CAN ASCITES AND SERUM ANALYSES DIFFERENTIATE DELTA FROM HBV INFECTION IN CIRRHOTIC PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS?

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ABSTRACT

Aim: *We tried in this work to define laboratory differences in ascites and serum of cirrhotic patients with HBV or Delta infection*

Material and Methods: *We conducted a retrospective study in a large hospital experienced in hepatology by including 46 patients with HBV and HDV between January 2018 and September 2020. Data of age and gender-matched 24 patients with HBV and 22 patients with HBV/HDV having SBP were analyzed.*

Results: *White blood cell, neutrophil counts, serum glucose, serum albumin, serum globulin, serum ascites-albumin gradient and serum albumin-globulin gradient levels were similar.*

Conclusion: *Cirrhotic patients with HDV infection had lower platelet and serum fibrinogen and higher INR levels than those with HBV infection.*

Keywords: *Cirrhosis, HBV, delta infection, ascites.*

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Introduction

Hepatitis D (delta) virus (HDV) has been discovered as an antigen in hepatocytes of Hepatitis B Virus (HBV) infected patients. HDV can only cause an infection with HBV surface antigen, so it can be considered as a defective virus[1, 2]. HDV is associated with more severe liver damage than HBV alone[1]. In developing countries such as Central Africa, parts of the Middle East, and the Amazon basin where HBV can not be controlled, HDV is highly endemic. Intermediate prevalence is seen in much of Eastern Europe, Turkey, and Central and South America[3, 4].

The end-stage of chronic liver disease is hepatic cirrhosis and is characterized by fibrosis. The most common causes of liver cirrhosis are alcoholism and chronic hepatitis B or C in developed and developing countries, respectively[5].

Physical examination findings (small, firm, nodular liver; jaundice) and laboratory test abnormalities (low platelet count, decreased albumin level, elevated INR, elevated bilirubin and/or transaminase levels) are used in diagnosis of hepatic cirrhosis. Some scoring methods are used to determine the prognosis with Child-Pugh score being the most used. This scoring system is based on bilirubin, albumin and INR levels, the presence

and severity of ascites, and encephalopathy[6]. There are three stages of the scoring system: A, B, and C according to the severity of the disease.

Hepatic cirrhosis can be divided as compensated or decompensated. Compensated cirrhosis is the relatively asymptomatic phase before the development of decompensating complications. Criteria of decompensated cirrhosis include new onset of ascites, non-obstructive jaundice, bleeding gastrointestinal varices and hepatic encephalopathy; which all are related to increased mortality[7]. Ascites, pathologic accumulation of peritoneal fluid, is a common clinical sign of decompensated cirrhosis, even though 15% of which is related to non-cirrhotic etiologies[8]. Cirrhosis is the most common cause of ascites. Infected ascites without a puncture are defined as spontaneous bacterial peritonitis (SBP) which is a well-known and mortal complication in patients with cirrhosis. Enteric organisms are the causative agents in more than 90% of cases, which suggests gastrointestinal tract as the source of bacterial contamination. The main microorganism responsible for infection is enterobacteriaceae[9].

In short, hepatic cirrhosis with SBP caused by HBV and HDV is a serious clinical problem and yields high mortality and morbidity. In this study, we tried to compare serum and ascites biochemical test findings in cirrhotic SBP patients infected with HBV or HBV/HDV.

Material and method

We conducted a retrospective study in a large hospital experienced in hepatology by including 46 patients with HBV and HDV between January 2018 and September 2020. Data of age and gender-matched 24 patients with HBV and 22 patients with HBV/HDV having SBP were analyzed. All underwent paracentesis, and fluid cell count plus biochemistry along with simultaneous blood tests were taken. All patients had portal Doppler ultrasonography. Data of both groups were compared statistically.

Statistical analysis

As descriptive statistics, average, standard deviation, minimum, maximum values were used for continuous variables, while number and percentage were used for categorical variables. Wilcoxon test was used to compare variables and, the Pearson's chi-square and Fisher's exact test were used to compare categorical variables. Variables with normal distribution in both groups were compared by t-test for independent samples comparison. Pearson correlation coefficients were calculated to determine the relationship between these variables. A Chi-square test was performed to determine the relationship between categorical variables and groups. The significance limit was taken as $P<0.05$ and duplex. Analyses were performed using SPSS 21 software.

