Natural history and risk factors in fulminant hepatic failure

U Poddar, B R Thapa, A Prasad, A K Sharma, K Singh

Background: The natural history of fulminant hepatic failure (FHF) without liver transplantation is not well known.

Aims: To study the natural history and prognostic factors, especially the presence of ascites and spontaneous bacterial peritonitis (SBP) in children with FHF.

Methods: FHF was defined by the onset of encephalopathy within 12 weeks of onset of jaundice. From August 1997 to December 2000, 67 children (≤12 years) were diagnosed with FHF. Their clinical features, investigations and outcome were noted. Viral markers A to E (IgM, anti-HAV; IgM, anti-HEV, HBsAg, and anti-HCV) were determined by ELISA. SBP was defined by the presence of ≥250 neutrophils with or without a positive culture in ascitic fluid.

Results: Mean age of the children was 5.8 years with an almost equal sex distribution. Viral markers were positive in 63 (94%) cases: hepatitis A in 34 (54%), E in 17 (27%), A+E in seven (11%), and B in five (8%). Thirty-one children presented with grade I or II encephalopathy and all recovered. Among 17 of 36 children who had grade III or IV encephalopathy, ascites was detected (both clinically and ultrasonically) in 34 (51%) cases, nine (26%) of which had SBP. Overall mortality was 25%. Mortality was higher in those who had ascites than in those who did not (32% v 18%); among those with ascites it was maximum in those who had SBP (78% v 16%). Total serum bilirubin and grade of encephalopathy were significantly higher, serum albumin was significantly lower, and prothrombin time was significantly prolonged in those who died than in those who recovered.

Conclusion: The natural history of FHF in Indian children depends on age, grade of encephalopathy, ascites, and SBP. SBP depicts worse outcome. In all cases of FHF with ascites, the presence of SBP should be investigated.

Fulminant hepatic failure (FHF) is a rare but potentially fatal complication of acute hepatitis. With the availability of liver transplantation, the natural history of FHF has changed. However, in developing countries such as India, where liver transplantation is not widely available, it is possible to study the natural history of the condition and risk factors in relation to outcome. Recently it has been shown that ascites and spontaneous bacterial peritonitis (SBP) are poor prognostic factors in FHF in adults. Although ascites is an important feature of decompensated chronic liver disease, it has been reported infrequently in patients with fulminant hepatic failure. SBP, which occurs in 15–25% of patients with cirrhosis, has occasionally been reported in FHF in adults. Though studies in children with FHF have shown a prevalence of ascites in 32–55%, SBP has not been reported. We prospectively studied the natural history and prognostic factors, and especially the occurrence of ascites and SBP in children with FHF.

METHODS

The study was carried out in a tertiary care hospital in North India where liver transplantation is not available. FHF was defined according to the criteria laid down by O’Grady and colleagues: onset of hepatic encephalopathy occurring within 12 weeks of onset of jaundice in the absence of pre-existing symptomatic liver disease. This was further subclassified depending on the interval between the onset of jaundice and the onset of encephalopathy into hyperacute liver failure (HALF; interval 0–7 days), acute liver failure (ALF; interval 8–28 days), and subacute hepatic failure (SAHF; interval 29 days to 12 weeks). A viral aetiology was presumed if there was a classical prodromal illness, with or without positive viral markers, in the absence of history of exposure to drugs or toxins. Underlying chronic liver disease was excluded by clinical, biochemical, and abdominal ultrasound examination.

From August 1997 to December 2000 consecutive cases admitted to our unit with a diagnosis of FHF as a result of viral hepatitis were studied. A structured proforma comprising clinical features, results of investigation, and outcome was maintained. The peak grade of encephalopathy during hospitalisation was noted. Encephalopathy was graded from grade I to IV according to the criteria of Teasdale and Jennett. Baseline liver function, kidney function tests, full blood count, prothrombin time (PT) and partial thromboplastin time were checked and repeated twice a week. For comparison a prothrombin time index (PTI) was calculated (PTI = standard PT/observed PT × 100).

Viral markers for hepatitis A to E (IgM, anti-HAV; IgM, anti-HEV, HBsAg, anti-HCV) were determined by ELISA with commercial kits. Acute hepatitis B was diagnosed if there was HBsAg positivity together with IgM-anti HBc positivity. When all viral markers were negative, the case was labelled as non-A to E hepatitis. The diagnosis of ascites was made clinically and ultrasonically. An ascitic tap was performed in all cases with ascites and fluid was analysed for total leucocyte count, differential count, and serum ascites albumin gradient (SAAG). Ascitic fluid was cultured in blood culture bottles.

Abbreviations: ALF, acute liver failure; CNNA, culture negative neutrocytic ascites; FHF, fulminant hepatic failure; GI, gastrointestinal; HALF, hyperacute liver failure; PT, prothrombin time; PTI, prothrombin time index; SAAG, serum ascites albumin gradient; SAHF, subacute hepatic failure; SBP, spontaneous bacterial peritonitis
SBP was defined as the combination of a positive culture, an ascitic fluid neutrophil count of $\geq 250$ cells/mm$^3$, and no evidence of a source of infection.$^{12}$ Culture negative neutrocytic ascites (CNNA) was defined as ascitic fluid infection in which the neutrophil count was $\geq 250$ cells/mm$^3$ with no growth of ascitic fluid culture.$^{13}$ All cases of SBP and culture negative neutrocytic ascites were treated with parenteral cefotaxime (100 mg/kg/day). Clinically significant ascites was treated with salt restriction and diuretics (spironolactone 2–8 mg/kg/day and furosemide 1–2 mg/kg/day) for as long as there was ascites.

