Our Experience with Fulminant Hepatic Failure in Turkish Children: Etiology and Outcome

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Summary

Fulminant hepatic failure is a rare and devastating event during childhood. The etiology of liver failure is reported to change according to age and geographical location. We aimed to investigate, retrospectively, causes and outcome of fulminant hepatic failure in Turkish children. Thirty-four children with fulminant hepatic failure were analysed by means of etiology and outcome. Etiological factor, clinical presentation, encephalopathy stage and biochemical parameters were correlated with outcome. Acute viral hepatitis was detected in 12 cases (35.2 per cent) and hepatitis A was the most commonly detected cause among cases with fulminant hepatic failure (n = 9, 26.4 per cent). Hepatitis B and non A-E infection were diagnosed in two (5.8 per cent) and one (2.9 per cent) cases, respectively. Wilson's disease was defined in four patients (12.5 per cent). Budd–Chiari syndrome (2.9 per cent), autoimmune hepatitis (2.9 per cent) and mushroom poisoning (2.9 per cent) were other detected causes of fulminant hepatic failure in this group. No viral, metabolic, toxic or anatomic reason could be detected in the remaining 15 (44.1 per cent) patients and they were evaluated as cryptogenic. Mortality was 67.6 per cent (23 cases). Encephalopathy grade, total and indirect bilirubin levels were found to be significantly higher in patients who died (p = 0.004, p = 0.03, p = 0.04). Seven patients could have been transplanted (two cadavaric, five living related) and the mortality of this group was 28.5 per cent (n = 2). It was concluded that fulminant hepatitis A virus (HAV) infection is the most common detectable cause of fulminant hepatic failure in Turkish children.

Introduction

Fulminant hepatic failure (FHF) is a clinical syndrome of sudden and severe liver impairment associated with encephalopathy and coagulopathy in a previously healthy person. Etiology of liver failure depends on age in a pediatric population and it is reported to vary with geographical location.[1] However, viral agents tend to be the leading cause worldwide.[2] FHF is a relatively rare, but devastating event in children. Attempts to correlate clinical and laboratory data with outcome failed in prospective studies.[2] Mortality is reported to change between 18 and 80 per cent with progressive degree of encephalopathy.[3,4] Supportive treatment and artificial liver support systems have limited therapeutic value in patients with advanced coma.[5] Liver transplantation is the only available solution for these patients.

The aim of this retrospective study was to investigate causes and outcome of FHF in Turkey, a developing country. The second purpose was to examine clinical and laboratory variations with outcome.

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Materials and Methods

We retrospectively analysed 34 patients (23 boys, 11 girls) referred to the Pediatric Gastroenterology and Nutrition Department at Ege University who had a diagnosis of FHF between January 1994 and May 2002. FHF was classified as hyperacute, acute, and subacute if the time interval between the onset of jaundice to encephalopathy was less than 7 days, 8–28 days, and more than 28 days, respectively.[6]

All patients were followed-up in intensive care settlement. Encephalopathy stage was clinically assessed and patients were also assessed by a pediatric neurologist. Hepatocellular functions by aminotransferases, bilirubin, total protein, albumin, ammonia (NH_3), prothrombin time (PT), international normalization rate (INR), blood glucose, and cholestatic markers were studied. Baseline renal functions were assessed by urinary output, serum urea, creatinine, urinary sodium, and fractional sodium excretion (FeNa). Total blood count and cultures from sputum, urine, stool, and blood were also taken.

Acute viral serology with anti-hepatitis A virus immunoglobin (Ig) M, anti-hepatitis B virus core antigen Ig M, hepatitis B surface antigen, anti-hepatitis C virus, cytomegalovirus Ig M, anti-herpes simplex virus 1-2 Ig M, Epstein–Barr virus nuclear

TABLE 1
Clinical and biochemical characteristics of the study group (mean ± SD)

