Anti-HDV seroprevalence in patients with decompensated liver cirrhosis due to hepatitis B

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Abstract
Aim: Hepatitis B (HBV) and Hepatitis D (HDV) viruses are among the two important causes of end-stage liver disease today. In this study, we aimed to increase HDV awareness in people infected with HBV by examining the prevalence of HDV in patients with end-stage liver disease due to HBV and who were evaluated for liver transplantation.

Materials and Methods: The study was designed as a retrospective single-center and cross-sectional. Patients with HBV decompensated liver cirrhosis were divided into two groups as anti-HDV positive and negative. Child-turcott pugh (CTP), Model for End-Stage Liver Disease (MELD) score, complications of liver cirrhosis, viral hepatitis serology, and platelet count variables were statistically compared between the groups.

Results: A total of 147 patients with decompensated liver cirrhosis due to HBV were included in the study. Anti-HDV positivity was detected in 46 (31.3%) patients, and anti-HDV negative in 101 (68.7%) patients. The mean age of HDV positive patients (48.39±9.20) was statistically significantly lower than HDV negative (54.37±7.80) patients (p<0.001). Although MELD and CTP scores were slightly higher in the anti-HDV negative group, there was no statistically significant difference between the groups in terms of both scores (p=0.401; p=0.782, respectively). The platelet count was found to be significantly lower in the anti-HDV positive group than in the anti-HDV negative group (p=0.008).

Conclusion: The rate of encountering HDV in end-stage liver disease due to HBV was found to be quite high. HDV is an important factor in the development of end-stage liver disease in HBV-infected individuals, especially at an early age, and taking precautions for this is of great importance.

Keywords: Anti-HDV; hepatitis B; hepatitis D; liver cirrhosis

INTRODUCTION
Hepatitis B virus (HBV) maintains its significance today as an important public health problem considering its dramatic consequences such as acute and chronic hepatitis, acute liver failure, end-stage liver disease and hepatocellular carcinoma (HCC). Although there are regional differences all over the world, it has been reported that approximately 240 million people are HBV carriers (1). Hepatitis B surface antigen (HBsAg) positivity and anti-HBc IgG positivity against HBV core antigen, which is an indicator of HBV infection, were found to be 4% and 30.6%, respectively, in a multicenter study conducted in Turkey (2). Although hepatitis D virus (HDV) is not seen with the same frequency as HBV, it draws attention that it is an important cause of mortality and morbidity when compared to HBV. HDV is a small, defective hepatotropic RNA virus that needs the help of HBV for replication (3). Because HDV enters hepatocytes through the surface antigen envelope of HBV, it needs HBsAg to infect. Two types of HDV-related infections have been named; the first is superinfection with the subsequent addition of HDV in those with HBV infection, and the second is co-infection in which HBV and HDV are transmitted simultaneously and cause infection. HDV superinfection in HBsAg-positive individuals is characterized by exacerbation of hepatitis. HDV superinfection causes chronic delta hepatitis (CDH) in 70-90% of cases (4,5). CDH is the most severe form of viral hepatitis and causes an increased risk of progression to cirrhosis and HCC, and early decomposition in patients with cirrhosis (6). It has been shown that the risk of progression to cirrhosis and development of HCC is significantly increased in patients infected with both HDV and HBV compared to patients with HBV infection alone (7,8).

The diagnosis of HDV infection is mainly based on the demonstration of antibodies to the HDV antigen.
Immunoglobulin G antibody (anti-HDV) is a marker of HDV exposure and can be seen as serological evidence of past infection. Active HDV infection was diagnosed by the presence of anti-HDV IgM antibodies in the past, but it is now confirmed by detection of serum HDV RNA by PCR tests (9).

Our recent clinical observation is that HDV is more prominent in HBV-related end-stage liver disease. Thus, this study was planned to investigate the HDV exposure rates of patients with decompensated liver cirrhosis due to HBV.

MATERIALS and METHODS

Patient selection and study design
This study is a retrospective single-center cross-sectional study. Between 2015-2020, the files, online hospital data and endoscopy records of patients who were followed up with decompensated liver cirrhosis due to HBV in the gastroenterology clinic of the institution, were scanned. Age, gender, etiology of cirrhosis, a Model for End-Stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) scores, platelet counts, viral serology records, esophageal variceal bleeding, ascites and hepatic encephalopathy history in the last year were recorded.

Inclusion and exclusion criteria
Patients with decompensated liver cirrhosis due to HBV were included in the study.

Patients under 18 years of age, those with child A cirrhosis and those with non-HBV liver cirrhosis were excluded from the study.

Laboratory Analysis
Routine biochemistry analyzes of the patients were performed with the original kits of the Roche brand Cobas 8000 model biochemistry and hormone modular analyzer series (Roche Diagnostics, California, U.S.). For viral serological examinations of the patients, blood samples were analyzed by macro enzyme-linked immunosorbent assay (ELISA) method in the central clinical microbiology laboratory of our hospital (Abbott, Axsym, Ireland). The presence of anti-HDV was studied in accordance with the manufacturer’s recommendations using the micro-ELISA (HDV Ab, Enzyme Immunoassay Test Kit, Delta Biologicals, Italy) method.

Statistical Analysis
Statistical analyzes in our study would be performed using the SPSS Version 22 program. Frequencies were stated for the variables in the categorized data type (qualitative), and for the numerical data type (quantitative) variables, the means ± standard deviation if appropriate for the normal distribution, and the median (min-max) values if not for the normal distribution. Whether the variables fit the normal distribution or not was evaluated with the Kolmogorov Smirnov test. Parametric tests (Independent Sample T Test) were used for the variables that matched the normal distribution, and nonparametric tests (Chi-Square, Mann-Whitney U Test) were used for those that did not. The statistical significance of this study was accepted as p≤0.05.

