

Risk factors for Fulminant Hepatic Failure and their relation with outcome in children

Nazia Latif,¹ Khalid Mehmood²

Department of Paediatrics, Civil Hospital, Karachi,¹ National Institute of Child Health, Karachi.²

Abstract

Objective: To identify the risk factors for fulminant hepatic failure (FHF) and their relation with the outcome in children.

Methods: Descriptive case study was conducted at National Institute Of Child Health. Fifty patients having clinical and biochemical markers suggestive of FHF were included in this study and data was extracted from files, retrospectively. Their outcome was noted as expiry or recovery during hospital stay.

Results: The most common etiology found was viral in origin present in thirty-seven (74%) cases. Out of them twenty-eight (56%) had HAV and nine (18%) had HBV. Thirteen (26%) patients were negative for acute serology of hepatotropic viruses, out of them four (8%) had Wilson's disease and one (2%) had autoimmune hepatitis. Etiology could not be established in eight (16%) cases. Thirty (60%) patients expired and twenty (40%) patients recovered.

Conclusion: FHF is not uncommon in children. Hepatitis A is most common cause in paediatric age group. Age less than 4 years, higher degree of encephalopathy, INR >4, higher serum bilirubin with lower SGPT has poor outcome and mortality is high without liver transplantation (JPMA 60:175; 2010).

Introduction

Fulminant hepatic failure remains a rare but devastating disease.¹ FHF is the most feared complication of hepatitis in children. Clinically, the syndrome was described as sudden and severe impairment of hepatic function resulting in jaundice and followed by hepatic encephalopathy within eight weeks of the onset of jaundice, in absence of prior liver disease.²

In Pakistan, viral hepatitis is endemic and is punctuated by periodic outbreak. Almost all known hepatitis viruses, A to G are prevalent here.³ Aziz et al⁴ in their study, demonstrated prevalence of hepatotropic virus in population of age 14 years and above and 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%. HAV is seen mostly in childhood due to substandard hygienic conditions leading to feco-oral transmission. In young children HAV is either sub clinical or results in mild clinical jaundice lasting for 2 to 3 weeks. However, sometime HAV is also associated with progressive hepatic failure and death.⁵ One to two percent of patients with viral hepatitis experience liver failure.⁶

Establishing the underlying disease may be important because it can influence treatment options, determine prognosis and help to counsel families as illustrated by the following observation:

Acetaminophen overdose is treated with N-acetylcysteine. Herpes virus hepatitis is treated with acyclovir

and autoimmune hepatitis is treated with prednisolone and azathioprine.⁷ Family members of patients with Wilsons disease require screening for presymptomatic disease.⁸ The maximum International Normalized Ratio (INR) reached during the course of illness is a sensitive predictor of outcome. With an INR of 4 or more than 4, the mortality rate reaches 86%, with an INR of less than 4, it is as low as 27%.⁷

Survival rate of 50 to 75 % is being achieved in-patients with poorest prognosis after orthoptic liver transplantation.⁶

FHF and its consequences must be readily recognized, so that appropriate management can be administered. Supportive care remains the main stay of treatment and liver transplantation has provided the means to rescue such patient from death.⁹

There is very scarce data available regarding FHF in children. This study was conducted to identify the risk factors for FHF and their relation with high mortality in children presenting with FHF.

Patients and Methods

A descriptive study was conducted at National Institute Of Child Health (NICH) Karachi from September 2006 to February 2007. Retrospective data from previous files was collected. Patients of ages between 1 to 15 years, who presented with FHF in absence of pre-existing liver disease were included in this study. Diagnosis of FHF was clinically suspected in jaundiced patients who developed encephalopathy within 8 weeks of onset of Jaundice and

having evidence of coagulopathy i.e. prothrombin Time (PT) deranged >4 seconds of control and deranged liver function i.e. total serum bilirubin more than 1.5 mg/dl, SGPT more than 40 IU/L. Patients having preexisting decompensated liver disease and cirrhosis were excluded.

