6 – TOM 5 – SON / 2023 - YIL / 15 - MAY

ETIOPATHOGENETIC ASPECTS OF LIVER DAMAGE IN PATIENTS WITH COVID-19

A.K.Soliev
Candidate of Medical Sciences, associate professor
Numonova G.D
Master of the 3rd year
Andijan State Medical Institute

This article discusses epidemiological characteristics, mechanisms of damaging effects, as well as strategies for the management and prevention of liver damage in patients with COVID-19.

Clinical manifestations (characteristics) of liver damage in COVID-19

Currently, there are a large number of studies that describe in detail the main symptoms characteristic of the defeat of the respiratory system and determine in most cases the prognosis of the disease. However, with COVID-19, other organs and systems of the body, including the digestive organs, can also be affected. The gastrointestinal tract (gastrointestinal tract), along with the respiratory tract, can serve as the initial "the entrance gate of infection." Thus, such clinical symptoms of damage to the digestive system as diarrhea were registered (1.25–10.10%), nausea and vomiting (1-10.1%), loss of appetite (43%).

In addition, liver dysfunction was observed in 16-53% of COVID-19 cases, with mostly isolated increases in transaminase levels – alanine aminotransferase (ALT), aspartate aminotransferase (AST) – and LDH.

Thus, it was reported that the first case of COVID-19 in the United States during hospitalization had a progressive increase in ALT, AST, alkaline phosphatases (ALP) and LDH, while bilirubin levels and prothrombin time remained normal.

According to published data, secondary liver damage in patients with COVID-19 It is most often found in patients with diabetes mellitus and arterial hypertension, is hepatocellular, not cholestatic, and manifests itself mainly in an increase in ALT, AST and LDH levels. Patients with mild forms of COVID-19 rarely have secondary liver damage, even if they suffer from chronic liver diseases. It is noteworthy that COVID-19 can cause damage to several organs, including the myocardium, skeletal muscles and kidneys, which also leads to an increase in the level of hepatic transaminases and LDH. In this case, LDH is more likely to be increased compared to ALT.

Etiology of liver damage in COVID-19

Virus-induced damage

The defeat of the gastrointestinal tract by the virus is evidenced by the fact that already at an early stage of coronavirus infection, about 2-10% of patients have positive

SARS-CoV-2 RNA in fecal and blood samples, which is simultaneously accompanied by gastrointestinal symptoms such as diarrhea, abdominal pain, nausea and vomiting. Infection with the SARS-CoV-2 virus of hepatocytes and cholangiocytes was revealed, which is associated with the presence of angiotensin converting receptor 2 (ACE2) in them, which the SARS-CoV-2 virus uses to enter the cell. At the same time, the expression level of ACE 2 in cholangiocytes is comparable to the expression level of alveolar type 2 cells and is ten times higher than in hepatocytes. Cholangiocytes are multifunctional and play a significant role in liver regeneration and immune responses, indicating that virus-induced liver damage may occur in patients with COVID-19. However, clinical and laboratory data have shown that COVID-19 has elevated levels of AST, ALT and LDH, while levels of Alkaline phosphatase and gammaglutamyltranspeptidase (GGTP), which are markers of cholangiocyte damage, did not increase significantly in patients with COVID-19. This discrepancy with changes in biochemical parameters suggests that direct viral exposure to the liver is not the main damaging mechanism. A key role in the development of hepatocellular lesions is played by a combination of several factors, such as systemic inflammatory reactions, hypoxic disorders and the use of a large number of medications intended for the treatment of coronavirus infection.

Drug-induced liver damage

The clinical picture of drug-induced liver damage varies from pure hepatocellular and cholestatic, to mixed variants. Due to the fact that the initial symptoms COVID-19 is mainly represented by fever, cough, fatigue and shortness of breath, then most of the patients have a history of using antipyretic drugs, most of which contain paracetamol, the direct hepatotoxicity of which is widely known. According to a number of authors, it has been shown that hydroxychloroquine, antibiotics (macrolides, fluoroquinolones), steroids and other drugs used to treat patients with COVID-19 can also cause liver damage. So, Falcao M.B. et al. (2020) presents the case of a patient with pneumonia caused by SARS-CoV2, who after receiving two doses (800 mg) of hydroxychloroquine were noted a 10-fold increase in the activity of aminotransferases and their decrease to normal levels after discontinuation of the drug. It has been suggested that the use of higher doses of hydroxychloroquine may lead to drug damage to the liver when COVID-19. In addition, due to the fact that, as before, there are no antiviral drugs with proven anticovid activity, various antiviral drugs (favipiravir, lopinavir, ritonavir, enisamia iodide) with a damaging effect on the liver have been widely used and are being use. In addition, hemolysis caused by ribavirin can cause or exacerbate tissue hypoxia, which can also cause increased levels of liver enzymes in the blood serum. Thus, for patients with concomitant liver diseases (viral hepatitis, cirrhosis of the liver, non-alcoholic fatty liver disease (NAFLD), alcoholic fatty liver disease) and patients with elevated levels of transaminases before treatment, when using antipyretic, antiviral and other potentially

hepatotoxic drugs, doctors should take into account the risk of liver damage in order to take timely measures to prevent drug damage to the liver.

Hypoxic damage

The liver is characterized by high metabolic activity and active blood supply, which makes it particularly vulnerable to circulatory disorders. Hypoxia caused by complications associated with COVID-19, such as systemic inflammatory response syndrome, respiratory distress syndrome and multiple organ damage, can lead to liver ischemia and reperfusion dysfunction.