RESULTS
A total of 147 patients with decompensated liver cirrhosis due to HBV were included in the study. Anti-HDV positivity was detected in 46 patients (31.3%), while HDV was negative in 101 (68.7%) patients. The mean age of HDV positive patients (48.39±9.20) was statistically significantly lower than the mean age of HDV negative (54.37±7.80) patients (P<0.001). It was determined that male gender was significantly higher in both anti-HDV positive patients (n:35, 76.1%) and anti-HDV negative patients (n:86, 85%). While the rate of hepatic encephalopathy, one of the complications of liver cirrhosis, was higher in the anti-HDV positive group than in HDV negative patients, the difference between them was not statistically significant (p=0.054). The rates of ascites and esophageal variceal bleeding were similar between the two groups (p=0.671; p=0.938, respectively).

It was observed that anti-HBe positive patients were significantly higher in both groups, and there was no statistically significant difference between the groups.

<table>
<thead>
<tr>
<th>Table 1. Clinical findings of the study population</th>
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<tbody>
<tr>
<td>Anti-HDV (+) n= 46</td>
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<tr>
<td>Age, mean±sd</td>
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<tr>
<td>Gender, male</td>
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<tr>
<td>35 (76.1)</td>
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<tr>
<td>Hepatic encephalopathy</td>
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<tr>
<td>27 (58.7)</td>
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<tr>
<td>Ascites</td>
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<tr>
<td>35 (76.1)</td>
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<tr>
<td>Esophageal variceal bleeding</td>
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<tr>
<td>17 (37.0)</td>
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<tr>
<td>HBsAg (+)</td>
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<tr>
<td>46 (100)</td>
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<tr>
<td>Anti-HBs (+)</td>
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<tr>
<td>HBeAg (+)</td>
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<tr>
<td>Anti-HBe (+)</td>
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<tr>
<td>Anti-Hbc IgG</td>
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<tr>
<td>Anti-Hbc IgM</td>
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<tr>
<td>CTP score, mean±sd</td>
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<td>MELD score, mean±sd</td>
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<td>Platelets (10⁹/L), median (min-max)</td>
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</table>

HDV: hepatitis D virus; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e antigen; Anti-HbcIgG: hepatitis B core antigen; MELD: model for End-Stage Liver Disease, CTP: Child Turcott Pugh.

† P-values from Student’s t-test. ‡ P-values Mann-Whitney’s U-test. All other p-values are obtained from chi-square analysis and results are given as n and %
Anti-HBs negative, HbsAg positive, anti-HBc IgM negative, anti-HBc IgG positive were detected in all patients in both anti-HDV positive and anti HDV negative groups. MELD and CTP scores were slightly higher in the anti-HDV negative group, but there was no statistically significant difference between the groups in terms of both scores (p=0.401; p=0.782), respectively. The platelet count was found to be significantly lower in the anti-HDV positive group than in the anti-HDV negative group (p=0.008). The findings are summarized in Table 1.

**DISCUSSION**

In large-scale studies conducted for HDV, the number of people with HDV infection worldwide was reported to be approximately 74 million (10). HDV positivity with a rate of 13.02% in HbsAg positive individuals and a global prevalence of 0.98% in general has been reported (11).

In various studies conducted in HbsAg-positive patients in our country, anti-HDV positivity rates have been found to vary between 2% and 15%, although it varies regionally (12-14). In similar periods, anti-HDV positivity was detected in 6% of asymptomatic HBV carriers and 27.5% of chronic active hepatitis B patients (15). In recent studies, HDV antigen or antibody positivity was found in 5.2% of HbsAg positive patients in the Izmir region (16). In a study examining patients with chronic hepatitis B, anti-HDV positivity was found at a rate of 8.8% (17).

In a study conducted in our country, including patient groups with HBV-related liver cirrhosis in 2001, the rate of anti-HDV was 18.8% (18), and in a meta-analysis in 2008, HDV prevalence was reported to be between 12% and 46% according to regions (19). In a recent and global meta-analysis, the prevalence of HDV was found to be 25.77% in HBV-induced liver cirrhosis and 19.80% in HCC (20).

In the present study, a more homogeneous patient group was examined by using the CHILD and MELD classifications. Thus, the incidence of HDV in decompensated liver cirrhosis due to HBV was given accurately on the basis of our country.

In the current study, the rate of encountering HDV in patients with end-stage liver cirrhosis infected with HBV was found to be quite high (31.3%). In addition, HDV positive patients were found to be decompensated at an earlier age. Platelet counts were found to be lower in anti-HDV positive individuals, which may mean that they more easily have thrombocytopenia, one of the signs of severe portal hypertension.

Considering both the loss of workforce and costly treatment methods due to end-stage liver failure, the implementation of a vaccination program against HBV can be a cost-effective approach. Based on this analysis, it is stated that an HBV vaccination coverage of more than 80% is sufficient for the final eradication of both HBV and HDV infection (21).

**CONCLUSION**

In conclusion, in addition to chronic HBV infection, which still has an important place among the causes of end-stage liver failure, HDV infection is also of considerable importance. Considering that the eradication of HBV has not been realized yet, we believe that it is necessary to raise awareness of the society against HDV with more effort.

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**Ethical Approval:** Ethics committee approval was obtained from the ethics committee of Basaksehir Cam and Sakura City Hospital with the number 2021/140.

**REFERENCES**


