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# PATHOGENESIS, DIAGNOSTICS AND TREATMENT OF ANEMIA IN VIRAL HEPATITIS AND LIVER CIRROSIS

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✓ ***Resume***

***In chronic liver disease, mild to moderate anemia is usually detected, which can be normochromic, macrocytic, and hypochromic with gastrointestinal bleeding. The pathogenesis of anemia in hepatitis and cirrhosis of the liver is complex and diverse.***

***In the development of anemia, the violation of proliferation processes and the maturation of erythroblasts in the bone marrow with the release of defective erythrocytes into the peripheral blood, as well as the toxic effect of viruses, drugs, and toxins on erythron, is important. A certain role in the development of anemia in liver cirrhosis is played by a violation of the absorption and metabolism of iron, a deficiency of folic acid and vitamin B12.***

***Key words: viral hepatitis, liver cirrhosis, anemia, treatment, diagnosis.***

# ПАТОГЕНЕЗ ДИАГНОСТИКА И МЕТОДЫ ЛЕЧЕНИЯ АНЕМИИ ПРИ ВИРУСНЫХ ГЕПАТИТАХ И ЦИРРОЗАХ ПЕЧЕНИ

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✓ ***Резюме***

***При хронических заболеваниях печени обычно выявляется легкая или умеренная анемия, которая может быть нормохромной, макроцитарной и гипохромной при желудочно-кишечных кровотечениях. Патогенез анемии при гепатитах и циррозах печени сложный и многообразный.***

***В развитии анемии имеет значение нарушение процессов пролиферации и созревание эритробластов в костном мозге с выходом в периферическую кровь неполноценных эритроцитов, а также токсическое воздействие на эритрон вирусов, лекарственных средств, токсинов. Определенную роль в развитии анемии при циррозах печени имеет нарушение процессов всасывания и метаболизм железа, дефицит фолиевой кислоты и витамина В12.***

***Ключевые слова: вирусные гепатиты, цирроз печени, анемия, лечения, диагностика.***

# VIRUSLI GEPATIT VA JIGAR SIRROZRAIDA KUZATILADIGAN ANEMIYALARNI PATOGENEZI, TASHXISLASH VA DAVOLASH USULLARI

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✓ ***Резюме***

***Jigarning surunkali kasalligida odatda me'da-ichak qon ketishi bilan normoxromik, makrositik va gipoxromik bo'lishi mumkin bo'lgan engil va o'rtacha anemiya aniqlanadi. Gepatit va jigar sirrozida anemiya patogenezi murakkab va xilma-xildir.***

***Anemiya rivojlanishida proliferatsiya jarayonlarining buzilishi va periferik qonga nuqsonli eritrotsitlar chiqishi bilan suyak iligidagi eritroblastlarning yetishishi, shuningdek, viruslar, dorilar va toksinlarning eritronga toksik ta'siri muhim ahamiyatga ega. Jigar sirozida anemiya rivojlanishida temirning so'rilishi va metabolizmining buzilishi, foliy kislotasi va B12 vitaminining etishmasligi ma'lum rol o'ynaydi.***

***Kalit so'zlar: virusli gepatit, jigar sirrozi, anemiya, davolash, diagnostika.***

**Relevance**

Recently, there has been a tendency in the world to increase the number of patients with chronic diffuse liver diseases (hereinafter referred to as CDLD) among people of working age [3,7]. CDZD is distinguished by a severe course, an unfavorable prognosis, which often becomes the main reason for the disability of patients.

In this regard, the study of the peculiarities of epidemiology, clinic, diagnosis, treatment of liver disease remains one of the urgent problems of modern hepatology. Anemia in CDZD is characterized by a complex pathogenesis and is caused by complex disorders of erythropoiesis in the form of a violation of iron metabolism with its deficiency, increased autohemolysis and an increase in the content of fetal hemoglobin (HbF) in erythrocytes, changes in the qualitative and quantitative composition of proteins of erythrocyte membranes [6]. Anemia in liver disease is traditionally referred to as anemia of chronic diseases.

In patients, the number of erythrocytes, the value of the color index, the content of reticulocytes, hemoglobin at the level of 80 - 100 g / l decrease, and an increase in anemia is observed with the progression of chronic hepatitis into cirrhosis of the liver. In addition, the level of serum iron and total iron-binding capacity decreases, and serum ferritin increases. At the same time, there is an increased consumption of iron by the cells of the RES, which leads to a violation of erythropoiesis due to insufficient supply of iron to the progenitor cells [1].

