulation of hematopoiesis, and antimicrobial activity has been established. However, iron can be an extremely toxic element if it is present in the body in concentrations

that exceed the capacity of iron-containing proteins. The potential toxicity of free ferrous iron (Fe + 2) is explained by its ability to trigger free radical chain reactions leading to lipid peroxidation of biological membranes and toxic damage to proteins and nucleic acids. Iron metabolism in the body consists of several stages: absorption in the gastrointestinal tract, transport, intracellular metabolism and deposition, utilization and reutilization, excretion from the body. According to modern concepts, the key functional compounds that determine the metabolism of iron in the body are the membrane-bound specific divalent cation transporter 1 (DCT1), transferrin, transferrin receptors, and ferritin.

The key regulator of iron metabolism is the hepatic bactericidal protein (hepcidin), a hormone synthesized primarily in the liver. Hepcidin contains 25 amino acids, is rich in cysteine, with 4 disulfide bridges. Human hepcidin is derived from the Sternal portion of an 84-amino acid precursor. The synthesis and secretion of hepcidin is controlled by three proteins: HFE (hereditary hemochromatosis protein), hemouvelin, transferrin receptor 2. Hepcidin is excreted in the urine, where it was first excreted.An excess of iron induces the synthesis of hepcidin by hepatocytes. Hepcidin inhibits intestinal absorption of iron, blocks the transport of iron everywhere, including internal epithelium, macrophages, placenta and other cell types, and the transfer of iron across the placenta.

Hepcidin induces the immersion of ferroportin into the cell cytoplasm, blocking the only pathway for iron transport from the cell (Fig. 5). Removal of ferroportin from the membrane leads to a blockade of the removal of iron from the cell into the blood plasma.

Hepcidin has antibacterial activity to gram-negative, gram-positive bacteria and antifungal activity. Like other antibacterial peptides, hepcidin is able to rupture the bacterial membrane, which is due to its structure - the spatial separation of side chains: hydrophilic (positively charged) and hydrophobic (negatively charged).

Hepcidin is capable of destroying bacterial membranes, affecting the accumulation of iron by macrophages. In this case, microorganisms are deprived of the necessary component for the production of superoxide dismutase, which, in turn, protects them from the host's oxygen radicals. Iron promotes the development of inflammation and catalyzes the formation of destructive reactive

oxygen species for tissues. Decreased serum iron is an important defense mechanism to avoid inflammatory organ damage. In infections, this is also part of the immune strategy. bacteria need iron - a deficiency of iron in the blood serum leads to inhibition of their growth. The level of hepcidin in the urine with the development of a systemic infection increases by a factor of 100 or more. Hepcidin inhibits the synthesis of IL-6 and TNF α in macrophages, and thus has an anti-inflammatory effect.

Bacteria and pathogen-specific macromolecules act on macrophages, including hepatic Kupffer cells, and induce increased production of IL-6. This cytokine, in turn, initiates the synthesis of hepcidin by hepatocytes through the induction of its mRNA. Simultaneously with increased expression of hepcidin, it increases serum ferritin and IL-6 levels. The same situation is observed with tumors: anemia develops, hepcidin, ferritin and IL-6 levels increase.

The opposite situation occurs with anemia and hypoxia. Under these conditions, a decrease in the expression of the hepcidin gene is observed, which leads to an increase in the uptake of iron, both from macrophages and from the intestine. The suppressive effect of hemolytic anemia on the production of hepcidin is observed even when the body is overloaded with iron, thus confirming that the requirements of erythropoiesis in the gland are a stronger stimulus than an excess of iron, which should cause hepcidin induction. This hierarchy of effects explains why hemosiderosis develops in hemolytic anemias. Since in such cases, a decrease in hepcidin production leads to an overload of the body with iron, only chelation therapy can prevent the increasing excess of iron.

People with hepcidin-producing adenomas develop iron deficiency anemia that is resistant to iron therapy. Mutations in the hepcidin gene are the cause of hemochromatosis. Overproduction of hepcidin during infection and inflammation may be responsible for anemia of inflammation or anemia of chronic disease. Inflammatory anemia is caused primarily by hepcidin-induced iron deposition in macrophages.

