Subacute hepatic failure

B. N. TANDON, Y. K. JOSHI, S. K. ACHARYA

ABSTRACT
Subacute hepatic failure is a clinical entity distinct from acute liver failure, due to fulminant hepatitis, and from chronic liver failure, due to chronic active hepatitis. Viral hepatitis is the commonest cause of this disease in India. The main clinical feature is the persistence of jaundice, which often progresses for four weeks after its appearance and is associated with the development of moderate or severe ascites. Liver function tests show a low serum albumin and moderately elevated serum bilirubin, serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels and a prolonged prothrombin time. The clinical course is a progressive deterioration leading to death in 70% to 80% of patients. Liver biopsy shows acute viral hepatitis with bands of bridging necrosis and no evidence of regenerative activity. The pathogenesis of this disease is not known. Continued viral replication with extensive hepatocyte necrosis on an autoimmune basis has been suggested to be a possible mechanism for the progressive liver damage.

INTRODUCTION
Liver failure is a serious and often fatal complication of hepatitis. It may present as acute, chronic1-4 or subacute failure. There are several good descriptions of acute and chronic liver failure1-4 but owing to its rare occurrence in most English-speaking countries only a few papers have been published in the English language on subacute hepatic failure (SAHF). In fact a group of experts meeting on the classification of liver diseases omitted the term altogether in their report.5 In an earlier publication6 we have argued that SAHF is a distinct clinical entity and deserves thorough clinical and laboratory investigations. A few other hepatologists have supported our observations on this condition but have used different terms to describe it, e.g. subfulminant liver failure,7 late onset hepatic failure (LOHF),8 and protracted viral hepatitis with impaired regeneration.9

DEFINITION
A workshop on subacute hepatic failure held in 1983 at the All India Institute of Medical Sciences (AIIMS)10 identified the following four diagnostic criteria for this condition:

1. Persistent progressive jaundice for four weeks after its first appearance in a patient with acute hepatitis.
2. Development of unequivocal ascites four weeks after the appearance of jaundice.
4. Submassive or bridging necrosis on liver biopsy.

In 1974 Redeker11 described a disease similar to 'subacute hepatitis' which had the following characteristics: 'features of liver failure appear 1 to 2 months after illness and have a gradual onset unlike the explosive onset of fulminant hepatitis. In addition, ascites is common and may be the first clinical sign. These patients do not show temporary improvement but instead gradually develop hepatic coma and die.'

We recommend the term subacute hepatic failure in preference to subacute hepatitis as it focuses on the clinical status rather than on the histopathological changes in the liver. Our major concern in this condition is to differentiate the pattern of subacute liver failure from that of acute and chronic liver failure.

PREVALENCE
The prevalence of the three types of liver failure at the Raigarhia Liver Unit in the Department of Gastroenterology at the AIIMS, a referral centre in northern India, has been recorded in the following order of frequency. The annual admission rate for acute, subacute and chronic liver failure is 36, 34 and 6 cases respectively. In contrast, western literature reports chronic liver failure (CLF) as the commonest complication of hepatitis, followed by acute liver failure (ALF) and SAHF. According to published figures, the liver unit at King's College Hospital, London, admits annually about 20 patients with ALF and 2 to 3 cases of LOHF.8 Peters et al. collected a series of 21 similar cases over several years and classified them as protracted viral hepatitis with impaired regeneration.9 Bernau et al. have labelled this condition subfulminant hepatic failure but do not comment on its prevalence rate.7 Along with non-cirrhotic portal fibrosis12 and Indian childhood cirrhosis,13 it would appear that SAHF has a high prevalence rate amongst Indians.

CLINICAL PICTURE
We recorded 148 cases of SAHF at the Raigarhia Liver Unit over a period of six years (June 1981 to June 1987). These included 104 males and 44 females. The peak age group for the disease was 40-49 years. The disease was uncommon below the age of 20 years (2.1%). Its clinical
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Indian series are supported by Redeker,\textsuperscript{11} as well as by two reports from Peters \textit{et al.}\textsuperscript{9} and Bernaua \textit{et al.}\textsuperscript{7} These reports have emphasized that encephalopathy is either infrequent or a terminal manifestation. Redeker\textsuperscript{11} and Bernaua \textit{et al.}\textsuperscript{7} have stressed that ascites and leg oedema are important features. (3) While Indian patients with SAHF had either normal or enlarged livers, Gimson \textit{et al.}\textsuperscript{8} have emphasized a small liver to be a feature of LOHF.

