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ORIGINAL ARTICLE

Risk Factors of Mortality in Children with Hepatic Encephalopathy

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Abstract:

Background: *Hepatic encephalopathy is a serious but potentially reversible complication in children with liver disease. The aim of this study is to evaluate the risk factors of mortality in children with hepatic encephalopathy.* ***Method:*** *Totally 42 patients including 22 boys and 20 girls with clinical diagnosis of hepatic encephalopathy who admitted to Pediatric Intensive Care Unit at Nemazee Hospital affiliated to Shiraz University of Medical Sciences, during 5 years period were enrolled in this study. Demographic features, cause of hepatic failure, grade of hepatic encephalopathy, predisposing factors, concurrent clinical manifestations and laboratory data, as possible prognostic factors were evaluated. The survival states of the patients (survivors or non-survivors) as final outcome were also documented.* ***Results:*** *The most common underlying liver diseases were cryptogenic (57.2%), hepatitis A (23.8%), Wilson disease (7.1%), and autoimmune hepatitis (7.1%). The total mortality rate was 54%. There was no statistically significant difference in age, weight and hospital stay between survivors or non-survivors groups. Only gastrointestinal bleeding had significant association with mortality (37% vs 92%; p=0.001). The most common predisposing factor was infection (52.5%). Patients with higher international normalized ratio and partial thromboplastin time and lower serum sodium and bicarbonate on admission and those with higher bilirubin, international normalized ratio, partial thromboplastin time, aspartate aminotransferase and lower platelets and serum bicarbonate level on last day were more likely to die.* ***Conclusion:*** *Poor prognostic factors for hepatic encephalopathy were included gastrointestinal bleeding, higher international normalized ratio, partial thromboplastin time, bilirubin, and aspartate aminotransferase, and lower serum sodium and bicarbonate levels and platelet counts.*

Keywords: *Hepatic encephalopathy; Mortality; Risk factors*

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Introduction

Hepatic encephalopathy (HE) is a serious and progressive but potentially reversible complication of liver disease with a wide spectrum of neuropsychiatric abnormalities and motor disturbances including mild alteration of cognitive and motor function to coma and death (1). It is estimated that HE occurs in 30% to 45% of patients with liver cirrhosis (2). The frequency of hospitalization for HE has nearly doubled over the last decade, with lengths of stay between 5 and 7 days (3). Patients with HE often have other manifestations of end-stage liver disease, such as ascites, jaundice, or gastrointestinal variceal bleeding. HE can also

develop as an isolated manifestation of decompensated cirrhosis. HE usually signals advanced liver failure, and is often considered a clinical indication for evaluation of the patients for liver transplantation (4). The risk factors which can precipitate HE consists of dehydration, infections, gastrointestinal bleeding, constipation, excessive dietary protein intake, renal failure, hypokalemia, urinary obstruction, hypernatremia, and surgery. There is few data about HE in children in the literature, because the early stages of encephalopathy are difficult to assess, and in infancy encephalopathy may not be apparent until terminal stages of liver failure (5).

In this study, pediatric HE considering demographic features, causes of hepatic failure, predisposing factors, concurrent clinical manifestations, laboratory data and risk factors of mortality will be evaluated.

Patients and Methods

Totally 42 patients including 22 boys and 20 girls with clinical diagnosis of HE who were admitted to Pediatric Intensive Care Unit (PICU) at Nemazee Hospital affiliated to Shiraz University of Medical Sciences during 5 years period were enrolled. Demographic features, cause of hepatic failure, grade of HE, predisposing factors, concurrent clinical manifestations and laboratory data, as possible prognostic factors were evaluated. The survival state of the patients (survivors or non-survivors) which considered as the final outcome was also documented. All patients had received supportive medical care.

Hepatitis A, defined as positive hepatitis A IgM antibody, registered in medical records. Wilson disease was defined as presences of Keiser Fleischer ring clinically, high urine copper content or low plasma ceruloplasmin level consistent with this diagnosis in medical records. Positive autoantibodies such as anti-smooth muscle, anti-liver-kidney-microsomal and anti-nuclear antibodies, high serum globulin level and compatible liver histology set the patients in the autoimmune causal group. And finally, the patients with no proven etiological cause were considered as cryptogenic.

