Clinical and Biochemical Profile of Acute Liver Failure with Hepatic Encephalopathy in Children from Eastern Nepal

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Abstract

Introduction: Hepatic encephalopathy is a potentially reversible neurophyschiatric abnormality in the setting of liver failure. Acute liver failure (ALF) is a potentially life-threatening disorder in children. **Objectives**: The present study evaluated the clinical profile, outcome and factors influencing the outcome of children presenting with acute liver failure and hepatic encephalopathy presenting to a referral hospital of Eastern Nepal. M**ethodology**: Thirty children (17 males and 13 females) were admitted with this diagnosis during two year period.Prospective study. **Results**: The most common cause of acute liver failure was mushroom poisoning seen in 30% of cases. Only 37% (11 out of 30) children survived, most of them in early stages (Stage I and II) of encephalopathy. Bleeding manifestations were significantly more common (P=0.002) in deaths as compared to survivors. **Conclusion**: As liver failure is associated with high mortality rates especially in absence of facilities for liver transplantation, efforts should be directed in favor of implementing preventive measures such as vaccination and community education to prevent toxin ingestion.

Key Words: Acute liver failure, Hepatic encephalopathy, Mushroom poisoning

Introduction

Hepatic encephalopathy is a potentially reversible neurophyschiatric abnormality in the setting of liver failure. Acute liver failure (ALF) is a potentially life-threatening disorder in children with diverse etiology including hepatotropic viruses (A-E), metabolic disorders, drugs and toxins[1]. The exact cause of the illness remains unestablished in a significant proportion of children especially in the underprivileged settings due to lack of advanced diagnostic modalities. The outcome of the disorder also remains poor in absence of the facilities for liver transplantation[2]. It is thus important to study the clinical profile and factors influencing the outcome of children with hepatic encephalopathy in different settings. There is a paucity of data regarding the profile and outcome of children with hepatic encephalopathy in Nepal. This study was thus planned at a tertiary care referral center of Eastern Nepal to evaluate the clinico-biochemical profile, outcome and factors influencing the outcome in children admitted with a diagnosis of acute hepatic encephalopathy.

Methodology

For this hospital based descriptive study, we extracted the case records of children admitted to the Department of Paediatrics and Adolescent Medicine at B. P. Koirala Institute of Health Sciences with a diagnosis of Acute Liver Failure (ALF) with hepatic encephalopathy between July 2006 and July 2008. The diagnosis of hepatic encephalopathy was made in children who presented with altered sensorium in a setting of acute liver disease manifesting as jaundice due to conjugated hyperbilirubinemia.

A detailed history including possible exposure to toxins and drugs was elicited from the parents. Detailed clinical examination including neurological examination was done in all subjects. Based on the neurological history and examination, a clinical staging was done for hepatic encephalopathy[3]. The investigations performed in every child included blood counts, peripheral smear for malarial parasite, liver function tests [Serum Asparatate aminotrasferase (AST), Alanine aminotransferase

(ALT), Direct and Total Bilirubin levels, Serum Albumin], Prothrombin time (PT), INR, Serum electrolytes, urea, creatinine and blood culture. Viral markers included hepatitis B surface antigen (HBsAg) and antibodies against hepatitis C virus (HCV). An ophthalmological examination for Kaysner-Fleisher ring (K-F ring) was done if the child's condition allowed so. Chest x-ray, ultrasonography of the abdomen, and urine examination were done as and when required. We could not evaluate for many causes of hepatic encephalopathy in detail such as Hepatitis A, Hepatitis E and metabolic disorders because of lack of diagnostic facilities and the patients' unaffordability. All children were admitted in the Paediatric Intensive Care Unit (PICU) or paediatric wards. Monitoring was done for vital parameters and the treatment included intravenous fluids, intravenous antibiotics, ranitidine, mannitol and bowel washes. Fresh frozen plasma and blood transfusions were given whenever indicated.

The outcome was reported in terms of survivors (those who improved and successfully discharged after resolution of encephalopathy), deaths and those who left against medical advice (LAMA). Descriptive analyses were used for reporting most of the results. Student's't' test was used for comparing numeric data whereas Chi-square and Fischer exact tests were used for comparing proportions.

Results

Thirty children (17 males and 13 females) were admitted with a diagnosis of acute liver failure with hepatic encephalopathy during the study period. Ages ranged from 1 year to 14 years with mean (SD) age of 7.4 (4.2) years. The mean (SD) duration of jaundice before hospitalization was 12.5 (16.5) days whereas the mean (SD) duration of altered sensorium was 1.6 (1.8) days. Six children presented in Stage I encephalopathy, four children in stage II, eleven children in stage III and nine in stage IV of encephalopathy. Bleeding manifestations were seen in most (22 out of 30) of the children.

