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THE MAIN CAUSES OF ANEMIA IN IRON AND VITAMIN B 12 DEFICIENCY ASSOCIATED WITH HELICOBACTER PYLORI

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Abstract:
The article is generally devoted to anemia and iron deficiency associated with HELICOBACTER PYLORI. The causes of the disease, world statistics, types and treatment modules are also given. The most common consequence of H. pylori infection is iron deficiency. It occurs primarily due to chronic blood loss in erosive gastritis, ulcerative defects, cancer, defects in the gastric mucosa in MALT lymphoma. Another mechanism for the development of iron deficiency is similar to the mechanism for the development of anemia in chronic disease. The synthesis of hepcidin (a peptide that regulates iron absorption) is increased, as a result of which the absorption of iron and its increased deposition in macrophages are blocked at the level of enterocytes. The reason for the development of iron deficiency may be a decrease in the absorption of non-heme iron (iron from plant products) at the level of enterocytes - achlorhydria.
Key words: helicobacter pylori, iron deficiency, B12-deficiency anemia, Reprogramming model of crypt epithelium, Hepcidin model, apotransferrin, monotransferrin, and diferrotransferrin, ferroprotein.

Introduction:

Iron deficiency is one of the most common diseases in the world. According to the WHO, the prevalence of such a manifestation of iron deficiency as anemia is 32.9%. In Europe, there are about 14% of cases of iron deficiency anemia per 100,000 population. Iron deficiency leads not only to the development of anemia, but also to the development of symptoms that worsen the quality of life, such as: weakness, increased fatigue, impaired attention, anxiety, forgetfulness, irritability, morning headaches, fainting, dizziness, increased susceptibility to infections, changes skin and mucous membranes, dyspeptic disorders.

According to the results of many epidemiological studies, one of the risk factors for iron deficiency is the presence of H. pylori infection [13]. H. pylori infection leads to a decrease in ferritin levels regardless of gender, age and other risk factors for iron deficiency, increasing the risk of anemia in this category of patients [22]. The presence of H. pylori infection also affects the effectiveness of iron therapy; most studies demonstrate an increase in the effectiveness of IDA therapy with successful eradication of H. pylori. With successful eradication, the use of iron preparations led to an increase in the level of ferritin, hemoglobin, and normalization of MCV and MCH.

The main results and findings:

To solve the set tasks, the following methods were used: descriptive method, interpretation method, method of conceptual analysis, method of thematic systematization. Clinical laboratory, molecular genetics and statistical methods were used in the work.

The mechanisms of the influence of H. pylori infection on the development of iron deficiency remain unclear. Several studies have suggested different biological mechanisms by which H. pylori infection can deplete a person's iron stores. One of these mechanisms is the effect on inflammation caused by Helicobacter pylori infection, on the hepcidin-ferroportin mechanism of iron metabolism regulation

[24]. An increase in hepcidin levels decreases the absorption of iron from the intestine [21]. Published studies show that hepcidin is elevated in patients with infection

H. pylori, rising as an acute phase marker in response to inflammation in the gastric mucosa, leading to a pathology known as "anemia of inflammation or chronic disease" [2, 6]. At the same time, the eradication of H. pylori leads to a decrease in the level of hepcidin, which increases the effectiveness of therapy for iron deficiency in this group of patients.

Most studies on the relationship between iron deficiency and H. pylori include patients with anemia, and only a few studies include patients with latent iron deficiency. In this regard, there are no reliable data on the frequency of latent and pre-latent iron deficiency in patients infected with H. pylori. It is also necessary to clarify the role of the hepcidin-ferro sportive mechanism for the development of iron deficiency in patients with varying severity of this condition. It is required to determine an algorithm for the treatment of iron deficiency and H. pylori infection in order to increase the effectiveness of therapy and to reduce the risk of developing adverse reactions while simultaneously treating iron deficiency and eradication of H. pylori.