All patients were subjected to history, clinical examination and investigation. Chronic liver disease (CLD) was excluded by absence of chronic history and sign of CLD (ascites, splenomegaly). Encephalopathy was classified in four grades; Grade I included patients who presented with period of lethargy and reversal of sleep pattern, Grade II included the patients who presented with drowsiness and inappropriate behaviour, Grade III included the patients who presented with confused and incoherent speech with hyperreflexia and rigidity and Grade IV included patients who were comatosed with areflexia and flaccidity. Baseline liver function test (serum bilirubin, SGPT), coagulation screening (Prothrombin Time PT, International Normalized Ratio INR) 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 disease (24 hour urinary copper, serum ceruloplasmin) and Autoimmune hepatitis (Antinuclear antibody ANA) were done in those cases who were negative for acute serology of hepatitis A to E virus. None of the patients had history of ingestion of hepatotoxic drugs therefore drug levels were not done. Outcome of patient was noted as recovery or expiry during hospital stay. The outcome was related clinically with respect to their age and grade of encephalopathy and biochemically with respect to their Bilirubin, SGPT and INR. The collected data was analyzed by using statistical program SPSS Version 13.0. Frequency and percentages were computed to present all categorical variables including sex, grade of encephalopathy, causes and outcome of patients while quantitative variables like age, SGPT, Serum Bilirubin and INR were presented by Mean \pm Standard deviation.

Results

During the study period, 50 patients were enrolled. There were 29 (58%) males and twenty one (42%) females. The mean age was 6.7 ± 3.5 years (range 1-14 years).

The most common cause of FHF was viral hepatitis present in 37 (74%) cases, while 13 (26%) patients were negative for acute serology of hepatotropic viruses, 4 (8%) of them had Wilson's disease, one (2%) had autoimmune hepatitis while etiology could not be established in 8 (16%) cases. Among the viral hepatitis (74%), Hepatitis A was found in 28 (56%) and hepatitis B in 9 (18%). Hepatitis C, D and E were not found in any patient.

Conservative management was given to all patients, Thirty patients expired and mortality was 60%, while twenty

Figure-1: Age distribution and outcome of FHF (n=50).

(40%) patients recovered.

Patients with FHF were divided in to three age groups (i.e. 1-4 years, 5-9 years and 10-14 years). Most of the patients were between 5-9 years, however, mortality was seen more among children below 4 years of age (Figure-1).

Among 50 patients with FHF, 28 (56%) patients presented with grade III encephalopathy, followed by 15 (30%) presenting with grade II. Six (12%) presented with grade IV and one (2%) patient with grade I. All patients with grade IV and 24 (85.7%) out of 28 patients with grade III encephalopathy expired (Figure-2).

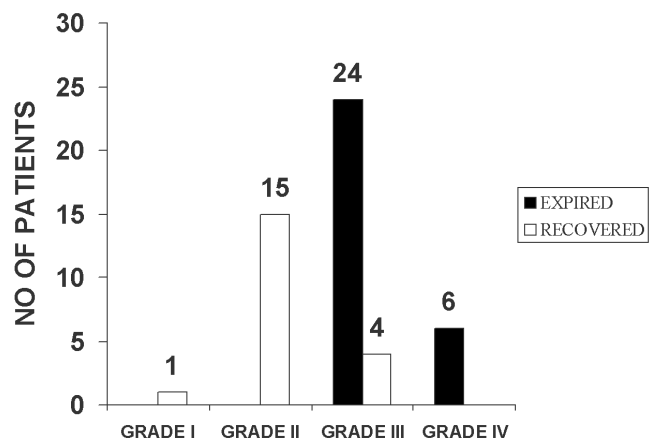


Figure-2: Grade of encephalopathy and outcome of FHF (n=50).

Regarding biochemical profile of patients with FHF, the expired patients had higher serum bilirubin level i.e. 13.5 ± 8.2 mg/dl as compared to 7 ± 3.1 mg/dl in recovered patients. SGPT was lower in expired patients i.e. 457 ± 385.7 IU/L as compared to 1824.3 ± 1556.8 IU/L in recovered patients.

Patients with FHF were sub grouped regarding INR value 4. With an INR of 4 or more than 4, the mortality rate reached 84%, while an INR of less than 4 the mortality was as

Table: Correlation of INR value in FHF with outcome (n = 50).

| INR | Outcome | | Total n (%) |
|---------|------------------|--------------------|----------------|
| | Expired n (%) | Recovered n (%) | |
| Up To 4 | 9(36%) | 16(64%) | 25(100%) |
| >4 | 21(84%) | 4(16%) | 25(100%) |

INR: International Normalized Ratio.

low as 36% (Table).

Outcome of patients with FHF depends on age, grade of encephalopathy and biochemical variables like serum Bilirubin, SGPT and INR. Mortality rate was found higher in patients less than 4 years of age, who were with grade III or IV encephalopathy and who had higher bilirubin, with lower SGPT and INR value more than 4.