All cases received supportive treatment without corticosteroids or specific antiviral agents. Hepatic encephalopathy was managed with a standard protocol including a protein free diet, oral antibiotics (ampicillin 50 mg/kg/day), and lactulose, either orally or by retention enema. All cases with grade III and grade IV encephalopathy received parenteral mannitol (20%) and when appropriate, hyperventilation. Fresh frozen plasma was infused if bleeding occurred.

**Statistics**

Results were expressed in terms of mean (SD). Comparisons were made using Student’s t test and the $\chi^2$ test.

**RESULTS**

During the study period 67 children ($\leq$ 12 years of age) had FHF. The mean (SD) age of the study population was 5.8 (3) years (range 3 months to 12 years). There was just one child aged 3 months; the others were more than 1 year old. The male to female ratio was 39:28. Prodromal symptoms (fever, anorexia, vomiting) were present in 64 (95.5%) cases. Thirty children had grade I or II, and 36 had grade III or IV encephalopathy. Table 1 presents the outcome according to aetiology. Viral markers were positive in 63 (94%) cases; the remaining four (6%) had non-A to E hepatitis.

The overall mortality in the study population was 25% (17 deaths). All children with grade I or II and 19 (53%) with grade III or IV encephalopathy recovered within an average period of 3 days (range 2–5 days). Table 2 shows outcome according to the various subtypes of FHF. Two thirds of cases were in hyperacute liver failure; mortality was lowest in them.

Table 3 compares those who survived and those who did not. The non-survivors had more severe disease indicated by significantly higher serum bilirubin, higher grade of encephalopathy, lower serum albumin, and more prolonged prothrombin time (low PTI). Interestingly, non-survivors were significantly younger than survivors. Five children had gastrointestinal (GI) haemorrhage; despite fresh frozen plasma infusion, bleeding continued and all five died.

Ascites was detected clinically in 34 (51%) cases and ultrasonically in 36 (54%). Ascites was high gradient (serum ascites albumin gradient $>1.1$) in all (mean (SD) SAAG = 1.8 (0.5)). Thirteen children (40%) with ascites required diuretic therapy for a brief period (3–14 days); in the remaining 23 (60%) cases, ascites improved spontaneously. Nine children with ascites (25%) had SBP, three had culture positive SBP ($E$ cell in two and $A$cinobacter in one), and six had culture negative neutrocytic ascites. Table 4 shows the outcome of the various clinical subsets of cases. Mortality was higher in children with ascites compared to those without.

**DISCUSSION**

Subclassification of FHF into hyperacute, acute, and subacute liver failure carries a prognostic significance. In a study of 376 cases of FHF in adults, O’Grady and colleagues$^{14}$ found that 60% of cases were hyperacute, 24% acute, and 16% subacute. The best chance of survival was in the hyperacute group (36%) compared to acute (7%) or subacute (14%). This classification has not previously been validated in children. We found that in children, 64% of cases were in the hyperacute group and 31% in the acute liver failure group, with significantly higher mortality in acute and subacute groups.

Although it has been shown that HEV alone or in combination with other hepatotropic viruses can produce more severe hepatitis in children, we found only 10% of children with mixed infection with HAV and HEV, and none died. The same...
kind of aetiological spectrum has been documented in a study of 261 Egyptian children with sporadic acute hepatitis where mixed infection was documented in <1% of cases.\(^8\)

The outcome in FHF is altered by the availability of liver transplantation. In the absence of liver transplantation, outcome depends on various clinical and biochemical factors. Psacharopoulos and colleagues,\(^1\) in a study of 31 cases of FHF in children, showed that poor outcome was related to the grade of encephalopathy, prolonged prothrombin time (>90 second), GI haemorrhage, and renal failure. Arora and colleagues\(^2\) found infection to be a marker for poor prognosis. Another study by Srivastava and colleagues\(^3\) in 41 children with FHF, showed the presence of GI bleeding, the degree of coma, and serum bilirubin to be independent predictors of mortality. In this study we found that those who died were younger, suffered GI bleeding, had higher bilirubin, a higher grade of encephalopathy, and a lower prothrombin time index than survivors.

Ascites has been reported in 16.5–55% of children with FHF.\(^4\)\(^5\)\(^6\)\(^7\)\(^8\) In our study, 54% had ascites. Portal hypertension has been implicated in the pathogenesis of ascites in FHF. Portal hypertension is an universal feature of FHF and its frequency is much higher in those with ascites.\(^9\)\(^10\)\(^11\)\(^12\) Valla and colleagues\(^12\) suggested that sinusoidal collapse caused by liver cell dropout was a major factor in acute viral hepatitis. The high serum ascites albumin gradient (≥1.1 g/l) in all of our cases further supports portal hypertension as the cause of ascites. SBP has been defined as culture positivity with a neutrophilic response (≥250 cells/mm\(^3\)) in ascitic fluid.\(^13\) However, in almost one third of cases of suspected SBP, culture is negative despite a neutrophilic response.\(^14\) In our series two thirds of cases had CNNA. The reason for culture negativity may have been our routine use of oral ampicillin for gut sterilisation.

Although there are some reports of SBP in FHF in adults,\(^15\)\(^16\)\(^17\) this has not been reported in children. It has been shown that the mortality was 2.5-fold and morbidity twofold higher in patients with SBP than in those without. In our study, the presence of SBP was associated with an increased mortality.

In conclusion, the natural history of FHF was dependent on age, subtype of FHF, grade of encephalopathy, presence or absence of GI haemorrhage, ascites, and SBP. Ascitic fluid analysis should be carried out in all children with FHF and ascites.

Authors’ affiliations
U Poddar, B R Thapa, A Prasad, A K Sharma, K Singh, Division of Pediatric Gastroenterology, Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

REFERENCES