

Etiology, outcome and risk factors for fulminant hepatic failure in children at a tertiary care hospital, Sukkur, Pakistan

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Objective: To study the etiology, outcome and risk factors for Fulminant Hepatic Failure (FHF) in children at a tertiary care hospital, Sukkur.

Methodology: Retrospective review of patients 1-14years, admitted with FHF from July 2007 to June 2012, at Pediatric department of Ghulam Muhammad Mahar Medical College Hospital Sukkur. Fulminant hepatic failure was defined as coagulopathy (PT > 20 sec or INR > 2) with or without hepatic encephalopathy within 8 weeks of the onset of symptoms.

Results: Eighty patients with FHF (50 males and 30 females) were admitted in our Pediatric department. The most common cause of FHF was viral hepatitis in 62 (77.5%) and in 11 (13.75%) cases etiology was not established. Among 62 cases of viral hepatitis, HAV was found in 50 (80.65%), and HBV in 11 (17.74%).

Encephalopathy grade 3 was most common in 30 (37.50%), and grade 2 in 25 (31.25%). Forty five (56.25%) patients expired. Patients with bilirubin 13.0 ± 8.0 mg/dl vs 6.7 ± 3.3 mg/dl recovered. ALT was lower in expired patients 467 ± 381 IU/L vs 1834.3 ± 1550.2 IU/L in recovered children. 45 (52%) expired with INR of 4 or more. The risk factors of FHF patients were grade 3 or 4 encephalopathy, high bilirubin, low ALT and INR >4.

Conclusion: HAV and HBV were the most common etiologic agents of FHF. Children with FHF, high grade encephalopathy, high bilirubin, low ALT and INR >4 had poor outcome. (Rawal Med J 2013;38: 219-222).

Keywords: Fulminant hepatic failure, etiology, outcome, risk factors and children.

INTRODUCTION

Fulminant hepatic failure (FHF) is a potentially fatal disease. The currently accepted definition in children includes biochemical evidence of acute liver injury (usually <8 weeks duration), no evidence of chronic liver disease and hepatic based coagulopathy defined as prothrombin time (PT) >15 sec or International normalized ratio (INR) >1.5 not corrected by vitamin K in the presence of clinical encephalopathy or a PT >20 sec or INR >2 regardless of the presence of clinical hepatic encephalopathy.¹ The etiology includes infectious, metabolic diseases and toxic causes that may differ depending on age and geographical location. In the developing world and in certain communities in developed countries, hepatitis A is the most common etiological agent causing FHF in children.^{2,4} Hepatitis B virus infection is the most important cause of FHF in endemic areas.⁵ In Pakistan, viral hepatitis is endemic and is

punctuated by periodic outbreak. Almost all known hepatitis viruses A to G are present here. Aziz S et al⁶ in their study, demonstrated prevalence of hepatotropic viruses in population of age 14 years and above, 100% of them were positive for anti-HAV, 26% for anti-HEV, and 1.4% for anti-HCV while HBsAg was positive in 1.9%. In English infants younger than 2 years, hemophagocytic lymphohistocytosis, cryptogenic hepatitis and metabolic diseases account for 75% of cases of FHF and infectious causes were rare.⁷ The FHF can also be caused by autoimmune hepatitis in 5% of cases and an idiopathic form accounts for 40/50% of cases in children.^{1,5}

Establishing the underlying cause may be important because it can influence treatment options, determine prognosis and help to guide families. Family members of patients with Wilson's disease require screening for presymptomatic disease.^{8,9} In different studies, etiology, age, neurologic status,

INR ratio, ammonia, bilirubin and creatinine levels were found to be related to prognosis.^{3,10} With an INR of 4 or more than 4, the mortality rate reaches 86%.¹¹ There is very little data available in our tertiary care hospitals regarding FHF in children. The objective of this study was to determine etiology, outcome and risk factors of FHF in children at our tertiary care hospital.

METHODOLOGY

The medical records of all patients of both genders, age ranging from 1-14 years admitted in pediatric department of SMBBM University at GMMMC Hospital Sukkur, Pakistan with FHF from July 2007 to June 2012 were reviewed. FHF was defined as the presence of acute liver failure (coagulopathy PT > 20 sec or INR > 2), hepatic encephalopathy without pre-existing liver disease, within 8 weeks of the onset of clinical liver disease. Patients with pre-existing systemic disease such as hemophagocytic lymphohistocytosis, leukemia and chronic liver disease were excluded. Encephalopathy was classified in 4 grades. The grade 1 include patients alert, periods of lethargy, reversal of day-night sleep, slow mentation, grade 2 include drowsiness, inappropriate behavior, fetor hepaticus, grade 3 stupor but arousable, hyperreflexia, rigidity, grade 4 unarousable, areflexia or flaccidity.

Baseline liver function test (serum bilirubin, ALT), coagulation profile (PT, INR ratio) and hepatitis serology were done in all patients. Viral markers for hepatitis A to E (anti-HAV IgM, HBsAg, anti-HCV antibody, anti-HEV IgM) were determined by ELISA method. Test for Wilson's disease (24 hour urinary copper, serum ceruloplasmin) and autoimmune hepatitis (Antinuclear antibody ANA) were done in those cases that were negative for acute serology of hepatitis A to E virus. Outcome of patient was noted as recovery or expiry during hospital stay. The outcome was related clinically with grade of encephalopathy and bio-chemically to their serum bilirubin, ALT, and INR. The data was analyzed by SPSS v 11.

RESULTS

During the 5 year period, 80 patients with FHF were admitted. There were 50 males and 30 females. The

mean age was 6.3 years (range 1-14 year), majority were in age group of 5-9 years (Table 1). The most common cause of FHF was viral hepatitis in 62 (77.5%) of cases, followed by autoimmune hepatitis and Wilson's disease (Table 2).