It has been found that with CDKD, the production of pro-inflammatory cytokines increases, which have the ability to change iron metabolism, the production of erythropoietin and shorten the life span of erythrocytes.

In addition, proinflammatory cytokines stimulate the production of free radicals, in particular nitric oxide or superoxide anion, thereby exerting a direct toxic effect on erythron [5]. Also, anemia may be one of the side effects of antiviral treatment of CDKD predominantly with ribavirin, while hemolysis of erythrocytes develops, which is completely reversible at the end of therapy [8].

In addition, the ability of ribavirin metabolites to accumulate in erythrocytes has been established, thereby reducing their lifespan. A separate cause of anemia is bleeding from varicose veins of the stomach and esophagus, leading to the development of post-hemorrhagic iron deficiency anemia of varying severity.

All of the above suggests a differentiated approach to the treatment of anemia in CDDD. Treatment of the underlying disease is the foundation of the therapeutic approach. In addition, transfusion therapy, iron preparations, folates, erythropoietins are used. With portal hypertension, surgical treatment is indicated. In chronic anemia, transfusion of donor blood or erythrocyte-containing components is prescribed only for the purpose of correcting the most important symptoms caused by anemia, which are not amenable to the main pathogenetic therapy [9].

Life-threatening anemia with hemoglobin content <65 g / l or anemia caused by bleeding and accompanied by a decrease in hemoglobin level below 70-80 g / l and hematocrit below 25% with the occurrence of circulatory disorders is an absolute indication for transfusion of erythrocyte mass or washed erythrocytes [2 ].

Iron preparations are indicated in case of an established deficiency of iron in the blood. Deterioration in the functioning of the duodenum, which is often found in anemia of chronic diseases, leads to poor absorption of iron preparations when taken orally. Let the main introduction be parenteral. However, it must be remembered that an excess of iron leads to the formation of highly toxic hydroxy radicals, which can cause tissue damage and increase the risk of acute cardiovascular diseases [4].

There is information that iron-containing free radicals can stimulate the development of malignant tumors. In addition, an excess of iron is associated with impaired neutrophil function, at the same time, precisely because of the immunosuppressive effect, treatment with iron preparations can be indicated in patients with an autoimmune component of the disease [3].

Folic acid deficiency is the most common cause of megaloblastic anemia in chronic diffuse liver disease and occurs in almost half of alcohol abuse patients. The lack of vitamin B9 is mainly due to the nature of the diet of this group of patients, in addition, alcohol reduces the levels of the enzyme methylenetetrahydrofolate reductase, thereby creating a functional deficiency of folates in the body [7].

Among other things, the consumption of large doses of ethanol leads to direct damage to the bone marrow with the development of megaloblastic changes in erythrocytes. Disruption of cyanocobalamin metabolism is also the cause of megaloblastic restructuring of erythrocytes in CDZD, although to a lesser extent. Erythropoietins are effective for correcting anemia and improving the quality of life of patients [5].

An indication for therapy with recombinant human erythropoietins is considered a hemoglobin level below 100 g / l. It has been established that

the regulation of erythropoiesis is not the only function of erythropoiesis-stimulating agents. For example, they are involved in the most important metabolic processes in myocardiocytes and brain cells.

Currently, the problem of anemia is extremely relevant in the management of patients with chronic diffuse liver diseases. Determination of the mechanisms of anemia in CDDD is very important for timely diagnosis, correction and prevention of the progression of both pathological changes in red blood and underlying liver disease.

**Purpose of the study.** To study in detail the pathogenesis and clinical manifestations of CBT-associated anemia in patients with CHC and LC.

## Material and methods

The paper analyzes the results of examination of 94 patients with viral hepatitis and liver cirrhosis, who were treated in the clinic of the State Medical Institute in Andijan. The average age of the patients was 38.5 (28; 39) years, the duration of the disease was 4.5 (1.2; 6.4) years.

## Result and discussion

Of 94 patients with CHC and LC, 67.9% completed the course of combined antiviral therapy (CBT). Sustained virological response (SVR) was achieved in 66.1% of patients, of which 28.6% were infected with the 1st; 14.3% - 2nd and 23.2% - 3rd HCV genotypes. Among those who received peg-IFN-α, the SVR rate was 55.2%; who received "short" - 77.8%. In CHC patients with HCV genotype 1, SVR was observed in 51.6% of cases; with HCV genotypes 2 and 3 - in 88.9% and 81.3% of cases, respectively.

