Factors Differentiating Acute Hepatitis B from Acute Exacerbation of Chronic Hepatitis B in Prospective-retrospective Cohort

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Abstract

Introduction and Aim: It is difficult to distinguish acute hepatitis B (AVH-B) from chronic hepatitis B with an acute exacerbation (CHB-AE) in patients whose prior history of HBV infection is unknown. The present study aimed to screen laboratory parameters at presentation to discriminate between these two conditions.

Materials and Methods: A prospective study was conducted in patients presenting clinically as AVH-B without known previous chronic hepatitis B status. Patients were divided into AVH-B and CHB-AE at end of six months follow up. Clinical and laboratory profiles were compared between these two groups at presentation.

Results: There was no significant difference in clinical presentation and risk factors profile in patients of both the groups. Mean age of presentation in AVH-B was 31.8 ± 14.9 years while, 47.2 ± 17.3 years in CHB-AE group (p=0.005). Mean IgM anti-HBc levels were higher in AVH-B than in the CHB-AE group (p=0.001). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IgM anti-HBc (>12.14 S/CO (Sample/Cut-off)) for diagnosis of AVH-B was 76.9%, 71.4%, 76.9% and 71.4 % respectively. Quantitative HBV DNA levels were significantly higher in CHB-AE group than in AVH-B group (p=0.015). Sensitivity, specificity, PPV and NPV of HBV DNA (> 15390 IU/ml) for diagnosis of CHB-AE was 78.6%, 46.2%, 44% and 80% respectively.

Conclusions: A high percentage of patients with apparent AVH-B might be cases of CHB-AE. Elderly patient (mean 47.2 years), high titers of HBV DNA (>15390 IU/mL) and low IgM anti-HBc titer (<12.14 S/CO) favours CHB-AE over AVH-B.

Introduction

Hepatitis B virus (HBV) infection is a global health problem. Cirrhosis and/or hepatocellular carcinoma (HCC) are found in 25%-40% of patients with chronic hepatitis B (CHB) infection. 1,2 Natural history of HBV infection is a dynamic state of interactions between HBV, hepatocytes, and immunity of the host.

Acute viral hepatitis B (AVH-B) resolves completely in 90–95% of the adult patients. Persistence of hepatitis B surface antigen (HBsAg) beyond 6 months is considered as chronic hepatitis which develops in about 1-5% of the adult patients who had presented with AVH-B. 3,4 Chronic hepatitis B with exacerbation (CHB-AE) is defined as “Abrupt elevation of serum ALT to >5 ULN (Upper limit of normal) or a greater than 3-fold increase in baseline ALT, whichever is higher” in known hepatitis B carrier. 5,6 Acute exacerbations are due to spontaneous viral activation (immune clearance) in 50-90 % patients, the remaining being due to super-infection by non-B hepatitis virus. 5,6 Reactivation following immunosuppression is characterized by the initial phase of enhanced viral replication during the immune suppression followed by immune-mediated destruction of HBV infected hepatocytes, resulting in hepatitis when immunosuppression is withdrawn. 5,6 In 40–50% of hepatitis B e antigen (HBeAg) positive patients, CHB-AE can occur during the immune-clearance phase; it can be repeated when there is an unsuccessful clearance of HBeAg. 6,7 In HBeAg-negative patients, reactivation occurs in 15–30% cases and is occasionally associated with HBeAg seroreversion. 6,7

Endemicity for chronic hepatitis B is defined as, high (>8%), intermediate (2-7%) and low (<2%) according to the percentage of population positive for HBsAg. 5,8 In countries with intermediate and high endemicity, the possibility of exacerbation of chronic HBV infection is high. It may be the first presentation of chronic hepatitis B or compensated cirrhosis, which was asymptomatic before exacerbation. Hence, a possibility exists that a proportion of patients with suspected AVH-B might actually be suffering from CHB-AE. At the first presentation, it is difficult to differentiate between these two conditions especially when the chronic hepatitis status is not known.

This study was undertaken to assess the clinical, biochemical, and virological characteristics of patients presenting clinically as AVH-B and to find features that could differentiate them from patients having the first episode of symptomatic CHB-AE.

Materials and Methods

Study design

This was a prospective-retrospective...
observational study of patients presenting with features of AVH-B admitted at a tertiary health care centre in the gastroenterology department during August 2016 till July 2018. The study was approved by the institutional ethics committee.

**Patient selection**

Patients presenting clinically with acute viral hepatitis with HBsAg positive status were assessed for eligibility. Data was collected on a predesigned proforma. History of previous episodes of jaundice, known chronic hepatitis B, contact with chronic HBV infected patient, blood transfusion, surgery, dental procedures, tattooing, high-risk sexual behavior, and intravenous drug abuse were noted. Information was obtained regarding the onset of symptoms, altered sleep pattern, and the presence of ascites. Detailed physical examination was performed and the presence of pallor, icterus, pedal edema, hepatomegaly, splenomegaly, ascites, and flaps was noted. All routine investigations were performed like complete blood count, renal function tests and serum electrolytes. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, total protein, albumin, prothrombin time and an international normalized ratio (INR) were done in all patients.