	Total (n = 34)	Survived[a] (n = 6)	Died[a] (n = 21)	p
Encephalopathy				
Grade I	9 (26.5%)	5 (83.3%)	2 (9.5%)	0.004
Grade II	11 (32.4%)	1 (16.7%)	8 (38.1%)	
Grade III	10 (32.4%)	–	8 (38.1%)	
Grade IV	4 (11.8%)	–	3 (14.3%)	
Clinical presentation				
Hyperacute	12 (35.3%)	3 (50%)	5 (23.8%)	>0.05
Acute	18 (52.9%)	2 (33.2%)	13 (61.9%)	
Subacute	4 (11.8%)	1 (16.7%)	3 (14.3%)	
ALT (U/l)	857.9 ± 731	1050.6 ± 1348.1	585.5 ± 597.4	>0.05
Total bil. (mg/dl)	20.7 ± 15.7	16.9 ± 20.9	22.2 ± 13.5	0.03
Direct bil. (mg/dl)	8.5 ± 7	5.7 ± 6.4	9.3 ± 7.2	>0.05
Indirect bil. (mg/dl)	13.3 ± 11.5	11.8 ± 15.8	14 ± 9.7	0.04
PT (s)	40.6 ± 20.3	29.4 ± 17.5	45.3 ± 20.3	>0.05
NH_3	188.2 ± 105.1	201 ± 153.4	182.4 ± 79.2	>0.05
Blood glucose (mg/d)	82.4 ± 64.5	85.9 ± 43.3	80.9 ± 72.1	>0.05
HCO_3	21.3 ± 4.9	20.8 ± 4.3	21.3 ± 5.1	>0.05

[a]Analyses include patients on supportive care.

antigen, and Parvovirus B19 Ig M were studied. Serum ceruloplasmin, copper, urinary copper excretion, and Kayser–Fleischer ring were looked for in all cases. A diagnosis of Wilson's disease was supported by liver copper content measurements. Autoantibodies, alpha 1 anti-trypsin (AAT) level and metabolic screening were performed when clinically suspected. FHF patients with no proven etiological cause were accepted as cryptogenic.

Prophylactic beta-lactam and aminoglycoside combination was started as soon as the cultures were collected. Intestinal decontamination with oral and rectal lactulose and oral non-absorbable antibiotics were started. Plasmapheresis was performed in four patients until donor liver was available or during potential living donor work-up.

Results were performed using SPSSWIN (Statistical Package for Social Sciences for Windows). The data were evaluated by chi-squared test and Student's *t*-test.

Results

The study group consisted of 23 boys and 11 girls, with a median age of 6 years (1 month–17 years). Hyperacute, acute, and subacute presentation was detected in 12 (35.3 per cent), 18 (52.9 per cent) and four (11.8 per cent) cases, respectively. Encephalopathy stage was grade I in nine (26.4 per cent), II in 11 (32.3 per cent), III in 10 (29.4 per cent) and IV in four (11.7 per cent) patients.

The biochemical analyses of the patients are summarized in Table 1. All patients, other than one boy with normal alanine aminotransferase (ALT), showed hepatocyte injury biochemically. Our unit is a referral hospital so that most of the patients were on plasma support on admission and seven (20.5 per cent) patients had a PT of less than 20 s (mean 17.7 s, range 14–20 s). Severe cholestasis was documented in all cases except one girl with normal alkaline phosphatase and γ-glutamyl transpeptidase. Hypoglycemia (blood glucose <40 mg/dl) and metabolic acidosis were detected in seven (20.5 per cent) and three (8.8 per cent) of the cases, respectively. Three patients (one with grade I, one with grade II, and one with grade III encephalopathy) had normal serum NH_3 levels (NH_3 < 80 μg/dl).

Etiologic distribution is summarized in Table 2. Anti-HAV Ig M and anti-HBc Ig M were detected in nine (26.4 per cent) and two (5.8 per cent) cases. Non-A non-B non-C (NANBNC) hepatitis was assessed in another case (2.9 per cent) with acute hepatitic histology in the explant liver. Four patients had Kayser–Fleischer rings, increased urinary copper excretion (median 1960 μg/day, range 1010–2180), low ceruloplasmin level (median 11 μg/dl, range 8–19), and histological confirmation of Wilson's disease with increased liver copper content (median 480 U/g; range 432–550). Budd–Chiari syndrome was detected by Doppler ultrasound in one patient (2.9 per cent). Autoimmune hepatitis was diagnosed by acute phase response, antinuclear antigen (ANA) and liver–kidney microsomal antibody positivity in one patient. Mushroom poisoning was defined and confirmed by histological evaluation. AAT deficiency was suspected in an infant (AAT level 47 mg/dl); however, phenotypic and genotypic confirmation could not be done, so the patient was included in the cryptogenic group. No cause could be detected in the

TABLE 2
Etiologic distribution and outcome of FHF

Disease	No. of patients (%)	Outcome
Viral hepatitis	12 (35.2%)	
HAV	9 (26.4%)	3 R, 6 NR
HBV	2 (5.8%)	2 NR
NANBNC	1 (2.9%)	1 NR
Wilson	4 (11.7%)	4 NR
Autoimmune hepatitis	1 (2.9%)	1 NR
Budd–Chiari	1 (2.9%)	1 NR
Mushroom poisoning	1 (2.9%)	1 R
Cryptogenic	15 (44.1%)	2 R, 13 NR

R, recovered; NR, died or required liver transplantation

remaining 15 (44.1 per cent) patients and they were evaluated as cryptogenic.

