New Opportunities in the Diagnosis of Anemia of Chronic Diseases

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ABSTRACT

The paper presents its own data on the study of hepcidin content in the blood in iron deficiency anemia and anemia developed in patients with rheumatoid arthritis and bacterial infections. The authors present their own data on the content of hepcidin in practically healthy people. The results of the study indicate an extremely low level of hepcidin in iron deficiency anemia, while in patients with anemia of chronic diseases, the content of hepcidin is significantly high. There were no differences in hepcidin levels in people with ACD with rheumatoid arthritis and bacterial infections of various localization. The study of hepcidin levels in blood serum can be used in the algorithm of differential diagnosis of iron deficiency anemia and functional iron deficiency.

Keywords: iron deficiency anemia; anemia of chronic diseases; hepcidin; cytokines

Introduction

A number of proteins are involved in the regulation of iron metabolism, which control its absorption from food in the small intestine and the recycling of iron from macrophages. The proteins responsible for iron metabolism are expressed according to the needs of the body. About 20 regulatory molecules have been discovered that control this highly organized process. In recent years, the role of hepcidin as a key regulator of iron metabolism has been widely discussed. Hepcidin is a cysteine–rich polypeptide (molecular weight 470 kDa). Its precursor, a prepropeptide (84 amino acids), is converted to The prohormone is progepsidin (60 amino acids), which is proteolytically cleaved to the bioactive hepcidin – hepcidin-25. Hepcidin is synthesized mainly by hepatocytes and excreted by the kidneys. For the first time, hepcidin was isolated from urine and described by S.N. Park et al.. Subsequently, this peptide was also isolated from plasma. Hepcidin has pronounced antibacterial properties. A.A. Levina et al. It was found that in humans, hepcidin expression in the liver is noted as early as the 5th week of intrauterine development. The same authors showed that in fetuses that died due to bacterial infection The expression of the peptide was ten times higher than in fetuses without signs of infection. At the same time, in fetuses that died from a viral infection, the expression of hepcidin increased slightly, on average by about 1.5 times, which confirms the predominantly antibacterial orientation of this link of innate immunity. In recent years, it has been found out that the role of hepcidin in the body is much more multifaceted than just antibacterial protection, since disorders in the expression of the hepcidin gene are associated with clinical abnormalities in iron metabolism, as well as with anemia. The relationship between hepcidin and iron metabolism was first presented by S. Pigeon et al., who proved that

excess iron contributes to the expression of the hepcidin synthesis gene, and it was shown that mRNA is expressed not only under the influence of an iron-rich diet, but also under the influence of lipopolysaccharides. In studies conducted both in model experiments on transgenic mouse lines and in humans with infectious diseases and inflammation, it was shown that hyperproduction of hepcidin during infection and inflammation, it causes hypoferrymia and may be responsible for anemia in chronic diseases. E. Nemeth et al. It was shown that 3 hours after administration of the inflammatory agent, there is an increase in the values of the proinflammatory cytokine interleukin–6, and after 6 hours the peak of hepcidin expression and a decrease in the level of the iron in the serum.

The leading role of IL-6 in the regulation of hepcidin production is confirmed by data that when treated with monoclonal antibodies to the interleukin-6 receptor, hepcidin levels rapidly decreased in patients The level of hepcidin significantly affects the treatment of anemia in chronic kidney disease, when inflammation and, possibly, a decrease in hepcidin clearance leads to an increase in its plasma level, which helps to limit the participation of iron in erythropoiesis and resistance to erythropoietin. Accordingly, the high level of hepcidin dictates the need for parenteral administration of iron to prevent erythropoiesis disorders and increase doses to suppress hepcidin production. Low hepcidin levels may be an indicator of a better response to iron supplementation. Quite It is likely that the level of hepcidin can become a unique marker that determines the tactics of therapy with iron preparations. We conducted a study of the serum hepcidin content in hypochromic anemia of various origins in order to assess the role of hepcidin in the formation of anemic syndrome and the possibility of using this indicator in the differential diagnosis of hypochromic anemia.

Materials And Methods

The study included women (n = 375) aged 16 to 60 years; 16 of them were practically healthy and made up the control group, 59 people had anemic syndrome, 21 of them suffered from iron deficiency anemia (IDA), 38 from anemia of chronic diseases (ACD). 24 women with ACD was diagnosed with anemia that developed against the background of autoimmune connective tissue diseases (rheumatoid arthritis), 72 – anemia of chronic diseases with bacterial infections (chronic tonsillitis, bacterial endocarditis, chronic pyelonephritis).

The nature of anemia was determined based on the results of a study of iron metabolism indicators, taking into account clinical and hematological data. In women with ACD on the background of rheumatoid arthritis (RA), anemia of mild severity was recorded in 14 cases, the average – in 10 patients. The duration of RA ranged from 1.5 years to 15 years, the onset of the disease in all patients was subacute and subsequently took a prolonged progressive course. Extra-articular symptoms involving the kidneys, heart and other organs were found in 19 patients, 14 had moderate (II) and 10 had a high (III) degree of activity with functional joint insufficiency of stage II–III. 9 women with ACD with infectious and inflammatory diseases had mild anemia, and 5 had moderate anemia. The inflammatory reaction was confirmed by high levels of acute phase proteins: C-reactive protein, α1-acid glycoprotein, neopterin.