Serological tests for HBV like HBsAg, hepatitis B e-antigen (HBeAg), quantitative hepatitis B virus DNA (HBV DNA), and hepatitis B core antibody titers (IgM anti-HBc) were requested in all cases. Blood samples for antibodies to hepatitis A virus (IgM anti-HAV), hepatitis E virus (IgM anti-HEV), and hepatitis C virus antibody (Anti-HCV) were also collected. Serological tests were done using the enzyme-linked immunosorbent assay (ELISA) technique. Serum IgM anti-HBc was done using the fully automated chemiluminescent microparticle immunoassay, measured as a sample to the cut-off ratio (S/CO). Serum HBV DNA was done using the real-time polymerase chain reaction (PCR). All the patients underwent an abdominal ultrasound examination performed by a single observer with Xario 100, platinum series, Canon medical system USA. Esophagogastroduodenoscopy (EGD) was done with (GIF Q150 Olympus, Japan) in all patients.

**Inclusion criteria**

Patients with clinical features of acute viral hepatitis and HBsAg positive status, presenting within four weeks of the onset of symptoms and completing at least 6-months of follow-up were included in the present analysis. All the patients included were above 18 years of age.

**Exclusion criteria**

Patients with antibodies against hepatitis A, C or E virus, superimposed alcoholic liver disease, clinical, radiologic or endoscopic evidence of chronic liver disease at presentation were excluded from the study. HIV patients and pregnant females were also excluded from the study.

**Follow-up**

Patients were followed up after the initial diagnosis of acute hepatitis for at least 6 months. Data were obtained suggesting the clearance or persistence of HBsAg and development of clinical, radiologic and endoscopic evidence of chronic liver disease. At 6 months follow-up, all the patients underwent ultrasound abdomen and fibroscan (Fibroscan, echosens Abbott India Limited) and EGD scopy.

**Study groups**

The diagnosis of acute hepatitis B was made on the basis of clinical features, compatible liver function tests and exclusion of other causes of jaundice. Patients were divided into 2 groups. Group 1 included patients, who on follow-up lost HBsAg antigen and did not develop evidence of chronic liver disease on ultrasound abdomen, fibroscan or EGD scopy. These patients were considered as AVH-B. Group 2 patients included those who on follow-up remained HBsAg-positive for at least 6 months and developed clinical, biochemical, radiologic, or endoscopic evidence of chronic liver disease. These patients were considered to be having CHB-AE. Laboratory parameters at the time of first presentation analysed retrospectively between these two groups. Out of the 53 patients presenting as acute icteric viral hepatitis B, 40 fulfilled the inclusion criteria. Thirteen patients were excluded from the study: 3 had
Table 1: Symptoms, signs and risk factors for infection in both groups (AVH-B and CHB-AE)

<table>
<thead>
<tr>
<th>Symptoms, signs and risk factors</th>
<th>Final Diagnosis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>AVH-B 26/26 (100%) CHB-AE 14/14 (100%)</td>
<td>-</td>
</tr>
<tr>
<td>Fever</td>
<td>17/26 (65.3%) 8/14 (57.14%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20/26 (76.9%) 9/14 (64.2%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Anorexia</td>
<td>23/26 (88.5%) 12/14 (85.7%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>8/26 (30.8%) 7/14 (50%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>0/26 (0%) 2/14 (14.2%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>3/26 (11.5%) 0/14 (0%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Past history surgery</td>
<td>3/26 (11.5%) 2/14 (14.3%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Tattoo</td>
<td>3/26 (11.5%) 2/14 (14.3%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Dental procedure</td>
<td>1/26 (3.8%) 0/14 (0%)</td>
<td>0.32</td>
</tr>
<tr>
<td>High risk behavior</td>
<td>2/26 (7.7%) 1/14 (7.1%)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Associated acute hepatitis E, 1 had acute hepatitis A, 4 had a history of significant alcohol intake and 5 had evidence of chronic liver disease at the time of admission.

Statistical methods

Statistical analysis was done with SPSS version 22.0 statistical software [IBM Armonk NY, USA]. Comparisons of continuous variables were done by unpaired t-test and discrete variables by χ² test and Fischer exact test as required. Sensitivity, specificity, PPV, and NPV of various tests were also calculated. Variables at the presentation that could predict the persistence of HBsAg with the development of chronic liver disease were assessed by regression analysis.

