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A MODERN VIEW OF ANEMIA IN CHILDREN WITH CHRONIC KIDNEY DISEASE

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Tayanch so‘zlar: surunkali kasalliklar anemiyasi, nefrogen anemiya, eritropoetin, sukrosomal temir.
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Anemia is a common complication in children with chronic kidney disease (CKD). It significantly worsens the quality of life and affects the growth and development of the child. Understanding the mechanisms of anemia development and its diagnosis is important for effective treatment. In this regard, anemia in children with CKD requires a comprehensive approach to diagnosis and treatment. Early diagnosis and adequate therapy can significantly improve the quality of life of children with this condition and contribute to their normal development.

ANEMIYANING ZAMONAVIY KO‘RINISHI SURUNKALI BUYRAK KASALLIGI BO‘LGAN BOLALARDA

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Anemiya surunkali buyrak kasalligi (SBK) bo‘lgan bolalarda keng tarqalgan asoratdir. Bu hayot sifatini sezilarli darajada yomonlashtiradi va bolaning o‘sishi va rivojlanishiga ta’sir qiladi. Anemiya rivojlanish mexanizmlarini tushunish va uni tashxislash samarali davolash uchun muhimdir. Shu munosabat bilan, SBK bilan og‘rigan bolalarda anemiya tashxis qo‘yish va davolashda kompleks yondashuvni talab qiladi. Erta tashxis qo‘yish va etarli terapiya ushbu kasallikka chalingan bolalarning hayot sifatini sezilarli darajada yaxshilaydi va ularning normal rivojlanishiga hissa qo‘shadi.

СОВРЕМЕННЫЙ ВЗГЛЯД НА АНЕМИЮ У ДЕТЕЙ С ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК

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Анемия является распространенным осложнением у детей с хронической болезнью почек (ХБП). Она существенно ухудшает качество жизни и влияет на рост и развитие ребенка. Понимание механизмов развития анемии и ее диагностики важно для эффективного лечения. В связи с этим, анемия у детей с ХБП требует комплексного подхода к диагностике и лечению. Ранняя диагностика и адекватная терапия могут существенно улучшить качество жизни детей с данным состоянием и способствовать их нормальному развитию.

This article is devoted to the main factors contributing to the development of anemia syndrome during chronic kidney disease in children. It examines in detail the prevalence and significance of this disease in the modern world, shows the role of hepcidin and the contribution of cytokine markers in the formation of anemia in children with chronic kidney disease. Modern approaches to the treatment of children with anemia in chronic kidney disease with the use of erythropoietin-stimulating drugs and antianemic drugs such as sucrosomal iron are also presented.

The main factors of development, prevalence and significance of anemia in chronic kidney disease. Iron deficiency anemia (IDA) is a disease that has a hereditary character and is characterized by a decrease in the iron content in the body: in the blood, bone marrow and tissues. As a result, the formation of hemoglobin and erythrocytes is disrupted, hypochromic anemia and trophic disorders in tissues develop [1]. According to the World Health Organization, about 1.62 billion people, or 24.8% of the world's population, have various variants of anemia. The prevalence of anemia in 2008 was published by WHO: high levels were found in preschool children (76.1%), pregnant women (69.0%) and non-pregnant women (73.5%). In the field of anemia, which concerns children and adults, two groups prevail: 90% are anemia in childhood, and 80% are in the age group over 10 years [2]. In the presence of anemia, which occurs in chronic inflammatory situations, it is customary to conditionally designate it as anemia in chronic diseases (ACD). Due to the fact that iron deficiency anemia has many chronic diseases, it is often associated with a large number of chronic pathologies. The pathogenetic variants of IDA include nephrogenic anemia, which is a natural complication of chronic kidney disease [3]. According to data provided by National Registrars, there are approximately 6.5-58.3 cases of impaired renal filtration function per 1 million children under the age of 18. With the help of scientific literature data, it can be concluded that epidemiological studies among children with chronic kidney diseases have not

been conducted in the Republic of Uzbekistan [4]. The modified classification used in KDIGO allows us to divide 5 stages of chronic kidney disease: from I-III (IIIa - IIIb - moderate and slight decrease, respectively) to IV-V (ESRD), taking into account the glomerular filtration rate (GFR) [5]. GFR is an integral indicator of the functional state of the kidneys. This method of estimating GFR, which is proposed by G.J. Schwartz, is convenient and accurate and widely used in pediatric practice.

