Subacute Hepatic Failure: Unresolved Issues

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Introduction
Over a decade ago Tandon et al. described the clinical entity of subacute hepatic failure (SAHF) from Delhi. Apart from this group, the only other sizable experience of this disease has come from the King’s College, London. Since most other clinicians have not reported enough of such cases, it is important to look at the data and views of these two groups of workers critically and see if we could work out an acceptable definition or else we run the risk of labeling this entity an enigma wrapped inside mystery.

In this article we will attempt to address two basic questions: a) is the disease described from Delhi the same as that reported from London and b) is SAHF often unrecognized and misdiagnosed by others? The answer to the first question is not easy. The main reason for confusion in the minds of clinicians seems to be the varying definitions given by various workers. SAHF is a disease with no specific temporal sequence of particular symptoms (jaundice and ascites or encephalopathy) supported by clear biochemical and histological criteria. No wonder most clinicians are confused about labeling their patients with this set of symptoms.

Definition of SAHF
There is no doubt that different authors who have described cases with SAHF are referring to a group of patients, who are distinct from uncomplicated acute viral hepatitis on one hand and chronic liver disease on the other. These authors have further narrowed down their consideration to patients with a delayed occurrence of certain complications following acute onset of jaundice. The crux of the matter seems to be which complication should be accepted as criterion for diagnosing SAHF—ascites, encephalopathy or both. The different original definitions may be briefly reviewed here. Tandon et al. pioneered, proposed that SAHF be diagnosed under the following situations:

1. Persistence or progressive jaundice 10 weeks after the first appearance of icterus in a patient with acute hepatitis.
2. Development of unequivocal ascites and/or encephalopathy 10 weeks after the appearance of icterus.

4. Submassive or bridging necrosis on liver biopsy whenever tissue is obtained.

The European workers on the other hand, have laid emphasis on encephalopathy as the main diagnostic criterion. The King’s College group have used the term ‘late onset hepatic failure’ (LOHF) which they define as hepatic encephalopathy and other evidence of hepatic decompensation occurring between 8-24 weeks after the first symptom of illness. Bernau et al. substituted SAHF with the term subfulminant liver failure (SFLF) which they defined as acute liver failure complicated by encephalopathy 2 weeks to 3 months after the onset of jaundice. An American study defines SAHF as irreversible liver failure developing between 8-28 weeks from the onset of symptoms in an individual without prior evidence of chronic liver disease.

Ascites or encephalopathy
Certain glaring discrepancies exist in these definitions which make interpretation of the existing data difficult. First, if encephalopathy was to be used as the diagnostic criterion, 85% of the patients from Delhi would fail to be classified as LOHF or SFLF. The Delhi workers on the other hand, stressed the importance of ascites in diagnosis. If their criteria were to be applied to the King’s College patients, then only 15% of their patients would qualify for this diagnosis of SAHF. In their recent update, Tandon et al. have altered the original diagnostic criteria with regards to the duration of jaundice and the interval between the appearance of ascites from the onset of jaundice. It is not clear however why the authors have now shortened this interval from ten weeks to four weeks. Another minor change from the earlier definition is the deletion of encephalopathy, understandably because encephalopathy was present in only 16% of their cases.

Time of appearance of ascites/encephalopathy
It could well be true that SAHF as diagnosed in India is distinct from either SFLF or LOHF. Although encephalopathy was considered as an essential diagnostic criterion by the French, British and American workers, the exact time of its clinical appearance was different in these series. Whereas the British workers estimated the interval between the first symptom and encephalopathy, the French used the interval, between the onset of jaundice and encephalopathy, taking the outer limits of both the intervals, encephalopathy in SAHF can occur any
time between 2-28 weeks after the onset of jaundice or prodromal symptoms; this wide range may seriously vitiate the correct labeling of cases. Another practical point worth considering is if inclusion of one criterion or the other or of accepting a particular time period in the basic definition would have bearing on the ultimate outcome of the patients with SAHF. To answer this question, it is essential to have adequate follow up of patients with ascites or encephalopathy. Unfortunately currently available data are insufficient to throw light on the long term consequences of these conditions.

From the above discussion we believe that SAHF, SFLF and LOHF are not synonymous terms as was suggested by Tandon et al.6

What is the true prevalence of this disease?
Tandon et al.6 have suggested that SAHF has a high prevalence in India. The annual admission rates in their center for acute, subacute and chronic liver failure were 36, 34 and 6 patients respectively.6 There is a definite referral bias in these figures and these may not be representative of the whole country. We, in Lucknow, admit 250-300 patients with liver disease every year. SAHF has accounted for only about 1% of these. Our figures are similar to those from the King's College, London where 2-3 cases of LOHF are seen annually. Since both Lucknow and Delhi fall in the same geographical area and serve similar population groups, it is difficult to explain why SAHF is so much more common in Delhi than in Lucknow. Prevalence data from other regions in India and abroad are scanty.

