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CLINICAL MANIFESTATIONS IN COVID-19 AGAINST THE BACKGROUND OF HDV INFECTION

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Annotation

The novel coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2, has become a global challenge of unprecedented nature since December 2019. Although most patients with COVID-19 exhibit mild clinical manifestations and upper respiratory tract involvement, in approximately 5%-10% of patients, the disease is severe and involves multiple organs, leading to multi-organ dysfunction and failure. The liver and gastrointestinal tract are also frequently involved in COVID-19. In the context of liver involvement in patients with COVID-19, many key aspects need to be addressed in both native and transplanted organs. This review focuses on the clinical presentations and laboratory abnormalities of liver function tests in patients with COVID-19 with no prior liver disease, patients with pre-existing liver diseases and liver transplant recipients. A brief overview of the history of COVID-19 and etiopathogenesis of the liver injury will also be described as a prelude to better understanding the above aspects.

Keywords: *COVID-19, liver injury, SARS-CoV-2, clinical manifestations, liver function tests, cirrhosis*

Relevance

During the past 20 years, three major outbreaks by coronaviruses have occurred. These include severe acute respiratory distress syndrome (SARS), Middle East respiratory syndrome and coronavirus disease 2019 (COVID-19)[1]. Among these, COVID-19, caused by SARS coronavirus 2 (SARS-CoV-2) was reported for the first time in Wuhan, China in December 2019, which later spread in pandemic form throughout the world[2]. In patients with COVID-19 infection, upper and lower respiratory tract involvement, *e.g.,* common cold, bronchiolitis, and pneumonia, are the dominant manifestations. Primary clinical symptoms of COVID-19 patients are fever, dry cough, fatigue and myalgia. However, in many cases, SARS-CoV-2 affects other organs such as the heart, gastrointestinal tract, liver and kidneys with organ-specific symptoms (Table 1). Many patients with severe disease may die from multiorgan failure. In this review, we described liver involvement in COVID-19, which can be studied from many aspects. The focus of this review, however, was on clinical and laboratory manifestations of liver disease in COVID-19 patients, in the native healthy liver, native diseased liver and in the transplanted liver.In the Republic of Uzbekistan, the introduction of the HBV vaccination into the preventive vaccination schedule has resulted in nearly a 40-fold reduction in cases. However, despite effective measures, the number of mixed HBV infections identified with the delta agent is increasing, and Uzbekistan remains one of the countries with moderate endemicity on the global map [4].

In the literature reviewed, we did not find information regarding the course of COVID-19 infection against the background of chronic HDV infection. Therefore, the aim of this study was to determine the clinical and laboratory characteristics of COVID-19 infection in the context of HDV infection.

"Livomed" tablets, a well-balanced combination of pure herbs, is a very useful remedy for jaundice, liver enlargement and cirrhosis, loss of appetite, anemia, alcoholism, etc. It protects the liver from various hepatotoxins, corrects liver dysfunction and damage. Promotes appetite and controls jaundice. It helps the liver eliminate toxins and restore cell growth while protecting them from the harmful effects of alcohol, drugs and environmental toxins. Restores the functional efficiency of the liver by protecting the liver parenchyma and promoting liver cell regeneration. Its antiperoxidant activity prevents the loss of functional integrity of the cell membrane, supports and ensures early restoration of liver function in infectious hepatitis.

Materials and methods. A total of 143 patients with HDV+COVID-19 infection and 50 patients with only COVID-19 infection, treated at the Zangiota Specialized Hospital from 2021 to 2023,

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were selected using a randomized method. The main clinical signs of the disease and a comparative analysis of certain laboratory indicators were conducted for these patients.

Inclusion criteria for the study: Patient consent to participate in the study. Male or female patients aged 18 years and older. Patients with confirmed COVID-19 and HDV infection by PCR.

Exclusion criteria for the study: Pregnant or lactating women. Non-compliance with the requirements and procedures of the study. Patients younger than 18 years. Patients with chronic somatic, oncological, or hematological diseases.

