

Evaluation of Serum Ammonia in Hepatic Encephalopathy Patients and Its Correlation with Clinical Severity

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Received: July 13, 2016

Revised: September 6, 2016

Accepted: September 10, 2016

Published online: October 21, 2016

ABSTRACT

AIM: To study serum ammonia levels and its correlation with clinical status in patients of hepatic encephalopathy.

METHODS: A total number of 84 patients diagnosed clinically as Hepatic encephalopathy (HE) were grouped into 3 groups, due to cirrhosis of liver ($n = 40$), due to acute viral hepatitis ($n = 34$), due to drug induced hepatitis ($n = 10$). The diagnosis of HE was based on clinical criteria, and its severity was graded according to the West Haven Criteria for grading of mental status. Serum ammonia levels were estimated using enzymatic UV-method (RANDOX LABS). Ammonia levels were correlated with the severity of hepatic encephalopathy in all the three groups. All data obtained were assessed and statistically analyzed. ANOVA (ANalysis Of VAriance between groups) was used to find the statistical significance between the groups. TUKEY-KRAMER multiple comparison testswere used to compare meanbetween the groups.

RESULTS: The mean serum ammonia levels in each study group were found to be as follows [($\mu\text{g/dL}$) \pm SD]: 118.12 \pm 48.87 in cirrhosis, 222.76 \pm 74.73 in acute viral hepatitis, 134.6 \pm 37.8 in drug induced hepatitis. Serum ammonia levels in acute viral hepatitis

group were significantly higher than cirrhosis group ($q = 10.59, p \leq 0.001$). In all 3 groups, an increase in mean serum ammonia levels were associated with worsening clinical status. Out of 84 patients, 12 patients (14.29%) of cirrhosis group, 18 (21.43%) of acute viral hepatitis group, 4 (4.76%) of drug induced hepatitis expired during the course of illness. A higher risk of mortality was observed with an increase in serum ammonia levels. In cirrhosis group, 100% mortality was found with serum ammonia $> 200 \mu\text{g/dL}$. In acute viral hepatitis, 70% mortality was observed with serum ammonia levels $> 200\mu\text{g/dL}$. In drug induced hepatitis, 100% mortality was observed with serum ammonia values $> 150 \mu\text{g/dL}$.

CONCLUSION: An elevated serum ammonia level is an important laboratory abnormality in patients with HE. Both the mortality and severity of HE increases with an increase in serum ammonia levels. This could be useful in identifying patientswith higher grades of HE, suggesting that estimation of serum ammonia could be a useful tool in assessing the severity of illness and to plan for aggressive detoxification measures.

Key words: Hepatic encephalopathy; Ammonia; Cirrhosis; Acute viral hepatitis

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Thangasami SR, Lalchandani A, Mathiyalagan N. Evaluation of Serum Ammonia in Hepatic Encephalopathy Patients and its Correlation with Clinical Severity. *Journal of Gastroenterology and Hepatology Research* 2016; 5(5): 2185-2190 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/1787>

Abbreviations

HE: Hepatic encephalopathy
ALF: Acute liver failure
FHF: Fulminant hepatic failure
CLD: Chronic liver disease
AVH: Acute viral hepatitis
DIH: Drug induced hepatitis

INTRODUCTION

Hepatic Encephalopathy [HE] refers to a complex, potentially reversible or progressive syndrome of cerebral dysfunction, which consists of neuropsychiatric, cognitive and motor disturbances, characterized by a broad etiological spectrum. It is observed in patients with decompensated liver function such as in Cirrhosis and in those with Acute Liver Failure [ALF], in the absence of other known brain disease^[1]. HE can be a complication after insertion of a trans-jugular intrahepatic porto-systemic shunt [TIPS]^[2]. Hepatic Encephalopathy [HE] is one of the most serious complications of liver failure, either chronic or fulminant. It can be either acute and reversible, or chronic and progressive leading to coma and death^[3-4]. Although accurate data on the incidence of HE is lacking; majority of patients with cirrhosis will develop some degree of HE at some point during the course of the illness. The true incidence and prevalence of hepatic encephalopathy is difficult to establish because of variable differences in the etiology and severity of hepatic encephalopathy. Therefore, a true picture of this complication is not fully known^[5]. In patients with cirrhosis, acute encephalopathy occurs mostly due to precipitating factors such as electrolyte disturbance, medications, gastrointestinal bleeding or infections^[6]. The acute form of HE is often associated with fulminant hepatic failure [FHF] and can rapidly progress to seizures, coma, de-cerebrate posturing and death^[7].