The laboratory data consisting of total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, direct bilirubin; prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), blood urea nitrogen, creatinine, blood sugar, sodium, potassium, white blood cell (WBC) count, hemoglobin, platelet count, and serum bicarbonate level were also collected.

The predisposing factors of encephalopathy were included gastrointestinal bleeding, constipation, infections, use of sedatives, and electrolyte imbalance. The first four factors were registered on clinical evidence that were documented in admission note. Electrolyte imbalances were defined as contributed abnormality in admission serum sodium and potassium. Other clinical manifestations and findings such as ascites, edema, jaundice, esophageal varices, hepatopulmonary and hepatorenal syndromes and spontaneous bacterial peritonitis were registered and documented in the medical records. Esophageal varices were diagnosed endoscopically. Hepatopulmonary syndrome was diagnosed as arterial oxygen pressure of <70 mmHg in room air with alveolar/arterial gradient of >20 mmHg. Abdominal paracentesis with polymorphonuclear cells more than 250/mm3 was considered as spontaneous bacterial peritonitis.

Patients were arranged in two groups according to final outcome, survivors (n=19) and non-survivors (n=23). Collected prognostic factors were compared in these two groups to find statistical differences.

Statistical Analysis

Statistical analysis of the results was performed

using ANOVA and Student t- test with the SPSS version 19.0 software.

If the number of data regarding prognostic factors were insufficient to statistically compare analysis, only descriptive presentations were done. Multiple regression analysis was used where appropriate to define strength of association between mortality and the different risk factors.

Results

There were 22 boys (52.4%) and 20 girls (47.6%). The mean age of the patients was 9.2±4.6 years (range; 3-18 years). The mean weight of the patients was 25±13.6 kilograms (range; 8-50 kilograms). The mean duration of hospital stay was 7±5 days (range; 1-22 day).

There were no statistically differences in age; weight and hospital stay of two outcome groups ($p > 0.05$).

The most common underlying liver diseases were hepatitis A (n=10; 23.8%), Wilson disease (n=3; 7.1%), autoimmune hepatitis (n=3; 7.1%) and hepatorenal tyrosinemia (n=2; 4.8%). The 24 cases (57.2%) that didn't have any known etiology classified as cryptogenic comprised the majority group.

The most common clinical manifestations and complications on admission in decreasing order of frequency were jaundice (n=41; 97.6%), ascites (n=19; 45.2%), gastrointestinal bleeding (n=13; 31%), edema (n=7; 16.7%), hepatorenal syndrome (n=4; 9.5%), spontaneous bacterial peritonitis (n=3; 7.1%), and hepatopulmonary syndrome (n=3; 7.1%). None of these clinical presentations had statistically significant impact on outcome except gastrointestinal bleeding. (37% vs 92%; p=0.001).

The most common predisposing factors were infection (n=22; 52.4%), constipation (n=18; 42.9%), gastrointestinal bleeding (n=13; 31%), electrolytes imbalance (n=11; 26.2%), and use of sedatives (n=3; 7.1%). Some patients had multiple predisposing factor of encephalopathy.

Table 1. Comparison of laboratory data between survivors and non-survivors on the first day of admission

Laboratory data	Survivors	Non-survivors	*P*
INR	2.5	5.6	0.009
PTT (Second)	47.8	66.2	0.04
Sodium (meq/L)	136.8	131.8	0.049
Bicarbonate (meq/L)	19.8	13.6	0.001

The total mortality rate was 54% (23 patients). Unfortunately because of small sample size, we could not evaluate the relation between cause of hepatic failure and outcome of the patients, so we have presented only the percent of mortality in each causal group. The case mortality rate were 100% in autoimmune hepatitis, 66% in Wilson disease, 58% in cryptogenic, 50% in tyrosinemia, and 30% in hepatitis A groups.