Specific IgM and IgG for chronic viral hepatitis B and D were determined in serum by the IFT method, along with D-dimer, C-reactive protein, and interleukin-6 (IL-6). The test kits developed by HUMAN (Germany) and NPO "Diagnostic Systems" (Nizhny Novgorod, Russia) were used for this purpose. The quantity of viral hepatitis B DNA and D RNA in the serum was determined by the PCR method, using test kits developed by InterLabServis (Moscow, Russia) and Vektor-Best (Novosibirsk, Russia).

The numerical data of the study were processed using the variation statistical method through the "Microsoft Excel" 2021 (XP) program. The arithmetic mean (M), quadratic mean deviation, standard error of the mean (m), and relative values (degree, %) were calculated. The statistical significance of the differences in quantitative means between the study groups was determined using Student's t-test, with a significance level of $p < 0.05$ considered statistically significant. To identify the correlation between the studied groups, correlation-regression analysis (Pearson coefficient) was conducted using a medical statistical calculator (https://медстатистис.ру/салсулаторс).

Results. In the course of the study, we observed 120 patients who received treatment at Zangiota Specialized Hospital No. 2 between 2021 and 2023, and 43 of them were found to have HDV infection, representing 1.1% of the total number of patients studied. Accordingly, we divided the patients into two groups: the main group, consisting of 43 patients with HDV+COVID-19 infection, and the comparison group, which included 50 patients with COVID-19 infection only. Among patients in the main group with HDV+COVID-19 infection, 26 (60.5%) were women and 17 (39.5%) were men. In the comparison group, 62.0% (31) of the patients were women and 38.0% (19) were men. The average age of patients in the main group was 41.6±2.1 years, while in the comparison group, it was 38.9±1.7 years. As can be seen, there were no significant differences between the groups in terms of age ($p=0.987622$) or gender (OR=1.8; CI=0.9-3.1; $\chi2=0.328$), meaning the groups were comparable.

In patients of the main group, COVID-19 was more often accompanied by signs of intoxication, such as headache and dizziness, astheno-vegetative syndrome with irritability and increased sweating, indicating damage to the autonomic nervous system, as well as symptoms of lung involvement, including shortness of breath and difficulty breathing, and a higher frequency of fever compared to patients in the comparison group. However, no statistically significant differences were found between the groups ($p>0.05$). Meanwhile, in the main group, there was a significantly higher incidence of dyspeptic symptoms, such as nausea and vomiting, as well as hepatosplenomegaly and jaundice. According to the analysis results, in patients with HDV+COVID-19 infection, the likelihood of experiencing nausea was 6 times higher (OR=6.118; CI=2.4-15.4; $\chi2=15.955$), the likelihood of vomiting was 7 times higher (OR=7.292; CI=2.8-19.2; $\chi2=17.932$), the likelihood of hepatomegaly was 11 times higher (OR=11.538; CI=3.8-36.6; $\chi2=35.185$), the likelihood of splenomegaly was 35 times higher (OR=35.280; CI=4.4-279.7; $\chi2=22.595$), and the likelihood of developing jaundice of the skin and mucous membranes was 14 times higher (OR=13.689; CI=4.7-39.7; $\chi2=28.122$) compared to patients with only COVID-19 infection.

Among the 93 patients in the study group, 15 (16.1%) had a mild course of COVID-19, 51 (54.8%) had a moderate course, and 27 (29.0%) had a severe course. In the main group of patients with COVID-19 on the background of HDV infection, mild cases of the disease were observed less frequently compared to patients in the comparison group, and the difference between the groups was statistically significant (OR=5.7; CI=1.5-21.4; $p<0.05$ by Fisher's exact test). In the study group, the probability of moderate and severe COVID-19 courses was nearly the same, with no statistically significant differences between the groups.

