RESEARCH BRIEF

Etiology and Prognostic Factors of Acute Liver Failure in Children

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Acute liver failure (ALF) is a life-threatening condition characterized by jaundice, encephalopathy and coagulopathy leading to multiorgan failure in a patient with no prior history of liver disease. Forty three consecutive patients of ALF admitted in Pediatric ICU were studied for etiology and prognostic factors. Etiology was established in 91% cases. Viral infections were the most common cause. Mortality rate was 44%. Increasing grade of encephalopathy, >7 days interval between the onset of prodromal symptoms and encephalopathy, blood glucose <45mg/dL, serum bilirubin > 10mg/dL and pH <7.35 or >7.45 on admission were found to be associated with increased risk of mortality.

Key words: *Fulminant liver failure, Hepatic encephalopathy, Outcome, India.*

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Acute liver failure (ALF) is a rapidly progressive, potentially fatal syndrome caused by a large variety of insults. It is defined as presence of biochemical evidence of liver injury (deranged transaminases) and coagulopathy not corrected by parenteral vitamin K administration with International Normalized ratio (INR) ≥1.5 in the presence of encephalopathy or an INR >2 with no evidence of encephalopathy [1]. The etiology of ALF varies according to the age of patient and development of the country [2-4]. The survival rate of ALF also varies according to etiology – survival is better in few etiologies like paracetamol poisoning whereas it is poor in metabolic diseases [4,5]. Because of the shortage of facilities of liver transplantation (LT), a large number of patients of ALF die without undergoing LT. Determining the prognosis of ALF is vital when considering the patient for LT so as to identify those patients who are unlikely to survive without LT and assessing the probability of successful LT. The present study was undertaken to study the underlying etiology and prognostic markers of ALF in children under 18 years.

METHODS

It was a prospective cohort study conducted in Pediatric Intensive Care Unit (PICU) of a tertiary care teaching hospital from November 2008 to March 2010 after obtaining institutional ethical clearance. All consecutive children <18 years old, fulfilling the case definition of acute liver failure were recruited [1]. Patients with a past history of liver disease or features of chronic liver disease on examination were excluded. After receiving informed consent, the patients were subjected to hematological and biochemical investigations. All patients were tested for viral markers for hepatitis. Investigations for other infections like dengue, malaria and enteric fever were conducted, wherever clinically indicated. All children less than 1 year age were investigated for Galactosemia and neonatal hemochromatosis; the former by detection of urinary reducing substances and by Galactose 1 phosphate uridyl transferase assay and the latter by serum ferritin levels. All children more than 1 year old were screened for autoimmune hepatitis and Wilson disease (serum ceruloplasmin, presence of KF ring and 24 hours urinary copper levels). All the patients were monitored for hypoglycemia and were managed according to the standard ICU protocols. This included maintaining fluid and electrolyte balance, euglycemia maintainence, protein restriction, bowel wash and lactulose. The standard treatment for clinical evidence of cerebral edema included: head end elevation, maintaining normotension, fever control, limiting non-essential physical examination, correction of hypoxemia and hypercapnia by mechanical ventilation, and mannitol infusion. Fresh-frozen plasma was infused for bleeding manifestations as per standard recommendations. Broad spectrum antibiotics were given empirically. Prognostic factors were studied by dividing cases into two groups according to the final outcome: Group A comprised of those patients who expired while group B comprised of those who improved and were discharged.

Data were analyzed using SPSS statistical software version 13.0. Univariate and multivariate analysis was used for comparison

RESULTS

During the study period 58 children were admitted with liver failure. Fifteen patients were excluded due to past history of liver disease or physical signs of chronic liver disease, expiry within few hours of admission and refusal of consent. The study population included 43 children (30 boys) with a mean age of 4.8 year. ***Table* I** depicts baseline clinical and biochemical characteristics of patients. Etiology was established in 39/43 (91%) children (***Table* II**). Infections were the most common cause (77%) with viral hepatitis (hepatitis A-E) in 72% cases. 19 patients (44%) constituted Group A and 24 patients (56%) constituted Group B. Patients in whom the interval between onset of prodromal symptoms and onset of encephalopathy was >7 days had a significantly higher mortality rate (77%) in comparison to those with an interval of < 7days (34%; *P*=0.015). ***Web Fig.*1** shows the ROC curve plotted. An interval of >4.5 days was found to be predictor of mortality with a sensitivity of 77.8% and specificity of 66.7% (Area Under Curve 0.718, *P* value 0.026). Mortality rate increased in proportion to stage of encephalopathy. The mortality in children with blood glucose ≤45mg/dL was higher than those with levels >45mg/dL. On applying multiple logistic regression analysis, interval of greater than 7 days between prodromal symptoms and encephalopathy and blood glucose ≤45mg/dL were found to be predictors of mortality.

DISCUSSION

Since ALF is a potentially fatal condition, estimating the likelihood of spontaneous recovery and identifying patients who cannot be salvaged without LT is necessary. Prognostic factors that predict mortality and need for early LT are required. Our study results highlight the fact that viral hepatitis remains the most common cause of ALF in India. The presence of following factors was found to predict mortality: subacute presentation, higher grade of encephalopathy, higher bilirubin, hypoglycemia and deranged pH.