Chronic kidney disease (CKD) of stage I-II can include chronic pyelonephritis, glomerulonephritis, tubulointerstitial nephritis, obstructive nephropathy, early stages of diabetic nephropathy and others. As a result, it is at these stages that timely and correct therapy of a particular disease can completely prevent the process of renal failure [6, 7]. When CKD appears, it usually progresses to the terminal stage, which is inevitable. For the treatment of CKD at the stage of III-IV, it is necessary to take into account the nature of previously existing pathologies that may affect the course of the disease. The therapeutic strategy should be aimed at slowing the progression of CKD, ensuring normal growth and development of the child [8, 9].

Diagnosis of anemia in children with chronic kidney disease. Anemia and CKD have a close relationship. A mild degree of anemia is observed in children in the initial stages of the disease. Severe anemia is observed in children at stages IV and V. Anemia in patients with CKD develops due to a decrease in the production of erythropoietin, a hormone that activates the proliferation of stem cells into erythroblasts and promotes the synthesis of protein necessary for the formation of hemoglobin. Stimulation of erythropoietin synthesis at the initial stages of CKD leads to inhibition of its synthesis in the future, which is one of the main reasons why anemic syndrome is formed in children [10-15].

The nature of anemia in children with CKD. Iron deficiency is considered as one of the causes of anemia in CKD in children [16]. There are two types of iron deficiency: absolute and functional. In the case when iron reserves are exhausted, their depletion occurs as a result of loss or decrease in dietary intake, an absolute iron deficiency occurs. A functional deficiency of iron can be detected if there is an increased level of the body's need for iron for the synthesis of hemoglobin, which can be obtained from iron reserves [17]. With a lack of iron in the bone marrow, red blood cell production decreases, and with a deep iron deficiency, hemoglobin synthesis is disrupted and iron deficiency hematopoiesis is formed. Low hemoglobin levels are based on low blood iron levels, high serum ferritin levels, and transferrin saturation [18]. When assessing the availability of iron for erythropoiesis, the transferrin saturation formula (HCT-TSAT) is most often used, which is the ratio (serum iron × 100÷ (total serum iron binding capacity)).

In order to assess iron reserves, serum ferritin levels are used. The level of serum ferritin, which is an "acute phase reactant", is important for patients with CKD, especially in dialysis patients who may have subclinical inflammation [20]. If serum ferritin is less than 30 mcg/l, this may mean severe iron deficiency and a high probability of lack of iron reserves in the bone marrow. Among children with high ferritin levels, a link was found between low hemoglobin values and their level in the group. In the presence of iron-deficient hematopoiesis, a decrease in serum iron levels in combination with normal or elevated ferritin and hemoglobin levels below average is an indicator for iron deficiency [19].

The role of hepcidin as a hemoregulatory factor in the development of anemia in CKD. According to numerous studies, hepcidin is a universal humoral regulator of iron metabolism [26]. This peptide hormone contains 25 amino acids and is saturated with cysteine. It is synthesized in the liver with the help of enzymes. After hepcidin was first isolated from urine, it was described by C.H. Park. [21]. This hormone was subsequently isolated from plasma as well. Non-heme trivalent iron, located in the duodenum and in the upper jejunum, is converted to divalent by duodenal cytochrome b. During the absorption of ferrous iron, it interacts with a bivalent metal transporter, which has the ability to suppress hepcidin, an acute–phase protein that is produced in the liver. With iron overload and the presence of an inflammatory process, including CKD, the hormone hepcidin is produced. Thus, increased production of this hormone causes functional iron deficiency, then the concentration of ferritin becomes higher, iron absorption decreases, iron absorption by the bone marrow is disrupted and its sequestration from enterocytes and macrophages. The main work of hepcidin is the binding and assimilation of iron due to the transporter protein ferroportin produced by enterocytes, macrophages and hepatocytes. There are regulators of hepcidin levels in

the blood, such as iron stores, anemia and hypoxia, as well as inflammation [22].

