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Original Research Article

Does stroke messed up with a serum hepcidin levels in therapy of anemia in rheumatoid arthritis patients?

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Abstract

Anemia in rheumatoid arthritis is a process associated with chronic inflammatory disease. It occurs as iron deficiency, mostly due to drug-induced gastrointestinal bleeding and disorders as well as iron redistribution into inflamed joint structure. Oxidative stress plays an important role in neuronal injuries caused by cerebral ischemia. It is known that free iron increases significantly during ischemia and is responsible for oxidative damage in the brain. For a period of two years 46 patients (8 male and 38 female), diagnosed with rheumatoid arthritis from the Department of Rheumatology at "St. Ivan Rilski" hospital were observed. Acute stroke were diagnosed in Neurology Dept. at University "Aleksandrovska" hospital. Thalassemia patients were monitored in Intensive Cardiology Dept. at the same hospital. Serum hepcidin levels statistically differ in three RA groups: RA no anemia 15.8 ± 0.7 µg/L (in the reference ranges), RA with IDA 0.7 ± 0.2 µg/L and RA with ACD 96.7 ± 1.9 µg/L (P < 0.001). In patients with acute stroke hepcidin concentrations were significantly elevated compared to thalassemia cases 87.8 ± 1.6 µg/L to 0.95 ± 0.3 µg/L (P < 0.001). Our study in patients with rheumatoid arthritis and different anemia plus additional acute stroke cases confirms the ability of verified immunochemical method to differentiate the increase and decrease in serum hepcidin in patients with RA. It provides a basis for choosing the correct therapeutic approach in the treatment of anemia.

Key words: Anemia, Anemia on chronic inflammation, Hepcidin, Iron deficiency, Rheumatoid arthritis, Stroke

INTRODUCTION

Anemia in rheumatoid arthritis is a process associated with chronic inflammatory disease. It occurs as iron deficiency, mostly due to drug-induced gastrointestinal bleeding and disorders as well as iron redistribution into inflamed joint structure. Identifying and finding the right treatment approach for iron deficiency in patients with anemia of chronic disease is of great clinical importance because it can prevent unnecessary spelling of therapy with iron preparations.

Proinflammatory stimuli lead to the development of anemia of chronic disease by directly inhibiting erythropoesis and indirectly through reduced iron supply for the synthesis of heme (Weiss and Goodnough, 2005). This process is associated with increased levels of regulatory peptide hepcidin due to inflammation. Elevated hepcidin decreases intestinal iron absorption, due to the changes in the molecule of the cell iron exporter – ferroportin, together with iron retention in macrophages and iron sequestration in the reticuloendothelial system (Kemna et al., 2008; Goodnough et al., 2010).

Table 1. Age distribution of patients in different groups

Group	M:F	Age
RA no A	3 (20%): 12 (80%)	52.1 ± 9.2
RA with IDA	2 (14.3%): 12 (85.7%)	54.6 ± 10.3
RA with ACD	3 (17.6%): 14 (82.4%)	55.5 ± 7.0
RA and stroke no A	1 (25%): 3 (75%)	50.2 ± 2.2
RA and stroke with IDA	1 (33.3%): 2 (66.7%)	52.2 ± 6.1
RA and stroke with ACD	1 (25%): 3 (75%)	52.5 ± 4.0
Thalassemia	8 (53.3%): 7 (46.7%)	35 ± 3.2
Acute stroke	9 (69.2%): 4 (30.8%)	51.9 ± 2.7

