

HEPCIDIN: A PROMISING MARKER FOR DIFFERENTIAL DIAGNOSIS OF ANEMIA AND MACROPHAGE ACTIVATION SYNDROME IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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Resume. Hepcidin is a 25-amino acid peptide, which is a key systemic regulator of iron metabolism. As considered, overproduction of hepcidin in the liver is controlled by high levels of proinflammatory cytokines. It is known that interleukin-6 play a key role in the development of anemia in patients with juvenile idiopathic arthritis (JIA). However, IL-6 blockers itself may provoke the onset of Macrophage Activation Syndrome (MAS), manifesting, particularly, also with anemia. In view of the fact that macrophages involved in MAS express CD163 — a scavenger receptor that binds hemoglobin-haptoglobin complexes — and activate the pathways which are important for adaptation to oxidative stress induced by free iron, we can consider hepcidin as a welcome challenge to predict the development of MAS early in the course of the disease. During the study of 35 patients with JIA treated with biological disease-modifying drugs (tocilizumab and golimumab), direct relations between the level of hemoglobin and hepcidin were not found. However, it was found that the mean corpuscular hemoglobin level is associated with hepcidin concentration in patients with JIA. It was found that concentration of serum hepcidin may be used for early differential diagnosis of anemia and MAS in patients with JIA. High probability of evolution of anemia to MAS was found when concentration of hepcidin was <140 ng/mL and ferritin >160 g/L. The following combinations were associated with high probability of evolution of slight anemia to a severe form, but not to MAS: 1. hepcidin >200 ng/mL and ferritin <140 g/L; 2. hepcidin >140 ng/mL and soluble transferrin receptor <1.6 mg/L; 3. hepcidin >140 ng/mL and total iron binding capacity >46 mcmmol/L. Misclassification should be assessed during further studies.

Key words: hepcidin; anemia; macrophage activation syndrome; juvenile rheumatoid arthritis.

INTRODUCTION

Anemia of chronic disease, the anemia that is the second most prevalent after anemia caused by iron deficiency, occurs in patients with acute or chronic immune activation [15]. It is believed that anemia in patients with chronic illness can significantly worsen the prognosis and quality of life of these patients.

For the first time this condition was described by Cartwright G.E, Wintrobe M.M. in 1952 [3]. However, the key pathogenic moment became clear after the discovery of the peptide hepcidin in 2000 [19]. The name of the new peptide was formed by abbreviation of the Latin word *hepar* (lat. — liver — the site of synthesis of peptide) and *cidin* (lat. — destroy — emphasizing antibacterial properties of this peptide). It was shown that hepcidin synthesis occurs in renal tubules. In addition, low levels of expression were found in other cells, tissues and organs, including macrophages, adipocytes, and brain cells, which may indicate the important role of hepcidin in the autocrine and paracrine control of iron metabolism at the local level [12]. Hepcidin is encoded as an 84-amino acid prepropeptid. The active form of the hormone circulates in plasma and can bind to α_2 -macroglobulin [20]. The main route of elimination of hepcidin is renal clearance.

Currently, hepcidin is known to be the main regulator of systemic iron metabolism in the organism [7]. Hepcidin reduces dietary iron absorption by reducing iron transport across the gut mucosa, it reduces iron exit from macrophages, which is the main site of iron stor-

age and it reduces iron exit from the liver. Hepcidin acts by modulating of ferroportin-mediated iron transport. Ferroportin — is a receptor of hepcidin and is the only known cellular iron exporter in vertebrates [4]. Hepcidin injected into mice causes a significant reduction of iron in serum within just 1 hour. Even though usually hepcidin is rapidly eliminated from plasma, the effect of a single dose lasts for up to 72 hours. Probably, this time is required for the re-synthesis of sufficient amounts of the hepcidin receptor — ferroportin [21]. Hepcidin synthesis rapidly increases during infection and inflammation. Interleukin-6 (IL-6) is a major inducer of hepcidin and acts through STAT3-dependent transcriptional mechanism. In volunteers urinary hepcidin excretion increased several times and serum iron levels decreased in 2 hours after infusion of IL-6 [17].

Thus, IL-6 plays a significant role in the pathogenesis of juvenile idiopathic (rheumatoid) arthritis (JIA) and anemia. Production of IL-6 is known to be significantly increased in patients with JIA. It correlates with the degree of disease activity [18] and is associated with anemia. The level of serum pro-hepcidin in patients with rheumatoid arthritis is significantly higher being compared to patients with systemic lupus erythematosus and healthy control group [11]. In addition, serum pro-hepcidin was significantly lower in patients with iron deficiency anemia than in patients with rheumatoid arthritis and anemia without iron deficiency, and in a control group of healthy volunteers [10].