Discussion

The present series has provided information regarding etiology; presentation and prognosis of patients with FHF admitted in NICH a tertiary care hospital.

The etiology of FHF shows interesting pattern in various age groups and various geographical areas in different countries and even within the same country. Viral hepatitis is uncommon in Western Europe and other developed countries where the chief offenders are drugs and toxins especially acetaminophen.¹⁰ While viral hepatitis is the commonest cause of FHF in developing countries as reported from India by Poddar et al,¹⁰ where viral hepatitis was positive in 94% of cases including HAV in 51%, HEV in 25%, HAV + HEV in 10% and HBV in 7.5%. In this study, it was also noted that viral hepatitis is the major cause of FHF, which constituted 74% of cases, including HAV in 56% and HBV in 18%.

There is no local published data regarding etiology of FHF in children, however, some local studies reported in adults have shown predominantly HBV. A study in adults showed HBV in 40%, HEV in 25% and HAV in 15% among 18 patients.² Another study conducted at Civil Hospital Karachi showed HBV in 47.5% and HCV in 7.5% among 40 patients.¹¹

The study highlights that children are more prone to acquire hepatitis A virus in our population due to high prevalence and poor socioeconomic condition. Almost 100% of population in developing world has been exposed to HAV by age of fourteen years.⁴ Hepatitis A accounts fifty to sixty percent of all cases of acute viral hepatitis in children in Pakistan. Although 90% of hepatitis A infection is sub clinical but there is <1% chance of developing fulminant hepatitis.⁵

Among non-viral causes, metabolic and drug-

induced hepatitis are major causes. In this study, 4 (8%) patients had Wilson's disease and one (2%) had autoimmune hepatitis. Bandre et al¹² also found Wilson's disease in 2 out of 36 children with FHF. In another study Squires et al¹³ observed metabolic induced FHF in 10% and autoimmune hepatitis in 6% cases among 348 children with FHF.

Although drug induced fulminant hepatitis is a major cause of FHF in western world, no case of drug-induced hepatitis was detected in this study. A few cases have been reported in some studies such as Bandre et al¹² who found drug induced FHF in 2 out of 36 children with FHF. In another study Squires et al¹³ also observed acetaminophen toxicity in 14% and non acetaminophen drug related hepatotoxicity in 5% out of 348 children with FHF less than 18 years.

We could not find any definite cause of FHF in 8 (16%) of our patients. No cause could be identified in twenty two percent cases by Bandre et al,¹² six percent cases by Poddar et al¹⁰ and forty nine percent cases by Squires et al.¹³ Obviously, some unknown environmental toxins, metabolic disorder, non A-E viruses or other infectious agent have to be investigated as causative agents.

Mortality of patients in this study was sixty percent that is high as compared with the centers not doing liver transplant. Mortality was thirty nine percent in a study by Bandre et al,¹¹ twenty five percent by Poddar et al.¹⁰ Squires et al¹³ observed mortality of 20.8% among 235 children who were not transplanted as compared to 7% among 113 children who were transplanted. Mortality in this study was higher than other studies due to the fact that most of the patients presented in grade III and IV encephalopathy.

Patients' outcome was influenced by number of factors including age, grade of encephalopathy, severity of cougulopathy and liver function test such as serum bilirubin and SGPT.

In this study, mortality was highest among children below 4 years of age. Other studies also observed higher mortality in younger age group such as Squires et al¹³ showed higher mortality among children less than 3 years of age. Poddar et al¹⁰ also found mean age of expired patients was 4.4 ± 2.9 years as compared to mean age 6.2 ± 3 years in recovered patients.

Grade of hepatic encephalopathy remains an important predictor of outcome. Grade III and grade IV has poor outcome because these stages are commonly associated with cerebral oedema. In the present study, 85.7% of patients with grade III and 100% of grade IV expired as compared to none of patients with grade II or I. Other studies also reported higher mortality in higher grade of encephalopathy such as Bandre et al¹² who showed that 12 out of 14 children with grade III and grade IV

encephalopathy expired as compared to only 2 out of 22 patients with grade I and II. Similarly Poddar et al¹⁰ observed that all patients with grade I or II and 19 (53%) with grade III or IV recovered while 17 (47%) with grade III or IV expired. Squires et al¹³ observed that only 25% of grade III or IV had a spontaneous recovery.

