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Original Article

Validity of Serum Ammonia Level for Diagnosis of Severity of Hepatic Encephalopathy in Children

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Abstract

Hepatic encephalopathy is a broad spectrum neuropsychiatric abnormalities of liver dysfunction. Ammonia level may correlate with the severity of liver failure. The brain is very sensitive to the toxic effects of ammonia. As a result patient may manifests with irritability, slurring of speech, reversal of sleep-awake cycle, flapping tremor, confusion, stupor or even deep coma. This study was aimed to validate the ammonia level in children with liver failure for the assessment of its severity considering hepatic encephalopathy. This cross-sectional comparative study was conducted among 64 children aged 1-15 years of both sexes (study subjects) diagnosed as acute or acute on chronic liver failure in the Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh during the period of November 2017 to September 2019. The subject were divided into two groups for the comparison of ammonia level to assess the severity in contrast to hepatic encephalopathy. In the first group 32 were liver failure with encephalopathy and in the second group 32 were liver failure without encephalopathy. Hepatic encephalopathy was diagnosed on the basis of West Haven Criteria. The analysis was done by the Receiver Operating Characteristic Curve with SPSS-20. Among the 64 patients female were 45% whereas male patients were 55%, male female ratio was 1.2: 1. Regarding etiology, Wilson disease was the most common cause and it was nearly two-third (65.6%) of children, cryptogenic cirrhosis was 10%, Hepatitis A was 9.4%, Autoimmune Hepatitis (AIH) was 3.10%, Hepatitis E, Hepatitis B, Hepatitis C, biliary atresia and lipid storage were 1.60% respectively. This study showed that, ammonia of ≥71 µmol/L is an indicator for presence of hepatic encephalopathy in children. The analysis by the Receiver Operating Characteristic Curve showed area under the curve (AUC) is 0.86 with upper bound 0.96 and lower bound is 0.77. It was observed that about half (48.4%) of the children had positive blood ammonia level (≥71.0 umol/L) and among the children of positive blood ammonia level most of them (80.65%) had hepatic encephalopathy and 19.35% had no encephalopathy. More than half (51.6%) children had negative (<71.0 umol/L) blood ammonia level, among them 21.21% children had encephalopathy and 78.79% patients had no encephalopathy. Sensitivity of blood ammonia was found 78.1%, specificity 81.2%, positive predictive value 80.6%, negative predictive value 78.8% and accuracy 79.7%. In conclusion, high level of ammonia is found with higher grade of encephalopathy and hyperammonia is also found in liver failure without encephalopathy.

Keyword: *Serum ammonia level, hepatic encephalopathy, west haven criteria.*

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INTRODUCTION

Hepatic encephalopathy is characterized by personality changes, intellectual impairment and a depressed level of consciousness[1]. The pathogenesis of hepatic encephalopathy

is not completely understood but ammonia plays a key role among the neurotoxic substances[2]. About 85% of ammonia is detoxified through the liver and excreted in the urine as urea. Whereas 15% is metabolized in the muscle and brain through the synthesis of glutamine from glutamate[3]. Normally the gut produces ammonia as a byproduct of bacterial urease activity, protein digestion, and amino acid deamination. This ammonia in the systemic circulation is regulated by urea cycle in a healthy liver. So, when there is any pathology in liver that causes decreased functioning of urea cycle. It increase the concentration of ammonia in the systemic circulation. This excess ammonia convirt to glutamine in astrocytes, increase intracellular osmolarity that results fluid retention and develop brain edema[4]. However hyperammonia in circulation can also be a result of high protein diet, parental nutrition, and congenital defects in the urea cycle or drugs like sodium valproate[5]. The American and European Associations for the Study of the Liver 2014 practice guidelines recommend that HE will be classified according to four factors: (i) the underlying etiology– Type A, B or C; (ii) severity – using the grading system such as West Haven Criteria; (iii) time course – episodic, recurrent (>1 episode in 6 months) or persistent[1]. (symptoms always present and can have episodes of acute exacerbations); and (iv) non precipitated or precipitated by factors such as infections, medications or electrolyte disorder[6]. Type- A encephalopathy is associated with acute liver failure. Type B HE with portal-systemic bypass and no intrinsic hepatocellular disease. Type C HE with cirrhosis and portal hypertension or portosystemic shunts[7]. Common laboratory testing for hepatic encephalopathy includes assessment of liver and renal function, electrolytes, glucose, complete blood count, cultures and drug screening and ammonia levels may correlate with the severity of hepatic encephalopathy[8]. Blood should be place immediately on ice and centrifuged within 15 min of collection. If left at room temperature the concentration of ammonia can increase about 20% within 1 h and up to 100% within 2 hour[9]. The Pediatric Acute Liver Failure Study Group (PALF) define as follows: (a) evidence of liver dysfunction within 8 weeks of symptoms onset, (b) uncorrectable (6–8 h after administration of one dose of parenteral vitamin K) coagulopathy with international normalized ratio (INR) >1.5 in patients with hepatic encephalopathy (HE) or INR> 2.0 in patients without HE and (c) no evidence of chronic liver disease[10]. The definition of Acute-On-Chronic Liver Failure (ACLF) indicates acute deterioration in patients with chronic liver disease or cirrhosis as a result of an underlying precipitating event[11].

