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MARKERS OF INFLAMMATORY AND HYPERCOAGULATION SYNDROMES IN PATIENTS WITH LIVER DAMAGE IN THE REHABILITATION PERIOD OF COVID-19

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ABSTRACT: - ***Purpose of the study:*** to study some biochemical parameters of mesenchymal-inflammatory and hypercoagulable syndromes in patients with liver damage who underwent SARS-COV2 infection.

Materials and research methods. 243 patients who had COVID-19 at the age of 18-60 were under observation. Inclusion criteria in the study were: transferred no earlier than 10 days prior to entry into the COVID-19 study; at the time of inclusion in the study PCR-negative COVID-19, negative PCR and markers of replication of hepatitis viruses. As a control group (CG), 20 healthy volunteers were examined. Enzymes were determined in the blood serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl aminotransferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (AP), total and direct bilirubin, albumin, ferritin, C reactive protein and complete blood count.

Research results The activity of blood liver enzymes in patients who underwent COVID-19 was significantly increased compared to CG: ALT exceeded the average values in CG by almost 10 times, AST = almost 3 times, LDH - 3 times, GGT and ALP - almost 1 .5 times. The level of bilirubin in the CG was significantly higher ($p<0.001$). The concentration of albumin in the peripheral blood of patients was reduced ($p<0.001$ significance of the difference from CG). The level of hemoglobin and

erythrocytes in peripheral blood was significantly lower than in the CG ($p<0.001$ and $p<0.05$). The platelet count was reduced ($p<0.001$ significant difference from CG). The ESR and CRP concentrations were significantly increased compared with the CG ($p<0.001$ significance for both indicators).

Conclusion

In patients who have undergone COVID-19, functional changes in the liver are noted, characterized by cytolytic, cholestatic syndrome, and a decrease in protein-synthesizing function. Also, these patients have signs of redistributive anemia and sideropenia, thrombocytopenia, and persistent activity of mesenchymal-inflammatory and coagulopathic syndromes. ALT activity significantly positively correlates with the activity of systemic inflammation and hypercoagulability indices.

KEYWORDS: Covid-19, liver demage, hypercoagulation.

INTRODUCTION

Coronaviruses (CoV) SARS-CoV, MERS-CoV, and SARS-CoV-2 are known to be highly pathogenic and cause respiratory disorders, up to acute respiratory distress syndrome [1]. However, CoV affects not only the respiratory system, but also the gastrointestinal tract, cardiovascular and endocrine systems [2,3]. Statistical data on patients with SARS-CoV-2 infection demonstrate the frequency of liver damage in 14.8-53% of patients [4,5]. The pathogenesis of liver damage in COVID-19 and in the post-COVID period is poorly understood. Possible mechanisms include direct viral damage to hepatocytes, autoimmune damage, hypoxia, coagulation disorders, and drug toxicity.

Purpose of the study: to study some biochemical parameters of mesenchymal-inflammatory and hypercoagulable syndromes in patients with liver damage after SARS-COV2 infection.

Material and research methods. Under observation were 243 patients who underwent COVID-19 at the age of 18-60 years. Inclusion criteria in the study were: PCR-verified COVID-19 transferred no earlier than 10 days before inclusion in the study; PCR-verified COVID-19-negative status at the time of inclusion in the study, negative PCR and markers of hepatitis viruses replication and PCR. The control group consisted of 20 healthy individuals. Serum enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl aminotransferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (APF), total and direct bilirubin, albumin, C reactive protein (CRP), ferritin were determined on the automatic analyzer BS-200.

An increase in the concentration of bilirubin was noted mainly due to the direct fraction ($p<0.001$). Also, the markers of cholestatic syndrome used in this study were the activity in the peripheral blood of ALP and GGT, which were significantly higher than in the CG ($p<0.001$). These patterns indicate a pronounced cholestatic syndrome due to the

presence of ACE receptors on the membrane. Results and discussion.

The results of the study showed that the activity cholengiocytes, which makes them a target for direct viral damage during coronavirus infection [8]. Peripheral blood albumin concentration in patients with COVID-19 was reduced (p<0.001 significant difference from CG), which is probably due to albumin consumption in the exudative phase of inflammation, leakage into the intercellular space due to increased vascular permeability associated with high concentration of pro-inflammatory mediators and endothelial dysfunction, and also, in addition to "consumption hyperalbuminemia", a decrease in albumin concentration can be pathogenetically associated with a violation of the protein-synthesizing function of the liver, as a component of liver cell failure.

Table 1

Biochemical indicators of the functional state of the liver in patients with COVID-19

Index	CG (n=20)	Main group (n=243)
ALT, units/l	26,00±1,82	254,67±7,99***
AST, units/l	24,85±1,09	83,07±2,04***
GGT, units/l	28,10±2,33	88,32±0,93***
ALP, u/l	80,75±4,57	187,84±7,25***
LDH, u/l	115,70±12,57	472,33±36,46***
total bilirubin, mmol/l	16,95±0,69	41,78±0,60***
direct bilirubin, mmol/l	1,80±0,22	14,65±0,35***
Albumin, g/l	50,20±1,77	33,70±0,48***

Note: * - significance of differences from CG. One sign - p<0.05, two signs - p<0.01, three signs - p<0.001.