As a result, it was found that at different stages of CBT, anemia in total developed in 37.5% of patients, while a mild degree was noted in 12.5%; moderate - in 19.6% and severe - in 5.4% of patients with CHC.

Among patients with mild anemia, 85.7% complained of general weakness and rapid fatigue. With the development of a moderate degree of anemia, 72.7% of patients with CHC additionally complained of shortness of breath with insignificant physical exertion. Patients with severe anemia also noted headache, dizziness, tinnitus - 66.7%, palpitations and chest pain - 33.3%. Objective changes in the form of acrocyanosis, tachycardia, extrasystole, edema of the lower extremities in the evenings were found exclusively in persons with severe anemia - 66.7% of patients with CHC. Splenomegaly developed in 21.4% of patients starting at week 20 of CBT. During CBT, 25.5% of patients repeatedly noted relapses of labial herpes, which is consistent with the scientific literature.

A mild degree of anemia after 4 weeks of CBT was recorded in 23.2%, after 8 weeks - in 30.4%, after 12 - in 24.1%, after 24 - in 28.9% and after 48 (patients with 1- m HCV genotype) - in 11.8% of patients with CHC. Moderate anemia after 12 weeks of CBT was observed in 5.6% of patients with CHC, after 24 weeks - in 13.2%, and after 48 weeks - in 29.4% of patients.

The development of severe anemia was first detected after 8 weeks of treatment in 1.8% of patients, which was the only reason for canceling CBT. In 3.7% of patients, severe anemia developed 12 weeks after the onset of CBT, coinciding with the absence of EVR, as a result of which the reason for discontinuation of therapy was “mixed”.

Correction of anemia was performed when the Hb level decreased <10.0 g / dl. In 2.2% of patients, the dose of ribavirin was gradually reduced to 600 mg / day, 1.3% of patients received recombinant EPO-α therapy as an alternative. In 16.1% of CHC patients during treatment, the Hb concentration also decreased <10.0 g / dl, however, the correction of CBT-associated anemia was not performed, since the corresponding Hb values were observed in patients or at the time of withdrawal of CBT due to the absence of EVR (n = 12 ), or by the end of the full course of antiviral therapy (n = 24).

All study participants, depending on the value of the minimum hemoglobin level recorded for the entire period of CBT (Hbmin), were divided into three groups. Group 1 (n = 140) included persons whose Hbmin remained within the permissible norm during CBT, i.e. > 11.9 g / dl. Group 2 (n = 28) included CHC patients with mild CBT-associated anemia: Hbmin in the range of 10.0-11.9 g / dl. Group 3 (n = 56) consisted of persons with moderate and severe anemia: Hbmin <9.9 g / dl. The average Hbmin in the 1st group was 12.44 ± 0.2; in the 2nd - 11.35 ± 0.26 and in the 3rd and - 9.15 ± 0.31 g / dl. Before starting CBT, women predominated among patients in group 3 compared to group 1 and 2; persons infected with HCV genotype 1; with a body mass index> 25; as well as peg-IFN-α-2a preparations in combination with ribavirin (p <0.05). At the start of CBT, the mean indices of Hb level and the number of erythrocytes in all groups did not statistically differ from each other (p> 0.05). However, in patients of the 3rd group, a significant decrease in these indicators was noted after 4 weeks of CBT, while in patients of the 1st and 2nd - only after 12. In general, the above indicators were significantly lower at almost all stages of CBT. in group 3 (p <0.05). As for the patients with CHC of the 1st and 2nd groups,

statistically significant differences were observed in them only at the 8th and 12th weeks of CBT. Among the changes in the average values of erythrocyte indices in the dynamics of CBT in all compared groups, only a significant increase in the MCV level can be distinguished. All patients showed an increase in the absolute and relative number of reticulocytes during treatment, which was most pronounced at 24-48 weeks of therapy. In addition, the so-called. "Shift of the formula to the left" with a predominance of immature forms of reticulocytes.

The average erythrocyte diameter before the start of CBT in CHC patients in all groups did not differ significantly, but after the completion or forced discontinuation of treatment, it significantly increased ($p < 0.05$). The proportion of normo-, micro- and macrocytes on average at the start of CBT in the compared groups practically did not differ from each other ($p > 0.05$). By the end of CBT, an increase in the relative number of macrocytes was observed, especially in the 3rd group of patients ($p < 0.05$).