A history of moderate alcohol ingestion was obtained in 3 (10%) children whereas a history of toxin ingestion before the onset of jaundice was reported in nine (30%) children. Poisonous mushrooms were the toxic substances responsible for acute liver failure seen in these nine children. None of the study children was positive for HbsAg or HCV antibodies. K-F ring was also not seen in any of the study child. The hematological and biochemical parameters of the study children are presented in Table 1**.** A prolongation of PT (INR > 1.5) was seen in 77% of cases. Out of the 23 cases in which PT was prolonged, INR was more than 4 in seventeen.

Out of thirty study children, 14 (47%) children died whereas 11 (37%) children improved and were successfully discharged from the hospital. Five (17%) children left the hospital against medical advice; most of them being critically sick. Table 2 presents outcome of these children in terms of their stage of encephalopathy. Overall, the survival rates were 100%, 50%, 27% and 0% in stages I, II, III and IV, respectively. Table 3 compares the profile of children who survived with those who died. It may be argued that the children who left against medical advice were also very sick and should be clubbed along with the deaths. Thus, this table also includes the analysis with LAMA included as deaths. In general, the hemoglobin and platelet count were lower whereas the bilirubin, hepatic enzyme levels and PT were higher in deaths in comparison to survivors but these did not reach statistical significance. The serum proteins and albumin levels were significantly lower (*p*-value = 0.04 and 0.03, respectively) in the children who died when the analysis included LAMA as deaths. The bleeding manifestations were significantly more common in deaths as compared to survivors irrespective of whether LAMA excluded from analysis (*p* value = 0.002) or included with deaths (*p* value = 0.000).

Table 1: Showing Characteristics of Children with Hepatic Encephalopathy (n=30)

Parameters	Mean	Standard Deviation (SD)
Age	7.40	4.18
Duration of Jaundice	12.53	16.48
Duration of Altered Sensorium	1.60	1.77
Hb	8.69	2.50
TLC	1.84	0.83
Platelet count	1.89	1.27
PT	54.66	33.24
INR	4.19	2.14
ALT	886.75	886.83
AST	701.39	629.61
Alkaline Phosphatase	847.50	442.68
Serum Bilirubin Total Direct	 17.03 8.00	 9.53 6.49
Serum Proteins Total Albumin	 5.99 3.36	 1.03 1.10
Na^+	130.20	8.79
K^+	3.97	0.86
Urea	54.50	40.32
Creatinine	1.19	0.96

Table 2: Showing the outcome in Relation to Stage of Encephalopathy

Stage	Deaths	Survivors	LAMA
I (n=6)	0	6	0
II (n=4)	2	2	0
III (n=11)	6	3	2
IV (n=9)	6	0	3

Table 3: Comparison of Clinical and Laboratory Parameters between Deaths and Survivors.

Parameter	Outcome			Outcome with LAMA included as deaths		
	Deaths (n=14)	Survivors (n=11)	*p* value	Deaths (n=19)	Survivors (n=11)	*p* value
Age (years)	8.4 (4.7)	6.6 (3.7)	0.31	7.9 (4.5)	6.6 (3.7)	0.43
Duration of jaundice days)	16.4 (22.4)	6.9 (8.3)	0.20	15.8 (19.2)	6.9 (8.3)	0.16
Duration of altered sensorium (days)	1.9 (2.3)	1.3 (1.3)	0.46	1.8 (2.0)	1.3 (1.3)	0.45
Sex (M:F)	9:5	4:7	0.19	13:6	4:7	0.09
Bleeding from any site	14	4	0.002	18	4	0.000
Hb	7.9 (1.8)	9.4 (2.9)	0.11	8.3 (2.2)	9.4 (2.9)	0.22
TLC	1.77 (0.80)	1.87 (0.96)	0.77	1.83 (0.76)	1.87 (0.96)	0.88
Platelet count	1.58 (0.97)	2.50 (1.53)	0.09	1.58 (1.02)	2.50 (1.53)	0.06
PT	61.8 (30.8)	40.6 (30.3)	0.10	63.2 (32.8)	40.6 (30.3)	0.07
INR	4.60 (1.71)	3.25 (1.91)	0.08	4.76 (2.11)	3.25 (1.91)	0.06
ALT	1145.3 (943.4)	706.2 (734.5)	0.22	1003.6 (882.9)	706.2 (734.5)	0.36
AST	981.5 (657.5)	516.7 (585.2)	0.08	820.9 (645.2)	516.7 (585.2)	0.22
Alkaline Phosphatase	992 (362.1)	772.4 (507.7)	0.23	896.1 (404.0)	772.4 (507.7)	0.48
Serum Bilirubin Total Direct	 16.5 (7.3) 7.6 (6.6)	 14.4 (10.6) 6.7 (5.7)	 0.58 0.73	 18.5 (8.8) 8.8 (6.9)	 14.4 (10.6) 6.7 (5.7)	 0.26 0.40
Serum Proteins Total Albumin	 5.9 (1.0) 3.2 (1.1)	 6.5 (1.1) 3.9 (1.1)	 0.13 0.12	 5.7 (0.9) 3.0 (1.0)	 6.5 (1.1) 3.9 (1.1)	 0.04 0.03
Na	126.7 (8.5)	133.7 (8.4)	0.05	128.2 (8.5)	133.7 (8.4)	0.09
K	4.1 (0.6)	4.0 (1.2)	0.91	3.9 (0.6)	4.0 (1.2)	0.73
Urea	49.6 (31.0)	44.7 (27.6)	0.69	60.2 (45.9)	44.7 (27.6)	0.32
Creatinine	1.2 (0.8)	0.9 (0.3)	0.16	1.4 (1.2)	0.9 (0.3)	0.15