The metal binding transport protein, transferrin, is a beta-1 globulin and has a molecular weight of approximately 88,000 daltons. Transferrin is synthesized in liver cells and in small amounts in lymphoid tissue, mammary gland, testes and ovaries. It consists of one polypeptide chain and two hydrocarbon side regions. The normal serum concentration is about 2-4 g / L,

which corresponds to about 4% of the total plasma protein. In addition to blood serum, under physiological conditions, transferrin is determined in lymph and tissue fluid, and under pathological conditions - in urine and effusion. In the vascular bed is about half transferrin, the other half is extravascular. The biological function of transferrin lies in its ability to easily form dissociating complexes with iron, which ensures the creation of a non-toxic pool of iron in the bloodstream, which is readily available and allows for the distribution and storage of iron in the body. Transferrin appears to be required by many cells as a growth promoter.

Disorders of iron metabolism in patients can be associated with both its deficiency and overload. Iron deficiency is clinically manifested by iron deficiency anemia, overload - by hemochromatosis.

In each case, iron deficiency is preceded, first of all, by the depletion of its reserves (latent iron deficiency), then the transport iron decreases, then the activity of iron-containing enzymes decreases, and last of all, hemoglobin synthesis is disrupted. There are three forms of iron deficiency conditions: iron deficiency without anemia (pre-latent and latent iron deficiency) and iron deficiency anemia. The first two are characterized by a decrease in the content of storage and transport iron with a preserved erythrocyte pool of iron, the third - by a decrease in the level of all metabolic iron pools.

Pre-latent iron deficiency is a condition preceding iron deficiency and is accompanied by increased absorption of iron in the gastrointestinal tract. There are no clinical symptoms. Laboratory parameters (peripheral blood picture, serum iron, transferrin, ferritin) usually remain within normal limits. The only test that can actually determine the depletion of deposited iron is the 59 Fe3 + absorption test. In about 60% of cases, an increase in absorption of more than 50% is determined at a rate of 10-15%.

Latent iron deficiency is accompanied by the so-called sideropenic symptoms due to iron deficiency in tissues. These include: dry skin, brittle nails, hair loss, changes in mucous membranes, muscle weakness. The variety of clinical symptoms of iron deficiency is explained by the breadth of the spectrum of metabolic disorders caused by dysfunction of iron-containing enzymes.

Among the laboratory data, attention is drawn to a decrease in the concentration

of ferritin (5–15 μg / l), serum iron in plasma, and an increase in transferrin. When iron stores are depleted, a lack of transported iron develops, although hemoglobin synthesis at this stage is not impaired and, therefore, red blood counts (Hb, RBC, MCV, MCH, MCHS) remain within normal limits. However, with additional stress or iron loss, latent iron deficiency can turn into iron deficiency anemia. The main cause of iron deficiency in pathology is blood loss, usually from the gastrointestinal tract, urinary tract, especially in women, and relatively rarely - as a result of bleeding from the kidney or bladder. The clinical picture of latent or manifest iron deficiency resulting from blood loss can be easily identified from the patient's history or during a diagnostic examination. So the test for occult blood in the stool easily detects bleeding from the gastrointestinal tract. However, there may be asymptomatic iron loss through the gastrointestinal tract, which is the cause of iron deficiency. Iatrogenic iron deficiency can be caused by medications such as nonsteroidal antirheumatic drugs or antacids. Frequent donation of blood by donors (2-4 times a year) depletes iron stores. The donation of 300 ml of blood immediately deprives his body of 150 mg of iron. Men who donate blood 4 or more times and women who donate 2 or more times a year should be tested for ferritin once a year.

Iron deficiency can result from malabsorption in the intestine (after extensive resection of the small intestine, with chronic enteritis). Violation of the acid and enzyme-forming function of the stomach (atrophic gastritis) may be an additional cause of the development of iron deficiency. Iatrogenic malabsorption with malabsorption syndrome can occur with prolonged use of tetracycline antibiotics.

Iron deficiency in adolescents, especially girls, is aggravated by fasting. A limited diet often leads to the fact that only about half of the recommended amount of iron is consumed with food and this, naturally, when combined with the onset of menstruation, leads to iron deficiency. Endogenous iron deficiency can occur in chronic infections (tuberculosis), intoxications, hypovitaminosis (especially Chypovitaminosis), and malignant neoplasms.