We were able to establish etiology in larger number of patients as compared to previous studies [5,6]. Our results were different from developed countries that showed that viral hepatitis account for < 10% cases of ALF but are consistent with previous Indian studies that showed that viral hepatitis is the most common cause of mortality [5,7,8]. It highlights that the burden of ALF can be decreased by decreasing viral hepatitis prevalence.

TABLE I DIFFERENCE IN CLINICAL AND LABORATORY PARAMETERS IN THE 2 GROUPS

Parameter	*Number N=43 (100%)*	*Group A (death) N=19 (44%)*	*Group B (discharged) N=24 (56%)*	*P value*
Age				
<1 yr	6 (14%)	4/6 (67%)	2/6 (33%)	0.714
1- 5 yr	19 (44%)	7/19 (37%)	12/19 (63%)	
5- 10 yr	14 (32.5%)	6/14 (43%)	8/14 (57%)	
>10 yr	4 (9.3%)	2/4 (50%)	2/4 (50%)	
Sex				
Male	30 (70%)	12/30 (40%)	18/30 (60%)	0.5
Female	13 (30%)	7/13 (54%)	6/13 (46%)	
Bleeding				
Yes	19 (42%)	11/19 (58%)	8/19 (42%)	0.1
No	24 (58%)	8/24 (33%)	16/24 (67%)	
Interval between onset of prodromal symptoms and encephalopathy				
<7 days	23 (56%)	8 (34%)	15 (66%)	0.015
>7 days	13 (34%)	10 (77%)	3 (23%)	
Encephalopathy grade				
0	7 (16%)	1/7 (14%)	6/7 (86%0	0.001
1	5 (11%)	1/5 (20%)	4/5 (80%)	
2	12 (28%)	2/12 (16%)	10/12 (84%)	
3	14 (32.5%)	10/14 (71%)	4/14 (29%)	
4	5 (11%)	5/5 (100%)	0/5 (0%)	
Blood glucose				
≤45mg/dL	8 (19%)	8/8 (100%)	0/8 (0%)	0.001
>45mg/dL	35 (81%)	24/35 (68%)	11/35 (32%)	
Mean ± SD		62.71± 24.73	89.17± 16.89	0.002
Total serum bilirubin(mg/dL)				
<10	18 (42%)	4/18 (22%)	14/18 (78%)	0.014
>10	25 (58%)	15/25 (60%)	10/25 (40%)	
pH				
<7.35	11 (26%)	7/11 (54%)	4/11 (36%)	0.038
7.35-7.45	25 (58%)	7/25 (28%)	18/25 (72%)	
>7.45	7 (16%)	5/7 (72%)	2/7 (28%)	

We also found that higher grade of encephalopathy and <7 days duration between onset prodromal symptoms and encephalopathy predict mortality similar to previous studies. [4,5,7]. Total serum bilirubin has been proposed to be a predictor of mortality in various studies [4,9,10]. We found that the prognosis of ALF worsens if total serum bilirubin levels increase beyond 10mg/dL. Also, the mortality was higher when indirect bilirubin was more than direct bilirubin, although the result was not statistically significant.

WHAT THIS STUDY ADDS?

- Viral hepatitis remains the commonest cause of acute liver failure in Indian children.

Srivastava, *et al*. [9] proposed that hypoglycemia (blood glucose < 45mg/dL) predicts mortality [9]. We also found that hypoglycemia is an independent predictor of mortality. It highlights the fact that early detection and appropriate treatment of this potentially treatable complication can improve the outcome. Deranged pH was also found to be a marker for poor prognosis similar to previous studies [11].

INR was comparable in both the groups showing that INR cannot be used as a prognostic factor in contrast to previous studies [4,9,11] The difference in results can be explained by the fact that the liver is the source of all clotting and anticoagulant factors. This balanced reduction in both factors explains the relative infrequency of clinically significant bleeding in ALF in the absence of provocative factor like infection or portal hypertension [12].

As viral hepatitis was the most common etiological agent, it highlight the fact that simple interventions like improving hygienic practices and immunization coverage can substantially decrease ALF. Our study carries various limitations because of the small sample size and hence generalization of our study results needs further research using a larger sample size.

Contributors: SK collected data, prepared the manuscript. PK conceived, designed the study and revised the manuscript for important intellectual content. VK and SKS reviewed the design and revised the manuscript. PK, VK and SKS will act as guarantor of the study. AK helped in preparation of the manuscript and analysis of data. The final manuscript was approved by all authors.

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TABLE II ETIOLOGY AND ITS RELATION TO MORTALITY

Etiology	*Number N=43*	*Group A (death) N=19*	*Group B (discharged) N=24*
HAV	25 (58%)	12 (48%)	13 (52%)
HBV	2 (4.6%)	0	2 (100%)
HCV	0	0	0
HEV	2 (4.6%)	2 (100%)	0
Other infections	2 (4.6%)	0	2 (100%)
HAV plus HEV	2 (4.6%)	0	2 (100%)
Hemochromatosis	1 (2.3%)	1 (100%)	0
Galactosemia	2 (4.6%)	2 (100%)	0
Wilson's disease	2 (4.6%)	0	2 (100%)
Autoimmune hepatitis	1 (2.3%)	1 (100%)	0
Indeterminate	4 (9.2%)	1 (25%)	3 (75%)

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