\section*{DIFFERENTIAL DIAGNOSIS OF ALF AND CLF}
Though acute, subacute and chronic liver failure are complications of hepatitis, it is nevertheless possible to identify them as distinct entities. As suggested by Bernaua \textit{et al.}\textsuperscript{7} this distinction leads to a more accurate description of the course of liver failure and identifies important clinical manifestation; thus helping in the management of patients. Acute liver failure caused by fulminant hepatitis, in persons without any pre-existing liver disease, is characterized by a rapid onset and a dramatic clinical course. Encephalopathy is a prime manifestation in all cases. The liver is shrunken and can barely be percussed in 2 or 3 intercostal spaces. Ascites is rare. Severe coagulation defects and cerebral oedema result in death. Associated infection and hepatorenal syndrome are less common causes of fatality. There is no general agreement on the time interval between the development of encephalopathy and the onset of icterus. Different authors have specified the interval to be two,\textsuperscript{7} three\textsuperscript{14} or eight weeks.\textsuperscript{15} We, however, use a limit of four weeks as 99\% of patients with ALF develop encephalopathy within this period.\textsuperscript{16} Compared to this, SAHF is characterized by a gradual onset of symptoms and a slowly deteriorating clinical course. Ascites and jaundice are the main manifestations and the liver is either enlarged or normal. Encephalopathy is uncommon but in some cases it is noted as a terminal development. Cerebral oedema and coagulation defects are also rare. The hepatorenal syndrome and associated infection, including spontaneous bacterial peritonitis, lead to death in most cases.\textsuperscript{5-9} The interval between jaundice and ascites—the two most important characteristics of the disease—is usually 10 to 12 weeks.

Chronic liver failure is defined as hepatic decompensation six months after acute liver injury. Major complications of hepatic decompensation leading to death include gastrointestinal haemorrhage, ascites and the hepatorenal syndrome, spontaneous bacterial peritonitis and hepatic coma. The interval between the onset of illness and development of advanced features of portal hypertension and liver failure easily differentiates CLF from SAHF.

\section*{AETIOLOGY AND RISK FACTORS}
Viral hepatitis is the most common cause of SAHF.\textsuperscript{11} Other hepatotoxic agents, e.g. alcohol, plant toxins, drugs, Wilson's disease, are less common aetiological factors. All 148 cases of the present series were attributed to viral hepatitis. Viral serological markers were studied in 79 patients and the aetiology was established to be virus A (HAV) in 4\%, virus B (HBV) in 34\%, non-A non-B in 58\%, and the delta agent in 4\%. No patient had Wilson's

\section*{Table I. Symptoms of subacute hepatic failure (148 patients)}

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>145</td>
<td>98</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>132</td>
<td>89</td>
</tr>
<tr>
<td>Anorexia</td>
<td>122</td>
<td>82</td>
</tr>
<tr>
<td>Pedal oedema</td>
<td>110</td>
<td>74</td>
</tr>
<tr>
<td>Fever</td>
<td>83</td>
<td>56</td>
</tr>
<tr>
<td>Nausea</td>
<td>81</td>
<td>55</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>76</td>
<td>51</td>
</tr>
<tr>
<td>Itching</td>
<td>44</td>
<td>30</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>19</td>
<td>13</td>
</tr>
</tbody>
</table>

