UDC: 616.61-036.12-053.32:616.155.194

BIOCHEMICAL AND REGULATORY MECHANISMS OF IMPAIRED IRON TRANSPORT IN ANEMIA OF CHRONIC DISEASE IN CHILDREN

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БОЛАЛАРДА СУРУНКАЛИ КАСАЛЛИКЛАР АНЕМИЯСИДА ТЕМИР ТРАНСПОРТИНИНГ БУЗИЛГАН БИОКИМЁВИЙ ВА РЕГУЛЯТОР МЕХАНИЗМЛАРИ

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БИОХИМИЧЕСКИЕ И РЕГУЛЯТОРНЫЕ МЕХАНИЗМЫ НАРУШЕННОГО ТРАНСПОРТА ЖЕЛЕЗА ПРИ АНЕМИИ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЙ У ДЕТЕЙ

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Резюме. *Сурункали касалликлар анемияси (СКА) болаларда, айниқса сурункали буйрак касаллиги ва яллиғланиш жараёнлари билан кечувчи ҳолатларда кенг тарқалган. Бу ҳолатда умумий темир захиралари етарли бўлса ҳам, темирнинг тўқималардан чиқиши ва унинг қондаги миқдори камаяди. Ортиқча интерлейкин-6 (IL-6) жигардаги гепсидин синтезини кучайтиради. Гепсидин ферропортин билан боғланиб, унинг парчаланишига ва темирнинг қонга чиқишини тўсилишига сабаб бўлади. Натижада темир ҳужайра ичида "тутиб қолинади" ва эритропоэз учун етарли бўлмайди. Ферритин ва С-реактив оқсил (CRP) даражалари ошган, қондаги темир ва трансферрин тўйинганлик кўрсаткичлари пасайган бўлади. Гепсидин, ферритин ва CRP даражаларини баҳолаш СКАни темир танқислиги анемиясидан фарқлашга ва болаларда даволаш усулларини такомиллаштиришга ёрдам беради.*

Калит сўзлар: *сурункали касалликлар анемияси, гепсидин, ферропортин, ферритин, С-реактив оқсил, темир транспорти, болалар, сурункали буйрак касаллиги.*

Abstract. *Anemia of chronic disease (ACD) commonly occurs in children with chronic kidney disease and inflammatory disorders. It is characterized by functional iron deficiency caused by impaired iron release from storage sites. Excessive interleukin-6 (IL-6) stimulates hepatic synthesis of hepcidin, which binds to ferroportin, leading to its degradation and blocking iron export into plasma. As a result, iron becomes unavailable for erythropoiesis despite normal or increased stores. Elevated ferritin and C-reactive protein (CRP) levels with reduced serum iron and transferrin saturation (TSAT) are typical for ACD. Evaluating hepcidin, ferritin, and CRP helps distinguish ACD from iron deficiency anemia and optimize therapy in children with chronic diseases.*

Keywords: *anemia of chronic disease, hepcidin, ferroportin, ferritin, C-reactive protein, iron transport, children, chronic kidney disease.*

Introduction. Anemia of chronic disease (ACD), also referred to as anemia of inflammation, is one of the most common forms of anemia in children suffering from chronic pathological conditions such as chronic kidney disease (CKD), autoimmune disorders, inflammatory diseases, and prolonged infections [1, 2].

Despite having sufficient or even elevated iron stores, these patients exhibit low serum iron levels and impaired iron utilization, leading to the develop-

ment of functional iron deficiency that is poorly responsive to conventional oral iron therapy [3, 4].

The pathogenesis of ACD is multifactorial and largely associated with immune-inflammatory regulation of iron metabolism. During chronic inflammation, there is an overproduction of interleukin-6 (IL-6), which stimulates hepatic synthesis of hepcidin - the key peptide hormone that regulates systemic iron homeostasis [5,6]. Hepcidin binds to the membrane protein ferroportin located on enterocytes and macrophages, causing its internalization and degradation [7,8]. As a result, iron becomes "trapped" within cells, its release into the plasma is blocked, and it becomes unavailable for erythropoiesis, despite normal or elevated total body iron stores [9].