Results

Case definition

Out of 53 patients, 13 were excluded from the study because they failed to fulfill the inclusion criteria (Figure 1). Out of the 40 patients available for final analysis who underwent investigations at 6 months, 25 (62.5%) patients had negative HBsAg, 1 (2.5%) patient had positive HBsAg with a normal abdominal ultrasound examination, normal EGD scope and normal fibroscan were defined as AVH-B patients. Fourteen (35%) patients had positive HBsAg and abnormal abdominal ultrasound and/or EGD scope and/or fibroscan were defined as CHB-AE. Laboratory parameters at the time of first presentation analysed retrospectively between these two groups.

Demographic characteristics

Mean age of presentation in AVH-B group was 31.8 ± 14.9 years and 47.2 ±17.3 years in CHB-AE group. Age of presentation was significantly higher in the CHB-AE group (p=0.005). Male to female ratio was 1:8.1 and 1:1 in AVH-B and CHB-AE group respectively. Baseline clinical features and risk factor profile for acquiring hepatitis B infection were comparable in both study groups (Table 1).

Biochemical parameters at the time of admission

Among the biochemical parameters at the time of admission, platelet count, AST, ALT, total bilirubin, direct bilirubin, and INR were not significantly different in both groups. Mean serum albumin levels in AVH-B (3.63 ±0.44 gm/dl) was significantly higher than CHB-AE (3.01 ± 0.5 gm/dl) group (p=0.001) (Table 2).

Virus serology at the time of admission

Four (15.3%) out of 26 patients of the AVH-B group and 3 (21.4%) out of 14 in CHB-AE group were HBeAg positive. HBeAg positivity was not statistically different between the two groups (p=0.65).

Mean IgM anti-Hbc levels in the AVH-B group was 21.4 ± 10.78 whereas 10.48 ± 4.75 in the CHB-AE group (Figure 2). IgM anti-Hbc levels were significantly higher in the AVH-B group (p=0.001) as compared to CHB-AE. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IgM anti-Hbc (>12.14 S/CO) for diagnosis of AVH-B was 76.9%, 71.4%, 76.9%, and 71.4 % respectively. Receiver operating characteristics curve (ROC) of IgM anti-Hbc is shown in (Figure 3). The area under the curve was 0.82.

Mean quantitative HBV DNA levels were 119723.69 ± 212067.18 in the AVH-B group, While 1200572.14 ± 2158872.79 in the CHB-AE group (Figure 4). Quantitative HBV DNA levels were significantly higher in the CHB-AE group than in the AVH-B group (p=0.015). Sensitivity, specificity, PPV and NPV of HBV DNA (cut-off >15390 IU/ml) for diagnosis of CHB-AE was 78.6%, 46.2%, 44% and 80% respectively. ROC of HBV DNA is shown in (Figure 5).

EGD, Ultrasound abdomen and Fibroscan at 6 months

Ultrasound abdomen at 6 months was normal in all patients of the AVH-B group. Six (42.8%) out of the 14 patients in the CHB-AE group showed signs of chronic liver disease on ultrasound examination. (Four (28.5%) patients had coarse liver echotexture and dilated portal vein > 13 mm and 2 (14.3 %) had coarse echotexture and mild ascites (p=0.008)). EGD scope was normal in...
all 26 patients of the AVH-B group with no evidence of esophageal varices while four (28.5%) out of 14 patients in the CHB-AE group had esophageal varices (p=0.04). On fibroscan examination, mean of median stiffness of liver in the AVH-B group was 5.5 ± 1.1 Kpa, while in CHB-AE group it was 8.8Kpa ± 2.6 (p=0.0003).

Discussion

Differentiation between AVH-B and CHB-AE has always been a task for the hepatologists.

Management in these two conditions differs considerably. Acute hepatitis B is usually a spontaneously recovering disease and does not require antiviral treatment except patients with ‘severe acute hepatitis B’ who have a protracted severe disease characterized by bilirubin >5 mg/dl plus INR >1.5, for >4 weeks or acute liver failure (ALF). However, antiviral treatment is required for CHB-AE which can present as hepatitis, ALF, decompensated liver disease or acute on chronic liver failure (ACLF).

In high prevalent areas for chronic HBV infection, the cases of CHB-AE might account for an appreciable percentage of cases presenting clinically as AVH-B. Kumar et al reported an occurrence of CHB-AE in 37.9% of all clinical acute presentations. Chu et al found 63% of CHB-AE actually presenting as acute hepatitis. In the present study, 35% of the patients presenting as apparent AVH-B, actually had CHB-AE.