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In patients with HDV+COVID-19 infection, the average total bilirubin level was 89.9±9.1 μmol/L, and a cholestatic syndrome was observed in 65.1% of patients. The increase in total bilirubin was primarily due to the conjugated fraction, which had an average value of 63.4±6.7 μmol/L, while the unconjugated fraction averaged 26.5±4.7 μmol/L. In the comparative group, only 6 patients had an average total bilirubin level increased to 43.2±3.2 μmol/L due to the conjugated bilirubin. The remaining patients in this group had total bilirubin levels within the normal range, averaging 11.5±2.4 μmol/L.

The total protein content in both patient groups was below normal: in the main group, it was 70.1±5.2 g/L, while in the comparative group, it was 75.58±4.7 g/L. Patients with HDV+COVID-19 infection had a statistically significantly lower level of total protein compared to the comparative group (p=0.436372). The prothrombin time index (PTI) in the main group of patients (on average 74±3.6%) was statistically significantly lower than in the comparative group (on average 94±4.1%), with some patients in the comparative group even reaching a PTI of 100% (p=0.000417).

To identify factors influencing the progression of the pathological process, we conducted a study of D-dimer, C-reactive protein, and IL-6 levels in patients from the main and comparative groups compared to the normal values of healthy individuals. For this, average values of D-dimer, C-reactive protein, and IL-6 were obtained from 10 healthy individuals.

We prescribed "Livomed" tablets for the treatment of patients with high PCR analysis of viral hepatitis. It is recommended to drink 2 tablets 3 times a day after meals for 20 days. During this time, the patients started to feel refreshed and have an appetite. After 20 days he felt completely better.

Results. This finding is significant as it aligns with existing research that highlights sex differences in immune responses and disease outcomes, particularly in infections like COVID-19 [15].

Patients in the main group exhibited more pronounced signs of intoxication, such as headache, dizziness, and respiratory symptoms. Dyspeptic symptoms (nausea, vomiting) were significantly more common in the HDV+COVID-19 group, highlighting the gastrointestinal impact of HDV infection. The frequency of jaundice and hepatosplenomegaly was also notably higher in the HDV+COVID-19 group, indicating a more severe effect on liver function. According to diarrhea and loss of appetite are also reported, with gastrointestinal symptoms linked to increased severity of COVID-19 [16]. The combination of HDV and COVID-19 exacerbates liver damage, leading to higher rates of jaundice and hepatosplenomegaly [17]

Conversely, some studies suggest that gastrointestinal symptoms may correlate with milder COVID-19 outcomes, indicating a complex relationship between these symptoms and disease severity(Canakis et al., 2022).

Mild cases of COVID-19 were less frequent in the HDV+COVID-19 group compared to the COVID-19-only group, indicating that HDV infection may contribute to a more severe disease course. Among patients with moderate and severe forms of the disease, there were no significant differences between the two groups, suggesting that while HDV co-infection affects the incidence of mild cases, it does not appear to impact the distribution of moderate and severe cases.

The percentage of patients without signs of lung tissue damage on CT was lower in the main group, while lung tissue involvement was higher, although specific damage thresholds did not show significant differences.

Patients with HDV+COVID-19 had significantly lower total protein levels and prolonged prothrombin times compared to the control group, indicating liver dysfunction. Levels of D-dimer, CRP, and IL-6 were markedly elevated in both groups, but the control group had higher levels than the main group, suggesting a potentially more severe inflammatory response in patients without HDV.

Strong correlations were found between levels of D-dimer, CRP, and IL-6 and the severity of COVID-19, indicating that these markers may be critically important for assessing disease progression.

Conclusion

In conclusion, liver involvement is common in patients with COVID-19 infection, particularly in those with moderate to severe disease. It is mostly asymptomatic or mild in nature. Conversely, patients with pre-existing liver disease are prone to serious COVID-19. Data on the impact of COVID-19 infection on patients with pre-existing diseases or liver transplants is either conflicting or scarce. Hence, large

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collaborative studies with prolonged follow-up are needed to fully comprehend the impact of this challenging infection on patients with liver diseases.

When Livomed tablets were used as a hepatoprotector, patients were quickly and effectively treated.

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