Rarely, iron deficiency develops due to a lack of transferrin (hereditary atransferrinemia). In each case, iron deficiency leads primarily to the depletion of iron reserves. With the development of iron deficiency, the iron deposited in the organs first decreases, then the transport iron, then the activity of iron-containing enzymes and, last of all, the synthesis of hemoglobin. An early sign of iron deficiency is the progressive accumulation of protoporphyrin IX in maturing erythroid cells and the

detection of excess protoporphyrin in mature erythrocytes. Iron deficiency in older people is associated with a lifestyle: with a monotonous poor diet, mainly cereals and broths. In athletes, iron deficiency can be considered an occupational disease. In long distance runners, iron deficiency is mainly associated with losses from the gastrointestinal tract. Latent iron deficiency is typically found in long-distance swimmers. Occupational physical overload is, apparently, additional factors of hemolysis.

The human body is not able to actively excrete iron. The increased intake of iron is accompanied by an increase in the concentration of iron-binding proteins ferritin and hemosiderin.

If the ability of these proteins to bind iron is exceeded, it begins to be deposited in the parenchymal organs. Iron poisoning, unlike iron deficiency, is relatively rare. This is a serious condition that can be life threatening. An increased ferritin content always accompanies iron overload. However, ferritin cannot be a differential diagnostic indicator of primary or secondary hemochromatosis. At the same time, the cause of the iron overload must be established, as it is necessary for informed treatment.

Primary hemochromatosis. Hereditary hemochromatosis is a serious disease with a genetically determined disorder of iron metabolism. The primary functional defect in hereditary hemochromatosis is an abnormality in the regulation of iron uptake by the cells of the gastrointestinal mucosa (there is no limitation of absorption), which leads to a massive intake of a trace element into the body, followed by the deposition of iron in various organs (liver, spleen, heart, pancreas, gonads, adrenal glands). Hemochromatosis is inherited in an autosomal recessive manner. A close relationship with the HLA-A locus was found. Primary hemochromatosis occurs about 10 times more often in men than in women. Usually clinical manifestations are observed at age 35 - 55 years old, there are liver dysfunctions up to cirrhosis, diabetes mellitus, pigmented dermatosis, cardiomyopathy and heart rhythm disturbances. The classic triad of primary hemochromatosis is melasma, liver cirrhosis, diabetes mellitus. Sometimes symptoms of secondary hypogonadism and adrenocortical insufficiency occur. Hepatocellular carcinoma develops in about 15% of cases.

Hereditary hemochromatosis is characterized by clinical polymorphism due to excessive iron load to one degree or another in all organs and tissues. Therefore, these stages of the disease are conditional. Dysfunction and the corresponding clinical manifestation occur with advanced morphological changes in organs, after

decompensation occurs. Laboratory diagnostics of the disease should be early, in connection with which widespread introduction of screening tests is necessary (hemogram in combination with a complete study of iron metabolism). If hereditary hemochromatosis is suspected, HLA typing and liver biopsies should be performed. In order to remove excess iron from the body, patients are treated with desferal and regular bloodletting.

Secondary acquired hemochromatosis. Hemosiderosis (secondary hemochromatosis) is possible with hemolytic anemias, with ineffective erythropoiesis (including with sideroblastic and aplastic anemia, thalassemia), malaria, intoxication (lead, tin, etc.), alcoholic cirrhosis, chronic viral hepatitis, some types of porphyria , after repeated blood transfusions.

At the beginning, excess iron is concentrated practically only in the cells of the RES and does not cause organ damage, which occurs later during the redistribution of iron from the cells of the RES to the cells of the parenchymal organs.

Therefore, only with prolonged chronic iron overload conditions arise for the development of diseases of iron accumulation with damage to organs.

The duration of chronic iron overload is a determining factor in organ pathology in secondary hemochromatosis.

Iron, which enters the body during blood transfusions, brings a significant addition to the iron that has already entered the intestine.