Laboratory studies (Table 2) found that in patients who underwent COVID-19 in the early rehabilitation period, the level of peripheral blood hemoglobin was significantly lower than in the CG (p<0.001). The number of erythrocytes per liter of blood was also lower than in healthy individuals, but with a lower degree of certainty (p<0.05). These findings indicate hypochromic anemia, which, in the context of COVID-19, is probably associated with a redistribution mechanism and the use of iron stores for the functioning of inflammatory effectors. This position can be confirmed by the analysis of the concentration of ferritin in the peripheral blood. The average ferritin concentration in the group was comparable in patients included in the study and in the CG. However, a detailed study revealed a very large scatter of values (1 - 684 µg/l) and the distribution in the group does not correspond to normal (the median of the indicator is 13 µg/l, and the arithmetic mean is 56.27 pmg/ml). Taking reference values of 8-

143 µg/l as a conditional norm, in 36 patients the indicator exceeded normal values, and in 114 patients it was below normal values. This distribution indicates the presence of iron deficiency in a significant proportion of patients, confirming the iron-deficient variant of erythropoiesis. The other end of the series indicates the preservation of active systemic inflammation, one of the markers of which is ferritin, which binds iron and provides inflammatory effectors with this cofactor. The number of leukocytes in the peripheral blood was lower than in the CG ($p<0.001$), although it remained within the normal range. This is probably due to the excessive consumption of leukocyte cells in the foci of inflammation. The platelet count was also reduced ($p<0.001$ significant difference from CG), reflecting consumption thrombocytopenia. COVID-19 is characterized by damage to the endothelium with a violation of its functional activity towards the expression of endothelins that activate platelet aggregation. In addition, hypoxia and inflammatory cytokines also change the properties of the platelet membrane, leading to platelet activation, formation of aggregates, which leads to microvascular thrombosis. One of the reflections of this phenomenon is thrombotic thrombocytopenia [7].

The ESR and CRP concentrations are nonspecific markers of inflammation, initially, at the time of inclusion of patients in the study, they were significantly increased compared to the CG ($p<0.001$, the significance of the difference from the CG of both indicators). An increase in the level of inflammation markers indicates an incomplete restoration of the immune system and is a consequence of the monocyte activation syndrome, which contributes to the development of post-COVID syndrome [6].

Table 2.

Complete blood count and inflammatory markers in patients with COVID-19

Index	CG (n=20)	Main group (n=243)
Hemoglobin, g/l	141,40±3,23	109,57±1,01***
Erythrocytes, *1012/l	4,26±0,18	3,76±0,05*
Leukocytes, *109/l	6,65±0,27	4,60±0,11***
Platelets, *109/l	246,05±9,87	198,40±3,70***
ESR, mm/h	9,00±0,78	22,00±0,46***
CRP, mg/l	2,60±0,24	12,78±0,38***
Ferritin, mcg/l	41,45±3,83	56,27±7,03

Note: * - significance of differences from CG. One sign - $p<0.05$, two signs - $p<0.01$, three signs - $p<0.001$.

Studies on the analysis of the main indicators of the coagulogram found that the concentration of D dimer in the peripheral blood was significantly increased in patients of the main group (p<0.001, the significance of the difference from CG), despite the anticoagulants used in the infectious period, which indicates the ongoing process of microvascular thrombosis. The duration of APTT significantly exceeded the CG index (p<0.001), which may be a reflection of consumption coagulopathy, as well as a decrease in the protein-synthesizing function of the liver. The concentration of fibrinogen in the peripheral blood was increased compared to CG (p<0.001), which is the physiological role of fibrinogen in the third phase of inflammation. The INR index exceeded the value in the CG, which may be due both to the effect of anticoagulants and to the coagulopathy of damage and impaired protein-synthesizing function of the liver (p<0.01 significance of the difference from the CG).

Table 3

Coagulogram parameters in patients who have undergone COVID-19 and have signs of impaired liver function

Index	CG (n=20)	Main group (n=243)
D dimer, mg/l	0,26±0,03	1,11±0,05***
Fibrinogen, g/l	3,46±0,13	4,16±0,14***
INR, units	1,01±0,03	1,11±0,01**
APTT, sec	16,90±0,38	19,40±0,24***

Note: * - significance of differences from CG. One sign - p<0.05, two signs - p<0.01, three signs - p<0.001.

Correlation analysis showed that ALT activity significantly positively correlates with the activity of systemic inflammation (with the ESR value r=+0.30, ferritin concentration r=+0.89, p<0.01), the tendency to hypercoagulability and hyperaggregation (with a concentration of d dimer r=+0.24, and platelet count r=+0.48, p<0.01).

CONCLUSION

In patients who have undergone COVID-19, functional changes in the liver are noted, characterized by cytolytic, cholestatic syndrome, and a decrease in protein-synthesizing function. Also, these patients have signs of redistributive anemia and sideropenia, thrombocytopenia, and persistent activity of mesenchymal-inflammatory and coagulopathic syndromes. ALT activity significantly positively correlates with the activity of systemic inflammation and hypercoagulability indices.

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