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Burden of Acute Liver Failure in India and Treatment Options

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Acute hepatic failure (AHF) in India almost always presents with encephalopathy within 4 weeks of the onset of the first symptom of hepatic injury. It is commonly due to viral hepatitis or drug use. Infectious diseases such as sepsis, severe malarial fever, or typhoid fever may present rarely with AHF. Unlike the West, viral hepatitis is the cause in approximately 95-100% of patients in India and therefore this constitutes a more homogeneous population than AHF in the West.

In northern India, hepatitis E (HEV) and hepatitis B (HBV) viruses are the important viral causes of AHF; approximately 60% of cases are caused by these two viruses. At a tertiary referral centre from the northern part of India, Acharya et al reported Hepatitis B virus core mutants as important agents in hepatitis B related AHF. Approximately, 50% of the patients were women and one-quarter of them were pregnant, in their series. Thus it is apparent, that pregnant women 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. Approximately one-third of AHF patients survive with aggressive conservative therapy, while death occurred within 72 h of hospitalization in the remaining two thirds. Cerebral oedema and sepsis (Both fungal and gram-negative bacteria) were the major fatal complications.

Another publication by Dhiman et al, highlighted the prognostic factors of AHF under the 3 categories of hyperacute, acute and subacute hepatic failure. They studied early indicators of prognosis by multivariate analysis in 204 consecutive patients with AHF admitted with hepatic encephalopathy over five years on classifiying them into hyperacute, acute and subacute hepatic failure. The etiology was virus related in 186 (91.1%), drug induced in 15 (7.4%), Wilson's disease in one (0.5%), acute Budd-Chiari syndrome in one (0.5%), and malignant infiltration in one (0.5%).

Sixty (32.3%) patients with viral hepatitis survived. Univariate analysis showed that the interval between onset of encephalopathy and onset of jaundice, grade of encephalopathy, raised intracranial pressure, prothrombin time, and serum bilirubin levels on admission correlated with outcome in these patients.

JSRM/001010700013/Dec 26, 2006.

Multivariate logistic regression analysis showed that the presence of raised intracranial pressure at the time of admission, prothrombin time >100 sec on admission, age (>50 yr), and onset of encephalopathy seven days after onset of jaundice were associated with poor prognosis. Forty seven (37.0%) of 129 patients with hyperacute survived compared with 9 (22.5%) of 40 with acute and 4 (21.1%) of 19 with subacute liver failure (P = NS). Raised intracranial pressure was more frequent in patients with hyperacute (48.8%) than in patients with acute (32.5%) and subacute liver failure (15.8%; P = 0.01), while clinically detectable ascites was more frequent in patients with subacute (78.9%) compared with hyperacute (19.7%) and acute liver failure (37.5%; P< 0.0001).

Khuroo from Kashmir, studied the early prognostic indicators for acute liver failure in endemic zones for hepatitis E virus. Of the total of 180 [69 males and 111 females: age (mean +/- SD) 31.1 +/- 14.7 years] with acute liver failure, 131 (72.8%) patients died. Hepatitis E virus was the aetiological cause in 79 (43.9%) patients, in one-third the cause remained unknown. Of 83 women in childbearing age, 49 (59.0%) were pregnant, 33 (67.3%) of them were in the third trimester. Forty-seven (95.8%) pregnant women had HEV infection. The four variables which predicted the adverse outcome on multivariate analysis were non-hepatitis-E aetiology, prothrombin time >30 s, grade of coma >2 and age >40 years in that order of significance. Pregnancy per se or duration of gestation did not adversely affect the prognosis.

Kar et al, from Delhi, studied the HGV infection in acute viral hepatitis, fulminant hepatic failure (FHF) and in normal healthy blood donors. HGV-RNA was detected in 6 (37.5%) of 16 patients with fulminant hepatic failure, in 7 (19.4%) of 36 acute viral hepatitis, and two (4%) in 50 control blood donors. In both AVH and FHF, HGV was more frequently detected in (8/13; 61.5%) patients co-infected with other hepatotropic viruses and the most common co-infections were found to be HEV (6/8; 75%) and HBV (5/8; 62.5%). The authors concluded that frequency of hepatitis G virus is found to be certainly higher (37.5%) in fulminant hepatic failure than that in any other type of viral hepatitis in India. But since the virus is often detected in co-infection with either hepatitis B or E virus, which are known potential hepatitis agents, the role of HGV as an independent hepatitis agent is uncertain.

Pregnancy and AHF:

Studies from India, Iran, Africa and Middle East have found the incidence of fulminant hepatitis to be higher in pregnancy. Malnutrition superimposed on the normal demands of pregnancy and inversion of T and B lymphocytes in early pregnancy have been postulated to be the contributing factors. Beniwal et al from North India studied 97 consecutive pregnant patients in third trimester with acute viral hepatitis (AVH) or fulminant hepatic failure (FHF). Hepatitis E virus (HEV) was the causative agent in 47.4% of the cases of viral hepatitis and 52.6% were caused by non-E viruses (HAV-5.2%,HBV-7.2%,HCV-0%,non A-E 47.4%). HEV was responsible for 36.2% of the cases of AVH and 75% of the cases of FHF. The mortality was 24.7% (24/97). All of them had FHF. Eighteen of 24 cases (75%) who expired were HEV positive. The mortality rate was 39.1% in HEV group and 11.7% in non HEV group. Majority of patients (87.5%) who expired had died undelivered. Hepatitis E was the commonest etiological agent in those who had fulminant disease during pregnancy and was associated with high mortality rate.