As a result, serum iron and NTFA levels are significantly increased. Serum ferritin concentration closely correlates with the corresponding degree of iron overload in the reticuloendothelial system. Ineffective erythropoiesis. Heme is formed in various tissues of the body, in the most significant quantities it is synthesized in the bone marrow for inclusion in hemoglobin and in the liver for use in the form of cytochromes.

Stages of heme synthesis:

1. Formation of 5-aminolevulinic acid. 5-Aminolevulinate synthase, the first enzyme on the heme biosynthesis pathway, catalyzes the condensation of glycine with succinyl coenzyme A to form 5-aminolevulinic acid. This enzyme is localized on the inner mitochondrial membrane; its cofactor is pyridoxal-5-phosphate. In the cells of the erythroid and non-erythroid series, synthase is encoded by different genes.

2. Formation of porphobilinogen. Under the action of aminolevulinate dehydratase (this enzyme is localized in the cytosol), two molecules of 5-aminolevulinic acid are converted into mono-pyrrolporfobilinogen with the release of two water molecules. Lead inhibits aminolevulinate dehydratase, displacing zinc, which is necessary for the enzyme to function. The most potent inhibitor is succinylacetone (a structural analogue of aminolevulinic acid), which is present in the urine and blood of patients with hereditary tyrosinemia.

3. Formation of hydroxymethylbilane. Porphobilinogen deaminase catalyzes the condensation of four porphobilinogen molecules to form a linear tetrapyrrole - hydroxymethylbilane. In the absence of the next enzyme, uroporphyrinogen cosynthase III, hydroxymethylbilane spontaneously cyclizes with the formation of the first tetrapyrrole, uroporphyrinogen I. In the presence of uroporphyrinogen cosynthase III, uroporphyrinogen III is formed, in which the pyrrole ring D has a “reverse” sequence of side chains. There are two isoforms of porphobilinogen deaminase; one is present only in erythroid cells, and the other in non-erythroid cells. These isozymes are encoded by different messenger RNAs, which are transcribed from the same gene, but in different ways and undergo different splicing.

4. The formation of uroporphyrinogen III from hydroxymethylbilane is catalyzed by uroporphyrinogen III-cosyntase. This stage consists in intramolecular rearrangement, affecting only the D ring of the porphyrin "large ring".

5. Formation of coproporphyrinogen. Cytosolic enzyme uroporphyrinogen decarboxylase catalyzes the sequential removal of four carboxyl groups from the carboxymethyl side chains of uroporphyrinogen to form coproporphyrinogen.

6. Formation of protoporphyrinogen IX. The mitochondrial enzyme coproporphyrinogen oxidase catalyzes the removal of the carboxyl group and two hydrogen atoms from the propionic groups of the pyrrole rings A and B of coproporphyrinogen with the formation of vinyl groups at these positions.

7. Formation of protoporphyrin IX. The oxidation of protoporphyrinogen IX to protoporphyrin IX is catalyzed by protoporphyrinogen oxidase, which removes 6 hydrogen atoms from the porphyrinogen core.

8. Formation of heme. The last stage of heme biosynthesis is reduced to the incorporation of iron into protoporphyrin IX. This reaction is catalyzed by the mitochondrial enzyme ferrochelatase.

The synthesized heme, combining with the α and β-polypeptide chains of globin, forms hemoglobin. The initial stages before the formation of porphobilinogen and the final links with the participation of protoporphyrinogen and protoporphyrin occur in mitochondria, and the enzymes that catalyze the middle part of the heme synthesis process are localized in the cytosol.

The rate-limiting enzyme that determines the intensity of porphyrin synthesis in all organs is the enzyme 5-aminolevulinate synthase. Glycine and succinyl coenzyme A are substrates for the reaction with the participation of 5-aminolevulinate synthase, their availability modifies the enzyme activity and determines the intensity of heme synthesis. Heme (as well as hematin) is able to inhibit the activity of 5-aminolevulinate synthase. Since heme is not a direct product of the reaction with the participation of 5-aminolevulinate synthase, the inhibition appears to be due to the steric effect.

Nevertheless, this effect is a negative feedback mechanism that controls the hemoglobin content in the circulation system. About 100 different drugs and metabolites are known that can affect the activity of 5-aminolevulinate synthase, in particular 3,5-dicarbethoxy-1,4-dihydrocollidine 40 times increases the activity of the enzyme in the experiment.

