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IRON DEFICIENCY ANEMIA IN THE STRUCTURE OF CHRONIC DISEASES (LITERATURE REVIEW)

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Abstract. Iron deficiency anemia is an important problem in modern medicine. The disease is common among the population around the world and accompanies many diseases, especially common against the background of chronic diseases. Timely diagnosis and treatment of this pathology is an important element of the therapy of chronic pathological processes, since anemia aggravates the course of the underlying disease, worsening the quality of life of patients. This literature review considers a number of chronic diseases accompanied by iron deficiency anemia.

Key words: *iron deficiency anemia; chronic disease.*

ЖЕЛЕЗОДЕФИЦИТНАЯ АНЕМИЯ В СТРУКТУРЕ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЙ (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме. Железодефицитная анемия — важная проблема современной медицины. Заболевание распространено среди населения во всем мире и сопровождает многие острые и хронические патологические процессы. Своевременная диагностика и лечение данного клинико-гематологического синдрома является важным элементом терапии хронических болезней, поскольку анемия усугубляет течение основного патологического состояния, ухудшая качество жизни пациентов. В данном литературном обзоре рассмотрен ряд хронических заболеваний, сопровождающихся железодефицитной анемией.

Ключевые слова: *железодефицитная анемия; хроническое заболевание.*

INTRODUCTION

Iron deficiency disorders (IDD) are an important problem in pediatrics. Primarily, it is determined by the widespread prevalence of these conditions worldwide [1, 2]. Iron deficiency anemia (IDA) is a medical and social problem due to its impact on growth, development, cognitive function, intelligence, and behavioral responses in children [3, 4].

Iron is an essential element involved in many biological processes, one of the most important components of the mitochondrial respiratory chain. It is absolutely necessary for the proper functioning of the organism [5]. Iron is capable to

give and receive electrons and plays an important role in fundamental biological processes, including oxygen and electron transport, cellular respiration and DNA synthesis [4]. Iron deficiency (even in the absence of anemia) aggravates the course of many chronic diseases and increases the risk of mortality. The main organs regulating iron metabolism are liver and kidneys [6].

Iron deficiency anemia is an acquired disease characterized by a decrease in iron content in blood serum, bone marrow and tissue depots which resulting in impaired formation of hemoglobin and erythrocytes, hypochromic anemia and trophic disorders in tissues. The disease is polyetiologic [7]. Hermic hypoxia progresses and, subsequently, secondary metabolic disorders develop within this condition. IDA can develop in children with chronic inflammatory diseases even without persistent blood loss [8–10]. Anemia associated with such conditions is commonly referred to as anemia of chronic diseases (ACD), although this term is arbitrary since anemia can also occur in acute inflammation, particularly in suppurative processes (apostematous nephritis, lung abscess, etc.).

EPIDEMIOLOGY

According to the World Health Organization (WHO), about 1.62 billion people, or 24.8% of the total world population, suffer from various pathogenetic forms of anemia. In 2008, the WHO published a report analyzing the prevalence of anemia syndrome, with high rates among preschool children (76.1%), pregnant (69.0%) and non-pregnant women (73.5%). Iron deficiency anemias account for 90% of all anemias in childhood and 80% of all anemias in adults [11].

Iron deficiency anemia is associated with a large number of chronic pathologies:

1) autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, vasculitis, sarcoidosis, Crohn's disease, nonspecific ulcerative colitis) [12–15];
2) infections (acute ones: sepsis, pneumonia, septic endocarditis, peritonitis; chronic ones: osteomyelitis, tuberculosis, lung abscess, HIV);
3) tumors [16];
4) chronic heart failure (anemia is found in 17% of patients with first diagnosed CHF; it is an independent prognostic factor of mortality);
5) critical patients (intensive care patients);
6) endocrine pathology;
7) liver diseases;
8) chronic non-inflammatory diseases (severe trauma, thermal burns);
9) mixed diseases — alcoholic cirrhosis of the liver, circulatory insufficiency, thrombophlebitis, ischemic heart disease [17, 18].

PATHOPHYSIOLOGY

Three pathophysiological mechanisms of anemia development are distinguished:

A slight shortening of erythrocyte lifespan which is attributed to increased hemophagocytosis by macrophages occur in patients with inflammatory diseases;

Erythropoiesis is impaired due to decreased erythropoietin (EPO) production and reduced bone marrow response.