MATERIALS AND METHODS

Study design was cross sectional comparative. Study place was Pediatric Gastroenterology and Nutrition Department of BSMMU, Dhaka Bangladesh. The duration of the study was 22 months from November 2017 to September 2019. Data were collected from children of liver failure with or without encephalopathy attending in the Department of Pediatric Gastroenterology and Nutrition, BSMMU. Sampling technique was Purposive sampling.

Inclusion criteria for cases:

Pediatric patients aged 1-15 years of both sexes diagnosed as acute liver failure or acute on chronic liver failure were selected as the study population.

1. Patients of liver failure with encephalopathy were taken in one group.
2. Patients of liver failure without encephalopathy were taken in another group.

Exclusion criteria:

The following patients were excluded from the study.

Parents who were unwilling to give consent.

2. Encephalopathy other than the liver disease.

Written informed assent from the parents was taken before enrollment of children. Details history was taken and a standard data form was filled up for every children. Past history of illness and any systemic disease was inquired cautiously. A complete physical examination including general physical examination and systemic examination was done. Hepatic encephalopathy was diagnosed on the basis of West Haven Criteria and liver failure on the basis of PALF. After patient selection 3 ml of fasting venous blood was collected, during blood collection fist clenching and tourniquet use was avoided. After collection, blood sent immediately (within 30 minutes) in ice pot to the Department of Biochemistry. Base line investigations along with other investigations to identify the causes of liver failure such as HBV, HEV, HAV, Slit-lamp eye examination, 24 hours urinary copper, Serum ceruloplasmin, CBC with PBF, coomb`s test for Wilson disease and autoimmune screening like ANA, SMA, LKM1 were done. Liver function as prothombine time (PT), Serum albumin, Serum bilirubin were also investigated. Investigations results were collected and recorded in the structured data sheet. Data cleaning validation and analysis was performed using the SPSS (Statistical Package for Social Science) Version 20 (SPSS

Inc., Chicago, IL USA) and graph and chart by MS excel, result was presented in tables in mean, standard deviation (SD) and percentages.

RESULT

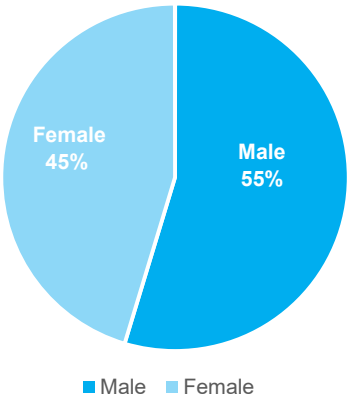

Figure-1: Sex distribution of children with as acute liver failure (n=62)

Figure 1 is shows the sex distribution of the studied patients. Among 64 patients female were 45% whereas male patients were 55%. Male female ratio was 1.2: 1