Hypoxic (ischemic) hepatitis, often observed in severe and extremely severe coronavirus infection, develops as a result of hypoxia and hypovolemia against the background of respiratory and cardiovascular insufficiency. In situations of systemic stress, there is a compensatory decrease in peripheral and splanchnic blood flow, leading to a decrease in blood supply to the liver, and, consequently, to hepatocellular hypoxia. Reperfusion injury is mediated by the formation of reactive oxygen species as a result of strengthening of lipid peroxidation processes. In addition, Kupfer cells can produce cytokines in response to ischemia and initiate activation of polymorphic leukocytes. This phenomenon usually progresses rapidly and is accompanied by a significant increase in the level of transaminases (20 or more norms), and LDH, which can normalize as hypoxia is corrected. Hospitalized patients have varying degrees of hypoxemia, and, as a rule, need oxygenation support, which is carried out depending on the severity of hypoxemia, using a nasal cannula (66%), non-invasive ventilation (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. Therefore, hypoxemia, reperfusion and circulatory disorders that occur in cardiac and respiratory failure may be the causes of liver damage in patients with COVID-19.

Exacerbation of chronic liver diseases against the background of COVID-19

Chronic liver diseases, such as chronic viral hepatitis, alcoholic and non-alcoholic liver disease, autoimmune hepatitis, cirrhosis, are widespread diseases all over the world. Therefore, during the COVID-19 pandemic, it is extremely important to assess the degree of damage to liver tissue in patients with chronic liver diseases.

Conducted by Singh S. the study showed that patients with pre-existing liver diseases have significantly more a higher mortality rate than patients without liver disease, and the relative risk was markedly higher in patients with cirrhosis of the liver.

In a cohort study involving 1099 patients from 552 hospitals, 261 patients (23.7%) had at least one chronic concomitant liver disease, 23 of them (2.1%) had hepatitis B. At the same time, patients with hepatitis B were more likely to have a severe course of coronavirus infection, which indicates the relationship of this chronic liver disease with the worst clinical outcome in patients with COVID-19. Observed in severe during coronavirus infection, lymphocytopenia is associated with a decrease in the

immunotolerant status of the hepatitis virus, which can lead to reactivation of hepatitis B. For patients undergoing antiviral therapy, discontinuation of medication during COVID-19 or administration of glucocorticoids may also induce activation of hepatitis B and cause liver damage. The greatest adverse effects of the SARS-CoV-2 virus were observed in patients with cirrhosis who have systemic inflammation, hypoxia and circulatory disorders can cause secondary infection, decompensation of liver function, increased risk of bleeding and, according to the international registry of patients with chronic liver diseases and cirrhosis of the liver, an increase in the mortality rate to 40-63%.

Thus, the presence of chronic liver diseases should be considered as a prognostically unfavorable indicator for coronavirus infection, which requires close and long-term monitoring of this group of patients.

Treatment of liver damage in patients with COVID-19

The etiological treatment of COVID-19 is currently not developed. COVID-19 therapy is a complex of vital measures, such as intensive therapy, correction of hypoxemia by supporting oxygenation or artificial ventilation, continuous renal replacement therapy for cytokine storm syndrome and maintenance of effective blood circulation necessary for the prevention and treatment of multiple organ failure, including liver damage. Although some clinicians have suggested that the use of NSAIDs in early This period may have a negative impact on the outcome of COVID-19, the World Health Organization does not exclude the use of NSAIDs in the presence of clinical indications.

Liver damage in patients infected with SARS-CoV-2 is often transient and reversible without special treatment, and liver failure is rarely reported. However, in case of severe or acute liver damage, a thorough diagnosis of any underlying diseases and an assessment of the degree of liver damage is necessary to predict the onset the development of liver failure. Initial screening includes a thorough history of pre-existing liver disease, exposure to hepatotoxins (alcohol, medications, chemicals and herbs), assessment of hypoxia and circulatory status.

Patients with hypoxic hepatitis are recommended to strengthen blood circulation and respiratory support. In patients with suspected drug damage to the liver, the possibility of rapid withdrawal or reduction of doses of hepatotoxic drugs should be considered.

Therapy of patients with NAFLD in conditions The COVID-19 pandemic should include the use of hepatoprotective pleiotropic ursodeoxycholic acid (UDCA) drugs with a high safety profile and minimal risk (absence) of drug interactions. An additional advantage of using UDCA in the complex therapy of a new coronavirus infection is the universal ability of the molecule to inhibit the development of fibrosis and have a pronounced systemic immunomodulatory and anti-inflammatory effect not only in the liver, but also in other organs and systems that may be relevant for the prevention of

pulmonary fibrosis (a typical complication of COVID-19 infection). In patients with chronic alcoholic liver disease, ademethionine has been proven to be effective.

In addition, prebiotics and probiotics can be considered to ensure intestinal microecological balance and prevent bacterial infections. However, these medications are only adjuvant treatments and should not be overestimated.

Conclusion

Thus, the development of COVID-19 infection in some cases is accompanied by symptoms of hepatocellular or mixed liver damage, which correlate with the severity of the disease and are often transient.

The mechanisms of liver damage in coronavirus infection have not been fully studied, however, it is assumed that the most significant are drug damage and secondary damage caused by systemic inflammatory response syndrome or hypoxia. The possible connection of the SARS-CoV-2 virus with liver damage requires further study.

It is necessary to pay attention to the treatment of pre -existing chronic liver diseases, to monitor the liver function of patients with COVID-19. Timely treatment of severe cases is of great importance for the prevention of secondary liver damage. It is necessary to streamline treatment and prevent the use of unjustified medications, optimize the dosage regimen of recommended drugs in order to reduce the likelihood of liver damage caused by medications.

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