Results

A total of 46 cirrhotic SBP patients with Child Pugh's score B and C (with a male-female ratio of 1.09:1) was included. Delta hepatitis was isolated from 22 (47.8%) of 46 samples. The mean age was 58.8±14.5. Mean age of HDV group was 56.7±13.3 while that of HBV group was 60.8 ± 15.6; yielding no significant difference ($p>0.05$). Mean blood serum platelets and fibrinogen levels in HDV group were significantly lower compared to HBV group (91±49.2 versus 179.1±124.5; $p=0.003$; 188.7±135.6 versus 312±224.4; $p=0.04$ respectively). Furthermore, the mean international normalized ratio (INR) was found to be significantly higher in HDV group compared to HBV (20.8±10.4 versus 15.1±5.5; $p=0.024$) (Table 1).

	HBV group	HDV group	p value
Age (years)	60,83±15,6	56,77±13,3	0,351
White Blood Cell (/mm^3)	8675±5679	6940±5621	0,304
Neutrophil (/mm^3)	6095±4953	5195±5231	0,552
Hemoglobin (g/dl)	11,5±2,9	11,4±2,1	0,896
Platelet (/mm^3)	179130±124500	91090±49250	0,03
AST (U/L)	87±163,1	132±174,7	0,366
ALT (U/L)	195±673,4	87±71	0,457
INR	15,1±5,5	20,8±10,4	0,024
D-dimer (mcg/L)	137,6±420	56,5±60,7	0,398
Fibrinogen (mg/dL)	312,5±224,4	188,7±135,6	0,040
Albumin (g/L)	27,6±7	24,4±6,8	0,124
Globulin (g/L)	37,1±10,6	39,3±10,2	0,488
AFP (U/L)	4342±3822	2956±7915	0,363

Table 1: Comparison of serum biochemical tests according to HBV and HDV infection.

According to viral infection type (HBV or HDV); the ascites fluid biochemistry were compared, and there were no significant differences in white blood cell, neutrophil counts, serum glucose, serum albumin, serum globulin, serum ascites-albumin gradient, and serum albumin-globulin gradient

levels (Table 2). Portal and splenic vein diameters were measured using Doppler ultrasound. There was no statistical difference in portal vein diameters; however, the mean diameter of the splenic vein in HDV patients was statistically higher than that of HBV patients. (14.5±3.5 cm versus 9.3±0.5 cm; p=0.044) (Table 3).

	HBV group	HDV group	p value
Ascites WBC (/mm^3)	918±1155	762±903	0,691
Ascites neutrophil (/mm^3)	454±721	494±876	0,946
Ascites glucose (mg/dL)	131,9±41,2	142,6±91,9	0,619
Ascites albumin (g/L)	8,6±6,4	6,8±8,4	0,427
Ascites globulin (g/L)	7,4±4,9	7,1±5,2	0,815
Serum/ascites albumin gradient	19±7,7	19,4±7,9	0,862
Serum/ascites globulin gradient	28,7±11,6	32,2±10,8	0,322

Table 2: Comparison of ascites biochemical tests according to HBV and HDV infection.

	HBV group	HDV group	p value
Mean portal vein diameter (cm)	12,7±2,7	13,2±3,4	0,827
Mean splenic vein diameter (cm)	9,3±0,5	14,5±3,5	0,044
Mean axial splenic diameter (mm)	139,8±45,1	164,4±42,7	0,102

Table 3: Comparison of splenic and portal vein diameters according to HBV and HDV infection.