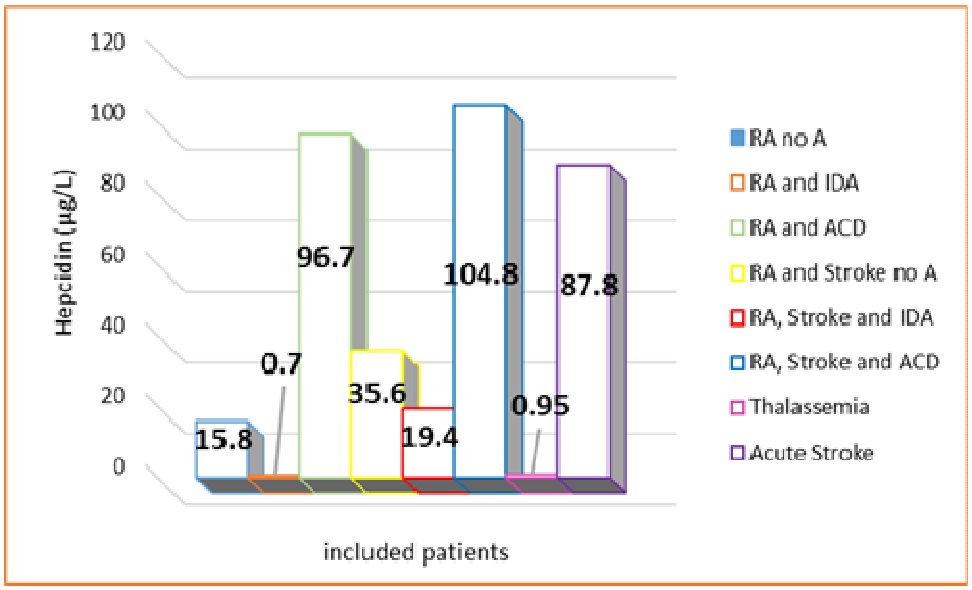

Figure 1. Serum hepcidin concentrations (in µg/L) in the different groups of patients included in this study.
*RA – rheumatoid arthritis; A – anemia; IDA – iron deficiency anemia; ACD – anemia of chronic disease

Consequently, the total content of iron in the body is normal, but less is supplied for erythropoesis. The opposite mechanism occurs for the development of iron deficiency anemia. When it is observed absolute iron deficiency, hepcidin secretion is suppressed, leading to stimulation of the absorption of iron in the intestine.

Oxidative stress plays an important role in neuronal injuries caused by cerebral ischemia. It is known that free iron increases significantly during ischemia and is responsible for oxidative damage in the brain.

METHODS

For a period of two years 46 patients (8 male and 38 female), diagnosed with rheumatoid arthritis from the Department of Rheumatology at "St. Ivan Rilski" hospital were observed. Disease activity was determined by Disease Activity Score calculator for rheumatoid arthritis [DAS 28-CRP]. Patients with anemia were divided into three groups by identifying clinical and laboratory indicators of inflammation and iron deficiency. 11 of them had an acute stroke. Their results were compared to 15 thalassemia patients and 13 cases with acute stroke. Acute stroke were diagnosed in Neurology Dept. at University "Aleksandrovska" hospital. Thalassemia patients were monitored in Intensive Cardiology Dept. at the same hospital. One patient with thalassemia and rheumatoid arthritis was also evaluated.

We quantify serum hepcidin levels using verified ELISA method (Manolov et al., 2014) from previous studies. Unpaired t-test and Pearson's correlation were used for statistical analysis.

RESULTS

Age distribution of patients in the different included groups is shown in Table 1.

Patients were signing the informed consent according

to the Declaration of Helsinki (Directive 2001/20 / EC). We found statistically different results into included groups for serum hepcidin levels. They differ in case if an acute stroke occurs during rheumatoid arthritis. The results obtained from the serum hepcidin quantification are presented in Figure 1.

Serum hepcidin levels statistically differ in three RA groups: RA no anemia 15.8 ± 0.7 µg/L (in the reference ranges), RA with IDA 0.7 ± 0.2 µg/L and RA with ACD 96.7 ± 1.9 µg/L ($P < 0.001$). In patients with acute stroke hepcidin concentrations were significantly elevated compared to thalassemia cases 87.8 ± 1.6 µg/L to 0.95 ± 0.3 µg/L ($P < 0.001$).

Occurrence of acute stroke in rheumatoid arthritis patients changes hepcidin concentrations. In cases of RA without anemia we observed elevated hepcidin 35.6 ± 1.4 µg/L; the results are above reference ranges for Bulgarian population. RA group with IDA and acute stroke also showed elevation in their serum hepcidin 19.4 ± 0.9 µg/L; already in the normal values! Hepcidin increased in rheumatoid arthritis patients with acute stroke and anemia of chronic disease 104.8 ± 2.2 µg/L.