Iron metabolism is altered due to increased levels of hepcidin, which inhibits iron absorption and recycling, resulting in iron sequestration. Hepcidin, a protein synthesized in the liver, plays an important role in iron homeostasis. Inflammation results in the release of large amounts of mediators such as interleukin-6, interleukin-13, which in turn leads to an increase of hepcidin levels. It induces ferroportin blockade, impaired function of duodenal enterocytes, liver kupffer cells, and spleen macrophages; such changes result in reduced iron absorption and recycling [19, 20].

DIAGNOSTICS

The diagnostic basis for IDA associated with chronic disease is the presence of a long-standing condition, such as tumor, infectious-inflammatory, or autoimmune disease. By the moment, diagnostic criteria for the pathology have been developed:

1) clinical signs (depend on the disease: inflammatory, tumor or infectious);
2) pathology (hypoproliferative anemia, impaired iron release from cells of the mononuclear phagocyte system for furhter hemoglobin synthesis, reduced life span of erythrocytes);
3) data of laboratory tests [21, 22].

Clinical manifestations of chronic IDA largely depend on the associated disease. There is a direct correlation between the degree of IDA and severity of an underlying disease.

IDA and diseases of gastrointestinal tract (GIT). Obviously, when searching for the cause of anemia, first of all, it is necessary to exclude diseases that create conditions for blood loss. However, iron deficiency may be caused by impaired intestine absorption of the element. Iron is absorbed in the duodenum and in the initial part of the jejunum. The element passes through the following stages: capture of divalent iron by the cells of the mucous membrane (villi) of the small intestine and its oxidation into trivalent iron in the membrane of

microvilli; transfer of iron to the proper membrane, where it is captured by transferrin and quickly passes into the plasma. In this regard, small intestinal pathology may cause iron deficiency anemia [23–25].

The debut of celiac disease may manifest with anemia; therefore, children with chronic IDA are at risk for celiac disease, so should be screened. Iron deficiency can be observed both in the typical manifestation of celiac disease and in the absence of diarrhea and weight loss. Anemia occurs in 23.75–50% of patients with celiac disease and may be the sole symptom [8, 26].

The stomach plays a major role in iron absorption processes.

Hydrochloric acid converts ionic trivalent iron into the divalent form. In this regard, atrophic gastritis may cause IDA. The second, most common form of atrophic gastritis is associated with prolonged exposure to *Helicobacter pylori* (*H. pylori) infection*, which has been considered as a trigger factor in the development of idiopathic anemia in recent years [9, 14, 27, 28].

At the same time, the peculiarities of IDA in children with Helicobacter infection are insufficiently explored. In the course of the study (67 children with IDA aged 11–15 years) the authors found out that *Helicobacter* infection was detected in every third child with anemia. Anemia associated with Helicobacter infection was characterized by a refractory course, lower increase of hemoglobin and erythrocyte levels compared to children with IDA without *Helicobacter* infection. After successful eradication of *H. pylori*, there was obtained a positive dynamic in treatment with a significant increase of hemoglobin level in children [29].

Anemic syndrome is a frequent companion of inflammatory bowel disease (IBD). About two-thirds of patients with IDA suffer from concomitant anemia, which significantly impairs their quality of life. As a rule, the etiopathogenesis of anemia in IBD is multicomponent since it has no isolated single cause. Anemic syndrome in IBD is a combined variant of iron deficiency and anemia of chronic diseases. The course of the disease is aggravated by additional metabolic disorders, vitamin deficiency, as well as the effect of drugs used for the treatment of IBD [30].

Hemocolitis is one of the main causes of IDA in children with IBD, the incidence is 83–84% in ulcerative colitis and 22–43% in Crohn's disease. In case full recovery of iron depot is not taken into account, the correction of iron deficiency might be inadequate which lead to latent iron deficiency, and then to recurrence of anemic syndrome. As a result, decreased iron intake and increased iron losses have a negative effect on the parameters of iron metabolism [31].

Iron deficiency in overweight. IDA and iron deficiency in excessive adipose tissue accumulation have long been recognized, however, the mechanisms of their interaction continue to be studied. In recent years, 3 main hypotheses of hypoferremia in obesity have been proposed. Nutritional hypothesis: iron deficiency is a comorbid condition in obesity due to insufficient dietary iron intake or insufficient absorption due to concomitant gastroduodenal pathology. Blood volume hypothesis: as body weight increases, blood volume increases. Inflammation hypothesis: based on the involvement of systemic inflammation in the disturbance of iron metabolism in obesity. This hypothesis is the most convincing, it logically fits with the data on low-active inflammation found in obesity [1, 4].