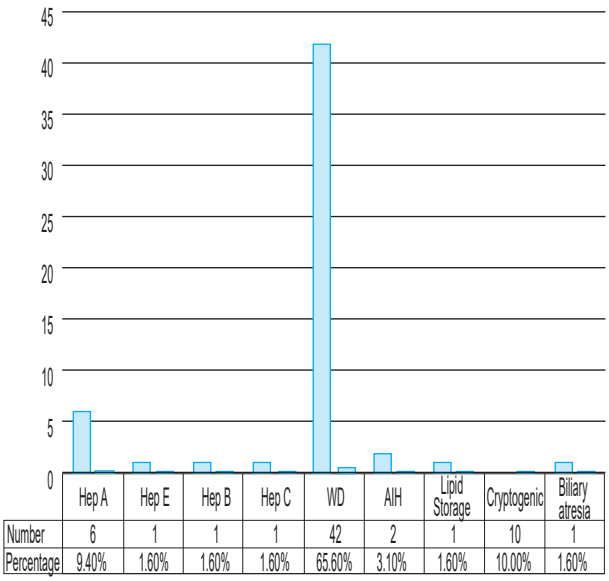

Figure-2: Etiology of acute liver failure in children (n=62)

Figure 2 illustrates the etiology. Regarding etiology Wilson disease was about 65.6%, cryptogenic 10%, Hep A were 9.4%, AIH were 3.10%, Hep E, Hep B, Hep C, biliary atresia and lipid storage were 1.60% respectively among the studied patients.

Table I contains the cut of value of blood ammonia for encephalopathy ≥71.0 (µmol/L); here sensitivity of blood ammonia for encephalopathy found 78.1%, specificity 81.2%, area under the curve (AUC) 0.86 with upper bound 0.96 and lower bound 0.77.

Table- I: Cut of value of blood ammonia level in children with hepatic encephalopathy (n=62)

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
Blood ammonia (µmol/L)	≥71.0	78.1%	81.2%	.862	.770	.955

Table II shows mean ammonia value was 106.3750 µmol/L in children of liver failure with hepatic encephalopathy (HE) and mean ammonia value 53.8438 µmol/L in children of liver failure without encephalopathy.

Table- II Mean value of ammonia in liver failure with and without hepatic encephalopathy (n=62)

HE	N	S. Ammonia Mean	Std. Deviation	Std. Error Mean
Present	32	106.3750	42.71870	7.55167
Absent	32	53.8438	21.60064	3.81849

Figure 3 showing the Receiver Operating Characteristic Curve for ammonia. This study showed that, ammonia of ≥71 µmol/L is an indicator for presence of hepatic encephalopathy in children.

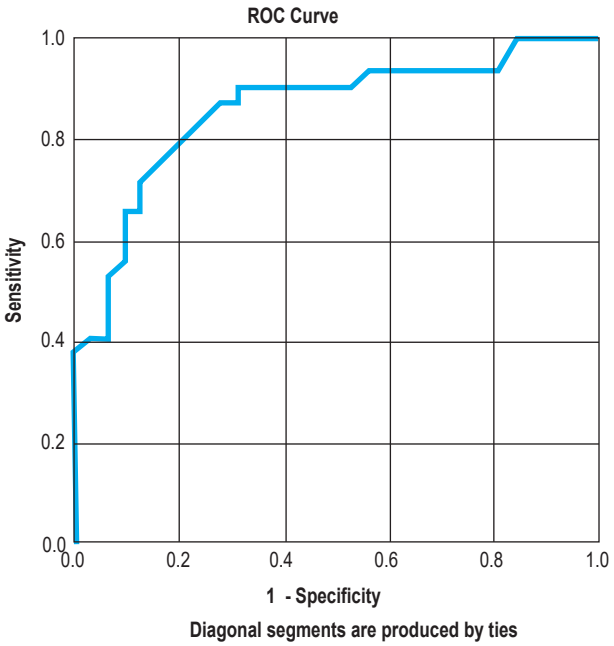

Figure-3: Relationship between ammonia and hepatic encephalopathy (ROC curve)

Table III shows thirty two (32) patients had liver failure with hepatic encephalopathy (HE) and 32 had liver failure without encephalopathy (HE). It was observed that 31 (48.4%) patients out of 64 had positive blood ammonia level (≥71.0 umol/L); among them 25 patients had hepatic encephalopathy and 7 had no encephalopathy. Remaining thirty three (51.6%) patients out of 64 had negative (<71.0 umol/L) blood ammonia level, among them 7 patients had encephalopathy and 26 patients had no encephalopathy. It is found that positive predictive value 80.6%, negative predictive value 78.8% and accuracy 79.7%.

