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THE NATURE OF LIVER INJURY IN COVID-19, AS WELL AS THE CLINICAL COURSE'S SPECIFICITY

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Annotation. *For many years, chronic liver diseases have been one of the main and urgent problems of the fields of Gastroenterology and Hepatology. In particular, statistical indicators show that in the last 20 years, the incidence of liver diseases in the population has increased significantly. In a single case, statistics obtained on the scale of the CIS countries show that as a result of observations conducted in the population for 12 months, from 500 to 1,000,000 people were registered liver diseases caused by damage to the liver by various etiological factors. Unfortunately, to date, about 2 billion residents on Earth suffer from liver diseases. From year to year, the reason for the increased damage to liver cells is the increased diversity of etiological factors. In particular, with the damage of liver cells to medicamentosis, viral, toxic, alcohol and autoimmune, 2-3 million inhabitants are being registered every year. For this reason, we can cite the fact that most drug preparations are metabolized in the liver, that carbohydrates, proteins, fats are metabolized in the liver, and that the liver plays an important role in external and internal disintoxication.*

Key words: *Hepatitis, liver fibrosis, aspartataminotransferase, alaninaminotransferase, gammagglutamiltranspeptidase.*

The clinical picture of liver damage as a result of medication varies from pure hepatocellular and cholestatic to mixed variants. Since the first signs of COVID-19 are mainly fever, cough, fatigue and shortness of breath, a large part of patients have a history of using fever-lowering drugs, most of which contain paracetamol, which have a direct hepatotoxic effect. According to a number of authors, hydroxychloroquine, antibiotics (macrolides, fluoroquinolones), steroids, and other drugs used to treat patients with COVID-19 have also been found to cause liver damage. So Falcao M.B. and other co-authors (2020) have witnessed a 10-fold increase in aminotransferase activity and a drop to normal levels only after the patient has taken two doses (800 mg) of hydroxychloroquine during the follow-up period for a patient with SARS-CoV2-induced pneumonia. It has been estimated that high doses of hydroxychloroquine in Covid – 19 can cause damage to the liver beyond the effects of drugs . In addition, due to the still absence of antiviral drugs that have been proven to be active against COVID-19, various antiviral drugs (favipiravir, lopinavir, ritonavir, enisamium iodide) that cause liver damage have been widely used and used. In addition, hemolysis resulting from ribavir can call or enhance tissue hypoxia, which can cause an increase in the amount of liver enzymes in blood plasma[1].

Most drugs used to treat Covid-19 , notably macrolides, quinolines, antiviral drugs, anti-inflammatory nonsteroidal drugs, steroids,and others, have hepatotoxic effects that can damage liver cells.The extent of liver cell damage in Covid – 19 depends on the rate of increase in blood transaminase levels,while

the concentration of transamylases in the blood will be significantly increased in mild to moderate Covid – 19, but the rate of increase in ALT and AST levels is higher than that of severe Covid – It will be lower than 19. Huang C.va observations by other co-authored scientists suggest that 8 (62%) of the 13 patients treated in the resuscitation unit had an increased AST indicator,while only 7 (25%) of the 28 patients treated in the therapy unit had an increased AST indicator.This is due to long-term and high-dose antiviral drugs in severe patients, in particular lopinavir / ritonavir , taking antibacterial drugs[2].

National manuals published in various states dedicated to the diagnosis and treatment of SARS-CoV-2 indicate that prolonged treatment or the use of large amounts of drug drugs can have side effects on liver function and cause liver cells to be damaged in the outcome of hepatotoxic effects of drugs.[3]

One of the most common causes of liver cell damage caused by drugs in Covid-19 is etiotropic treatment of SARS-CoV-2 infection and pathogenetic therapy in Covid-19.

Daslabki clinical guidelines published during the pandemic recommended a number of drugs to treat SARS-CoV-2 infection, and some of them, notably lopinavir/ritonavir, hydroxychloroquine, azithromycin, umifenovir, famipiravir, recombinant interferon betta-1B, have potential hepatotoxicity.