Porphyrin metabolism disorders manifest clinically as porphyrias. Porphyrias are hereditary and acquired anemias associated with impaired porphyrin synthesis, characterized by hypochromia, high serum iron, and organ hemosiderosis.

A form of the disease associated with a violation of the synthesis of 5-aminolevulinic acid is observed relatively more often. Violation of the formation of protoporphyrin causes the impossibility of binding iron and, as a result, its accumulation in the body. If iron enters the liver, cirrhosis develops, when iron is deposited in the pancreas, diabetes mellitus occurs, the accumulation of predominantly iron in the testes leads to the development of eunuchoidism, in the adrenal glands - adrenal insufficiency. The clinical manifestations of the disease depend on the severity of anemia and clinical signs of excessive iron deposition in the body. In young people, anemia in most cases is not expressed (80-90 g / l),

but hemoglobin gradually decreases to 50-60 g / l. The content of reticulocytes is normal or slightly reduced. Erythrocytes are hypochromic, there is anisocytosis, poikilocytosis, single target erythrocytes. In the bone marrow - a sharp irritation of the red sprout, increased basophilic polychromatophilic and decreased oxyphilic normoblasts, many sideroblasts. The iron content in the blood serum is significantly increased (up to 5.5 mg / l), transferrin is saturated with iron by almost 100%. When examining the content of porphyrins in erythrocytes in some patients, a decrease in protoporphyrin to 3-9 μmol / l (norm 18-90 μmol / l) and an increase in coproporphyrin to 60-75 μmol / l (norm to 12 μmol / l) are found, in some cases decreases both protoporphyrin and coproporphyrin. The content of 5-aminolevulinic acid and coproporphyrin in the urine is normal. Acquired disorders of porphyrin synthesis are most often associated with lead poisoning or occur with a lack of vitamin B6. Lead blocks the active centers of two enzymes involved in the synthesis of heme, reduces the rate of synthesis of the β-chain of globin. The patient's appearance is peculiar - an earthy pallor with a grayish tinge, associated with both anemia and vasospasm and deposition of porphyrins in the skin, there may be a purple border on the gums. The hemoglobin content gradually decreases to 40-60 g / l, the color index is sharply reduced, erythrocytes are sharply hypochromic, aniso-poikilocytosis is detected. In the bone marrow there is a sharp increase in annular sideroblasts. The serum has a high concentration of ferritin, the iron content reaches 350 - 550 mcg / dl, the iron transferrin saturation coefficient (NTI) is almost 100%.

The most characteristic biochemical sign of lead poisoning is an increase in the content of 5-aminolevulinic acid and coproporphyrin in the urine, while the content of protoporphyrin in erythrocytes is increased.

The quantitative determination of transferrin in serum is carried out by immunochemical methods based on the antigen-antibody interaction reaction. The serum transferrin concentration is high enough that the first reaction between antigen and antibody may be an agglutination or precipitation reaction. The result could be measured directly, often a reaction to the eye.

Direct reactions can be quantified by methods turbidimetry, nephelometry, radial immunodiffusion, radioimmunoassay, etc.

In contrast to these direct specific immunochemical methods for the determination of individual proteins, conventional chemical methods allow an

indirect and approximate determination of the concentration of transferrin by the total iron-binding capacity of serum (TIBC). TIBC is the amount of iron that can bind transferrin to about limit volume of serum.

In clinical diagnostic laboratories, due to the ease of implementation, TIBC is more often determined instead of transferrin. Modern methods for the determination of ferritin are based on immunological analysis. Ferritin is present in serum at very low concentrations (0.2-7 x 10-12 mol / L). Therefore, test kits of the first generation for the determination of ferritin were based on methods of indirect measurement - ELISA, RIA. In recent years, the sensitivity of direct methods (turbidimetry, nephelometry), therefore, turbidimetric latex agglutination test, ELISA-based ELISA kits, nephelometry, fluorescence analysis, luminescence immunoassay, RIA are used to determine ferritin.