Poor outcome is also related to severity of coagulopathy as evidenced by many studies such as Bandre et al¹² observed PT 32 seconds in expired patients as compared to 18.8 seconds in recovered patients. Squires et al¹³ identified INR ≥ 2.55 as risk factor to predict death. Similarly, the current study showed 86% mortality among patients with INR ≥ 4 as compared to 36% among children with INR < 4 .

Total bilirubin and SGPT are also predictive factors of mortality because high serum bilirubin with lower SGPT reflects the severity of liver dysfunction and liver injury. The current study showed higher bilirubin i.e. 13.5 ± 8.2 mg/dl in expired patients as compared to 7.1 ± 3.1 mg/dl in recovered patients while lower SGPT i.e. 457 ± 385.7 IU/L in expired patients as compared to 1824 ± 1556.8 IU/L in recovered patients. Similarly Bandre et al¹² observed higher bilirubin in expired i.e. 13.9 versus 10.9mg/dl in recovered patients and lower SGPT in expired i.e. 530.6 versus 1385IU/L in recovered patients. Poddar et al¹⁰ also reported a higher serum bilirubin in expired i.e. 434 μ mol/L versus 219 μ mol/L in recovered patients. While Squires et al¹³ identified serum bilirubin > 5 mg/dl as a risk factor to predict death.

Conclusion

Hepatitis A constitutes major bulk of causative organism of FHF. Younger age (< 4 year), Grade III and IV of encephalopathy, prolonged INR (INR ≥ 4) and elevated serum bilirubin with lower SGPT are associated with poor

outcome. The mortality rate is quite high, as we do not have the facilities of hepatic transplantation and methods of artificial liver support. It will be improved if these facilities are provided in our country.

Acknowledgement

Authors would like to acknowledge the help provided by Dr Ambreen and also grateful to Dow University Senior Research Officer Masood Hussain Rao for statistical advice.

References

1. Vaquero J, Bleit AJ. Etiology and management of fulminant hepatic failure. *Curr Gastroenterol Rep* 2003; 5:39-47.
2. Ali L, Fatima N, Shah MA, Hussain I. Fulminant Hepatic Failure: A devastating problem. *J Coll Physicians Surg Pak* 2000; 10:255-7.
3. Almani SA, Memon AB, Qureshi AF, Memon NM. Hepatitis viral status in Sindh. *The Professional* 2002; 9:36-43.
4. Aziz S, Muzaffar R, Hafiz S, Abbas Z, Zaar MN, Anwar SA, et al. Helicobacter pylori, hepatitis viruses A, C, E antibodies and HBsAg prevalence and associated risk factor in paediatric communities of Karachi. *J Coll Physician Surg Pak* 2007; 17: 195-8.
5. Shah U, Habib Z, Kleiman RE. Liver failure attributable to hepatitis A virus infection in a developing country. *Paediatrics* 2000; 105:436-8.
6. Suchy FJ. Fulminant hepatic failure. In: Behrman RE, Kliegman RM, Jenson HB Eds. *Nelson textbook of Paediatrics* 18th ed. Philadelphia: Saunders 2007; pp 1703-5.
7. Nazer H, Nazer D. Fulminant hepatic failure. [Online] 2008 [Cited 2008 Nov 12] Available from URL: <http://www.emedicine.com/ped/topic808.htm>.
8. Carey RG, Balistereri WF. Metabolic disease of the liver. In: Behrman RE, Kliegman RM, Jenson HB Eds. *Nelson textbook of paediatrics* 18th ed. Philadelphia: Saunders 2007; pp 1675-78.
9. Shakil AO, Mazariages GV, Karmer DJ. Fulminant hepatic failure. *Surg Clin North Am* 1999; 79: 77-108.
10. Poddar U, Thapa BR, Prasad A, Sharma AK, Singh K. Natural history and risk factor in fulminant hepatic failure. *Arch Dis Child* 2002; 87: 54-6.
11. Harron H, Fazal PA, Makki KU, Soomro IB. Causes and outcome of patients with fulminant hepatic failure. *Med Channel* 2006; 12: 6-9.
12. Bendre SV, Bavdekar AR, Bhavne SA, Pandit AN, Chitambar SD, Arankalle VA, et al. Fulminant hepatic failure: Etiology, viral markers and outcome. *Indian Paediatr* 1999; 36: 1107-12.
13. Squires RH Jr, Shneider BL, Bucuvalus J, Alonso E, Sokol RJ, Narkewicz MR, et al. Acute liver failure in children: the first 348 patients in the paediatric acute liver failure study group. *J Pediatr* 2006; 148: 652-8.