Mechanical ventilation was needed in 23 patients (67.7 per cent) during or after admission and all died. Hepatorenal syndrome (oliguria with azotemia) was assessed in eight (23.5 per cent) cases with a mortality of 87.5 per cent (seven cases) in this group.

Twenty-seven of the patients (79.4 per cent) were treated supportively. Pediatric cadaveric and living related liver transplantation were started in March 1997 and October 1999 in our unit, respectively. Two cadaveric transplants were made for NANBNC and Wilson's disease and five living related liver transplants were performed in two patients with HAV infection, two patients with Wilson disease, and one cryptogenic case.

The mortality of the whole group was 67.6 per cent (23 cases). Median hospitalization period of the mortal cases was 10.5 days (4 h–60 days). Eleven patients (32.3 per cent) survived; mean follow-up was 2.5 years (2 months–6 years).

Mortality was not found to be different in patients with hyperacute, acute, or subacute presentation ($p = 0.4$) (Table 1). Encephalopathy grade was significantly higher in mortal patients ($p = 0.004$) (Table 1). Correlation of clinical and laboratory variation with outcome is shown in Table 1. Total and indirect bilirubin levels were found significantly higher in patients who died ($p = 0.03$, $p = 0.04$). A correlation among hypoglycemia and mortality was found ($p > 0.05$). Mortality of the group on supportive treatment was 77.7 per cent (21 cases).

In the transplanted group, two patients transplanted from living related donor died of infection. The mortality of the group treated by transplant was 28.5 per cent. Mortality was found to decrease significantly with transplantation ($p = 0.03$).

Discussion

FHF is a rare, but highly fatal event during childhood. Sokol, *et al.*[1] emphasized the dependency of etiologic factors on age in a pediatric population; however, the most common cause in all series was viral hepatitis.[2] Viral hepatitis was also the leading defined cause among our FHF children. HAV infection appeared to be the most common cause (26.4 per cent). Although HAV infection has a case fatality rate of 0.14 per cent, its prevalence in pediatric FHF is reported to vary from as low as 1.5 per cent to as high as 31 per cent, depending on geographical location.[8–10] Our results indicate the importance of HAV infection in Turkey and emphasize the need for a national vaccination programme. Hepatitis B virus (HBV) infection is also reported to be a primary cause of FHF with a prevalence of 25–75 per cent, especially in highly endemic areas like Eastern Asia.[9,11] Turkey is an intermediately endemic area for HBV; HBV was found in 5.8 per cent of our fulminant cases.[12] A national vaccination programme was started in 1997 in our country; this may have had an impact on our results. NANBNC is reported to be the most common cause in developed countries.[13] We had only one patient (2.9 per cent) related to NANBNC infection that was documented by the histology of the explant liver. However, we could not always perform autopsy or necropsy, because of social and religious reasons, and hence it was not possible to clarify the exact incidence from patients with no identifiable cause, namely the cryptogenic group.

Wilson's disease was the second detected cause of fulminant hepatic failure in our group. Consanguinity is widely seen in our country and it might have been a reason for the high incidence of fulminant Wilson's disease among our FHF patients when compared with the literature.[4]

Cryptogenic cases consist of the majority of our FHF group. Toxic causes, such as insecticides, could not be excluded from these cases since Turkey is an agricultural country.

Encephalopathy grade and hyperbilirubinemia were found to be significantly increased in mortal cases ($p < 0.05$). Kings College criteria offering prediction of poor prognosis consist of non-A non-B hepatitis as an etiologic factor, acute and subacute presentation, age less than 11 years, and serum bilirubin level and PT exceeding 18 mg/dl and 50 s, respectively.[14] Neither clinical presentation, etiologic agent, PT, or other laboratory data correlated with outcome in our patients who were managed medically. More than 80 per cent of children were admitted when they could be transplanted. However, liver transplantation could be performed in seven of them. Organ donation is low in our country; liver transplantation from cadaver could only be done in two cases in the last 4 years, and five of them were transplanted from voluntary living related donors. Mortality was significantly decreased with transplantation when compared with medical treatment.

In conclusion, fulminant HAV infection is the most commonly detected cause of FHF in Turkish children. This emphasizes the need for a community vaccination programme against HAV in Turkey.

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