Recently, research has increasingly raised the question of the relationship between iron deficiency and the presence of H. pylori infection. The relationship between H. pylori (HP) infection and anemia has been proven by a number of epidemiological studies, which allows one to classify anemia as a complication of HP infection [13]. According to metanalysis data, there was a weak but significant relationship between H. pylori infection and anemia with an OR of 1.15 (95% CI; 1.00–1.32) [22]. Based on an analysis of 17,191 cases, the prevalence of anemia was 5.5% (428 / 7.804) in patients with H. pylori infection, compared with 5.2% (522 / 9.987) in the group with negative results for HP. The relative risk of anemia in patients with ADR was 1.19 (OR = 1.19; 95% CI), the risk of moderate to severe anemia in patients with ADR was also increased, the RR was 1.39 (95% CI: 1.06–1.54; p = 0.019). Epidemiological studies in children have also demonstrated an association between HP infection, decreased ferritin levels, and the incidence of ID [8]. Studies conducted both in developed and in developing countries have shown a lower ferritin content and / or a higher incidence of iron deficiency or IDA [5, 28] in children with positive NR. A review (NHANES) showed that 32.3% of cases of iron deficiency anemia (IDA) and 13.6% of iron deficiency (IR) in the United States could be associated with H. pylori infection [25].

We also conducted a study of 375 healthy children aged 10–15 years, in which the prevalence of H. pylori infection was 15.5% in children without IDA and 31.3% among children with ID (p = 0.022) [7].

In another large study, in 937 children, the prevalence of H. pylori was higher in the group of children with anemia, hyperferritinemia, and iron deficiency and was 34.2%, 29.5% and 35.3%, respectively, compared with 19.6% in the group. children without anemia (p = 0.003), 19.2% in the group without hyperferritinemia (p = 0.005) and 19.4% in the group of children with iron deficiency (p = 0.001) [119]. The prevalence of H. pylori in the group with IDA was 44.8% compared to 20.0% in the group without IDA (p = 0.001). Decreased iron levels were associated with HP infection more often among girls. In a follow-up study of the effect of H. pylori on iron metabolism, serum ferritin levels were measured in 753 schoolchildren aged 6–12 years. Ferritin levels were significantly lower in children with HP infection compared with the control group (p <0.001).

B12-deficiency anemia (megaloblastic anemia, pernicious anemia, Addison-Birmer disease), characterized by progressive hyperchromic, macrocytic anemia, hypersegmentation of neutrophil nuclei, megaloblastic erythropoiesis and morphological abnormalities of other hematopoietic growths in the bone marrow; Unlike other anemias, B12-deficiency anemia is often associated with the development of pathological psycho-neurological symptoms (funicular myelosis) [26, 4].

Deficiency of vitamin B12 leads to disruption of thymidine synthesis and metabolism of fatty acids, which, in turn, results in disruption of DNA synthesis, accumulation of a metabolite toxic to nerve cells - methylmalonic acid, and a decrease in the content of myelin in nerve fibers. Clinical manifestations of B12 deficiency are numerous disorders in the hematopoietic, nervous and endocrine systems, atrophy of the mucous membranes of the gastrointestinal tract and the development of a characteristic clinic of funicular myelosis.

The main reason for the development of vitamin B12 deficiency is a violation of its absorption in the intestine. The parietal cells of the body and the fundus of the stomach secrete a protein, the so-called.

"Internal Castle factor" (discovered by W. Castle in 1930), necessary for the absorption of vitamin B12 (cobalamin, "external factor"). Formation of a persistent complex;

"Cobalamin - internal Castle factor" begins in the alkaline environment of the duodenum, then the absorption of vitamin B12 occurs in the small intestine, mainly in the ileum, where cubulin is localized - a secific receptor protein for;

"Internal factor". In the process of absorption, the "complex" breaks down, vitamin B12 penetrates through the wall of the small intestine into the bloodstream, where it binds to transcobalamin, which delivers it to consumer cells, including bone marrow and liver cells.

The following pathological processes can lead to impaired absorption of vitamin B12:

- a decrease in production or absence of "internal Castle factor" due to the presence of autoantibodies to it or to parietal cells of the stomach, other atrophic gastritis, gastric resection;
- diseases of the small intestine (chronic enteritis with malabsorption syndrome, tumors, including lymphomas);
- competitive absorption (diverticulosis with changes in flora, diphyllobothriasis, “blind loop” syndrome with anastomosis of the small intestine);
- diseases of the pancreas, which contribute to an increase in the acidity of intestinal contents (tumor with the formation of gastrin, Zollinger-Ellison syndrome),
- long-term use of certain medications (proton pump inhibitors, metformin, etc.) [15,6]

Nutritional deficiencies in vitamin B12 can develop in people on a vegetarian or vegan diet. All of the above risk factors for the development of cobalamin deficiency should be considered in patients with hereditary forms of hemolytic anemia.