Physicochemical and immunological differences of isoferritins contribute to the fact that radioimmunological methods or enzyme-linked immunosorbent assay, depending on the type of antigens or antibodies used, can be accompanied by significant differences the results of measuring the concentration of ferritin in serum. International contacts on a single standard for ferritin were coordinated by the World Health Organization (WHO), the International Committee for Standardization in Hematology (ICSH), the International Federation of Clinical Chemistry (IFCC), and the Standardization Committee of the International Union of Immunological Societies (IUIS). A standardized sample of human liver ferritin is currently stored at the National Institute for Biological Standards and Control in London. The criteria for diagnostic kits for ferritin have been worked out, which, in particular, must meet the safety requirements (tested for the absence of HIV infection), sensitivity, specificity and accuracy, could be used on automatic machines, and be commercially available. Ferritin, like transferrin, does not have circadian rhythms. Based on the fact that the vertical position of the body affects the composition of high-molecular-weight proteins, it is recommended to take samples for ferritin with a standard position of the body from a vein. Preferably, the same blood sample is used for the determination of ferritin, transferrin and iron. Determining reference values for ferritin is always a challenge, as gender and age affect serum ferritin levels. For example, the ferritin content in newborns increases very sharply during the first month of life, since physiological hemolysis of erythrocytes takes place, then its

concentration in serum decreases significantly, reaching minimum values by 6 months of age, and then gradually increases up to 15 years of age. In adult women before menopause, the amount of iron and ferritin stores is significantly less than in men. In old age, the serum ferritin concentration is approximately the same in men and women. It is recommended to set the boundaries of "normal values" in the group of persons in whom latent iron deficiency can be suspected - these are permanent donors and young women. Naturally, people with a manifest form of iron deficiency and patients with infectious diseases should be excluded. An increased serum ferritin content, which does not correlate with the amount of deposited iron in the body, is often determined in Hodgkin's disease, acute leukemia, breast cancer, malignant gonadal tumors, melanoma and carcinoma of the gastrointestinal tract and liver. An increase in ferritin concentration depends on the type and stage of the disease and can be caused by the following reasons: increased synthesis of ferritin by tumor cells, release of ferritin during their destruction, nonspecific increase in serum ferritin concentration. In patients with malignant tumors, an increase in ferritin is due to a high concentration of acidic isoferritins. Normal serum ferritin concentration does not exclude malignant neoplasm. Therefore, ferritin is not used as a screening indicator for early diagnosis of tumors. In selected patients, an elevated serum ferritin concentration may be a useful parameter for detecting metastasis and relapse and, in part, for monitoring the effectiveness of treatment.

The value of ferritin determination in differential diagnosis causes of iron deficiency and anemia. Extremely important when differential diagnosis to distinguish iron deficiency anemia (primary) from other hypochromic anemias, since only with iron deficiency anemia is treatment with iron preparations indicated. Similar treatment for other hypochromic anemias can cause symptoms of secondary hemochromatosis. If iron deficiency is associated with a violation of its distribution in the body (movement of iron from the serum to the deposited form in the RES cells, an increased affinity of the deposited iron in the RES), then treatment with iron preparations will only increase the overload of the RES and will not lead to an increase in hemoglobin synthesis.

Most often, it becomes necessary to differentiate iron deficiency anemia from chronic anemias associated with tumors, infections, sideroblastic nemia, or thalassemia (Table 9). The most important diagnostic finding is the amount of

iron reserve, as measured by the serum ferritin concentration. All anemias, with the exception of iron deficiency, have normal or elevated ferritin levels. A combination of anemia of chronic diseases with iron deficiency anemia is possible. In cases of low ferritin content, treatment with iron preparations is indicated. It should be emphasized that the diagnostic significance of individual indicators of iron metabolism under physiological conditions and most pathological processes does not allow diagnosing the real cause of the violation of iron metabolism. To avoid an erroneous diagnosis, it is necessary to determine all clinical and biochemical parameters of iron metabolism and interpret them on the basis of (patho) physiological laws. The cost of a comprehensive examination is much less compared to the consequences of erroneous (incorrect) therapy. Recently, for the differential diagnosis of IDA and ACD, a new test has been used - the determination of soluble transferrin receptors. Iron deficiency anemia is accompanied by an increase in the synthesis of transferrin receptors, their expression on the surface of cells and an increased release into the blood, where an increased content of soluble transferrin receptors is determined. The synthesis of Hb starts from the pronormoblast stage. At this stage, the processes of formation of Hb, DNA and RNA are carried out with a high speed. With the accumulation of Hb, the synthesis of DNA and RNA is inhibited, as a result of which the mitotic cycle is lengthened. Normally, at the stage of the middle polychromatophilic normoblast, the Hb concentration reaches a critical value, which almost completely stops DNA synthesis and turns off the cell from the mitotic cycle. In this case, the rate of Hb synthesis also slows down. Further maturation of red cells occurs without division.