The hepatotoxicity of hydroxychloroquine in the treatment of patients with systemic lupus erythematosus, skin porphyria, rheumatoid arthritis and malaria has been described in separate clinical observations. According to LiverTox hydroxychloroxin belongs to Category C and can cause idiosyncratic damage to liver cells[4].

The interaction of Lopinavir/ritonavir – antiretroviral drugs with drugs with immunosuppressive effects is well studied, and its use with mTOR inhibitors (sirolimus, everolimus) is not recommended. The concentration of the drug should be carefully monitored when lopinavir/ritonavir is administered simultaneously with calcineurin inhibitors (cyclosporine, tacrolimus).Patients with cirrhosis of the liver have data on the use of the drug. Patients with chronic liver disease have a low risk of hepatotoxicity of the drug.It is not recommended for use in patients with decompensated liver cirrhosis. According to LiverTox , lopinavir is in Category D , ritonavir – C .

The liver is characterized by high metabolic activity and active circulation, which makes it especially vulnerable to circulatory disorders. Hypoxia, complications associated with COVID-19, notably Systemic Inflammatory Response Syndrome, respiratory distress-syndrome and polyorgan failure, can lead to liver ischemia and reperfusion dysfunction hypoxic (ischemic) hepatitis, often observed in severe and acute cases of coronavirus infection, develops as a result of hypoxia and hypovolemia resulting from respiratory and cardiovascular failure . In cases of systemic stress, there is a compensatory decrease in blood flow in the peripheral and internal organs, which leads to a decrease in the blood supply to the liver and, as a result, to hepatocellular hypoxia. Reperfusion injury occurs through the formation of reactive oxygen species as a result of increased lipid peroxidation processes. In addition, Kupffer cells can produce cytokines in response to ischemia and initiate the activation of polymorphic leukocytes. This phenomenon usually develops rapidly and a significant increase in transaminases (20 or more norms) and LDG levels can also be observed and this condition is normalized when the hypoxia condition is corrective. [5].

Hospitalised patients have different levels of hypoxemia that require oxygenation and, depending on the severity of hypoxemia, use nasal cannula (66%), noninvasive veltillation (24%), invasive artificial lung ventilation (5%) and extracorporeal membrane oxygenation (5%). Approximately 1.1-20% of patients with COVID-19 infection develop septic shock and 23% develop heart failure. For this reason, hypoxemia, reperfusion, and circulatory failure associated with heart and respiratory failure may be the cause of liver damage in patients with COVID-19.

One of the predictive mechanisms of liver damage in patients with coronavirus infection is considered to be an immunn-linked systemic inflammatory response to "cytokine storm". the occurrence of" cytokine storm " syndrome is associated with the release of various inflammatory markers and inflammatory cytokines, which include tumor necrosis factor, interleukin - 2, 6, 7, 18 (IL-2, IL – 6, IL-7, IL-18), granulocyte-colonastimulant factor, interferon-ɤ, and ferritin. Lightning and fatal hypercytokinemia can cause polyorgan damage, as well as a chain of destruction that leads to a pathological reaction of the liver. in the past, the activity of the over-immune system and inflammation leading to such changes in the cytokine-mediated liver have been described in some systemic viral infections(cytomegalovirus, herpevirus, Epstein-Barr virus). in turn, the anti-inflammatory response can lead to hepatocellular or mixed-type lesions, with increased serum transaminases, hepatomegaly, jaundice, and hepatic encephalopathy [6].