Anemia in rheumatoid arthritis is a typical example of the anemia of chronic disease [14]. The main mechanism of this kind of anemia is a disturbance of iron utilization in the bone marrow triggered by hepcidin, whose expression is increased due to overproduction of IL-6 [16]. Anemia is highly prevalent among patients with ineffective treatment of rheumatoid arthritis. Studies performed in 1966–2003 showed the prevalence of anemia in patients with rheumatoid arthritis ranged from 33.3 to 59.1% [22]. According to a multicenter study of patients with rheumatoid arthritis, the prevalence of anemia in the first year after onset of the disease was 5%, 3 years — 11%, 5 years — 13%, 7 years — 16%, 10 years — 7% [23]. In another study, the prevalence of anemia was 16.7% and was associated with the severity of rheumatoid arthritis [6]. In a placebo-controlled trial of infliximab anemia was observed in 39% of patients [9].

Treatment of anemia in rheumatoid arthritis requires understanding of pathogenic mechanisms underlying the development of anemia. The best way to correct anemia in a patient with rheumatoid arthritis is to control the systemic disease with corticosteroids and disease-modifying drugs [2, 13]. Combined therapies of rheumatoid arthritis with infliximab and methotrexate as a rule result in increase of hemoglobin level in blood right up till its normalization in 43% of anemic patients [5]. Tocilizumab selectively binds to and inhibits both soluble and membrane IL-6 receptor (sIL-6R and mIL-6R). In clinical trials of tocilizumab hemoglobin level increased by 17 g/L after 2 weeks of treatment in patients with rheumatoid arthritis and anemia [8].

OBJECTIVES OF THE STUDY

To determine the prevalence of anemia in patients with JIA receiving treatment with biological disease-modifying drugs and estimate the dependence of hemoglobin level in this group of patients upon the level of hepcidin and other indices describing the iron metabolism.

MATERIALS AND METHODS

35 children (12 boys and 23 girls) with juvenile idiopathic arthritis were enrolled in the study. 19 children had the diagnosis polyarticular juvenile arthritis (polyJIA), 16 — system onset JIA (soJIA).

All patients have been treated with biological disease-modifying drugs. Of these, 25 patients received tocilizumab — recombinant humanized IgG1 class monoclonal antibodies to human IL-6 receptor Ten patients received golimumab — recombinant humanized IgG1 class monoclonal antibody, forming high-affinity stable complexes “antigen-antibody” with soluble and transmembrane bioactive forms with tumor necrosis factor alpha (TNF-α), preventing binding of TNF-α

to its receptors. The study was approved by the Ethics Committee, prior to study the patients and their parents signed informed consent.

Together with clinical signs of JIA activity, the dynamics of the following laboratory parameters Have been monitored (number of samples): hemoglobin concentration (n=554), red blood cells count (n=554), reticulocytes count (n=135), mean corpuscular volume (n=236), mean corpuscular hemoglobin (n=241), mean corpuscular hemoglobin concentration (n=191), white blood cells count (n=554), platelets count (n=543), absolute neutrophils count (n=192), eosinophils count (n=191), monocytes count (n=192), basophils count (n=192), lymphocytes count (n=192), erythrocyte sedimentation rate (n=554), the level of C-reactive protein (n=383), soluble transferrin receptor concentration, sTFR (n=35), total serum iron concentration (n=76), ferritin concentration (n=154), total iron binding capacity of serum, TIBC (n=60), the level of serum hepcidin (n=25).

Anemia was diagnosed and classified according to the WHO criteria.

Statistical analysis was performed by means of Statistica for windows (ver. 6) package. We used common methods of statistical description, statistical hypothesis testing and multivariate exploratory techniques.

RESULTS

The prevalence of anemia in JIA patients treated with biological disease-modifying drugs was 60.0% (23.8% of them mild, 61.9% — moderate, 14.3% -severe) (Fig.1). The prevalence of anemia in patients with polyJIA was 42.1%, and in patients with soJIA — 81.3% (Table 1).

