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REVIEW

Acute hepatic failure in India: A perspective from the East

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Abstract Acute hepatic failure (AHF) in India almost always presents with encephalopathy within 4 weeks of the onset of acute hepatitis. Further subclassification of AHF into hyperacute, acute and subacute forms may not be necessary in this geographical area, where the rapidity of onset of encephalopathy does not seem to influence survival. Viral hepatitis is the cause in approximately 95–100% of patients, who therefore constitute a more homogeneous population than AHF patients in the West. In India, hepatitis E (HEV) and hepatitis B (HBV) viruses are the most important causes of AHF; approximately 60% of cases are caused by to these viruses. Hepatitis B virus core mutants are very important agents in cases where hepatitis B results in AHF in this country. Half of the patients with AHF admitted to our centre are female, one-quarter of whom are pregnant. Therefore, pregnant females who contract viral hepatitis constitute a high-risk group for the development of AHF. However, the outcome of AHF in this group is similar to that in non-pregnant women and men. No association with any particular virus has been identified among sporadic cases of AHF.

In our centre, approximately one-third of AHF patients survive with aggressive conservative therapy, whereas two-thirds of deaths occur within 72 h of hospitalization. Cerebral oedema and sepsis are the major fatal complications. Both fungal and Gram-negative bacteria are major causes of sepsis. Among patients with AHF, despite the presence of sepsis, its overt clinical features (i.e. fever, leucocytosis) may be absent and objective documentation of the presence of sepsis in such patients is achieved by repeated culture of various body fluids. It should be possible to develop simple, clinical prognostic markers for AHF in this geographical region, in order to identify patients suitable for liver transplantation.

Key words: acute hepatic failure, India.

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INTRODUCTION

Acute hepatic failure (AHF) is a fatal complication of acute hepatitic illness resulting from various causes.[1,2] The aetiologies of acute hepatitic illness differ geographically,[1–5] and affected people also differ in their phenotypic and genotypic characteristics depending on their geographical origin. The resultant interactions between various aetiologies of AHF and the susceptible host may be geographically distinct.[1] This article will address the characteristics of acute hepatic failure, with particular focus on our Eastern experience in the Indian Subcontinent.

DEFINITION AND NOMENCLATURE

In 1969, Trey and Davidson defined AHF as occurrence of encephalopathy within 8 weeks of the onset of acute hepatitic illness in an individual without pre-existing liver disease.[6] However, during subsequent years, this definition was not adequate to describe patients with AHF seen in both Western and Eastern populations. In the UK,[7] Japan[2,8] and France,[3] it was observed that patients with AHF presenting within 1 week or 10 days of the onset of jaundice had significantly higher survival rates than similar patients presenting with encephalopathy after 1 week or 10 days of onset of jaundice. This observation influenced the selection of patients with AHF for liver transplantation.[9,10]

In contrast to these observations, all the patients in an Indian study presented with encephalopathy within

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3 weeks of the onset of jaundice and 4 weeks of the onset of other symptoms. In this series, the rapidity of onset of encephalopathy did not influence survival.[1,5] At our centre, liver failure occurring more than 4 weeks after the onset of an acute hepatitic illness manifests with progressive ascites; encephalopathy is an extremely rare presenting feature at this stage. The mortality rate is 70%, and 60% of survivors develop chronic sequlae.[11,12] We identify such cases as subacute hepatic failure (SHF) because they are quite different from AHF, and the majority of patients do not survive beyond 6 months, to be described as liver failure due to chronic liver disease. Similar patients have been described from the West as having late onset hepatic failure (LOHF), with protracted viral hepatitis and impaired regeneration or subacute hepatic necrosis.[13–15]

To resolve the geographical differences on the these issues of definition, nomenclature and subclassification, the International Association for the Study of the Liver (IASL) formed a subcommittee in 1996 that, after careful analysis, has recommended a new set of definitions and subclassifications of AHF and SHF (Table 1).[6] These have recently been published in this Journal.[16]