SARS-CoV-2 RNA si positive result in stool and blood sample analysis of 2-10% of patients in the early stages of infection with COVID-19 infection is evidence of simultaneous gastrointestinal symptoms, including diarrhea, abdominal pain, nausea and vomiting, damage to the gastrointestinal tract by the COVID – 19 virus. The detection of SARS-CoV-2 virus in hepatocytes and cholangiocytes is indicative of the presence of an angiotensin-2 converting receptor, which is needed when SARS-CoV-2 virus enters the cell. However, angiotensin-2 converting receptor efficacy in cholangiocytes is expressed in Type 2 alveolar cell efficacy, and is 10 times higher than that of hepatocytes. Cholangiocytes are multifunctional and play an important role in liver regeneration and immune reactions, suggesting that patients with COVID-19 infection may have liver damage caused by the virus. However, clinical-laboratory indicators show that in COVID - 19 , the amount of alaninaminotransferase (ALT), aspartataminotransferase (AST) and lactatdegydrogenase (LDG) increased, while at the same time the amount of markers representing cholangiocyte damage-alkaline phosphatase (IF) and gammagglutamiltranspeptidase (GGTP) did not significantly increase. This discrepancy in biochemical indicator variation suggests that direct viral exposure to the liver is not the primary damaging mechanism. A combination of several factors, such as systemic inflammatory reactions, hypoxic disorders, and the use of many drugs designed to treat coronavirus infection, play an important role in the development of hepatocellular injury [7].

Currently, there are many studies that describe in detail the main symptoms characteristic of the respiratory system and, in most cases, determine the prognosis of the disease. However, COVID-19 can also affect other organs and systems of the body, including members of the digestive system. The gastrointestinal tract, together with the respiratory tract, can serve as the "gateway to infection". The following clinical signs have been observed in damage to the digestive system, diarrhea (1.25-10.10%), nausea and vomiting (1-10. 1%), loss of appetite (43 %)

In addition, in 16-53% of cases, patients with COVID – 19 have an increase in liver function disorders, mainly transaminases - alaninaminotransferase (ALT), aspartataminotransferase (AST), and lactatdegydrogenase (LDG). [8]

Thus, in the initial case of hospitalised COVID-19 cases in the US, it was observed that the indicators of alaninaminotransferase (ALT), aspartataminotransferase (AST), alkaline phosphatase (IF) and lactatdegydrogenase (LDG) had remained normal.

In California, Cholankeryl G. and in studies by other co-authors, patients with severe forms of COVID-19 will have a significantly higher percentage of liver damage compared to patients with moderate to severe levels of COVID-19 found. [127]. However, no fatal cases of liver failure have been observed in both critical and lethal cases of Covid-19. In a number of cases, there has been a decrease in the amount of protein-synthetic liver dysfunction – albumin-up to 30.9 g/L.

The results of a study involving 1,099 patients and 552 hospitals in China showed a correlation between covid-19 severity and liver damage and an increase in total bilirubin in 10% of patients, a significant and frequent increase in bilirubin in severe cases of COVID-19(20.5 %) compared to mild form (9.8%) [124]. The results of a study in 5,771 patients in Hubei province are inextricably linked with changes in the level of markers representing liver damage , especially increased levels of aspartataminotransferase (AST), with a high risk of death in patients with COVID – 19 [9].

According to published data , secondary liver damage in patients with COVID – 19 is most common in patients with diabetes mellitus and arterial hypertension, and is a non-cholestatic, hepatocellular condition, manifested mainly through increased indications of alaninaminotransferase (ALT) , aspartataminotransferase (AST) and lactatdegydrogenase (LDG).. In patients with a mild form of COVID-19 , even with chronic liver disease, secondary liver damage is observed in very rare cases. It is worth noting that COVID-19 can call for injury in several organs, including the myocardium , skeletal muscle, and kidney , among which causes increased levels of liver transaminases and lactatdegydrogenase (LDG). In this case, with a high probability, an increase in the amount of lactatdegydrogenase (LDG) compared to the amount of alaninaminotransferase (ALT) is observed[10].

Conclusion: New coronavirus infection COVID-19 continues to spread across the planet and New causing problems. The effects of the virus on the human body have not yet been sufficiently studied. Coronavirus damages the lungs, kidneys, vascular wall and digestive tract, and as a result the patient develops severe hypoxemia and polyorgan deficiency. Liver function in severe cases violations can also be observed. Fatal in severe acute liver failure cases have also been reported.To determine the degree and causes of liver damage in Covid-19, in this area to study the course of Covid-19 in patients with chronic liver diseases further research is required.

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