ABSTRACT

Background: Subacute hepatic failure (SAHF) is a complication of acute hepatitis (AH) characterized by progressive jaundice and development of ascites within 24 weeks of the onset of icterus. Its pathogenesis is unknown and its treatment is unsatisfactory. This study highlights on the possible pathogenesis of the disease.

Materials and methods: Thirty-two with SAHF among 798 patients of AH who had tests for markers of acute hepatitis A, B, C and E had blood and ascitic fluid study and ultrasonogram (US) of liver. US and risk factors for infection were compared with consecutive uncomplicated AH. Blood culture was done in consecutive 307 AH patients at the time of the first visit. Patients with SAHF and control were followed for at least 6 months.

Results: SAHF developed in 4% of the patients with AH. Bacteremia was detected in 50% and ascitic fluid showed features of hepatic venous outflow obstruction (HVVOO) and bacterial peritonitis. Thrombus was detected in IVC in all. Seventy-five percent of the patients who received antibiotic recovered. Recurrence of the symptoms in five and development of cirrhosis in seven patients were noted at follow-up but none among patients with uncomplicated acute hepatitis (AH). Bacteremia was also detected in 25% of consecutive AH patients presenting with fever, with high incidence in those with complications.

Conclusion: Bacteremia was common among patients with AH. Clinical features of SAHF could be explained by occurrence superadded bacterial infection that caused thrombophlebitis of hepatic portion of the IVC resulting in HVVOO.


Keywords: Acute hepatitis, Hepatic venous outflow obstruction, Hepatic vena cava syndrome, Budd-Chiari syndrome.

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INTRODUCTION

Acute hepatic failure (AHF), cholestasis and chronic hepatitis (CH) are three well-known complications of acute viral hepatitis (AH). Another complication of AH reported mainly from India and some Asian countries1-6 but not from the West is subacute hepatic failure (SAHF). International Association for Study of the Liver in 1996 defined SAHF as occurrence of ascites and/or encephalopathy beyond 4 to 24 weeks from the onset of symptoms in patients with no history of liver disease.7 SAHF is basically a clinical concept and its main clinical features are progressive jaundice with early development of ascites. So in this study instead of adopting a rigid early temporal cutoff point, its distinctive clinical features—development of progressive jaundice with occurrence of ascites within 24 weeks of the onset of symptom in patients with no history of liver disease was adopted to diagnose SAHF. SAHF is generally associated with high mortality or increased tendency to develop cirrhosis.1,2 Pathogenesis of SAHF is unknown and its treatment is unsatisfactory.8,9 Here we report 32 patients of AH with SAHF and discuss its pathogenesis.

MATERIALS AND METHODS

Diagnosis of AH in this study was based on acute illness with anorexia, nausea and jaundice associated with elevation of serum transaminase level at least 5 times above the upper limit of normal (X ULN) in persons with no history of liver disease or exposure to drugs. Patients with AH seen in the period 2002 to 2008 had laboratory tests that included serum bilirubin, ALT and AP, total and differential WBC count and serological or molecular markers of known viral hepatitis.10,11 The hepatitis viral markers tested were anti-HAV IgM for hepatitis A, anti-HBc IgM for hepatitis B, anti-HCV for hepatitis C, anti-HEV IgM and HEV RNA for hepatitis E (HE). HAV RNA was tested in patients positive for anti-HAV IgM and HCV RNA in patients positive for anti-HCV. Patient positive for anti-HAV IgM was labeled as hepatitis A (HA), positive for anti-HBc IgM as hepatitis B (HB), HCV RNA positive as hepatitis C (HC), anti-HEV IgM and or HEV RNA positive as hepatitis E (HE). Patients negative for these markers were labeled as non-A to E hepatitis.

Thirty-two patients with AH seen in the period 2002 to 2008 had progressive jaundice and developed ascites within 24 weeks of onset of jaundice. Fourteen (44%) of these patients were seen during HE epidemic in 2006 to 200712 and the reminder 18 (56%) were sporadic cases seen in 6 years period from 2002 to 2005 and 2008.