The patho-physiology of HE is multifactorial with several circulating neurotoxins being proposed, but ammonia is strongly considered as a central factor in the pathogenesis of HE^[8-10]. Ammonia is formed mainly from the nitrogenous products in the diet, bacterial metabolism of urea and proteins in the colon, and by de-amination of glutamine in the small intestine by glutaminase^[11]. From the gut, ammonia is carried to the portal circulation and is converted to urea by the liver, which is subsequently excreted by the kidneys^[9]. The ammonia elevation is mainly due to the inability of the liver to convert ammonia into urea via the urea cycle in peri-portal hepatocytes, reduced glutamine synthesis in centri-lobular hepatocytes and due to porto-systemic shunting. The contribution of each mechanism depends on the underlying condition, which may be ALF, cirrhosis or total liver bypass^[12]. Both vascular anatomic anomalies that result in blood flow to bypass the liver, and the presence of constipation, can allow increased absorption of ammonia into the mesenteric blood, overwhelming the hepatic excretory pathways causing hyperammonemia^[13]. The skeletal muscles and the kidneys compensate in ammonia metabolism with increased glutamine synthetase activity. However, astrocytes which play a pivotal role in regulating the blood-brain barrier and neuronal homeostasis are not able to increase its glutamine synthetase activity to cope with the increased ammonia load. Ammonia crosses the blood-brain barrier and directly depresses central nervous system functioning by inhibiting postsynaptic potentials^[14]. The normal blood ammonia levels are usually less than 50 $\mu\text{mol/L}$ ^[15]. Proton emission tomography [PET] studies have shown that there is an increased permeability of the blood-brain barrier [BBB] to ammonia in chronic liver disease, and it has shown that brain ammonia uptake is significantly elevated in both chronic and acute liver failure^[10]. Excess ammonia may reduce levels of brain adenosine triphosphate resulting in impaired cerebral energy metabolism^[9]. Additionally, the metabolism of ammonia to glutamine in the brain increases the intracellular osmolality of astrocytes, inducing both astrocyte swelling and vasodilation. Increased astrocyte hydration without overt increase in the intracranial pressure is considered a major factor in the development of HE in patients with chronic liver disease^[16]. Ammonia can alter both excitatory and inhibitory neurotransmission, affecting the

glutamergic, γ -aminobutyric acid [GABA]-ergic and dopaminergic systems^[17,18]. Other proposed mechanisms of neuronal dysfunction include ammonia-induced RNA oxidation, activation of mitogen-activated protein kinases and of nuclear factor-K β ^[19]. Although some studies show correlation of serum ammonia levels with grades of encephalopathy in chronic liver disease^[20-23] and in acute liver failure^[24,25], some studies are inconsistent^[26,27]. Further, there is no major study comparing serum ammonia levels in acute hepatic failure. So, this study was taken to study the correlation between serum ammonia levels and the clinical status of the patients of hepatic encephalopathy due to heterogeneous etiology.

MATERIALS AND METHODS

This analytical study included 84 patients admitted to the medicine wards of GSVM medical college, Kanpur. The study was initiated after obtaining permission from the ethical committee. Informed consent was obtained from patient's relatives. Patients with age above 18 years and less than 70 years with a clinical diagnosis of hepatic encephalopathy were included in the study. Being a diagnosis of exclusion, hepatic encephalopathy was diagnosed by evaluating history of existing acute or chronic liver disease, after excluding central nervous system infections, metabolic problems, and intracranial vascular events. Patients who had co-morbid conditions like stroke, previous heart failure, lung diseases, diabetes and chronic renal failure were excluded from the study. Patients were grouped into 3 groups, due to cirrhosis of liver ($n = 40$), due to acute viral hepatitis ($n = 34$) and due to drug induced hepatitis (DIH) ($n = 10$). Diagnosis of cirrhosis of liver was based on clinical features, radiologic and biochemical features. Diagnosis of fulminant hepatic failure following acute viral hepatitis and drug induced hepatitis was based on history, clinical and biochemical features. The diagnosis of HE was based on clinical criteria, and its severity were graded according to the West Haven Criteria for grading of mental status (Table 1). The severity of liver disease was assessed according to Child-Pugh score. A total score from 5-6, 7-9 and 10-15 was classified as class-A, B and C respectively. Apart from complete history and physical examination, all baseline investigations like Hemoglobin, Total leukocyte Count (TLC), Differential Leukocyte Count (DLC), Serum electrolytes (Na/K/Ca), Prothrombin time (PT), Liver function test (LFT), Blood urea, serum creatinine, blood sugar, abdominal ultrasonography and arterial blood gases were carried out in all subjects. The clinical profile and the biochemical profile of the study group were noted (Tables 2 and 3). Serum ammonia levels were estimated using enzymatic UV-method (RANDOX LABS). Ammonia levels were correlated with the severity of clinical status of hepatic encephalopathy.