Among 62 viral hepatitis cases, HAV was the most common in 50 (80.65%) (Table 3). Supportive management was given to all patients. Forty five patients expired and mortality was 56.25%. All patients had encephalopathy, the grade 3 was found most common in 30 (37.5%), and all patients with grade 4 and 25 (83.33%) with grade 3 expired (Table 4).

The biochemical profile of patients with FHF showed, that patients expired had high bilirubin level 13.0 ± 8.0 mg/dl vs 6.7 ± 3.3 mg/dl recovered. ALT was lower in expired patients i.e 467 ± 382 IU/L vs 1834.3 ± 1550.2 IU/L in recovered children. Patients with an INR value 4 or more was found in 50 (62.5%) of cases. Majority 45 (90%) of them expired. The risk factors in our patients with FHF were found grade 3 or 4 encephalopathy, high bilirubin level, low ALT and INR value 4 or more than 4.

Table 1. Age group and outcome of 80 FHF cases

Age (years)	Number	Percentage	Recovered	Expired
1-4 y	20	25%	10 (28.58%)	10 (22.22%)
5-9 y	35	43.75%	15 (42.85%)	20 (44.45%)
10-14 y	25	31.25%	10 (28.57%)	15 (33.33%)
Total no	80	100%	35 (43.75%)	45 (56.25%)

Table 2. Causes of FHF in 80 cases.

Etiology	Number	Percentage
Viral hepatitis	62	77.5%
Autoimmune hepatitis	03	3.75%
Wilson's disease	02	2.5%
Drug -induced hepatitis	02	2.5%
Idiopathic hepatitis	11	13.75%
Total no	80	100%

Table 3. Viral causes of FHF in 62 cases

Virus	Number	Percentage
HAV	50	80.65%
HBV	11	17.74
HCV	01	01.61
Total	62	100%

Table 4. Hepatic encephalopathy grades and outcome of 80 patients..

Grade	Number	Percentage	Recovered	Expired
Grade 1	09	11.25%	9 (100%)	00%
Grade 2	25	31.25%	21 (84%)	04 (16%)
Grade 3	30	37.50%	05 (16.67%)	25 (83.33%)
Grade 4	16	20.0%	00%	16 (100%)
Total	80	100%	35 (43.75%)	45 (56.25%)

DISCUSSION

FHF is a rare but potentially fatal disease. The etiology of FHF in children differs around the world. Viral hepatitis is uncommon in Western Europe and other developed countries where the chief offenders are drugs and toxins specially acetaminophen,^{1,3} while viral hepatitis is the commonest cause of FHF in developing countries.^{2,4,5} In our study, viral hepatitis was the most common cause of FHF in 77.5% of cases including HAV and HBV; similar to previously reported from Karachi Pakistan by Latif N et al.¹¹ The current study highlights that children are more prone to acquire hepatitis A virus in our population due to high prevalence and poor socioeconomic condition. Almost 96% of the population is exposed to HAV by the age of 5 years and 98-100% at adulthood.⁶ Acute viral hepatitis A is a common infection among children in Pakistan and accounts for 50-60% of all cases of acute viral hepatitis in children¹² although 90% of hepatitis A in children is subclinical but there is less than 1% chance of developing fulminant hepatitis.¹

In our study, other causes of FHF were autoimmune hepatitis in 3 cases, Wilson's disease in 2 cases and drug-induced hepatitis in 2 cases, while etiology could not be established in 11 cases. These results are similar to the previously reported in local and international studies.^{2-5,11} In contrast to our results of idiopathic cases, very high cases forty nine percent were reported by Squires et al^{3,5} and Suehy FJ.¹ The mortality was 56.25% nearly similar to the Latif N and Mauood K^{11,13} found in their series but higher than previously reported by Squires et al³ in 348 in children.

The high mortality was due to the fact that most of patients presented to us in grade 3 or 4 encephalopathy, high bilirubin, low ALT and INR value of 4 or more in majority of cases as reported in different studies^{3-5,11,13,14} The grade of hepatic encephalopathy remains an important predictor of

outcome. The higher grade of encephalopathy has poor outcome because deaths are commonly associated with cerebral edema. In our study similar results were found with high grade encephalopathy to the previous observation from other studies.^{3-5,11,13}

¹⁴ The outcome is also related to other factors like high bilirubin, low ALT and to severity of coagulopathy as evidenced by many previous studies.^{5,7,10,15} Latif et al¹¹ reported in their series, high mortality of 86% among patients with INR >4 as compared to 36% among children of INR <4 and our results are also comparable to the previous observations.

Squires et al³ identified INR >2.55 as risk factor to death. Serum bilirubin and ALT are also predictive factors of mortality because high serum bilirubin with lower ALT reflects the severity of dysfunction and liver injury. The results of our study showed that higher bilirubin i.e 13.0±8.0 mg/dl in expired patients as compared to 6,7±3.3 mg/dl in recovered patients, while lower ALT i.e 467±382IU/L in expired patients as compared to 1834±1550 in recovered patients These observations are similar to the previously reported studies.^{3,7,10,11,13}

CONCLUSION

Fulminant hepatic failure is a rare but potentially lethal disease. Viruses are one of the important causes of FHF in children and HAV and HBV were found the most common viruses causing FHF. Children with FHF with high grade encephalopathy, high bilirubin, low ALT and INR >4 had poor outcome and high mortality without liver transplant. Wide spread use of timely and proper vaccination against HAV and HBV can reduce the high mortality and morbidity.

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