\section*{Table II. Signs of subacute hepatic failure (148 patients)}

<table>
<thead>
<tr>
<th>Sign</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>148</td>
<td>100</td>
</tr>
<tr>
<td>Ascites</td>
<td>143</td>
<td>97</td>
</tr>
<tr>
<td>Pedal oedema</td>
<td>123</td>
<td>83</td>
</tr>
<tr>
<td>Hepatomegaly (Palpable liver)</td>
<td>63</td>
<td>43</td>
</tr>
<tr>
<td>Splenomegaly (Palpable spleen)</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Encephalopathy (Grades I and II)</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Spiders</td>
<td>25</td>
<td>17</td>
</tr>
</tbody>
</table>

characteristics and their frequency are given in Tables I and II. Icterus was present in all the cases and ascites on admission was recorded in all but 5 patients who developed it later. These two features have therefore been recommended to be the essential diagnostic criteria of SAHF. Ascites was either moderate or severe in all cases. Anorexia and fever persisted during the icteric stage of hepatitis in more than 50\% of patients. Haematemesis, melaena, and hepatic encephalopathy were uncommon. The spleen could be palpated in only 17\%. Hepatomegaly was recorded in 43\% on admission and as the ascites decreased after diuretic therapy, this finding was noted more frequently. A small contracted liver was not elicited by percussion in any of the cases.

The clinical features of SAHF in a smaller number of patients have been described by other investigators.\textsuperscript{7-9} Apart from the present series, the largest number of similar patients were reported from London by Gimson \textit{et al.}\textsuperscript{8} and were classified as LOHF. The series consisted of 476 cases collected over a period of 12 years and included 9 cases of Wilson’s disease. Peak prevalence was in the fifth and sixth decades of life. On admission all had jaundice, 62\% had ascites, and 68\% presented with encephalopathy. During a progressively deteriorating clinical course, encephalopathy developed in all patients and renal failure in 62\%. Spontaneous bacterial peritonitis was recorded in 38\%. While there are many similarities between the patients of these two series, there are three major differences: (1) Ascites was one of the two most important manifestations in Indian patients while it was absent in 38\% of the London series. (2) Encephalopathy was present in almost all the cases in Gimson’s series while it was absent in Indian patients. Both these observations in the
disease or toxic liver injury. Gimson et al.\textsuperscript{8} recorded an HAV and HBV aetiology in 8%.

A history of occasional alcohol intake was noted in 8% of the patients. Prolonged administration of hepatotoxic and indigenous drugs was recorded in 21% and 30% respectively; and 16% had known diabetes mellitus. While we consider these to be possible risk factors for liver injury in patients with viral hepatitis, other investigators do not. However, there is universal agreement that elderly patients with a reduced capacity for liver cell regeneration are at high risk for developing SAHF.

**LIVER FUNCTION TESTS**

Liver function in SAHF patients indicate continued hepatocellular necrosis. Hyperbilirubinaemia and hypoalbuminaemia are abnormalities recorded in almost all cases. The mean values for serum bilirubin, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT) in the present series were 17.0 mg\%, 151 Karmen units, and 145 Karmen units respectively; the mean serum albumin was 2.9 g\%.

The serum alkaline phosphatase was nearly normal with a mean value of 18.1 KA units. The prothrombin time was abnormal in all cases. Similar biochemical abnormalities have been reported in LOHF cases by Gimson et al.\textsuperscript{8} with a median value of serum bilirubin of 24.85 mg per litre, a low serum albumin in all except three cases (median 2.6 g\%) and mean SGOT levels of 230 I.U. per litre. Liver function abnormalities in patients with SAHF are very different from those with ALF, but are somewhat similar to the abnormalities with CLF. Serum transaminases and the prothrombin time are markedly elevated in ALF but the serum albumin is either normal or slightly lower. Abnormalities of serum albumin, transaminases and prothrombin time in subacute and chronic liver failure are similar. The serum bilirubin is more frequently elevated in subacute than in chronic liver failure.

Autoimmune markers and immunoglobulin levels were estimated initially in 15 patients with SAHF. As no abnormalities were detected, the tests were discontinued in the later part of the present study.

