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ORIGINAL ARTICLE

Clinical Spectrum and Etiology of Pediatric Fulminant Hepatic Failure in Pakistan

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ABSTRACT

Objective: To determine the clinical spectrum and etiology of pediatric fulminant hepatic failure (FHF) in Pakistan.
Study Design: Prospective, cross sectional study
Place and Duration of Study: Department of Pediatric Gastroenterology, Hepatology & Nutrition, the University of Child Health & the Children's Hospital, Lahore, from December 2013 to March 2016.
Materials and Methods: Patients 2 -15 years, admitted in the unit with FHF, were included after taking informed consent from the parents, employing consecutive sampling. FHF was defined as presence of acute liver failure (INR>2.0) with/without hepatic encephalopathy, without preexisting liver disease, within 8 weeks of the onset of clinical liver disease. Patients with preexisting liver disease, systemic disease such as hemophagocytic lymphohistiocytosis or leukemia were excluded.
Results: Total 85 patients, who fulfilled the inclusion and exclusion criteria, were admitted during the study period. There was a slight male predominance (54.1%) with mean age as 6.3±3.8 years. The largest age group (54.1%) comprised of younger children with age 2-5 years. Infectious causes were most common (52.9%) in our participants followed by undetermined etiology (15.3%). More than 50% of patients has good outcome.
Conclusion: Hepatitis A was the most common etiological agent of pediatric FHF. Majority of children improve with supportive care.
Keywords: Clinical spectrum, Etiology, Pediatric fulminant hepatic failure.

INTRODUCTION

Pediatric fulminant hepatic failure (FHF) is a multisystem, devastating disease of children that can lead to hepatorenal failure, hepatopulmonary failure, hemodynamic instability, cerebral edema, sepsis, coagulopathy and sometimes aplastic anemia[1]. It is defined as biochemical evidence of liver injury (less than 8 week duration) with no underlying coexisting chronic liver disease and coagulopathy which is not corrected by vitamin K with INR>1.5 or PT>15 seconds if patient has encephalopathy or INR>2.0 or PT>20 seconds regardless of presence of clinical encephalopathy[2]. Overall incidence of FHF in developed countries is 10 per million. However, in developing countries, the exact incidence is unknown, but it has estimated to be higher due to increased rates of hepatotropic infections[3].

Pediatric FHF has varied etiology with viral hepatitis being the most common followed by Wilson disease, autoimmune hepatitis and drugs[4-6]. Rapidly worsening jaundice, abdominal pain, anorexia, fever, vomiting, hypoglycemia, irritability, changes in sleep pattern and seizure are the most common clinical presentation[7,8]. Progression of severe symptoms and rapid deterioration of disease needs timely decision for liver transplantation, in absence of which the mortality could be as high as 80-90%. Due to scarce liver transplant centers in our country and insufficient number of liver donations, it is necessary to identify poor prognostic factors for the disease progression. Studies have suggested

grade of encephalopathy, raised bilirubin, deranged liver enzymes, coagulopathy, hyponatremia, and renal failure at presentation are important prognostic factors[9].

In developing countries like Pakistan, there is very little data about clinical spectrum and etiology of FHF in Pediatric population. In this study, we determined the clinical spectrum and etiology of Pediatric FHF as early detection of this condition could alert pediatrician for prompt management, and be vigilant for timely referral to specialist set up in country.

MATERIAL AND METHODS

This prospective cross-sectional study was conducted at the Department of Pediatric Gastroenterology, Hepatology and Nutrition at the University of Child Health & the Children's Hospital, Lahore from December 2013 to March 2016. All patients whom age was between 2 years to 15 years, who were admitted in the unit during study period fulfilling the FHF criteria, were included after taking informed consent from the parents, employing consecutive sampling. FHF was defined as presence of acute liver failure (INR>2.0) with/without hepatic encephalopathy, without preexisting liver disease, within 8 weeks of the onset of clinical liver disease. As the diagnosis of HE is difficult in infants younger than 1 year, they were not included. Similarly, patients with preexisting liver disease, systemic disease such as hemophagocytic lymphohistiocytosis or leukemia were excluded. Children, who expired during work up or in whom work up could not be completed, were also excluded.

Clinical history, examination findings, age, gender, height, weight, liver function tests, INR, serum albumin and blood sugar were recorded for individual patient through a predesigned proforma. Advanced work up to determine the specific etiology like serum ceruloplasmin, 24 hours urinary copper, autoimmune profile, metabolic work up, blood culture and septic work up was sent individually according to the standard departmental protocol. The data was entered and analyzed using SPSS 23.

RESULTS

85 patients, who fulfilled the inclusion and exclusion criteria, were admitted during the study period. There was a slight male predominance (54.1%) with male to female ratio of 1.1%, with mean age as 6.3±3.8 years. The largest age group comprised of younger children as shown in Table-I.