All data obtained were assessed and statistically analyzed using INSTAT software. ANOVA (ANalysis of Variance between groups)

Table 1 West haven criteria for semi-quantitative grading of mental status^[9].

Grade 1	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition
Grade 2	Lethargy or apathy
	Minimal disorientation for time or place
	Subtle personality change
	Inappropriate behavior
Grade 3	Impaired performance of subtraction
	Somnolence to semi-stupor, but responsive to verbal stimuli
	Confusion
Grade 4	Gross disorientation
	Coma (unresponsive to verbal or noxious stimuli)

was used to find the statistical significance between the groups. TUKEY –KRAMER multiple comparison test was used, a *p* value less than 0.05 is considered significant. Post hoc analysis was done, if *p* value is found significant.

RESULTS

Patient characteristics

All the 84 Patients were grouped into 3 groups, due to cirrhosis of liver (*n* = 40), due to acute viral hepatitis (*n* = 34), due to drug induced hepatitis (*n* = 10) (Figure 1). Mean age of the patients in cirrhosis group, AVH group, DIH group were found to be 47.76 ± 9.94, 38.36 ± 12.91, 32.1 ± 8.1 respectively. Average mean age of the study group was 39.40 ± 10.31. Baseline clinical and biochemical profiles of the study group were described as below (Tables 2 and 3). Alcoholics comprised 35.71% of the study group. 42.86% patients in the study group had Hepatitis B and Hepatitis C was positive in 9.52%. Among acute viral hepatitis patients, 88.24% were Hepatitis B positive and 11.76% patients were Hepatitis C positive. Of the 10 cases of DIH, 9 were ATT induced and 1 was valproate induced. 60% of the cirrhosis patients belonged to Child-Pugh class C, while class A & B were 20% respectively. Common precipitating cause of HE in cirrhosis patients were sepsis (35%), GI bleed (30%), constipation (15%), hypokalemia (10%), alcohol intoxication (5%) and alkalosis (5%). HE patients in each group were classified according to West Havens clinical grading of HE. Among the 40 cirrhosis patients, 8 (20%) patients had grade 1 HE, 6 (15%) patients had grade 2 HE, 20 (50%) patients had grade 3 HE and 6 (15%) patients had grade 4 HE. Among the 34 acute viral hepatitis patients, 2 (5.9%) patients had grade 1 HE, 8 (23.5%) patients had grade 2 HE, 6 (17.6%) patients had grade 3 HE and 18 (53%) patients had grade 4 HE. Among the 10 drug induced hepatitis patients, 2 (20%) patients had grade 1 HE, 4 (40%) patients had grade 2 HE, 4 (40%) patients had grade 3 HE and no patients had grade 4 HE (Figure 2).

Serum ammonia levels and clinical severity

Serum ammonia levels (µg/dL) ranged from 45-246 in patients of cirrhosis with a mean average of 118.12 ± 48.87 and ranged from 84-402 in patients of acute viral hepatitis with a mean average of 222.76 ± 74.73 and ranged from 86-210 in patients of drug induced hepatitis with a mean average of 134.6 ± 37.8. Serum ammonia levels in acute viral hepatitis were significantly higher than cirrhosis patients (*q* = 10.59, *p* ≤ 0.001). Serum ammonia levels in acute viral hepatitis were significantly higher than DIH patients (*q* = 5.78, *p* ≤ 0.001). In all 3 groups of patients, as the mean serum ammonia levels increase, there was a worsening of clinical status of the patients (Figure 3, Table 4).