As the condition is seen only in developing countries and as its clinical features simulate that of subacute type of hepatic vena cava syndrome (HVCS)13 we looked for evidence of bacterial infection and ultrasonographic (US)
evidence of HVCS in these patients. Risk factors for bacterial infection like diabetes, age above 40 years were assessed in this group and compared with AH patients without this complication. Chronic alcohol use of < 40 g/day for several months was also considered a risk factor. Patient with alcohol use at or above this level for more than a few years were considered candidate for alcoholic liver disease and were excluded from this study. The blood tests done in patients with SAHF included assay for serum protein, albumin and prothrombin time. Twenty-eight patients had blood culture for aerobic organisms. Diagnostic paracentesis was done in 22 patients. Ascitic fluid was collected in EDTA bottle for total and differential WBC count and estimation of protein and albumin levels, and 15 ml was inoculated at bedside in blood culture bottle for culture of aerobic organisms. Blood culture for aerobic organism was also done in all AH patients that presented with fever during 2006 and 2007.

Patients with SAHF had ultrasonography (US) and color Doppler study of liver and inferior vena cava (IVC). This was compared with US of serial 92 and 43 patients with HE and non-A to E hepatitis respectively without bacteremia. Patients that showed ‘recent’ thrombus on thickened posterior wall of the IVC near cavoatrial junction or a long segment were diagnosed acute hepatic vena cava disease (HVCS). Chronic HVCS was diagnosed in the presence of localized stenosis/obstruction of the IVC; and acute on chronic lesion when ‘recent’ thrombus occurred in patient with chronic lesion with old organized thrombus (Figs 1A and B). US diagnosis of cirrhosis was based on findings of increased coarse echotexture of the liver parenchyma with rounded edge with or without evidence of portal hypertension.

Patients were treated with oral antibiotic and diuretic. Antibiotic was used at initial high dose for 2 weeks followed by normal dose for further 6 weeks. Patients who developed encephalopathy were managed in intensive care unit. Patients were monitored closely for 1 month and then at monthly interval for 6 months with US and tests for serum bilirubin, ALT and AP. One hundred and thirty-seven serial patients with uncomplicated AH seen in 2006 to 2007 were also followed for at least 6 months.

**RESULTS**

**Patients**

Out of 798 patients of AH seen during 2002 to 2008, 32 (4%), 19 male and 13 female developed clinical features of SAHF. Among SAHF patients 15 had HE, one each had HA and HB and the reminder 15 had non-A to E hepatitis. The demographic and viral features of patients with SAHF and AH without SAHF are compared in Table 1. Majority (82%) of the patients with SAHF had two or more risk factors for infection. Age ≥40 years and prolonged alcohol use were common risk factors associated with SAHF (Table 2).

**Table 1: Demographic and viral features of patients with subacute hepatic failure and acute hepatitis seen in Nepal**

<table>
<thead>
<tr>
<th>Features</th>
<th>SHF (2002-08) (N = 32)</th>
<th>AH (2002-07) (N = 745)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) &gt;40 years</td>
<td>38 ± 17 (4-58)</td>
<td>29 ± 14 (1-82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>18 (58%)</td>
<td>140 (19%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HAV</td>
<td>3%</td>
<td>4%</td>
<td>0.0294</td>
</tr>
<tr>
<td>HBV</td>
<td>3%</td>
<td>2%</td>
<td>–</td>
</tr>
<tr>
<td>HCV</td>
<td>0</td>
<td>1%</td>
<td>–</td>
</tr>
<tr>
<td>HEV</td>
<td>47%</td>
<td>58%</td>
<td>–</td>
</tr>
<tr>
<td>Non-A to E</td>
<td>47%</td>
<td>35%</td>
<td>–</td>
</tr>
</tbody>
</table>

AH: Acute hepatitis, SHF: Subacute hepatic failure, HAV: Hepatitis A virus infection, HBV: Hepatitis B virus infection, HCV: Hepatitis C virus infection, HEV: Hepatitis E virus infection, Non-A to E: Non-A to E hepatitis
Clinical Presentation

Patients with SAHF had prolonged fever. Jaundice became progressively deep.Ascites developed within 4 weeks in eight patients and between 4 to 16 weeks in the reminder. Edema of legs occurred in 26 patients and minimal rightsided pleural effusion in four. Five patients complained of swelling of face and hands with sudden poor urine output just before the onset of ascites. All had hepatomegaly. Five patients terminally developed features of encephalopathy and coagulopathy with bleeding.