Hepatitis B is a ‘stealth virus’, does not activate the innate immune system which recognizes pathogen-associated molecular patterns (PAMPs) and results in clearance of the pathogen. Instead of that adaptive immunity comes into play in the form of high levels of circulatory CD 8 cells which react with HBV antigens and eliminate the virus by destroying infected hepatocytes. Control of the infection during the incubation phase leads to a marked fall in virus load before the onset of clinically evident disease in humans who were identified before acute icteric hepatitis B. On the other hand, in patients with exacerbation, the on-going liver injury is due to the increased level of HBV DNA. Non-cytolytic processes could contribute to the elimination of the virus from the hepatocyte during acute infection of hepatitis B.

Our study emphasizes the importance of HBV DNA in differentiating patients with AVH-B from CHB-AE. In the CHB-AE group, HBV DNA levels were high in 10 out of 14 (71.5%) patients with cut off of 15390 IU/mL. The sensitivity and specificity of HBV DNA levels (>15390 IU/mL) in the diagnosis of CHB-AE were 78.6% and 48.2% respectively. Higher levels of HBV DNA at admission predicted persistence of HBsAg antigen and development of chronic liver disease on follow-up. Close follow up and early introduction of potent antivirals could prevent the progression of liver disease in these patients. The study by Kumar et al showed high HBV DNA levels (> 0.5 pg/mL = 28751 IU/mL) had sensitivity and specificity of 86.6%, 95.9% respectively for diagnosis of CHB-AE. Han et al demonstrated HBV DNA (<105 copies/ml = 17857 IU/mL) had 75.4% sensitivity and 79.2% specificity for the diagnosis of AVH-B. Park et al showed HBV DNA <5.5 log10 IU/mL had a sensitivity of 81.1% and specificity of 72.4% for the diagnosis of AVH-B. Raising viral load in CHB-AE becomes detectable in the serum during spontaneous reactivation of chronic hepatitis B infection. Dao et al found a low or undetectable IgM anti-HBc level, with elevated HBV DNA to >5 log10 IU/mL, in a patient with ALF due to underlying chronic hepatitis B rather than acute infection.

Our results demonstrated the importance of the titre of IgM anti-HBc. Around 76.9% of patients in the AVH-B group had high IgM anti-HBc titre (>12.14 S/CO). On the other hand, low IgM anti-HBc titre (<12.14 S/CO) was seen in the majority (71.4%) of the patients in the CHB-AE group. The study by Kumar et al have found an incidence of high IgM anti-HBc titre (>1:1000) in 77.5% patients of AVH-B and low IgM anti-HBc titre (<1:1000) in 70% patients of CHB-AE group [8]. Han et al reported an incidence of high IgM anti-HBc titre (>1:10,000) in 96.2% patients of AVH-B and low IgM anti-HBc titre in 76.9% patients with CHB-AE group. Park et al showed cut-off values for IgM anti-HBc as >8 S/CO which had sensitivity and specificity of 96.2% and 89.7% respectively for diagnosis of AVH-B. Importance of IgM anti-HBc in the diagnosis of acute hepatitis has been well reported by Papaevangelou et al in 1984.

Serum alpha-fetoprotein (AFP) levels are usually raised in around 45-60% patients of CHB-AE. Peak elevation of AFP is usually seen after 1-2 weeks of elevation of serum aminotransferases and normalizes over 3-12 months. Han et al reported, lower cut off of serum AFP (< 5 times of normal) minimally improve the diagnostic accuracy of IgM anti-HBc for diagnosis of AVH-B.

Liver biopsies during hepatitis B flares invariably show unevenly distributed lobular necro-inflammatory changes, occasionally it may be so
extensive that bridging hepatic necrosis (BHN) might occurs.28-30 Liaw et al. showed that BHN is present in more than 80% of the patients with AFP >100 ng/ml during hepatitis B exacerbation.31 Age of presentation was a unique finding in our study, which has not been reported in the previous studies.32,33 Elderly age of presentation (mean 47.2 years) possibly represents CHB-AE presenting clinically as acute hepatitis (Mean age was 31.8 years in the AVH-B group).

Conclusion
A high percentage of patients with apparent AVH-B might be cases of CHB-AE in intermediate and high endemicity areas. Elderly age of presentation (mean 47.2 years), high titre of HBV DNA (>15390 IU/mL) and low IgM anti-HBc titre (<12.14 S/CO) favors CHB-AE over AVH-B. Exacerbation of chronic hepatitis in underlying cirrhotic patients always requires immediate antiviral therapy. Non-cirrhotic patients with decreasing HBV DNA trend may be followed for HBsAg or HBeAg loss and therefore, may be followed for 3-6 months for real indication of antiviral therapy.6

Limitations of the study
Quantitative HBsAg (qHBsAg), Quantitative HBeAg (qHBeAg), Anti-HBeAg and serum AFP levels which were used in previous studies could not be done due to logistic problems. Liver biopsies were not performed in CHB-AE patients owing to ethical concerns. We recommend prospective studies and longer follow-up trials for better differentiation between AVH-B and CHB-AE.

References