Discussion

Paediatric acute liver failure is a rare but potentially life-threatening disorder of diverse etiology. The clinical presentation of ALF includes jaundice, coagulopathy and encephalopathy. The etiology of paediatric ALF is diverse, the most common causes being viral infections and drugs. In this study, we could not find viral etiology of ALF in any case though we could not investigate for hepatitis A and E viruses because of economic constraint. Hepatitis A and E are common causes of Hepatic encephalopathy in developing countries[4,5,6] and it is possible that some of the study cases had infections with these viruses as a cause of liver failure. However, it appears that hepatitis B is no more a common cause of ALF in this part of the world. This seems to be the result of universal hepatitis B vaccination program. In nine (30%) of the cases in our series, poisonous mushroom ingestion was the cause of ALF with hepatic encephalopathy. All the nine cases in our series had initial gastrointestinal symptoms followed by apparent recovery and then progression to ALF which is reported to be the pathognomonic presentation of poisoning with cyclopeptide-containing Amanita mushrooms[7]. A high prevalence of poisoning due to different species of Amanita mushrooms including the most poisonous Amanita phalloides has earlier been reported from Nepal[8]. Chronic alcohol ingestion was reported by three children, a problem unique to children of this part of the world because of the cultural regions. It was unlikely that alcoholism was the cause of hepatic encephalopathy in these subjects as they did not have any evidence of pre-existing liver disorder, and the amount and duration of alcohol consumption were not sufficient enough to cause acute or chronic toxicity. We could not evaluate the cause of ALF in majority (70%) of the cases largely because of lack of diagnostic facilities. However, it is reported that the cause may not be apparent in 45-50% of the children with acute liver failure despite extensive investigations[2,9]. Rare metabolic disorders and unknown viral infections are postulated to be the reasons for these so called 'cryptogenic' cases[10].

Two-thirds (63%) of the study children either died or left the hospital against medical advice in a critical state Thus, the survival was only 37% which is comparable to reports from other centers in absence of liver transplantation[9,11]. More than half of our cases had a marked prolongation of PT (INR > 4), a prognostic factor associated with very high mortality[12]. Liver transplantation is usually indicated when the INR reaches four, particularly in young children. Survival after transplantation is 60% to 80% depending on patient profile and the available facilities and infrastructure[11, 12]. We tried to evaluate the factors influencing the outcome of hepatic failure. A higher stage of encephalopathy was associated with a poor outcome. Presence of bleeding manifestations was significantly more common in deaths. Coagulopathy is a common accompaniment of ALF and a marked prolongation of PT is said to be the strongest predictor of mortality[12]. Although we could not demonstrate any significant difference in the bilirubin levels, liver enzymes and PT between survivors and deaths, the interpretation is limited by small sample size of our study. In a study from Turkey, encephalopathy grade, total and indirect bilirubin levels were found to be significantly higher in patients who died[9]. In our study, serum sodium levels were also significantly lower in deaths in comparison to survivors. This could be related to the presence of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in the cases that had higher grades of encephalopathy.

Conclusion

ALF is associated with high mortality in children especially if bleeding manifestations are present. Mushroom poisoning is a relatively common cause of ALF in children from our region whereas hepatitis B virus infection has become rare. The other causes of ALF largely remain unestablished primarlily because of lack of advanced diagnostic facilities. In the absence of facilities and also because of unaffordability by the majority of patients in developing countries, liver transplantation still remains a distant dream and efforts should be directed in favor of implementing preventive measures such as vaccination and community education to prevent toxin ingestion.

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