Etiology of SAHF
Viral hepatitis is considered to be the commonest cause of SAHF although unequivocal evidence for this is lacking. Role of drugs, toxins and Wilson's disease is disputed. A recent report on drug-induced liver disease does not recognize this entity.7 Wilson's disease is considered as a cause by some8,9 but not by others.5,10 In the largest series on SAHF, all 148 causes were attributed to viral hepatitis, although viral markers were studied in only 70 patients (53%).6 Non-A, non-B hepatitis was postulated as the commonest incriminating agent by several groups.5,6 Gupta et al.8 reported that 58% of their patients with subacute hepatitis tested positive with first generation anti-HCV tests. As these authors did not specify the time during the illness at which the samples were tested, it would be premature to label HCV as the major cause of SAHF. The limitation of the first generation test for detecting HCV antibody to diagnose early HCV cases is well known; further studies using more sensitive tests (4-RIBA, or HCV RNA) are therefore necessary to clarify relationship of HCV with SAHF.

The role of HBV in SAHF is also controversial. It was held responsible for nearly one third of the cases seen in Delhi, but accounted for only 5% of cases in Gimson's study. A recent study from New Delhi showed that none of the 12 patients with SAHF had serum IgM anti-HBc.11 This effectively excludes acute hepatitis B as a cause of SAHF. The possibility of an unknown virus causing a superinfection in HBV carriers however cannot be excluded. Till date there is no detailed study of the various markers of HBV infection in patients with SAHF. We are still in the dark about HBsAg and HBV DNA status in these patients. There is thus a need for comprehensive virological tests on stored sera to know the relation of HBV with SAHF. Data on delta infection are even more scanty. Four percent of SAHF patients at New Delhi12 were attributed to delta infection. The authors do not clarify whether this was simultaneous infection or superinfection. Hepatitis A accounted for 4% of cases in two studies13,14. There are no data on the role of other viruses in SAHF.

Could we redefine SAHF?
Distinct differences exist between the views of Indian, British and French workers regarding the definition of SAHF or other related terms. The origin of the controversy possibly stems from the emphasis laid on ascites as an essential diagnostic criterion by the Indian workers. It is not widely appreciated that ascites may complicate acute liver disease. A recent study from Spain15 showed that ascites is present in 60% of patients with fulminant or subfulminant hepatic failure. The dilemma is whether to accept ascites or encephalopathy or both as a criterion for SAHF. If we choose ascites alone as the criterion, we are faced with the problem of clearly distinguishing cases with mild ascites (detected ultrasonographically) FROM those with clinically overt ascites in terms of their prognostic. Until this is done the very importance of diagnosing SAHF will remain in doubt. On the other hand, if we consider encephalopathy as the backbone of diagnosis of SAHF (or LOHF or SFLF), we get entwined in the controversy of distinguishing SAHF from FHF. FHF has been defined variously as the onset of encephalopathy within 2, 4, or 8 weeks after the onset of disease or jaundice.16-18 Both diseases have almost identical mortality rate and only minor differences in histology. The major difference between the two pertains to residual liver disease in survivors. A painstaking follow up of survivors of both the disease as well as post-mortem biopsies from fatal cases will provide answers to these questions. If both ascites and presence of encephalopathy are as a diagnostic criteria, the condition is likely to be confused with Wilson's disease, chronic active hepatitis or prolonged large bile duct obstruction with secondary biliary cirrhosis.
Table: Revised Diagnostic Criteria for SAHF

**Inclusion criteria**
1. Persistent jaundice for 4 weeks in a patient with acute hepatitis
2. Development of unexplained ascites 4 weeks after appearance of jaundice
3. Biochemical evidence of hepatocellular necrosis

**Exclusion criteria**
1. Kupffer-Fischer ring/Low serum ceruloplasmin
2. Presence of ANA/AM antibody
3. Presence of dilated common bile duct or intrahepatic bile duct radii on ultrasonography
4. Features of established cirrhosis or large bile duct obstruction on biopsy

**Supportive criteria**
1. History
   a) Typical prodrome of viral illness
   b) Ingestion of hepatotoxic drugs immediately prior to onset of illness
2. Histopathology: Submassive or bridging necrosis on liver biopsy
3. Serological: One of the following tests positive: IgM anti-HAV, IgM anti-HBe, IgM anti-delta, IgM anti-HEV or HCV RNA or RIBA

To overcome some of these shortcomings we propose to modify the criteria laid down by Tandon et al. The original criteria have been supplemented by strict exclusion criteria and serological evidence of viral hepatitis (Table). SAHF should be diagnosed only when all the inclusion and exclusion criteria are fulfilled and any one of the virological markers are present.

**Conclusion**
It is about time that supporters of different nomenclatures look afresh into clinical, pathological and prognostic issues. It is extremely important to decide the basis of drawing a line at a two-four- or six-week period to differentiate FHF from SAHF. Although the fond desire to achieve a unanimity in this matter may remain a distant dream, it is important to make an attempt so as to give a clear direction to clinicians who encounter delayed complications in patients with acute hepatitis.

**References**

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4 INDIAN J GASTROENTEROL 1993 Vol 12 (Suppl 3) SUBACUTE HEPATIC FAILURE - NAIK & PURI