AETIOLOGIES

Hepatitis viruses are the major cause

Causes of AHF in Eastern countries, particularly in developing countries, are predominantly due to the various hepatitis viruses.[1,17–22] All the published reports from the Indian Sub-continent have identified hepatitis viruses as the aetiological agent in 95–100% of patients with AHF (Tables 2,3).[1,17–22]

Other causes, including paracetamol overdose, other drug-induced liver diseases, metabolic liver diseases like Wilson's disease, acute fatty liver of pregnancy, and toxicities such as *Amanita* poisoning, are extremely infrequent in the East. These differences in aetiology in AHF between patients in Western and Eastern parts of the world are probably due to the following reasons.

1 Hepatitis viruses are endemic in the East. For example, HEV and hepatitis A virus (HAV) are endemic in India and many other Asian countries. There are approximately 40 million HBV and 10 million hepatitis C virus (HCV) carriers in India alone.[23,24]

Table 1 Recommendation of IASL Subcommittee for the definition and classification of AHF and SHF[16]

Nomenclature	Acute hepatic failure (AHF) (synonyms like fulminant hepatitis, fulminant hepatic failure and acute yellow atropy should not be used). Subacute hepatic failure (SHF) (Synonyms like subfulminant hepatitis, subacute hepatic failure and late onset hepatic failure should not be used).
Dignostic criteria of liver failure	AHF: Encephalopathy SHF: Encephalopathy and/or progressive ascites
Maximum interval between onset of icterus and features of liver failure	AHF: ≤ 4 weeks SHF: > 4 weeks to 24 weeks
Subclassification	i. Aetiological to indicate specific cause of AHF. ii. Temporal to indicate the rapidity of encephalopathy Hyperacute—Encephalopathy within 10 days of icterus. Fulminant—Encephalopathy between 10 days and 30 days of the onset of jaundice. iii. Not otherwise specified
Example	(AHF, hyperacute-A)

IASL, International Association for the Study of the Liver.

Table 2 Differences in aetiology of AHF in various geographical areas

	India	USA	UK	France
Viral (%)	95	60	30	50–60
Major cause	HEV/HBV	Cryptogenic	Non-A, Non-B	HBV/HAV
Drugs (%)	4.5	30–35	60	15–20
Major cause	INH/Rifampicin	Paracetamol	Paracetamol	NSAID/Paracetamol
Other	0.5	5	10	10–15

AHF, acute hepatic failure; HEV, hepatitis E virus; HBV, hepatitis B virus; HAV, hepatitis A virus; INH, isoniazid; NSAID, non-steroidal anti-inflammatory drugs.

Table 3 Causes of acute hepatic failure in India

Authors	Year	No. cases	Percentage aetiologies							
			HAV	HBV	HCV	HDV	HEV	Mixed infection	Non A–E	Drugs
Acharya *et al.* (see text)	1999	458	4	11	4	0	23	6	47	5
Khuroo *et al.*[22]	1997	119	3	15	3	3	38	NR	39	1
Jaiswal *et al.*[20]	1996	95	4	27	2	5	41	4	15	0

NR, Not reported; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; Non A–E, non-A, non-E, viruses.

2 Cultural practices differ sharply between geographical regions. In the UK, paracetamol is freely sold over the counter and nearly every household keeps a bottle of paracetamol in the medicine cabinet. In contrast, self-medication is unusual in India and access to drugs is limited. Because India is an agricultural country, access to organophosphorous compunds is easy, and these are used more frequently as suicidal agents.
3 Genetic and ethnic differences may be responsible for the infrequent occurrence of metabolic liver disease, such as Wilson's disease or acute fatty liver of pregnancy, in the East. The essential aetiological differences between AHF in the West and East are shown in Table 2.