Laboratory Findings

HEV RNA was positive in only three out of 15 HE patients. HAV RNA was negative in the patients with HA. Twenty three patients (72%) had WBC count $\geq 10,000/mm^3$. ALT was $\geq 10$ X ULN in 20 patients (62.5%), AP was elevated $> 2$ X ULN in 10 (31%) and bilirubin was $>20$ mg/dl in 24 (75%). Blood culture grew bacteria in 57% (16/28) patients. It was mainly Gram-negative organisms ($E. coli$ in nine, $Klebsiella$ species in five, $Salmonella typhi$ in one and $Staphylococcus aureus$ in one). Ascitic fluid had high protein content; serum ascitic fluid albumin gradient was $\geq 1.1$. Ascitic fluid culture grew bacteria in 95% (21/22), which included $E. coli$ in nine, $Klebsiella$ species in six, and $Staphylococcus aureus$ in six. The culture negative ascitic fluids also had bacterial peritonitis as indicated by high absolute neutrophil count.15,16 Of the 10 patients who did not have diagnostic paracentesis, five had bacteremia. Result of the blood culture in patients with AH in 2006 and 2007 showed high incidence of bacteremia in patients with AH which was significantly higher in patients with complications (Table 3).

Ultrasound

Ultrasound examination showed ascites and hepatomegaly in all and splenomegaly in four patients. Liver showed uniform normal or slightly increase echotexture with smooth and regular surface. Wall of small intrahepatic blood veins were echoic in many. Right side pleural effusion was detected in four. Gallbladder was grossly dilated four and in 17 its wall was thick and edematous. US examination of the hepatic portion of IVC showed ‘recent thrombus’ in all. It was localized in 11 and filled the hepatic portion of the IVC in 16. Five had recent and old organized thrombus filling the hepatic IVC. All showed mild localized narrowing of the IVC opposite the site of entry of hepatic veins with thickened posterior wall. US in consecutive 92 and 45 patients with HE and Non-A to E respectively without bacteremia seen in the period 2006 to 2007 showed features of chronic HVCS like mild localized narrowing of the IVC opposite the site of entry of hepatic veins in 80% but none had acute lesion. Biliary dilatation or infiltrative lesion or fatty changes in the liver were seen in none.

Outcome and Follow-up

Eight patients (25%) died, five early within a month, of which two had not received antibiotic reminder three already had encephalopathy when referred to our unit. Of those who died late, two died at home 3 months after discharge from recurrence of fever and ascites and third from esophageal variceal bleeding 8 months after discharge.

Among the 24 patients (75%) that recovered eight were lost to follow-up after 3 months and were not able to be contacted as they did not have telephone. Reminder

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Table 2: Risk factors associated with subacute hepatic failure

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 32)</td>
<td>(N = 137)</td>
<td></td>
</tr>
<tr>
<td>1. Age $\geq$ 40 years</td>
<td>18</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2. Prolonged fever</td>
<td>8</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>3. Alcohol use</td>
<td>12</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4. Invasive procedures</td>
<td>3</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>5. Steroid use</td>
<td>2</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>6. Diabetes</td>
<td>3</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>7. Persistent diarrhea</td>
<td>2</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>8. Infective focus</td>
<td>6</td>
<td>0</td>
<td>–</td>
</tr>
</tbody>
</table>

SHF: Subacute hepatic failure; AH: Acute hepatitis; NS: Nonsignificant

Table 3: Blood culture for aerobic organisms in serial patients with acute hepatitis seen in 2006-2007 (n = 307)

<table>
<thead>
<tr>
<th>Clinical types of AH</th>
<th>Total</th>
<th>Positive culture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Uncomplicated AH</td>
<td>246</td>
<td>80</td>
</tr>
<tr>
<td>AH with cholestasis</td>
<td>45</td>
<td>15</td>
</tr>
<tr>
<td>AH with SHF</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>AH with AHF</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>307</td>
<td>76</td>
</tr>
</tbody>
</table>