In children, the main causes of B12 deficiency are:

- a decrease in the intake of vitamin B12 from food (in infants whose mothers are deficient in vitamin B12 or follow a strict vegetarian diet;
- decreased absorption (deficiency of intrinsic Kastl factor, gastric resection, malabsorption in the ileum due to congenital diseases of the small intestine, bowel resection);
- increased loss of cyanocobalamin in the intestine (helminthic invasion, cecum syndrome);
- congenital genetic defects leading to impaired transport of vitamin B12 [20, 10].

B12 deficiency anemia is one of the most common anemias, the frequency of detection of which varies in different age groups: after 60 years, vitamin B12 deficiency is found in one out of 50 people, and after 70 years - in every 15th. In accordance with this, in some countries, the concentration of vitamin B12 in the blood serum is determined for the elderly in the order of clinical examination [3, 15].

B12-deficiency anemias are divided into:

- acquired
- hereditary (congenital)

Among the acquired B12-deficiency anemias, the primary form is distinguished, due to the presence of autoantibodies to the internal Castle factor (pernicious anemia), and the secondary,

associated with one or more risk factors for the development of B12 deficiency, for example, the presence of congenital hemolytic anemia and a strict vegan diet. The primary form, due to the autoimmune nature of B12 deficiency, often complicates the course of autoimmune thyroiditis and type 1 diabetes mellitus. Hereditary forms of B12 deficiency have been described in children with congenital genetic defects leading to impaired transport of vitamin B12 [11, 16].

The main clinical manifestations of B12-deficiency anemia include gradually increasing weakness, apathy, exercise intolerance, palpitations, heart pain, dyspeptic disorders, as well as weakness in the legs and paresthesias, migratory pain, numbness of the extremities and gradual loss of sensitivity in the fingers. Typical - puffiness of the face and amimicity, pale jaundice skin color, smoothness of the papillae of the tongue ("crimson lacquered tongue"). Young people often have early graying of hair. Subfebrile temperature and an increase in the size of the spleen are often noted, which often lead to diagnostic errors. In the absence of timely diagnosis and treatment of B12 deficiency, a violation of superficial and deep muscle sensitivity, hearing loss, vision loss, areflexia develop, in advanced cases - dysfunction of the pelvic organs and severe cognitive impairment. In severe cases of B12 deficiency, the lesion of the peripheral nervous system (funicular myelosis) dominates: ataxia, hyporeflexia, the appearance of pathological signs - the Babinsky reflex [26, 4].

To understand the role of H. pylori infection in the development of IDA, it is necessary to describe the processes of iron metabolism and the important molecules involved in them. Iron metabolism in the body is a semi-closed system that is critically regulated by several factors. Two-thirds of iron is found in the pool of red blood cells and is recycled by breaking down and transforming them. Only 1–2 mg of iron is absorbed from the intestinal tract and circulates in the blood. Since there is no active mechanism for removing iron from the body, the balance of iron is controlled by absorption. Almost all absorption of dietary iron occurs in the duodenum. Iron metabolism consists of several steps, such as the reduction of iron to the state of ferrous iron (Fe2 +), apical uptake, intracellular storage or transcellular transport, and basolateral release. Different groups of proteins are involved in these mechanisms. They can be roughly classified into 4 functional groups. The enzymatic function is performed by ferro reductase and heme oxygenase-1, the transport function is performed by the bivalent metal-1 transporter (DMT-1), lipocalin-2, ferroportin-1, heme iron transporter, transferrin, transferrin receptor 1/2, Nramp-1 protein and hefestin. Hemosiderin, ferritin and lactoferrin are responsible for iron storage, and IRP1 / 2, IRE proteins, and hepcidin are responsible for the regulation.