Table 1
Prevalence of anemia in JIA patients Yakutia in total [3]

	Anemia	No anemia	Total
polyJIA (prevalence,%)	8 (42,1 %)	11	19
soJIA (prevalence,%)	13 (81,3 %)	3	16
Total (prevalence,%)	21 (60,0 %)	14	35

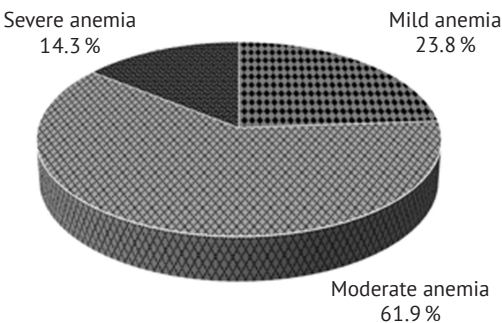


Fig. 1. Frequency of various degrees of anemia in JIA patients

To distinguish anemia in MAS from common anemia multivariate analysis was performed and the decision rules were formed. The best prognostic value had the combinations of concentrations of hepcidin, ferritin and soluble transferrin receptor. The response surfaces presented on figures 2–4 show non-linear patterns with ridges which make possible to predict evolution of anemia to MAS. It was found that concentration of serum hepcidin may be used for early differential diagnosis of anemia and MAS in patients with JIA. High probability of evolution of anemia to MAS was found when concentration of hepcidin was <140 ng/mL and ferritin >160 g/L. The following combinations were associated with high probability of evolution of mild anemia to a severe form, but not to MAS: 1. hepcidin >200 ng/mL and ferritin <140 g/L; 2. hepcidin >140 ng/mL and soluble transferrin receptor <1.6 mg/L; 3. hepcidin >140 ng/mL and total iron binding capacity >46 mmol/L.

Misclassification, particularly sensitivity and specificity, should be assessed during further studies.

CONCLUSIONS

Anemia is an often find among patients with JIA eligible for treatment with biologics. It can be explained by the fact that this group includes patients with severe polyJIA and soJIA, in which routine therapeutic programs have been proved to be ineffective. That is why the prevalence of anemia in this group is even higher than in patients with polyJIA and soJIA receiving routine treatment [1].

Anemia in JIA is a multifactorial disorder that develops as a result of hepcidin overproduction and difficulties of iron reutilization complicated with iron restricted erythropoiesis. Severe cases of anemia are associated with iron deficiency and/or with the MAS.

In order to assess the iron metabolism in patients with JIA in addition to standard indicators such as the level of serum iron, TIBC, transferrin saturation and ferritin levels, it is necessary to determine the level of plasma hepcidin and sTFR.

From the point of view of early differential diagnosis of anemia and MAS the most promising is the combination of declining hemoglobin concentration associated with high ferritin and low hepcidin levels in serum. We found this condition to be the most probable early marker of MAS in JIA patients.

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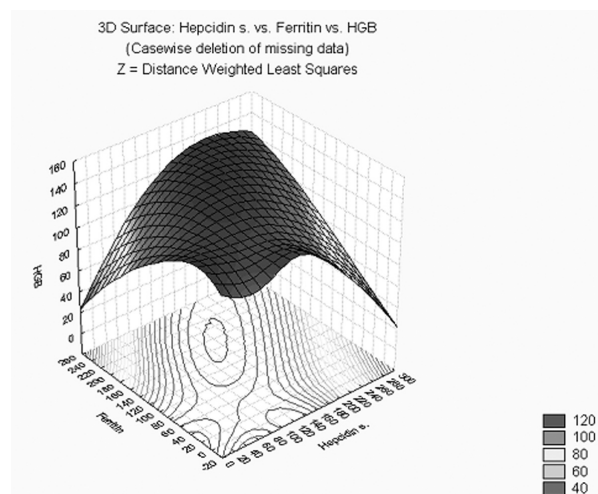