If the synthesis of Hb is impaired, it accumulates more slowly in the cells, as a result, at the stage of the middle polychromatophilic normoblast, the cells, having not received the required amount of Hb, enter additional mitosis. A population of cells with a smaller volume and lower Hb content (MCH) is formed. Counting the number of red blood cells, determination of hemoglobin and hemoglobin content per 1 erythrocyte (MCH), average erythrocyte volume (MCV) assess the processes occurring in erythron, and belong to the mandatory analyzes for various metabolic disorders of gland. If necessary, differential diagnosis of iron deficiency anemia with other types of anemias and impaired

iron metabolism, bone marrow puncture with a cytochemical reaction to sideroblasts is indicated.

Cytochemical determination of iron. Sideroblasts and siderocytes Siderocytes are erythrocytes containing ferric iron, the reserves of which are not associated with hemoglobin. Sideroblasts are the corresponding nucleated cells of the erythrocyte series. Iron granules are detected in reaction with Prussian blue.

Principle. The interaction of iron ions (Fe + 3), unbound with hemoglobin, with iron-cyanide potassium in a HCl solution is called the reaction of Prussian blue. The reaction product precipitates out as an insoluble complex in the form of turquoise-blue granules in blood cells, bone marrow or tissues, where free iron is localized.

4 Fe + 3 + 3K4Fe (CN) 6 ----> Fe4 [Fe (CN) 6] 3 + 12 K +

According to modern concepts, the most adequate tests for assessing iron metabolism in the body are the determination of the level of iron, transferrin, saturation of transferrin with iron, ferritin, the content of soluble transferrin serum receptors.

Conclusion Iron in the human body is necessary for redox reactions during energy production, peroxidation, oxygen transfer and other critical processes.

Both iron deficiency and excess cause severe disease. To ensure an adequate supply of iron to the body in the process of evolution, multilevel mechanisms of regulation of its metabolism have been developed, including the mechanisms of iron absorption in the intestine, transport through the circulation system, inclusion in cells in organs and tissues,intracellular metabolism, deposition and excretion from the body. Functional dysfunctions at each of these stages can affect overall iron metabolism. Nevertheless, the multistage metabolism allows the body to compensate to a large extent for metabolic shifts. Therefore, clinically there are both latent and, to varying degrees, clinically expressed states of iron deficiency or excess in the body. Moreover, blocking the utilization of iron at the stages of its utilization may be accompanied by the development of a clinical picture of iron deficiency and laboratory indicators of its excess. Incorrect interpretation of the results will be accompanied by incorrect prescription of iron-containing drugs and an even greater deterioration in the patient's condition. Limited access of iron for infectious agents is one of the most

effective mechanisms of infectious tolerance. This pathway is actively expressed in chronic pathology and is manifested by anemia of chronic diseases.

Therefore, the comprehensive laboratory analysis outlined in this study guide, aimed at analyzing the pathophysiological mechanisms of iron metabolism and the formation on this basis of algorithms for laboratory diagnostics and monitoring of the effectiveness of treatment with iron preparations. The offered laboratory technologies provide for the analysis of biochemical, immunochemical, hematological, cytological, general clinical studies.

For adequate laboratory diagnostics, it is necessary to introduce into practice and laboratory research standards such significant indicators of iron metabolism as the determination of transferrin, ferritin, soluble transferrin receptors, hepcidin, cytochemical indicators for hemosiderosis. Modern therapeutic approaches are able to significantly correct and normalize iron metabolism, but for this it is necessary to carry out both screening studies in groups prone to pathology of iron metabolism, and personalized laboratory studies of patients with clinically expressed pathology.

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