In addition to hepcidin, C-reactive protein (CRP) and ferritin play important roles in the regulation of iron metabolism, reflecting the interaction between inflammation and iron status. In children with ACD, ferritin levels are usually normal or elevated, while serum iron (Fe) and transferrin saturation (TSAT) are decreased, making differential diagnosis between iron deficiency anemia (IDA) and ACD difficult [10, 11, 17, 18]. Measurement of hepcidin and CRP levels allows for a more accurate assessment of the inflammatory blockade of iron transport and helps identify functional iron deficiency [12, 13, 18].

In children, anemia of chronic disease poses a significant diagnostic and therapeutic challenge, as it is often combined with both iron deficiency and chronic inflammation. Understanding the biochemical and regulatory mechanisms of impaired iron transport in these patients is essential for improving differential diagnosis and optimizing approaches to the treatment of anemia in chronic diseases [14, 15, 16, 19].

Objective. To evaluate biochemical and regulatory factors affecting iron transport in children with anemia of chronic disease, with particular emphasis on the relationship between hepcidin, ferritin, and C-reactive protein (CRP) levels.

Materials and Methods. The study was conducted at the Pediatric Department of the Samarkand State Medical University. A total of 60 children aged 5 to 15 years who underwent examination and treatment for anemia of various etiologies were included.

All patients were divided into two groups: Group I (n = 30) - children with anemia of chronic disease (ACD) associated with chronic kidney disease, rheumatic, or inflammatory disorders. Group II (n = 30) - children with iron deficiency anemia (IDA) without signs of chronic inflammation, serving as the control group.

The diagnosis of anemia was established based on clinical and laboratory criteria according to WHO guidelines (Hb below age-specific norms). Differential diagnosis between ACD and IDA was performed using a combination of iron metabolism indicators and markers of inflammation.

Inclusion Criteria: Age 5-15 years; Laboratory-confirmed anemia; Diagnosed chronic inflammatory disease (for ACD group); Informed parental (guardian) consent for participation in the study.

Exclusion Criteria: Acute infectious or inflammatory diseases at the time of study; Hemolytic or aplastic forms of anemia; Recent (within one month) administration of iron preparations or erythropoietin; Liver or gastrointestinal disorders affecting iron metabolism.

Methods of Investigation. All children underwent a comprehensive clinical and laboratory examination, including:

1. Complete Blood Count (CBC): measurement of hemoglobin (Hb), erythrocyte count, hematocrit, and mean corpuscular hemoglobin (MCH).
2. Biochemical markers of iron metabolism: serum iron (Fe, μmol/L); total iron-binding capacity (TIBC, μmol/L); transferrin saturation (TSAT, %); ferritin (ng/mL) - determined by enzyme-linked immunosorbent assay (ELISA).
3. Markers of inflammation: C-reactive protein (CRP, mg/L) - determined by immunoturbidimetric method; Erythrocyte sedimentation rate (ESR, mm/h) - determined by Panchenkov's method.
4. Regulatory marker of iron metabolism: serum hepcidin (ng/mL) measured by ELISA using certified diagnostic kits.

Statistical analysis was performed using SPSS Statistics 26.0. Results were expressed as mean ± standard error of mean (M ± m). To assess the significance of differences between groups, the student's t-test for independent samples was applied. Correlations between parameters were assessed using Pearson's correlation coefficient (r). Differences were considered statistically significant at $p < 0.05$.

Results and Discussion. As a result of the study, it was found that children with ACD exhibited pronounced alterations in iron metabolism and inflammatory markers compared with those suffering from IDA.

Both groups of children demonstrated moderate anemia (Hb 80-90 g/L); however, their metabolic profiles differed significantly. In the ACD group, serum iron (Fe) levels were significantly reduced, while total iron-binding capacity (TIBC) remained relatively low, indicating functional iron deficiency rather than absolute depletion of iron stores. In contrast, children with IDA exhibited the classical pattern of low Fe combined with elevated TIBC, which is typical of true iron deficiency (Table 1).