Table 2. Comparison of laboratory data between survivors and non-survivors on the last day

Laboratory Data	Survivors	Non-survivors	*p*
Total bilirubin (mg/dL)	12.4	24.7	0.031
AST (IU/L)	134	813	0.045
INR	1.5	6.7	0.021
PTT (Second)	36.5	69.5	0.029
WBC (/mm^3)	8700	20000	0.05
Platelet (/mm^3)	295000	130000	0.013
Bicarbonate (meq/L)	19.1	14.1	0.012

Eleven patients (26.2%) had grade I of encephalopathy, 17 patients (40.5%) grade II, 12 patients (28.6%) grade III and only two patients (4.8%) had grade IV of encephalopathy. Because of the small sample size, we combined grade I and II as a mild encephalopathy and grade III

and IV as a severe one. Then we compared the mortality rate in patients with mild and severe encephalopathy. The mortality rate were 46.6% and 69.2% in patients with mild and severe HE, respectively, which was not statistically significant.

Patients with higher INR (p=0.009) and PTT (p=0.04), and lower serum sodium (0.049) and bicarbonate (p=0.001) on the first day of admission in PICU had significantly higher mortality. Also patients with higher bilirubin (p=0.031), AST (p=0.045), INR (p=0.021), PTT (p=0.029) and lower platelet counts (p=0.013) and serum bicarbonate (p=0.012) on the last day were more likely to die. (Tables 1, 2).

Discussion

Hepatic encephalopathy is altered brain neuropsychiatric function which occurs as a consequence of liver failure. It may be due to acute or chronic liver diseases (6,7). HE is usually associated with a poor prognosis (8).

The mean age of the patients in the present study was 9.2 years that comparable with 7.1 years in Samanta T et al study (9) but higher than Sanchez MC et al study (5.3 years) (10).

The male to female ratio in the present study was 1.1:1 but in the Samanta T et al study was 1:1.25 (9).

The most common underlying liver diseases were hepatitis A (23.8%), Wilson disease (7.1%), and autoimmune hepatitis (7.1%) in this study, while the cause of liver disease was undetermined in 57.2%. In a study in Pakistan Latif N et al found hepatitis A in 56%, Wilson disease in 8%, and autoimmune hepatitis in 2% of their patients (11). Also hepatitis A was the most common cause in other studies (9,10).

In most cases of cirrhosis with acute or chronic HE, predisposing factors are found, such as gastrointestinal bleeding, infections, renal and electrolyte disturbances (renal failure, metabolic alkalosis, hypokalemia, dehydration, and diuretic effects), use of sedative medications, constipation, excessive dietary protein intake and acute deterioration of liver function in cirrhosis (12). In our study, infection and use of sedatives were the most and least predisposing factors for HE in children, respectively. Other factors include electrolytes imbalance, gastrointestinal bleeding and constipation.

Spontaneous recovery is more likely with lower grades of encephalopathy as 65-70% in grade I and II, 40-50% in grade III and less than 20% in grade IV encephalopathy (13). In this study the mortality rate was 46.6% in the patients with grade I and II encephalopathy that was lower than those with grade III and IV encephalopathy (69.2%), but their difference was not significant statistically. Patients older than 40 or less than 10 years of age may have a lower likelihood of spontaneous recovery compared to patients between these ages. Hepatitis A and hepatitis B have a better prognosis than those with idiosyncratic drug reactions and Wilson disease (14). In the present study, hepatitis A has the least mortality compared to other causes. All patients with autoimmune hepatitis and two third of patients with Wilson disease were died in our series.

Several other variables have been used to predict the probability of recovery but their predictive accuracy have not been well established such as PT, serum bilirubin concentration, arterial pH, the presence of a systemic inflammatory response syndrome and, in patients who received plasma exchange, the ratio of total to direct bilirubin (15). We found that higher INR, PTT, bilirubin, and AST, and lower platelet and serum bicarbonate levels were associated with poor prognosis. Hyponatremia is reported to be a risk factor of mortality in patients with cirrhosis and HE as we observed lower serum sodium in non-survivors (16). The relationship between serum sodium and overt HE has been recently suggested in another study (17).

The total mortality rate in this series was 54% that comparable to Latif N et al series (60%) (11), but higher than other studies (9,18,19). Due to high mortality the liver transplantation remains the therapeutic choice for fulminant hepatic failure in children (5).

We concluded that the presence of gastrointestinal bleeding and also admission INR, PTT, serum sodium and bicarbonate levels had significant impact on outcome ($p<0.05$). Total bilirubin, AST, INR, PTT, platelets count and serum bicarbonate levels on the last patient laboratory data had also significant difference between survivors and non-survivors ($p<0.05$).

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