Fig. 2. Dependence of hemoglobin level from hepcidin and ferritin levels

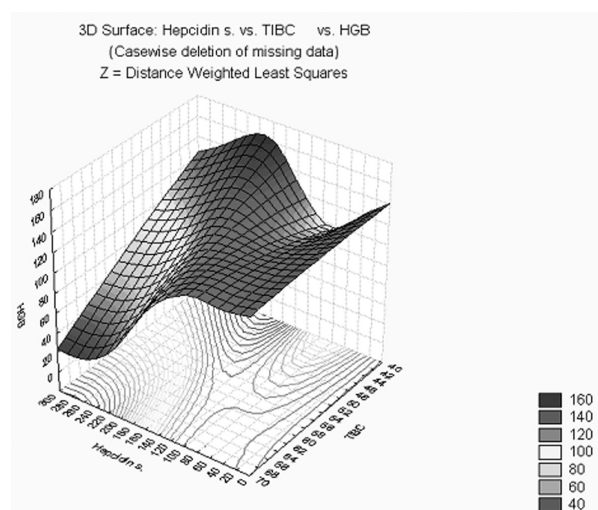


Fig. 3. Dependence of hemoglobin level from hepcidin and TIBC levels

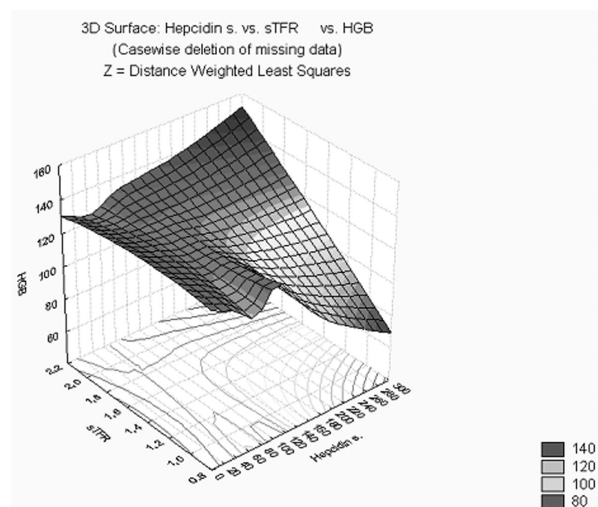


Fig. 4. Dependence of hemoglobin level from hepcidin and sTFR levels

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- ГЕПСИДИН – ПЕРСПЕКТИВНЫЙ ДЛЯ ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКИ МАРКЕР АНЕМИИ И СИНДРОМА МАКРОФАГАЛЬНОЙ АКТИВАЦИИ У ДЕТЕЙ С ЮВЕНИЛЬНЫМ ИДИОПАТИЧЕСКИМ АРТРИТОМ**
- Егоров А.С., Федорова Е.В., Часнык В.Г., Костик М.М., Снегирева Л.С., Калашникова О.В., Дубко М.Ф., Масалова В.В., Лихачева Т.С.*

◆ **Resume.** Гепсидин — 25-аминокислотный пептид, являющийся ключевым регулятором системного метаболизма железа. Гиперпродукция гепсидина, обусловленная влиянием провоспалительных цитокинов, в первую очередь интерлейкина-6 (ИЛ-6), приводит к перераспределению железа из циркуляции в хранилища и, как следствие, к ограничению железа для эритропоэза. Данный механизм лежит в основе патогенеза анемии при хронических болезнях (АХБ), в том числе и при ювенильном идиопатическом артрите (ЮИА). Однако лекарственные средства, блокирующие ИЛ-6, могут сами провоцировать развитие синдрома макрофагальной активации (МАС), который проявляется, в том числе и тяжелой анемией. Кроме того, было показано, что макрофаги, фигурирующие в МАС, экспрессируют на своей поверхности CD163 (рецептор связывающий комплекс гемоглобин-гаптоглобин) и участвуют в механизмах адаптации к окислительному стрессу, индуцированному свободным железом. В связи с этим можно рассматривать гепсидин сыворотки как предиктор развития МАС уже на ранней стадии заболевания. В ходе исследования, в которое были включены 35 детей, страдающих ЮИА и получающих биологическую болезнь-модифицирующую терапию (тоцилизумаб и голимумаб), непосредственной связи концентрации гемоглобина и сывороточного гепсидина не обнаружено. Вместе с тем было обнаружено, что характеристикой, в наибольшей степени сопряженной с концентрацией гепсидина в плазме, является среднее содержание гемоглобина в эритроците. Это явилось основанием для попытки использования концентрации гепсидина в качестве маркера, пригодного для дифференциальной диагностики анемии при ЮИА. Многофакторное моделирование позволило сформулировать решающие правила, пригодные для ранней дифференциальной диагностики анемии и МАС по сочетанию концентраций гепсидина, ферритина и гемоглобина, гепсидина, ТIBC и гемоглобина, гепсидина, sTFR и гемоглобина. В частности, высокая вероятность эволюции анемии в МАС выявлена при комбинации концентраций в плазме гепсидина <140 ng/mL и ферритина >160 g/L. Высокая вероятность эволюции легкой анемии и анемии средней тяжести в тяжелую анемию, но не в МАС выявлена при следующих комбинациях: 1) гепсидин >200 ng/mL и ферритин <140 g/L; 2) гепсидин >140 ng/mL и растворимый рецептор к трансферрину <1,6 mg/L; 3) гепсидин >140 ng/mL и общая железосвязывающая способность сыворотки >46 мстол/L. Ошибки прогноза при использовании этих решающих правил предстоит определить в ходе дальнейших исследований.

◆ **Key words:** гепсидин; анемия; синдром макрофагальной активации; ювенильный идиопатический артрит.

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