In a study of pregnant women with liver disease from Chennai, in 2004, none of the patients developed AHF. Viral hepatitis was the most common cause for jaundice. In a series of 290 cases of jaundice complicating pregnancy, Lahiri from Kolkata reported that 90% were due to viral hepatitis. Bhosale et al reported the incidence of viral hepatitis to be 0.28%. Viral marker study revealed that 45% women were affected with HEV, 21.4% with HBV, 19 % with HAV. Unlike the Chennai study, Bhosale reported that 57% women were

JSRM/001010700013/Dec 26, 2006.

referred in a state of encephalopathy with coma leading to high mortality. HEV alone was responsible for 52% of mortality. The over all maternal mortality was 59.2% and perinatal mortality of 51.5%.

In summary, HEV infection alone is responsible for 47.4% of the cases of viral hepatitis in pregnant females in the third trimester. This is corroborative with the fact that HEV infection accounts for 50-70% of all patients with sporadic viral hepatitis in India. In pregnant females in third trimester with viral hepatitis, the prevalence of HEV infection is reportedly between 40-57%. HAV infection was less common (0% vs 5.2%) and HBV infection more common (34.6% vs 7.2%) in central India. HCV infection was not seen in any case as was also observed by other groups.

Among the HEV positive pregnant females, the mortality rate was 39.1%. The mortality rate is in the range of 30-45% and may be as high as 70%. Majority of the cases die undelivered. Thus uniformly, viral hepatitis is the most common cause of jaundice in pregnancy, fulminant hepatic failure, atleast from southern and eastern parts of India are rare.

AHF in children:

In a study of 36 children admiited as AHF from Mumbai, a viral aetiology could be established in 22 children (61.1%). Hepatitis A (n=12), Hepatitis B (n=3), Hepatitis A and B (n=2), and Hepatitis A and E (n=4). Two children had enteric fever (1 with associated HEV), 2 had Wilson's disease, 1 had Indian Childhood Cirrhosis (ICC) and 2 had drug induced hepatitis. Etiological diagnosis was not possible in 8 children (22%). Fourteen children (39%) died. Poor outcome was associated with spontaneous bleeding, raised prothrombin time, lower transaminases and higher bilirubin on admission.(Bendre et al)

In conclusion, viral hepatitis is the most common cause of AHF, atleast in northern parts of India. Similar reports are not available for the southern states. Acute on chronic liver disease is a more common clinical presentation in south India. There is a need to develop simple, clinical prognostic markers for AHF in the Indian subcontinent, in order to identify patients suitable for liver transplantation, since patients with AHF, despite the presence of sepsis, overt clinical features (i.e. fever, leucocytosis) may be absent and objective documentation of the presence of sepsis can be achieved by repeated culture of various body fluids. Also, the uniform classification of hyperacute, acute and subacute recommended may not be applicable for the Indian subcontinent (Acharya et al), where the rapidity of onset of encephalopathy does not seem to influence survival.

The ultimate management of patients with AHF would be liver transplantation, when conservative supportive resuscitative measures fails. Today, there are several centres in India, like the Apollo Hospitals, New Delhi, Global Hospital, Hyderabad and Christian Medical College Vellore which are performing liver transplants. Transplants are being done at the rate of roughly two to three every year when atleast 60,000 persons in the country need a liver transplant. The approximate cost for liver transplant varies from Rs 10 to Rs 45 lakhs followed by post transplant expenditure.

Paucity of donors is one of the major handicaps hampering the growth and success of liver transplantation in the country. Even in the UK and US, there are as many as 4,000 recipients waiting for a liver transplant. There are several problems in obtaining a donor liver. Brain-dead patients almost always land up in neurological ICUs, since the majority are victims of road accidents or internal haemorrhage. In effect, the process of certifying the patient brain-dead has to begin with the neurologist. But in the end, this initiative gets lost and the real glory goes only to the transplant surgeon.

India's cadaver transplant programme is suffering from a chronic dearth of body parts that has ensured it never really takes off. After years of spirited campaigning, the Transplantation of Human Organs Act, passed

JSRM/001010700013/Dec 26, 2006.

in 1994, while banning trade in organs allowed doctors to certify patients brain-dead. It was a landmark. With better surgical techniques and a greater understanding of the body's immune system, it aroused in most doctors a sense of actually being able to help patients with failed organs instead of just looking on helplessly.

MARS has also served as a bridge to liver TX. There are very few centres in India wherein MARS is available and is often shared between centres performing liver transplant. It is an expensive modality of management.

Another major breakthrough has been in identifying the role of a tiny population of stem cells, called as "true" stem cells in management of these patients, in the UK. One-thousandth of the cells circulating in the blood are CD34 cells. Of these, 10 per cent are a sub-population of these CD34 cells, which are true stem cells, can differentiate into any specialised cells. While CD34 cells have certain limitations as stem cells, the sub-population can differentiate into all kinds of specialised cells. These when injected into the affected area can take over the function which a diseased cell can no longer perform. What makes the discovery significant is that the world over the number of donors is much less than those requiring a transplant. In India, the problem is even more pronounced. Habibullah et al, from India has done pioneering work on stem cell transplant and today liver cell therapy (both extra and intrahepatic source of stem cells) has been projected as a bridge and an alternative to ortho transplant. The author has reported success in isolated cases and both preclinical and clinical applications are in progress. If successful, the technique would solve the problem of finding donors, lower the cost and will not require a high level technology for treatment.

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