AH: Acute hepatitis; SHF: Subacute hepatic failure; AHF: Acute hepatic failure
16 who completed 6 months follow-up had remained well (four for 6-8 months, three for 2 years, two for 3 years and seven for 4 years). Prolonged minimal ALT elevation (within 2 X ULN) was observed in all. Recurrence of symptoms (fever, jaundice with or without ascites) occurred in five patients between 4 to 11 months. Of these one patient had three episodes of recurrence within 11 months. The symptoms of recurrence responded to treatment with antibiotic and diuretic. Total of seven (22%) patients (four non-A to E hepatitis and three HE) developed US features of cirrhosis in about 5 months time (2-11 months). Transition of initial uniform normal looking liver parenchyma to coarse echotexture in subsequent US distinguished SAHF from cases of chronic liver disease with acute viral hepatitis. Serial US examination was found helpful noninvasive procedure in recognition of development of cirrhosis. The acute lesion in IVC transformed to stenosis in five and complete obstruction in four within 4 months. Seventy-one percent (98/137) patients with uncomplicated AH could be followed-up for 6 months and none developed complications.

**DISCUSSION**

Four percent of the patients with AH in Nepal developed clinical features of SAHF. The biochemical profile of SAHF mild-to-moderate elevation of ALT, mild elevation of AP and PT and marked elevation of serum bilirubin were distinctive. Development of progressive jaundice; ascites and edema of legs in patients with AH with above biochemical profile; recurrent exacerbations, high mortality or progression to cirrhosis made SAHF a distinct clinical entity.

Subacute hepatic failure however is not specific to any particular type of AH. In other Asian countries it was reported commonly in HBsAg-positive AH, and HE. In Nepal it occurred predominantly in hepatitis E and non-A-E hepatitis, the common causes of AH in the community. Table 1. Thus the question arises what is this entity called SAHF? And what is its pathogenesis?

Viral factor was considered important in the pathogenesis of fulminant hepatitis. Hepatitis B virus variants with mutation in the precore region and/or the core promoter were implicated in AHF. Similarly nucleotide substitution in the 5'UTR of HAV genome was considered a possible cause of severity in hepatitis A. In Japan, patients infected with HEV genotype 4 tend to have more severe disease than those with genotype 3. However in developing countries, HEV genotype 1 prevails and it is associated with low mortality. There was no report of mutation of HEV in Nepal. The study of genetic changes based on observation of 412-nt sequences within ORF2 of HEV among 116 HEV-viremic samples from Nepal obtained at different periods from 1997 to 2002 showed no significant amino acid substitution. Further, only three out of 15 HE patients with SAHF were viremic and they all belonged to genotype 1. One fatal case of SAHF due to HA was not viremic. Absence of viral markers in the liver of HBV related SAHF was reported earlier. In contrasted to HBV related chronic liver disease where immunohistology showed presence of HBsAg and or HBeAg, these antigen were absent in the liver of HBV related SAHF. These observations suggested that probably the viral factor was not responsible for this clinical condition.

Prevalence of SAHF in older age group, presence of mild hepatocellular damage, absence of alpha-fetoprotein elevation and absence of viral antigen in HBV-related cases led Omata to suggest ‘impaired regeneration’ as the cause of SAHF in AH. In hepatitis E host factors like pregnancy, age or underlying disease were considered important in the severity of the disease. The epidemiological features of SAHF- its prevalence in South Asia but not in industrialized countries, its high incidence during period of HE epidemic and during rainy season when the extent of water pollution is high, and its predilection in elderly patients with other risk factors for infection (Table 2) led us to look for its association to bacterial infection. Outbreaks of AH in the developing countries had followed sudden increase in pollution of drinking water. Incidence of sporadic AH in Nepal paralleled with other water-borne bacterial infections like bacterial diarrhea and typhoid fever and the incidences of all these diseases were high during rainy season when pollution of drinking water was the highest. About 25% of AH patients presenting with fever in 2006 to 2007 had Gram negative bacteremia and its incidence was higher among those with complications (Table 3). High incidence of Gram-negative bacteremia observed in developing countries and among patients with AH in Nepal may thus be related to poor hygiene and sanitation. Above observations and high incidence of bacterial peritonitis and bacteremia observed in patients with SAHF in this study indicated to the association of bacterial infection to this complication.