The pre-laboratory clinical examination was carried out using a questionnaire, which included sections on complaints, anamnesis of life and illness, the presence of concomitant diseases, and objective examination data. Research methods

The assessment of indicators of the peripheral erythron link, iron metabolism, cytokine and hepcidin levels was included. The study of indicators of the peripheral erythron link and iron metabolism was carried out using standard conventional methods. Iron reserves were estimated by the level of serum ferritin, which was studied by the enzyme immunoassay using the company's test systems Orgentec diagnostika (Germany). The cytokine status (IL-6, TNFa, IFN-γ) was studied using the Vector-Best test systems by the method enzyme immunoassay. Hepcidin-25 in

the serum of the examined patients was determined by the method ELISA using Peninsula test systems Laboratories, LLC (USA).

Statistical processing of the obtained data was carried out using software packages MS-EXCEL, MS-WORD, BIOSTAT, Version 4.03. The research results were processed by the method of variational statistics, the t-criterion was used to assess the reliability of the research results A student. The normal distribution was determined using the Shapiro–Wilk criterion. Critical The significance level when checking statistical hypotheses was assumed to be 0.05.

Research Results And Their Discussion

When evaluating iron metabolism in all examined patients with iron deficiency anemia, there was a significant decrease in serum iron and CST levels with significantly increased OHSS and LVSS compared with those in healthy individuals (p = 0). Serum ferritin levels in patients with iron deficiency anemia averaged 4.91±0.66 ng/ml and was significantly lower compared to those in the control group (p = 0), which in combination with clinical data, results of hematological studies and indicators of iron metabolism indicated the microcytic, hypochromic, iron deficiency nature of anemia.

Impaired iron metabolism in patients with ACD was characterized by low serum iron levels, a reduced transferrin saturation coefficient with a high serum ferritin content. An increase in serum ferritin levels in patients with anemia of chronic diseases against the background of infectious and inflammatory processes and rheumatoid arthritis occurs in parallel with an increase in the levels of acute phase plasma proteins (C-reactive protein, α1-acidic glycoprotein, neopterin).

In practically healthy patients, the level of hepcidin varied from 5 to 12 ng/ml, averaging 8.07±0.2ng/ml. When using the Gaussian distribution law, the normal laboratory values are the average values for a healthy population of ± 2 standard deviations (± 2SD). In our studies, ± 2SD corresponded to a value of ± 3.74, respectively, the range of normal hepcidin25 values in healthy subjects ranged from 4.33 to 11.81 ng/ml.

In patients with IDA with verified iron deficiency, a significant decrease in hepcidin levels was revealed. The content of hepcidin in the blood serum of patients with IDA averaged 0.25±0.02 ng/ml versus that in the control group – 8.07±0.2 ng/ml. In patients with ACD, the level of hepcidin was significantly high compared with that in healthy and patients with IDA (p = 0), and the increase in hepcidin levels did not depend on the etiology of the disease and the localization of the inflammatory process. There were no significant differences in hepcidin levels in patients with ACD on the background of rheumatoid arthritis and ACD in bacterial infections of various localization. High hepcidin levels in patients with AHZ correlated with the severity of anemia syndrome in them, while there was an inverse correlation.

Along with By studying hepcidin, we conducted a study of the content of proinflammatory cytokines in the blood serum of the examined patients. We found the most pronounced increase when assessing the level of IL-6 with a significant increase in the level of TNFa and interferon-γ in ACD. Thus, the average values of IL-6 in the groups with ACD on the background of RA and in infectious and inflammatory diseases were significantly higher than in the control group and amounted to 43.39±11.93 pg/ml (p = 0.005) and 48.27±12.86pg/ml (p = 0), respectively, versus 2.78±0.23 pg/mlml in healthy patients.

We see that in ACD there is a direct correlation between serum concentrations of IL-6 and hepcidin. This is consistent with modern ideas about the activation and increased synthesis under the influence of IL-6 of the iron-regulatory protein hepcidin, which plays the role of a negative mediator in the regulation of iron metabolism and its incorporation into erythroid cells, which leads to iron deficiency erythropoiesis and anemia.

The obtained results of the study indicate that hepcidin serves as a regulator of iron metabolism and can be used in the algorithm of differential diagnosis of ACD (functional iron deficiency) and true iron deficiency – iron deficiency anemia. Increase in hepcidin-25 more than 11.81 ng/ml indicates anemia of

chronic diseases, and a value less than 4.33 ng/ml indicates iron deficiency anemia (4.33–11.81 ng/ml is the range of hepcidin-25 levels in practically healthy people).

Conclusion

Reduction of hepcidin levels in This is quite understandable from the point of view of the role of hepcidin in iron metabolism and the body's desire to replenish iron reserves to ensure hemoglobin synthesis in erythroid cells of the bone marrow and replenish the number of red blood cells. A low level of hepcidin can serve as an indicator of latent iron deficiency when there is still no change in other indicators of iron metabolism, such as ferritin levels. This is of great practical importance: incorrect interpretation of a patient with ACD as having an iron deficiency entails ineffective therapy with iron preparations with the risk of complications.

Modulation of the biological activity of hepcidin, which is a key factor in the regulation of iron homeostasis, determines the clinical possibilities of treating patients with anemia of chronic diseases and other hypochromic anemia associated with impaired iron metabolism.

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КАРДИОСКЛЕРОЗОМ И ДИЛАТАЦИОННОЙ КАРДИОМИОПАТИЕЙ. In *СОВРЕМЕННЫЕ ТЕХНОЛОГИИ: ПРОБЛЕМЫ ИННОВАЦИОННОГО РАЗВИТИЯ* (pp. 268-272).

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