According to a study published by the author J. Zaritsky (2009), serum hepcidin levels were compared with those in the control group of children and adults with stage II-IV CKD. As a result of this study, 48 children with stage II-V CKD, 26 patients on dialysis and 32 adults with stage II–IV CKD were identified. During the study, the level of hepcidin in the blood of children who were at the predialysis and terminal stages of the disease turned out to be significantly higher than in the control group of healthy children ($p < 0.001$) [23]. By filtering in the glomeruli, hepcidin can be freely excreted by the kidneys [24]. According to J. Malyszko (2007), a decrease in renal excretion of hepcidin is associated with a decrease in GFR, which is the mechanism by which anemia progresses in CKD [25].

The effect of cytokine markers on the formation of anemia in CKD. The main regulator contributing to the rapid release of hepcidin and, subsequently, to hypoferremia is inflammation. Interleukin-6 (IL-6) is the main inflammatory cytokine that mediates an increase in hepcidin levels [26]. In the work of E. Kemma, it was proved that an increase in IL-6 levels affects an increase in hepcidin values and subsequently iron deficiency occurs [27]. An increase in the content of pro-inflammatory cells in the body, such as tumor necrosis factor alpha (TNF-α), can also lead to negative consequences for EPO cells. Both IL-6 and TNF-α contribute to the inhibition of postreceptor signaling pathways in erythroid cells, and also contribute to increased hepcidin synthesis by the liver.

Thus, anemia-related inflammatory cytokines such as IL-6 and TNF-α contribute to a decrease in hematopoiesis and contribute to a decrease in iron availability, while they also contribute to inhibition of maturation of erythrocyte progenitor cells in the bone marrow [28]. Before the start of renal replacement therapy, i.e. already at the initial stages of CKD, an increase in the level of inflammatory markers was detected in children [28]. Inflammatory cytokines disrupt the intake and mobilization of iron in the body. They contribute to the inhibition of erythropoiesis in the bone marrow, as well as erythropoiesis, which promotes the production of EPO (or hepcidin) in the liver and kidneys.

A modern approach to the treatment of anemia in children with chronic kidney disease.

The use of sucrosomal iron formula for the treatment of anemia in children with CKD. Currently, there are several innovative technologies in the world for the delivery of iron to the human body. For example, sucrosomal iron (CI) preparations ("Sideral Forte" and "Sideral drops") are trivalent iron pyrophosphate with a shell of two layers of natural phospholipids, which are similar to the structure of the cell membrane. It is this shell, thanks to which atomic iron is rapidly and almost completely absorbed and has high bioavailability, contributes to rapid and complete absorption and high digestibility. Entering the lumen of the small intestine, liposomes with iron are able to penetrate into the M cells of the small intestine through the process of endocytosis and then transported to the lymph. From the lymph, liposomes enter the liver, where, due to the high tropicity to transferrin, release from the liposomal membrane occurs and trivalent iron is released from the liposome, after which it enters into active metabolism [29]. The mucous membrane of enterocytes and transfer enzymes (ferroportin), which are involved in the transfer of iron across the membrane, do not interact with CI, unlike traditional drugs. This means that its absorption does not depend on the composition of the inflammatory hormone hepcidin, which can inhibit the absorption of iron in the intestine. Due to the fact that the absorption of CI is carried out throughout the small intestine, this contributes to its better assimilation. According to the information presented above, when using traditional oral preparations, only 1.7-14.6% of atomic iron is absorbed. Due to the fact that fat is almost 100% bioavailable, it can reduce a single dosage to 30 mg and ensure that more iron is absorbed into the body than standard iron preparations. The use of CI helps to avoid undesirable effects that are characteristic of standard preparations of ferrous salts and complexes of trivalent iron-containing iron [30, 31]. In chronic blood loss associated with iron deficiency in the diet and anemia of chronic diseases, in which treatment with standard iron preparations is ineffective due to hyperproduction of hepcidin, high efficacy was established in patients with IDA after the use of CI [32]. According to the works of Pisani, A. and Tandoi F. (2015), CI was used in the treatment of mild or moderate anemia, which is the most common case in outpatient patients. In addition, it was better tolerated, safer and more economical to use (the drug was

taken once a day). No negative effects (allergic reactions, dyspeptic phenomena) were found [33, 34].