Ascitic fluid with high albumin gradient and bacterial peritonitis in SAHF was also reported from India. Ascites with high protein content and high albumin gradient indicated to hepatic venous outflows obstruction (HVVOO). The common cause of HVVOO in the east is the disease of the hepatic portion of the inferior vena cava (IVC) called hepatic vena cava syndrome (HVCS). It was previously thought to be a congenital vascular malformation but now found to be caused by bacterial infection. The disease is endemic in Nepal. The initial lesion in this disease is a...
localized thrombophlebitis at posterior wall of the IVC opposite the site where the hepatic veins join it. Recurrent bacterial infection led to deposition of thrombus at the site. On resolution, the lesion transforms into mild-to-severe stenosis or complete obstruction.\textsuperscript{13,34} Ascites in HVCS was associated with high incidence of bacterial peritonitis.\textsuperscript{14}

The clinical features of SAHF in AH thus may be explained by associated bacterial infection resulting in thrombophlebitis of the hepatic portion of the IVC. Because of the specific location of the lesion in the IVC it causes obstruction of the ostia of hepatic veins. Sudden obstruction of a large part of the hepatic outflow tract results in increase in sinusoidal pressure and formation of ascites. Ascites in this condition has high protein content and spread of infection from the infected IVC results in bacterial peritonitis.\textsuperscript{14} Peritonitis in this condition is not spontaneous bacterial peritonitis (SBP) as it occurs in cirrhosis due to other causes where the ascitic fluid has low protein content and the source of infection is unknown. Sudden increase in sinusoidal pressure results in sodium retention mediated by hepatic baroreceptors\textsuperscript{35} which would explain the occurrence of puffy face, swelling of hands and pleural effusion seen in some patients\textsuperscript{36} and this combined with caval obstruction would result in edema of legs.

Sepsis is known to cause deep jaundice. Bacterial cell wall component lipopolysaccharide (LPS) stimulated Kupffer cells to produce tumor necrosis factor and interleukin -1 and 6 that down-regulate the transport system for bile-salt-independent bile flow resulting in significantly reduced excretion of organic anions including bilirubin diglucuronide.\textsuperscript{37,38} Progressive deep jaundice with mild to moderate elevation of ALT in SAHF was likely to be due to sepsis rather than due to severity of viral hepatitis.

Bridging necrosis (BN) was considered a histological hallmark of SAHF.\textsuperscript{5,39} However BN is not specific to SAHF. It occurs in Budd-Chiari syndrome.\textsuperscript{40} Cells infiltrating the BN in SAHF consisted predominantly of polymorphonuclear leukocytes, a feature which was the converse of what is seen in acute viral hepatitis.\textsuperscript{39} In SAHF, the surviving hepatocytes arranges in a cord like fashion along the dilated sinusoids.\textsuperscript{8} Thus, histological features of SAHF are compatible with infection and HVVO.

HVCS is a chronic disease characterized by recurrent acute exacerbation with recurrent HVVO and thrombotic obstruction of intrahepatic veins. It is associated with bridging type of ischemic loss of hepatocytes and ultimate development of venocentric and venoportal cirrhosis.\textsuperscript{34,40} HVCS was complicated by high incidence of cirrhosis, which occurred more frequently in patients with prolonged severe disease or frequent acute exacerbations.\textsuperscript{34} Thus, the histological features of BN, thin cord like arrangement of the surviving hepatocytes with dilated sinusoids and rapid development of cirrhosis is more likely to be due to vascular lesion rather than to immunological damage of the liver by viral infection.

Based on these observations it is postulated that the entity called SAHF in AH is most probably caused by superadded bacterial infection resulting in acute or subacute HVCS. Development of acute/subacute HVCS appeared to explain not only all the cardinal clinical features of the disease-progressive jaundice with development of ascites and its progression to cirrhosis but also the histological changes. Good response to treatment with early and prolonged high dose antibiotic and diuretic appeared to support the hypothesis.

SAHF occurring in patients with AH is a distinct clinical entity. It is however not specific to viral hepatitis. It occurs in patients with other conditions. Clinical features of SAHF may be explained by occurrence of bacterial infection and HVVO rather than by primary hepatocellular failure. And it appears to be supported by long-term antibiotic therapy.

REFERENCES


34. Shrestha SM. Liver cirrhosis and hepatocellular carcinoma in hepatic vena cava disease, a liver disease caused by obstruction of the hepatic portion of the inferior vena cava. Hepatolo Intern 2009;3:392-402.


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