Iron metabolism in kidney disease. Iron metabolism is disturbed in any form of renal pathology. Nephrogenic anemia is one of the pathogenetic variants related to IDA, which naturally complicates the course of chronic kidney disease [5]. This pathology is usually characterized by normocellular, normochromic, hypoproliferative anemia.

Reduced production of erythropoietin produced by kidneys plays a leading role in the mechanisms of anemia development in chronic kidney disease (CKD). However, other factors also contribute to its formation: shortening of erythrocyte lifespan, chronic blood loss, iron or folic acid deficiency, secondary hyperparathyroidism, chronic inflammation and others. Hepsidine excess is considered to be the main cause of impaired iron homeostasis and anemia in CKD due to decreased absorption of dietary iron and mobilization of iron from the depot [32]. The highest incidence of IDA is registered when creatinine clearance is decreased to 40–60 ml/min, and sometimes at earlier stages of the disease. Early development of this form of anemia is most common for diabetic nephropathy [33].

The main causative agent of urinary tract infections currently remains Escherichia coli. This group secretes a number of toxins, including lipopolysaccharide (the main component of membranes of Gram-negative bacteria). Iron is an essential element for survival, reproduction, and virulence of intestinal microorganisms. Hypoferremia is a protective response to infection and inflammation which reduce the amount of iron available for pathogens. Lipopolysaccharide is known to

activate Toll-like receptors (TLRs). TLR activation causes hypoferremia mainly by increasing hepcidin levels. Progression of inflammatory processes in chronic pyelonephritis is accompanied by an increase in the proportion of divalent iron in the structure of sideremia against the background of a decrease in the total iron-binding capacity of serum and reticulocytes and an increase in the concentration of ferritin [5].

Anemia in autoimmune disease. Anemia associated with systemic connective tissue diseases is caused by impaired erythropoietin synthesis due to blood loss from ulcers and erosions of the gastrointestinal tract which develop during prolonged use of anti-inflammatory drugs [34]. Rheumatoid arthritis is accompanied by anemia in 16–65% of cases. The development of anemia in rheumatoid arthritis is promoted by an increased level of inflammatory cytokines. About half of patients with systemic lupus erythematosus have anemia with a hemoglobin content of less than 100 g / l, it is either hypo- or normochromic type. A close relationship between hepcidin levels and IDA in patients with rheumatoid arthritis (RA) has been demonstrated: patients with RA have higher hepcidin levels than healthy individuals, patients with RA and anemia have higher hepcidin levels compared to patients with normal hemoglobin levels, and finally, hepcidin levels in patients with RA and IDA are higher than in cases where systemic inflammation is combined with iron deficiency [35, 36].

IDA in endocrine disease Anemia is quite common in endocrine diseases. At the same time, all morphological forms of anemia might be developed. Thus, parathyroid hormone has a direct inhibitory effect on the synthesis of endogenous erythropoietin, as well as on erythrocyte precursors in the bone marrow and their life span, which determines the presence of anemic syndrome in parathyroid gland pathology. Hypothyroidism is accompanied by anemia in 30–60% of patients. As a rule, hypochromic anemia develops. It is caused by a reduced iron absorption in the small intestine and the lack of stimulating effects on erythropoiesis which is induced by thyroid hormones. Anemia in hypopituitarism occurs in 32–46% of cases [37]. The cause is neoplasms or pubertal underdevelopment of the pituitary gland, accompanied by deficiency of thyroid hormones, adrenal hormones, androgens [38]. Diabetes mellitus is a frequent cause of IDA. The etiology is multifactorial: decreased synthesis of erythropoietin (due to diabetic nephropathy), low absorption of iron and vitamins, medications. Falsely elevated hematocrit level is determined in the blood samples of patients with diabetes mellitus, ketoacidosis might cause acute hemolysis [39].

Thus, iron deficiency anemia is quite common, especially against the background of chronic pathology, often aggravating the clinical course of an underlying disease. Early detection of iron deficiency anemia can accelerate the diagnostic search for the underlying disease, which undoubtedly leads to an earlier start of therapy and improved prognosis.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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