The first sucrosomal iron preparation, named "Sideral forte", was registered under the name "Farmanutra" (Italy) and "Sideral drops" (Junia Pharma, Italy). The composition of Sideral and Sideral Forte contains 14mg / 30 mg of trivalent iron in the form of pyrophosphate, which is a combination with vitamin C and B12. In Italy, Sideral holds a leading position in the ranking of drugs that contain iron. Almost 70% of patients with IDA are children aged from infants to primary school age. Therefore, it is very important to provide them with effective and safe ferrotherapy. In the Russian Federation, unlike other countries, there are only isolated publications on the use of Sideral Drops in young children, and in the Republic of Uzbekistan no studies have been conducted on its use at all [35].

Based on the results of studies conducted by Zhukovskaya E.V., Anisimov V.N. and Sidorenko L.V. (2017), the researchers concluded that the alimentary mechanism for correcting symptoms of IDA using a specialized product of therapeutic and preventive nutrition for anemia "Sideral drops" in young children is a pathogenetically justified non-invasive technology. During their study, conducted on a group of 164 young children diagnosed with mild to moderate IDA, the effectiveness of using this drug was confirmed [36]. Another study by Antoine E. (2023) confirmed the effectiveness and safety of the therapeutic and preventive nutrition "Sideral drops" in order to correct mild and moderate IDA in infants and young children, which showed that after two months of taking the drug, an increase in RBC, Hb, MSV, MSN was achieved [37].

According to studies conducted by Dr. Bertani L. (2021), positive results were obtained in the treatment of IDA, which were carried out during the period of chronic inflammatory bowel diseases (n=24) [38]. With the help of Sideral Forte, which is an analogue of iron for intravenous administration, A. Pisani (2015) treated patients with IDA in CKD during predialysis. In his opinion, the drug was more effective than other iron preparations for intramuscular administration, but at the same time it is less traumatic and better tolerated [39]. Similar results were obtained by G. Giordano and A. Mafodda (2017) in studies in hematooncological patients. According to them, Sideral Forte was not only effective against iron preparations in such patients (n=96), but also gave a higher quality of life and had fewer side effects. In addition, MI therapy was 7.5 times cheaper than IV iron treatment [40, 41]. Due to the effects of LV for 1-2 months, the symptoms of IDA were stopped and the level of hemoglobin with serum iron and erythrocytes significantly increased in patients (n=75) with chronic bleeding (hemorrhoids, menorrhagia, bleeding from the gastrointestinal tract) [42].

Taking into account the obvious advantages of sucrosomal iron, Sideral can be recommended for use in a wide range of patients who have problems with iron deficiency conditions, including patients with anemia syndrome in chronic kidney disease [43, 44].

Conclusion. The provided literature review shows that iron and erythropoietin deficiency play a key role in the development of anemia in children with chronic kidney disease. Thanks to research, it can be concluded that the relationship between the progression of CKD and erythropoietin levels can be traced both with the level of red blood cells and with the state of iron metabolism (saturation of transferrin, serum ferritin and iron levels) and hepcidin. In case of detection of signs of anemia in CKD in children, cytokine profile indicators (IL-6 and TNF-α) should be used, which are markers for assessing the condition and determining the nature of anemia. In order to clarify the essence of the pathogenesis of anemia and improve the treatment of anemia at different stages of CKD in children, it is necessary to further study the relationship between the severity of anemia, the state of iron metabolism with hepcidin, erythropoietin deficiency and changes in inflammatory parameters in the blood.

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