Dietary iron occurs in two forms: heme iron (10%), obtained from meat and bound to hemoglobin and myoglobin, and non-heme iron (90%), which is ionic and excreted from plants. Both forms of iron are absorbed at the apical surface of duodenal cells through different mechanisms. Non-heme iron, taken with food, is initially present in the oxidized (trivalent Fe3 +) form. This form of iron is not bioavailable, and before it is absorbed by the enterocyte, it must be reduced to the form Fe2 + using ferro reductase [23]. Fe3 + recovery is optimized by the low pH in the stomach. Stomach acid, ascorbic acid, and reductase 969 enhance iron absorption [17]. Iron is transported through the intestinal epithelium using the bivalent metal transporter-1 (DMT-1), which also transports other metal ions [18]. There is also a siderophore-like lipocalin-2 mediated iron uptake pathway that appears to elicit an innate immune response against bacterial infection by sequestering iron. However, the physiological role of lipocalin-2 is not fully understood. Heme iron is better absorbed than the non-heme form. Heme iron is absorbed into enterocytes due to the heme iron transporter, which is a membrane protein located in the proximal intestine [14]. Heme iron is cleaved by hemeoxygenase-1 within the enterocyte. In the epithelial cell of the intestine, iron can be converted in two ways: 1) it can remain in the cell for use or storage, this iron is excreted from the body when the intestinal cells are slough off; 2) iron is transported into the bloodstream through the basolateral membrane of the

enterocyte. Fe2 + is transported from the basement membrane through ferroportin-1, after which it is oxidized to Fe3 + by hefestin, an enzymatic protein similar to plasma ceruloplasmin, before binding to plasma transferrin. Ferroportin-1 is also a putative iron exporter to macrophages and hepatocytes [10, 111]. Iron absorption is represented by two models. It increases with iron deficiency and increased erythropoiesis and decreases with inflammation and replenishment of iron stores. The regulation of iron absorption can be described in two models.

Reprogramming model of crypt epithelium:

The level of intracellular iron in the cells of the crypts of the duodenum communicates with the deposits of iron in the body, which, in turn, determines the amount of iron absorbed from the intestinal lumen. Crypt cells express transferrin-1/2 receptors. These receptors mediate the cellular uptake of transferrin-bound iron from plasma [23, 136]. The transferrin-1 receptor is ubiquitous, and transferrin-mediated iron uptake is believed to occur in most cell types. Despite this, the expression of the transferrin-1 receptor is limited in hepatocytes, duodenal crypt cells and erythroid cells, indicating a narrower function in the regulation of iron balance. IRE proteins act as iron sensors and regulate the translation of mRNA-encoding proteins. The interaction of IRE proteins with IRP proteins 1 and 2 is regulated by the level of intracellular iron. With iron deficiency, IRP1 binds to IRE and the synthesis of the transferrin receptor, DMT-1 and ferroportin-1 begins in the duodenum, thereby increasing the absorption of iron from food. Thus, the increased activity of IRP binding causes a decrease in iron stores in the body [23].

Hepcidin model:

Liver hepcidin is a cysteine-rich peptide of 25 amino acids. Numerous factors contribute to the regulation of hepcidin levels. These factors include liver iron levels, inflammation, hypoxia, and anemia. Hepcidin regulates the rate of iron absorption by controlling the expression of ferroportin-1 on the basolateral membranes of enterocytes. Internalization of ferroportin-1 and a decrease in its function occur after the binding of hepcidin to ferroportin-1. Ferroportin-1 molecules are also present in macrophages and in the liver. Therefore, iron release from crypt epithelial cells of the intestine, liver and macrophages is believed to be reduced when hepcidin levels are increased by iron overload or inflammation (via IL-6). On the contrary, it is likely that the expression of ferroportin-1 and iron release increase with a decrease in hepcidin levels, as is the case with ID, IDA, or hypoxia [24]. Iron in the bloodstream binds to transferrin and is transported to the loci of its use and storage. Three forms of transferrin can be found in plasma: iron-free apotransferrin, monotransferrin, and diferrotransferrin. Under normal physiological conditions, about 30–40% of these iron-binding transferrin pools are utilized. Transferrin-bound iron is the most important dynamic pool of iron transport [9]. Transferrin-bound iron enters target cells, mainly erythroid cells, as well as immune and hepatic cells during receptor-mediated endocytosis [23].