Serological profile in sporadic cases of AHF

The causes of AHF in 423 consecutive patients with AHF documented from January 1987 to June 1993 at the All India Institute of Medical Sciences were published in 1996,[1] and showed that non-A, non-B hepatitis viruses were the most important cause, being implicated in 62.4% (264/423) of patients.[1] The sera from these patients were not tested for serological markers of HEV and HCV for technical reasons. Between January 1992 and June 1998, 458 patients with AHF were hospitalized at our centre and they were tested prospectively for all available serological markers of hepatitis viruses (hepatitis B surface antigen (HBsAg), immunoglobulin (Ig)M, antibody to hepatitis B core antigen (IgM anti HBc), IgM antibody to hepatitis A virus, hepatitis C virus antibody (by using a second generation ELISA) and IgM HEV antibody). The data from these patients are presented in Table 4 and indicate their aetiological distribution. We also assessed the frequency of precore/core HBV mutants among patients with AHF without having any serological evidence of the these hepatotropic viruses. Table 3 depicts the serological profile of AHF in India from the present data at our centre and other published reports.[20,22] Table 4 indicates the details of serological profile among the AHF patients at our centre.

Table 4 Causes of acute hepatic failure among 458 cases admitted to a tertiary care hospital in northern india

Cause	No. cases (%)
Hepatotropic viruses	190 (42)
Isolated viral infection	
HAV	18 (4)
HBV	48 (10.5)
HCV	20 (4.4)
HDV	0
HEV	104 (23)
Mixed viral infections	29 (6.3)
Hepatitis (A + E)	7
Hepatitis (B + E)	13
Hepatitis (C + E)	4
Hepatitis (B + C)	1
Hepatitis (B + A)	1
Hepatitis (C + A)	1
Hepatitis (B + A + E)	1
Hepatitis (B + C + E)	1
*No identifiable viral markers but presentation like viral hepatitis (non A–E)	216 (47)
Antitubercular drugs	21 (4.6)
Mushroom poisoning	2 (0.4%)

Data based on serological markers of acute hepatitis virus infection. *The patients did not give any history of ingestion of alcohol, hepatotoxic drugs and toxins or any indigenous preparation. Their clinical presentations were similar to viral hepatitis. However 50 (23%) of these patients were positive for hepatitis B surface antigen only. HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; Non A–E, non A, non E viruses.

It is evident from Tables 3, 4 that HEV is the most frequently identifiable agent causing AHF in the Indian population. Large epidemics of hepatitis E are frequent in this country, and during such epidemics, cases of AHF have been well documented.[25] Studies from our

centre have also documented that HEV, either in isolation or in combination with HAV, is the cause in 40% of AHF cases among children.[17] Hepatitis B virus has been identified as the aetiological agent in 10–27% of AHF patients in India (Tables 3,4), and therefore constitutes the second most frequent cause of AHF. However, in a large proportion of Indian patients with AHF (15–47%), identifiable serological markers of known hepatitis viruses are absent (Table 3). These patients usually present with features suggestive of acute viral hepatitis, without having a history of ingestion of alcohol, hepatotoxic drugs or other hepatotoxins. The clinical features, and course (including outcomes) of these presumed non-A, non-E viral (non A–E) cases of AHF are similar to other forms of AHF.

Hepatitis B virus mutants in acute liver failure

The lack of serological markers for acute hepatotropic viral infections in a sizeable proportion of Indian patients with AHF (Tables 3, 4) could be due to various reasons.

1 A substantial proportion of apparent non A–E cases of AHF could have been due to cryptic HBV infection[26] or HBV mutants.[27–30] Wright *et al.* reported that during cryptic HBV infection, serological markers of acute HBV infection may be absent.[26] Mutations in the HBV core region that cause changes in the amino acid profile of the core protein could result in a production of anti-HBc that may not be detected by commercial ELISA kits designed to detect IgM anti-HBc against wild type HBV. Variants caused by a point mutation of nucleotide 1896 (G to A) resulting in a stop codon (TGG to TAG) at the end of the precore region have been implicated in AHF, and in these cases IgM anti-HBc is invariably detected. However, other forms of core mutation without IgM anti-HBc in a few patients may be a possibility.[31,32]
2 Superinfection of HCV without detectable anti-HCV has also been shown to cause AHF,[30] and this could have been the cause of AHF in many of these patients. Hepatitis E virus superinfection without the presence of serological markers is another possibility.[33–34]
3 Other as yet unidentified viruses could have been the cause.