Table 1. Indicators of iron metabolism and inflammation in examined children

Indicator	Control group (n=20)	ACD (n=30) (M ± m)	IDA (n=30) (M ± m)	p-value
Hb, g/L	125.0±4.74	85,4 ± 2,1	80,3 ± 1,8	>0,05
Fe, µmol/L	18.35±2.26	6,72 ± 0,31	4,23 ± 0,28	<0,001
TIBC, µmol/L	60.00±6.32	47,9 ± 2,4	68,4 ± 2,9	<0,001
TSAT, %	30.5±5.37	14,8 ± 0,9	10,2 ± 0,7	<0,01
Ferritin, ng/mL	38.6 ± 2.7	156,2 ± 9,4	18,7 ± 1,6	<0,001
Hepcidin, ng/mL	22.4 ± 1.8	118,6 ± 6,3	12,4 ± 1,1	<0,001
CRP, mg/L	1.9 ± 0.3	17,3 ± 2,1	3,1 ± 0,6	<0,001

Note: p - statistical results before treatment in children with ACD/IDA, compared with the healthy control group.

The key difference between the two groups was in ferritin and hepcidin levels. In children with ACD, ferritin levels were elevated (156.2 ± 9.4 ng/mL), reflecting preserved or excessive iron stores.

At the same time, hepcidin levels exceeded 100 ng/mL (118.6 ± 6.3), which was nearly tenfold higher than in children with IDA (12.4 ± 1.1; $p < 0.001$). This finding indicates pronounced activation of inflammatory regulation of iron metabolism, where excessive hepcidin secretion leads to ferroportin degradation and blockage of iron release from storage cells.

Role of Inflammation and Interrelations Between Parameters. High CRP levels in children with ACD (17.3 ± 2.1 mg/L) confirmed the presence of chronic inflammation.

Correlation analysis demonstrated:

1.a negative correlation between hepcidin and TSAT ($r = -0.65$; $p < 0.01$),

2.a positive correlation between hepcidin and CRP ($r = +0.62$; $p < 0.01$),

3.a positive correlation between ferritin and hepcidin ($r = +0.59$; $p < 0.05$).

Thus, the greater the inflammatory activity, the stronger the blockade of iron transport.

Discussion. An increase in hepcidin levels above 100 ng/mL in children with anemia of chronic disease represents a critical laboratory marker of inflammatory iron blockade.

Such levels are commonly observed in chronic kidney disease, juvenile arthritis, tuberculosis, and other chronic inflammatory or infectious conditions.

Elevated ferritin with low Fe and TSAT values creates the phenomenon of “trapped iron” - iron is present but unavailable for erythropoiesis due to hepcidin-mediated transport inhibition.

These findings are consistent with the data of international authors, who emphasize that hepcidin is a key mediator of anemia of chronic disease and reflects the degree of activation of inflammatory cytokines, primarily IL-6.

Conclusion. Children with anemia of chronic disease exhibit pronounced hepcidinemia (above 100 ng/mL), which correlates with the degree of inflammation and CRP levels.

1. Elevated hepcidin is accompanied by decreased transport forms of iron (TSAT) and blockade of its mobilization from depots, despite high ferritin levels.
2. The diagnostic combination “hepcidin + ferritin + CRP” serves as a reliable criterion for distinguishing functional from absolute iron deficiency in pediatric patients.

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БИОХИМИЧЕСКИЕ И РЕГУЛЯТОРНЫЕ МЕХАНИЗМЫ НАРУШЕННОГО ТРАНСПОРТА ЖЕЛЕЗА ПРИ АНЕМИИ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЙ У ДЕТЕЙ

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Резюме. *Анемия при хронических заболеваниях широко распространена у детей, особенно в случаях, сопровождающихся хронической болезнью почек и воспалительными процессами. В этом случае, даже если общие запасы железа достаточны, выделение железа из тканей и его концентрация в крови уменьшаются. Избыток интерлейкина-6 (IL-6) усиливает синтез гепсидина в печени. Гепсидин связывается с ферропортином, вызывая его распад и препятствуя выходу железа в кровь. В результате железо "задерживается" внутри клетки и становится недостаточным для эритропоэза. Уровни ферритина и С-реактивного белка (СРБ) повышены, а показатели насыщения железа и трансферрина в крови снижены. Оценка уровня гепсидина, ферритина и СРБ поможет дифференцировать анемию при хронических заболеваний от железодефицитной анемии и усовершенствовать методы лечения у детей.*

Ключевые слова: *анемия при хронических заболеваниях, гепсидин, ферропортин, ферритин, С-реактивный белок, транспорт железа, дети, хроническая болезнь почек.*