**CLINICAL COURSE AND PROGNOSIS**

The clinical course of SAHF is characterized by a progressive and gradual deterioration. The present series recorded a mortality rate of 72% while Gimson et al.\textsuperscript{8} reported a mortality rate of 81%. Other investigators\textsuperscript{9,11} have commented on the high rate of mortality. In our series all the deaths occurred within one year of the onset of the illness, and of these 64% died within six months. Age had no bearing on the mortality rate in our series. Renal failure was noted to be the commonest complication and was the cause of death in 44% of our cases and 62% of Gimson’s series. We include in these cases of renal failure only those with the hepatorenal syndrome, while Gimson et al.\textsuperscript{8} included those with hepatorenal syndrome and tubular necrosis. Gastrointestinal bleeding was the next important complication and led to a fatal end in 20%. This was also noted to be the second commonest complication in the London series.\textsuperscript{8} Infection was another complication recorded in 26% of patients in the London series.\textsuperscript{8} It was the precipitating cause of death in 14% of cases in our series. All the cases reported by Gimson et al.\textsuperscript{8} had encephalopathy during the course of illness though Grade IV encephalopathy was recorded in only 21%. We recorded Grade I or II encephalopathy in 10% and Grade IV was noted in only a few patients just before their death. Gimson et al.\textsuperscript{8} and others\textsuperscript{7,9} have emphasized that cerebral oedema is rare in SAHF.

There is some evidence in the literature to suggest that the survivors of SAHF continue to have liver damage which ultimately ends in chronic failure.\textsuperscript{8} Almost all the 42 patients (28%) who recovered from SAHF at our centre continue to have abnormal liver function over a follow-up period of less than one year (30 cases) and 1 to 2 years (12 cases).

**LIVER PATHOLOGY**

Most of the histopathological studies were carried out on post mortem liver biopsies. The biopsies conducted in 55 cases uniformly showed the morphological changes characteristic of acute viral hepatitis with a moderate to severe degree of bridging necrosis. The most striking and

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**Fig. 1.** Acute viral hepatitis with bridging necrosis (× 40)

**Fig. 2.** Acute viral hepatitis with bridging necrosis from central vein (× 40)
consistent findings were the bands of necrosis affecting the plates of the liver cells. These bands, which varied in width, severity and extent, were recorded in 99% of the cases. Only two cases showed linear inflammatory bridging which possibly represents a communicating 'spotty' necrosis of groups of hepatocytes. In most cases the bridging necrosis was central to central, or portal to central. Accompanying the bands of necrosis were collagen fibres but fibrous tissue septum formation was not seen in any of the cases. (See Figs. 1 and 2.)

Other histopathological features of acute viral hepatitis such as lobular inflammation, ballooning degeneration and cholestasis were observed. Ductular proliferation caused by prolonged cholestasis was a common finding. Portal inflammation with lymphocyte and polymorph infiltration was seen in almost all the biopsies. Gimson et al. recorded bridging necrosis in 94%. Peters et al. while reporting similar findings in a series of 21 autopsy cases emphasized the absence of morphological features of hepatic regeneration, cirrhosis of the liver, chronic hepatitis and HBsAg in the hepatocytes. Investigators working in a collaborative study sponsored by the Indian Council of Medical Research have reported similar findings under varying names such as acute viral hepatitis with bridging necrosis, subacute hepatic necrosis, and subacute hepatitis. Boyer and Klatskin have also reported similar patterns of liver damage under subacute hepatic necrosis.  

PATHOGENESIS
It is not known why in some cases of hepatitis the hepatocyte necrosis continues and there is inadequate regeneration of liver cells and consequent subacute hepatic failure. Most investigators have emphasized impaired hepatic regeneration, particularly in elderly patients, to be the main pathogenetic mechanism of this condition. Our observations showed the presence of DNA or HBeAg in 40% of HBsAg positive patients, suggesting active viral replication. We presume that viral replication provides a stimulus for cell-mediated immune injury and prevents the proper regeneration of hepatocytes that is necessary for the recovery.

TREATMENT
There is no specific treatment for SAHF. Supportive therapy includes an oral or parenteral 1200 to 1800 caloric diet, with a low sodium content, diuretics with proper monitoring of serum electrolyte levels, and antibiotics if there is evidence of infection. Bleeding, encephalopathy and the hepatorenal syndrome are managed according to the standard accepted modes of management. Initially we gave steroids to nine patients but this was associated with a high complication rate and mortality. Glucagon therapy was then tried in a group of ten patients but this also made no difference to the clinical course or the final outcome. We therefore discontinued the use of steroids and glucagon. Hepatic transplantation has been suggested by Gimson et al. At present the treatment of SAHF is altogether unsatisfactory.

REFERENCES