In light of these considerations, sera from 59 of the 216 apparent non A–E AHF patients (Table 4) at our centre were evaluated for the presence of HEV-RNA, HCV-RNA and HBV-DNA (using specific primers to detect the 662 bp precore/core region of HBV-DNA) by using polymerase chain reaction (PCR) techniques.[28–34] The results of the study revealed that 39% (23/59) of the presumed non A–E AHF patients had detectable HBV-DNA in their sera. Isolated HCV-RNA and HEV-RNA were detected in 3.3% (two of 59) and 1.6% (one of 59) of the non A–E AHF patients, respectively. Only one patient (1.6%) had both HBV-DNA and HCV-RNA in their sera.

Further cloning and sequence analysis of five of the HBV-DNA isolates mentioned revealed that none of the isolates had in-frame translational termination codons at the carboxy terminal end of the precore region (codon 28), which has been reported to be associated with AHF in certain geographical areas.[26–28] In contrast, these isolates had deletion/insertion of nucleotides in the core region, which might have changed the immunodominant epitope of the core peptide.[31–37] This might have been responsible for the lack of IgM anti-HBC in these patients. Therefore, HBV core mutants may be playing an important role in causing AHF in our patients, a possibility that needs further evaluation.

DEMOGRAPHY

There are three important demographic characterstics of patients with AHF in the East.[1]

1 Young age. The mean age of patients with AHF at our centre is 29.5 ± 0.6 years.[1]
2 More than half are female.[1,22] This fact is important, because, in the same unit, the predominance of males with all other forms of liver diseases has been documented.[1] In addition, among the general population in India, there are about 933 females for every 1000 males.[38]
3 Twenty-five to 30 per cent of the women patients are pregnant,[1,22] whereas the frequency of pregnancy among women in the general population at any time in India is 3%.[38] This fact may indicate that a pregnant female who develops acute viral hepatitis has an increased risk of developing AHF. Similar observations have also been made in India and other developing countries during epidemics of viral hepatitis.[39–43]

COMPLICATIONS

The survival frequency among the patients at our centre is approximately 33%.[18–22] Two-thirds of deaths occur within the first 72 h of hospitalization, indicating that any intervention or novel management strategy for such patients must be instituted at the earliest stages of hospitalization, or their early referral should be encouraged.[1] The median survival time was 4 days.[1]

Cerebral oedema and sepsis were the most important complications in these patients.[1,22] We had reported that 245/423 (58%) of the AHF patients had cerebral oedema at the time of hospitalization and 201 (82%) patients with cerebral oedema died, in contrast to 79 (44%) deaths among the remaining 178 patients.[1] Sepsis as a cause of death has been identified in 24–49% of Indian patients with AHF, whereas renal failure and gastrointestinal bleeding are rare.[1,22]

Sepsis in AHF needs special mention because: (i) due to liver failure, such patients are more prone to develop infection;[44–46] (ii) often they do not clinically manifest the overt features of sepsis such as fever and leucocytosis, and therefore this complication is often not recognized unless repeated cultures of various body fluids

are performed;[45] (iii) sepsis is one of the important causes of death in AHF;[1,21,22] and (iv) if sepsis is identified early and treated effectively it may further improve the survival rate.

Recently we evaluated the dynamics of sepsis in 125 patients with AHF.