Discussion

Hepatic cirrhosis is a dramatic clinical syndrome associated with high mortality. This disease can occur as a result of various etiologies, most common hepatitis viruses[10]. Hepatitis B is a viral infection caused by HBV, a DNA virus that may cause both acute and chronic liver disease. According to WHO, nearly 2 billion people around the world are estimated to have faced HBV, and 3% (240 million) are chronically infected with hepatitis B[11]. Chronic HBV infection is usually associated with progressive liver damage. Repeated repairs of damaged liver parenchyma can lead to fibrosis and cirrhosis[12]. HDV infection is associated with accelerated progression to cirrhosis and increased incidence of cirrhosis in hepatitis B virus carriers[13]. In European populations, 15% of patients with chronic hepatitis D virus infection progress to cirrhosis within 1-2 years, whereas the remaining 70-80% progress within 5-10 years[14]. Acute delta hepatitis is rare but may lead to fulminant hepatitis as a result of co-infection with hepatitis B. Chronic delta hepatitis develops as a result of superinfection of a hepatitis B surface antigen (HBsAg) carrier with hepatitis delta virus (HDV)[15]. Chronic Hepatitis D appears to result in the most severe form of viral hepatitis, causing cirrhosis and hepatocellular carcinoma more progressively[16]. Given these severe complications, early recognition of HDV is quite important. In our study, we compared HDV and HBV infections in patients with SBP. In HDV group, mean blood serum platelet count and fibrinogen levels were significantly lower (p=0.003; p=0.04) while mean international normalized ratio (INR) were found to be significantly higher (p=0.024).

Fibrinogen, a complex polypeptide synthesized in the liver, plays an important role in hemostasis along with platelets. Testing fibrinogen and platelet levels in serum may provide some key features about the hemostatic system in case of liver cirrhosis. Varnika Rai et al. reported that serum fibrinogen, protein C, and platelet count were lower in cirrhotic patients compared to chronic hepatitis[17]. Our study showed that patients with HDV infection had lower platelet and serum fibrinogen but higher INR levels than those with HBV infection.

One of the most common causes of ascites is hepatic cirrhosis caused by HBV and/or HDV infection[18]. SBP is diagnosed by a fluid neutrophil count of more than 250 cells/mm3 with paracentesis. Even in prolonged prothrombin time patients, paracentesis is a safe diagnostic method[19]. Paracentesis can be used to gain insight into the disease by performing some chemical tests on the fluid samples, and cultures can be obtained for diagnosis and treatment of SBP. Mortality and complications related to liver cirrhosis are both significantly higher in patients with SBP than without bacterial infections[20].

Karvellas et al. reported that septic shock secondary to SBP has a high mortality rate as approximately 80% in patients with liver cirrhosis, and bloodstream infections occur in 4%-21% of patients with liver cirrhosis, which is 10-folds higher than the rate in non-cirrhotic patients. The mortality of bloodstream infections in patients with liver cirrhosis ranges between 23% and 58%[21-23]. According to viral infection type (HBV or HDV) there were no significant differences in white blood cell, neutrophil counts, glucose, albumin, globulin, serum ascites albumin gradient, and serum ascites globulin gradient levels in ascites fluids samples in our study. It has been a well-known fact that HDV-related liver cirrhosis causes more severe liver damage than

those without HDV infection. Radiologic findings of advanced liver cirrhosis include shrunken liver, splenomegaly, and increased diameters of both portal and splenic veins detected by Doppler ultrasound[24]. Increased splenic vein diameters noted in our study may be a predictor of HDV infection in patients with SBP. This finding may be related to severe left -sided portal hypertension, possibly through effects on severe hepatocyte damage.

There were some limitations of the study. First, study findings may not be generalized for all patients with HDV infection due to the small sample size. Second, due to the The retrospective nature of the study, we could not obtain hospital data involving study patients' medical history.

On the other hand, the findings of this study demonstrate that HDV infection may be related to increased splenic vein size in SBP patients.

Conclusion

The current study showed that cirrhotic patients with HDV infection had lower platelet and serum fibrinogen and higher INR levels than those with HBV infection. These findings indicate in line with the literature that HDV is associated with more severe hepatic cirrhosis. It can also be advocated that in SBP patients with HBV infection, HDV super-infection should be suspected in case increased, higher than expected, splenic vein size is found, however; future research is needed.

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