Table- III: Performance of blood ammonia as a diagnostic test for presence of hepatic encephalopathy (n=64)

Blood ammonia	Hepatic encephalopathy		Total
	Present n=32 (%)	Absent n=32 (%)	
Positive ≥71.0	25 (78.1)	06 (18.8)	31 (48.4)
Negative <71.0	07 (21.9)	26 (81.2)	33 (51.6)
Total	32 (100.0)	32 (100.0)	64(100.0)

Sensitivity: 78.1 %
Specificity: 81.2 %
Positive predictive value: 80.6 %
Negative predictive value: 78.8 %
Accuracy: 79.7 %

DISCUSSION

Diagnosis of minimal HE is a challenge for the clinician where needs a sensitive, reliable and easy-to-use diagnostic tool. However neuropsychological evaluation and electrophysiological tests do not fulfill these requirements. So for screening of minimal HE in daily practice, a simple test would be welcome and greatly facilitate the diagnosis and as well as the management of HE[12]. The onset of hepatic encephalopathy in a person with cirrhosis is with poor prognosis and reduced survival if liver transplantation is not done. Overt hepatic encephalopathy also occur approximately 30 to 40% of individuals with cirrhosis. Overt HE need frequent hospitalizations, and pose a burden on the healthcare system. As ammonia has been regarded the key precipitating factor, so plasma ammonia levels are used widely in patients with cirrhosis and altered mental status to diagnose HE. However correlation between ammonia levels and the grading of HE continues to be controversial[8,13]. We found male 55% and female 45%. Different two studies found 63 (63%) males, 37 (37%) females and 85% patients (n = 51) males and 15% (n = 9) females[5,14]. In this study cut of value of ammonia for encephalopathy found ≥71.0 (µmol/L). Gundling et al, (2013) found cut of value of the blood ammonia level ≥ 55 µmol/L to diagnose HE, sensitivity and specificity was 47.2% and 78.3%, respectively. The positive predictive and negative predictive values of ammonia were 77.3% and 48.6%, with an overall diagnostic accuracy of 59.3%. In different two studies, an arterial ammonia level of 124 µ mol/L or higher predicted mortality with 78.6% sensitivity, 76.3% specificity, and 77.5% diagnostic accuracy; and arterial ammonia level higher than 100 µ mol/L (170 µg/dL) predicted the onset of hepatic encephalopathy and intracerebral hypertension with 59% sensitivity, 78% specificity, and 70% diagnostic accuracy[15]. In a retrospective study, grade of HE was found to be correlated with increased ammonia value in 39 patients with acute or acute on chronic liver failure (ACLF)[16]. In this study, some patients had high ammonia level but no encephalopathy, the explanation is that in CLD patients there is colonic dysbiota, that increase ammonia production and decreased ammonia detoxification due to reduced activity of urea cycle enzymes and portosystemic shunting in the liver. Two recent studies highlighted that ammonia levels on admission are important predictive factors for hospital mortality in decompensated cirrhosis[17]. Therefore, patients with advance stage of hepatic encephalopathy and a high

Child-Turcotte-Pugh score at the time of presentation should be considered at a higher risk of having hyperammonemia[18]. Another study shown risk of cerebral herniation increase when ammonia levels reach >200 μ mol/L[19].

CONCLUSIONS

High ammonia levels were a common finding among patients with hepatic encephalopathy. But patient without hepatic encephalopathy may also have raised ammonia level due to underlying CLD, liver dysfunction and high child pugh score.

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