Table 1: Demographic features and outcome of participants

Feature	n(%age)
Gender	
Male	46(54.1%)
Female	13(16.6%)
Age Group (mean 6.3±3.8 years)	
2-5 years	10(17.8%)
6-10 years	38(67.8%)
11-15 years	8(14.2%)
Outcome	
Discharge	53(62.4%)
Expired	32(37.6%)

The patients went through a series of various laboratory investigations whom mean value with

Among etiologies of FHF, infectious causes were most common (52.9%) in our participants. Table III shows the final breakup according to the causative agent.

Table 2: Laboratory investigations

Feature	Mean(Range)
Bilirubin (mg/dl)	21.7(4.8-41.6)
ALT (U/L)	1215.5(23-2150)
AST (U/L)	1546.2(28-2200)
ALP (U/L)	361 (90-3488)
Albumin (gm/l)	3.2(1.7-4.4)
PT (sec)	38.5(0-47)
INR	5.4(1.8-13.9)

Table 3: Etiology of pediatric fulminant hepatic failure

Etiology		n(%age)
Infective	Hepatitis A	32(37.6%)
	Hepatitis E	05(5.9%)
	Hepatitis B	04(4.7%)
	Enteric Fever	04(4.7%)
Undetermined etiology		13(15.3%)
Drug induced		11(12.9%)
Autoimmune hepatitis		08(9.4%)
Metabolic		08(9.4%)

DISCUSSION

FHF is a dramatic and challenging syndrome with rapid progression and high mortality. Therefore, it needs earlier diagnosis and expert management to avoid any irreversible loss[10]. Though different geographical areas might have different etiologies for FHF, the final common pathway leading to liver failure is similar[11]. Determination of specific etiology for FHF is necessary as specific treatment can reverse the worse scenario and patient can survive on native live. Nowadays orthotropic liver transplant is an established treatment option though the pediatric liver transplant centers in Pakistan are scarce. N-acetylcysteine therapy for FHF is another beneficial treatment option[12].

The mean age of our patients was 6.3±3.8 years with 54.1% children comprising of younger age group, 2-5 years. Jamro and colleagues performed a similar study, and their mean age was also 6.3 years (range 1-14 years)[13]. However, their major age group suffering from FHF was between 5-9 years. Silverio and colleagues also performed a similar study but they found infant age group to be mostly involved than other age groups. 8Males were predominant in our study (54.1%) which was similar to Talat and colleagues where males were 61%[14]. In contrast to us, female predominance (42.9%) was documented by Colleti et al[5]. The fatality rate of our patients was quite higher 37.6%. Similar higher fatality rates of 39% have been reported by Bender et al[15].

The mean bilirubin level in our patients was 21.7mg/dl, which was similar to Talat et al who recorded mean bilirubin to be 25.73mg/dl[10]. However much lower values of 13.0±8.0 mg/dl have been mentioned by Jamro and colleagues[13]. LFTs were markedly deranged in our study group, mean value of ALT & AST being 1215.5 and 1546.2, respectively. Mean values of ALT & AST up to half as compared to ours; have been documented by Silverio et al, which are in contrast to our findings[8]. Our findings of PT being 38.5 seconds was comparable to Talat et al[14], (36 seconds) but much prolonged when compared to 25 seconds recorded by Bendre et al[15]. Similarly, serum albumin levels of 3.2g/dl were higher when compared to Nabi et al and Talat et al and where generally mean serum albumin levels were less than 3mg/dl[10,14].

The most common cause of FHF in our study turned out to be Hepatitis A virus. Other local studies from our country[13,15] and neighbouring countries[16] too concluded Hepatitis A as the most common aetiologic for FHF in children. However, Nabi and colleagues found HEV to be most prevalent (22.5%) in their study cohort. Similarly, studies from UK found acetaminophen over dosage as the most common cause of FHF[17]. Drug induced FHF in our study were only 12.9%. The second major chunk comprised of undetermined aetiology, in which no cause could be ascertained by the available investigation's options. However, percentages as high as 30% and 31.2% has been mentioned for undetermined aetiology by Alonso et al and Nabi et al[18,10].

The study shows that the predominant cause of FHF in children are infectious aetiology, hepatitis A being the most common followed by undetermined aetiology. However, every effort should be done to determine the aetiology as outcome is dependent on proper management according to causative agent. This study also undermines the importance of improved sanitation indirectly to avoid the infective aetiology. The small sample size, lack of correlation between survivors and expired patients according to severity of clinical condition and labs, were the limitations of study.

CONCLUSION

Hepatitis A was the most common etiological agent of pediatric FHF. Majority of children improve with supportive care.

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