Yet, there was a statistical significance between hepcidin in three RA and stroke groups ($P < 0.001$).

One patient with rheumatoid arthritis and thalassemia showed hepcidin in serum 1.2 ± 0.3 µg/L.

DISCUSSION

Patients with inflammatory and reduced hepcidin are expected to have an iron deficiency. In contrast, those with high level of hepcidin are diagnosed with ACD.

Using serum hepcidin levels would help in assessing the need for the application of preparations containing iron. The results suggest that patients with IDA may be subjected to treatment with such drugs, while patients with ACD do not need them.

Rheumatoid arthritis is a multifactorial condition that is associated with ACD. It may also include iron deficiency due to bleeding in the gastrointestinal tract caused by applied therapy; distribution in synovial tissue. Establishment of iron deficiency in populations with ACD is clinically relevant because: 1) iron-deficiency anemia (IDA) is treatable, 2) diagnosis can precede further investigation of the cause of anemia, and 3) can prevent unnecessary supplementation with iron. Data from our study indicated a significant increase in serum hepcidin in RA and ACD compared with the control group.

On the other hand cases of acute stroke in thalassemia patients might seriously mask the anemia picture and clinicians might make an incorrect therapeutic choice (Julia Petrova, et al; accepted for publication in International Journal of Stroke).

Established changes of serum hepcidin in cases of acute stroke might lead to different evaluation of anemia in rheumatoid arthritis patients. Lower hepcidin levels in one patient with rheumatoid arthritis and thalassemia is probably due to the main hereditary disease. There was no acute stroke evidence in this case.

Future of hepcidin is related to the possibility hepcidin antagonists and agonists can be used as a therapeutic agent in the treatment of anemia in inflammation and iron-deficiency anemia. Reducing of hepcidin levels or counteracting the biological effects of hepcidin may lead to a reduction in inflammation on erythropoesis by mobilization of stored iron and increases intestinal absorption of the element. These new therapeutic approaches could reduce or eliminate all toxic effects of treatment with parenteral iron and Co-reduction needs erythropoetin stimulating agents (ESAs). In these cases, serum hepcidin is suitable therapeutic target in the management of therapy in CKD.

On the other hand the burden of iron overload in thalassemia-β were unaffected by treatment with chelators, which can have severe side effects. There are a few studies about micro-hepcidin as an alternative of chelation therapy, especially in patients without transfusion therapy (Preza et al., 2011). Treatment with hepcidin may have a beneficial effect and ineffective erythropoiesis.

Determination of serum hepcidin is still a novelty in Bulgarian medical practice. The introduction of a reliable routine method for the study of hepcidin in biological fluids is a step forward in the treatment of diseases with impaired iron homeostasis. Our study in patients with rheumatoid arthritis and different anemia plus additional acute stroke cases confirms the ability of verified immunochemical method to differentiate the increase and decrease in serum hepcidin in patients with RA. It provides a basis for choosing the correct therapeutic approach in the treatment of anemia.

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Conflict of Interest

The participants declare that there is no-conflict with any organization or institute during preparation of materials in short communication called “Does stroke messed up with a serum hepcidin levels in therapy of anemia in rheumatoid arthritis patients?” that is given to *MRJMMS*. All patients included in the trial have signed Informed Consent according to respective requirements from The Code of Ethics of the World Medical Association

(Declaration of Helsinki).

This article has been prepared after two years collection of samples from patients diagnosed with rheumatoid arthritis from the Department of Rheumatology at “St. Ivan Rilski” hospital was observed. Acute stroke was diagnosed in Neurology Dept. at University “Aleksandrovska” hospital. Thalassemia patients were monitored in Intensive Cardiology Dept. at the same hospital. One patient with thalassemia and rheumatoid arthritis was also evaluated. During this period no pharmaceutical or other company was involved in the trial.

All authors disclose that have no any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

There is no any potential Conflicts of Interest Related to Individual Authors' Commitments. All authors are responsible for disclosing all financial and personal relationships that might bias their work. All authors states that no potential conflicts exists.

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