Among the morphological forms of erythrocytes in patients with CHC in the PC, discocytes (biconcave discocytes, echinocytes, stomatocytes and spherocytes), elliptocytes, pathological (dacryocytes, codocytes and acanthocytes) and degeneratively altered cell forms were determined. After CBT, the mean incidence of biconcave discocytes in all groups significantly decreased. At the same time, the percentage of stomatocytes in the 1st group of CHC patients increased from the initial one by an average of 2.1; echinocytes - 2.5; spherocytes - 4.6; pathological forms - by 3.8 and degeneratively altered cells - by 4.7 times. In group 2 patients, the number of stomatocytes increased by an average of 2.9; echinocytes - 3.1; spherocytes - 7.3; pathological forms - 4.9 times and degeneratively altered cells - 10.6 times. Finally, in group 3, the relative number of stomatocytes during CBT increased by 3.6; echinocytes - 3.75; spherocytes - 13.3; pathological forms - by 6.3 and degeneratively altered cells - by 16.5 times.

During the study, in all compared groups, patients with various structural defects were identified as the cytoplasmic membrane of erythrocytes (local loosening, fragmentation, micro- and macrovesicles, formation of kidney-shaped protrusions), and their stroma (formation of cavities and endovesicles, the appearance of cells with uneven electron density and varying degrees of hemoglobinization). As shown by a comparative analysis, already at the start of therapy in the 3rd group of patients, people with the above defects were much more common. After the completion of CBT, the proportion of CHC patients with revealed structural changes in erythrocytes significantly increased in all three groups ($p < 0.05$).

As a result of the conducted antiviral therapy, the average concentration of MDA in the first two groups increased by 9.1% and 9.3%, respectively ($p > 0.05$), and VEG - by 9.1% and 9.3% ($p > 0, 05$). In patients with CHC of the 3rd group, much more pronounced changes in these indicators were noted: MDA increased by 92.1%, and VEG - by 47.4% ($p < 0.001$).

As for the level of anti-erythrocyte antibodies, in the 1st and 2nd groups of patients before the beginning of CBT, individuals were found with both the absence and the low and moderate level of fixed IgG, while there were no significant differences in their specific gravity between these groups. It was. In the third group of CHC patients, the relative number of patients with low and moderate levels of anti-erythrocyte IgG turned out to be statistically higher; in addition, individuals with a high level of autoantibodies were also identified.

After CBT in the 1st and 2nd groups of patients with CHC, the proportion of patients with moderate, and in the 3rd - a high level of anti-erythrocyte IgG significantly increased. In addition, in the 2nd group the appearance of persons with high, and in the 3rd - extremely high levels of the above antibodies was noted. The average EPO level in the 1st group of observed persons before the beginning of CBT was $7.3 \pm 1.2$ mU / ml, in the 2nd - $12.4 \pm 2.1$ mU / ml and in the 3rd - $30.8 \pm 5.3$ mU / ml.

After the end of CBT, the average EPO level increased statistically significantly in all compared groups. However, despite the general direction of the identified changes, the severity of the latter was clearly ambiguous. So, in the 1st group of CHC patients, the average EPO level increased from the initial in 7.7; in the 2nd - at 4.3; and in the third - only 1.9 times.

The frequency of occurrence of point mutations Ala16Val (rs4880) and -262C / T (rs1001179), respectively, in the genes responsible for the synthesis of SOD2 and CAT in all groups of observed individuals did not differ significantly ($p > 0.05$). A completely different situation developed with the 718C / T (rs713041) mutation of the GPX4 gene, so in the 1st group of CHC patients the "mutant" T / T genotype was recorded in $14.3 \pm 5.9\%$ of patients, in the 2nd group - in $17.8 \pm 6.3\%$ and finally in the third - in $78.6 \pm 5.3\%$ of patients with CHC, which turned out to be significantly higher than in patients of the first two groups ($p < 0.001$).

## Conclusion

In the course of our study, IDA was detected in patients with HAV and HBV (60.0% and 40.0% of patients, respectively). At the same time, out of 40 patients with concomitant IDA, the severity of anemia, based on clinical and laboratory data, was assessed as moderate in 21 (52.5%) patients, which was, pronounced - in 9 (22.5%) and severe - in 10 (25.0%) patients. All observed patients had such characteristic symptoms of anemia as pallor of the skin, ears, mucous membranes, dryness or roughness of the skin, fatigue, weakness and irritability, impaired appetite, etc. Our observations showed that iron deficiency anemia negatively affects the clinical course of GV in patients. So, in patients with hepatitis A, with concomitant anemia, the preicter period was predominantly of a mixed type.

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