1 Sixty-five of the 125 patients (52%) studied had either positive cultures ($n=35$) or clinical evidence of sepsis ($n=30$). Those with radiological evidence of pneumonia or a high-grade fever (≥39°C) and neutrophilic leucocytosis (total white cell count >15 000/mm^3 with >80% polymorphs), without positive cultures of any body fluids, were considered to have clinical evidence of sepsis.
2 Among the culture-positive patients ($n=35$), 69% ($n=24$) grew organisms from blood cultures, without any clearly identified site of infection. This is in sharp contrast to a report from the UK,[45] in which the respiratory tract was the commonest site of infection.
3 Six of the 24 patients (25%) with a positive blood culture, had *Aspergillus* infection.
4 Forty-three per cent ($n=15$) of the culture-positive patients had Gram-negative isolates and the remainder had Gram-positive isolates. In the UK report, more than two-thirds of the patients had Gram-positive infections.[45]
5 The mortality and the frequency of complications among AHF patients with sepsis were significantly higher than for similar patients without sepsis.

PROGNOSTIC MARKERS

The following variables present at admission have been identified as independent risk factors for patient outcomes[1]: (i) if patients are ≥40 years old; (ii) if their serum bilirubin is ≥15 mg/dL; (iii) if the prolongation of prothombin time is ≥25 s more than the control; and (iv) if they have clinical features of overt cerebral oedema.

The sensitivity, specificity and diagnostic accuracy of these factors are depicted in Table 5. With an increasing number of adverse prognostic factors, mortality increases, so that with three or more factors it was 93%.[1] Similar prognostic markers have been described from the West.[2,3,7,8,47]

Studies from the West have also identified that the cause of AHF and the rapidity of onset of hepatic encephalopathy are both important prognostic predictors.[2,3,7,8,47] In these reports, AHF due to non-A, non-B viruses and drugs had worse patient outcomes than cases due to other causes,[2,7,8] while patients with the most rapid onset of encephalopathy had the best chance of recovery.[3,47] However, at our centre the causative distribution and rapidity of onset of encephalopathy were similar among survivors and non-survivors.[1]

ACUTE LIVER FAILURE IN PREGNANCY

During epidemics of hepatitis in developing countries, the following important observations have been made.[40,48–52]

1 Pregnant women more often develop hepatitis (12–20%) during the epidemics than non-pregnant women and men (2–4%).[40,48,49]
2 The frequency of AHF is significantly higher (10–22%) among pregnant women with hepatitis than among non-pregnant women and men with hepatitis (1–2%). As a result, the mortality among pregnant women who contract hepatitis during epidemics is significantly higher (10–39%) than that of the general population (4–13%).[43–52]

Subsequently, all these epidemics had been shown to be due to HEV. Therefore, based on these observations, it has been suggested that hepatitis E preferentially affects pregnant women, and that the mortality amongst pregnant women with HEV-induced AHF is higher than in pregnant women with other hepatitis virus-induced AHF. However, these suggestions have not been documented in any study. In developing countries, epidemics of hepatitis among adults have been caused only by HEV. Thus, most adults in developing countries

Table 5 Prognostic indicators of outcome in patients with acute hepatic failure

Variable (at admission)	No.	Death	Sensitivity	Specificity	Positive prediction	Negative prediction	Diagnostic accuracy
Age ≥40 years	86	72	84	38	26	90	48
Cerebral oedema	240	196	82	54	70	69	70
Serum bilirubin (≥15 mg/dL)	182	141	78	47	57	70	61
Prothrombin time (≥25 s more than the control	154	126	82	43	45	80	57
Multiple adverse factors present							
Any one factor	146	82	56	80	86	44	63
Any two factors	115	93	81	80	88	70	80
Any three factors	86	80	93	80	86	90	87
All four factors*	13	12	92	80	48	98	82

All four factors were present only in 13 patients. This resulted in an apparently lower prediction of mortality in these patients. This is attributable to the small number of patients assessed in this group.

have protective antibodies against HAV, and do not succumb to HAV epidemics.[53–55] Hepatitis B virus and HCV epidemics are unknown due to the predominant parenteral routes of transmission for these agents. Therefore, prospective evaluation is needed to clarify the association between HEV and AHF in pregnant women. However, our data could not establish a special affinity of HEV for pregnant women.[56]

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