Transferrin binds to the transferrin receptor located on the plasma membrane. Siderosomes, clathrin-coated endosomes, are formed as a result of invagination of transferrin and receptor-ligand complexes on the cell membrane. Thereafter, the siderosomes are oxidized due to the ATP-dependent influx of protons. This process leads to conformational changes in the transferrin molecule and transferrin receptor 1 and promotes the release of ferric iron from transferrin.

Most of the body's iron is consumed in the production of hemoglobin by erythrone. Aging erythrocytes are phagocytosed, due to which iron is recirculated from hemoglobin. Hemoxygenase-1 metabolizes heme in the phagocytic vesicles of macrophages of the reticuloendothelial system. The iron is then released into the cytoplasm by Nramp-1, a DMT-1-like transport protein. Macrophages can also obtain iron from other cells undergoing apoptosis, as well as bacteria [10]. Iron is stored in the cell

in two forms: in the form of ferritin in the cytosol and in the form of hemosiderin, which is formed as a result of the decomposition of ferritin in lysosomes. Hemosiderin represents a small portion of the body's iron stores. It is found mainly in macrophages and increases with iron overload. The export of iron from macrophages to transferrin is carried out mainly by ferroportin-1, the same iron-exporting protein expressed in the enterocytes of the duodenum, and also by hefestin [23].

The amount of iron required for the daily production of 300 billion red blood cells (20–30 mg) is mainly provided through the reuse of iron by macrophages. The liver is the main storage organ for iron, in which excess iron is stored in the form of ferritin and hemosiderin. The uptake of transferrin-bound iron by the liver from plasma is mediated by transferrin receptors 1 and 2. In states of iron overload, transferrin is saturated, and excess iron is in the form of iron not bound to transferrin. This form of iron is transported along with the hepatocyte membrane and DMT-1 protein. Hepatocytes can also accumulate iron in the form of ferritin, hemoglobin-haptoglobin and heme-hemopexin complexes. Iron is oxidized by ceruloplasmin and binds to transferrin after it leaves hepatocytes. Iron is also found on mucous membranes in the form of lactoferrin. In addition to these proteins, cells contain an additional fraction of free iron in the form of a pool of labile iron.

The mechanisms by which H. pylori infection contributes to the development of IDA remain unclear. Several studies have proposed different biological mechanisms by which H. pylori infection can deplete a person's iron stores. Four possible mechanisms can be distinguished: 1) overt or latent blood loss due to lesions of the gastroduodenal tract; 2) decreased absorption of iron due to hypo- or achlorhydria [4]; 3) increased iron intake by H. pylori strains [16]; 4) sequestration of iron in the gastric mucosa.

Conclusion :

At the end of the research, the following conclusions were drawn:

— 19.9% (16.8–23.3; CI 95%) of patients with Helicobacter pylori infection develop iron deficiency. 4.95% (3.36–7.0; CI 95%) had pre-latent iron deficiency, 10.9% (8.5–13.7; 95% CI) had latent iron deficiency, 4.12 % (2.7–6.02; 95% CI) of patients - anemia. In 53% of patients, the development of iron deficiency is accompanied by symptoms of sideropenia.

— The development of iron deficiency in patients infected with Helicobacter pylori in 32.2% of cases occurs against the background of an increase in the iron-regulating protein hepcidin. There is an inverse correlation between the level of hepcidin and the level of iron (r = –0.595; –0.467 –701 95% CI).

— In the pathogenesis of iron deficiency, the leading role is played by the violation of iron metabolism under the influence of hepcidin, which leads to the development of iron deficiency of chronic inflammation in 32.2% of cases of ID. In 31.4%, the "true" variant develops, and in 36.4% - the "combined" pathogenetic variant of iron deficiency.

— A necessary component of effective therapy for iron deficiency in patients infected with Helicobacter pylori is successful eradication, in which the effectiveness of therapy is 96% versus 28% ($\chi 2 = 51.0$; $p < 0.001$) with negative results of eradication. The effectiveness of iron supplementation without eradication therapy is 59% (20.8; $p < 0.001$).

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