In cirrhotic patients, grade 1 HE patients had a serum ammonia levels (µg/dL) ranging from 48 - 122 with a mean average of 83 ± 26.42. Grade 2 patients had a serum ammonia ranging from 52-160, and a mean average of 86 ± 38.09, grade 3 HE had a serum ammonia ranging from 45-210, with a mean average of 122.85 ± 41.94, grade 4 HE had a serum ammonia ranging from 112-246, with a mean average of 177 ± 52.04. Tukey-kramer multiple comparison analysis in conjunction with ANOVA (Table 5) was done to compare the mean. The results showed increased serum ammonia values in grade 4 patients than the grade 1, 2, 3 patients. Serum ammonia levels of Grade 1 HE (83.66 ± 26.42) vs Grade 4 HE (177 ± 52.04) (*q* = 6.03, *p* ≤ 0.001) was highly significant. Grade 2 HE (86 ± 38.09) vs Grade 4 HE (177 ± 52.04) (*q* = 5.5, *p* ≤ 0.01), Grade 3 HE (122.85 ± 41.94) vs Grade 4 HE (177 ± 52.04) (*q* = 4.06, *p* ≤ 0.01) were

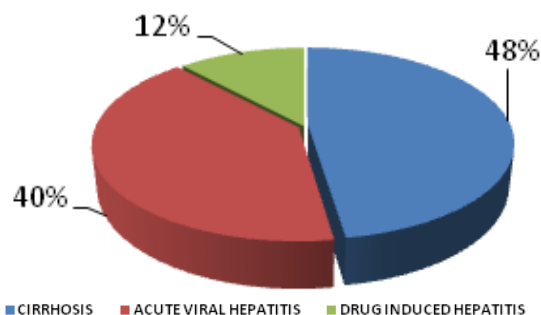


Figure 1 Classification of patients of HE.

Table 2 Clinical profile of the study group.

S.No	Parameters	Cirrhotics	AVH†	DIH‡	Total
1	No of subjects	40	34	10	84
2	Mean age	47.76 ± 9.94	38.36 ± 12.91	32.1 ± 8.1	39.40 ± 10.31
3	No of alcoholics	18	10	2	30
4	Asterixis+	18	10	6	34
5	HEP B + VE	6	30	-	36
6	HEP C + VE	4	4	-	8
7	Grade 1 & 2 HE	14	10	6	30
8	Grade 3 & 4 HE	26	24	4	54

† AVH-Acute viral hepatitis; ‡ DIH-Drug induced hepatitis.

Table 3 Bio-chemical profile of the study group.

S.NO	Parameters	Cirrhotics	AVH	DIH
1	SGPT(IU/L)	89 ± 41.6	275 ± 73.9	240 ± 34.6
2	SGOT(IU/L)	82.33 ± 43.2	254.6 ± 71.8	240.1 ± 71.86
3	Prothrombin time(sec)	20.2 ± 2.3	23.2 ± 4.9	20.4 ± 4.42
4	Sr. Bilirubin (mg/dL)	14.22 ± 3.14	14.5 ± 3.4	5.14 ± 1.46
5	Sr. Albumin (mg/dL)	1.96 ± 0.3	4.4 ± 0.4	4.4 ± 0.2
6	Sr. Globulin(mg/dL)	3.96 ± 3.6	2.4 ± 0.24	2.6 ± 0.19
7	Sr. Protein(mg/dL)	5.9 ± 0.2	6.8 ± 0.4	7.0 ± 0.17
8	Sr. Sodium (mEq/L)	124.62 ± 9.28	134.73 ± 9.62	135.7 ± 13.72
9	Sr. Potassium (mEq/L)	2.85 ± 0.53	3.64 ± 0.72	2.93 ± 0.77
10	Sr. Calcium (mg/dL)	4.80 ± 0.36	4.84 ± 0.36	4.67 ± 0.32
11	Sr. Ammonia (µg/dL)	118.12 ± 48.87	222.76 ± 74.73	134.6 ± 37.8

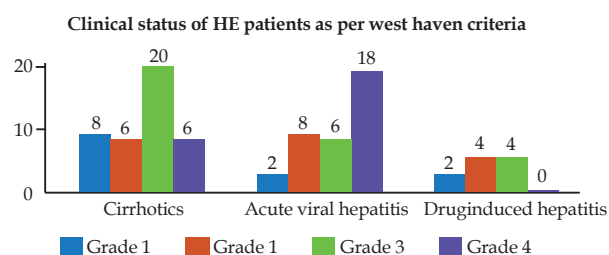


Figure 2 No of patients in each group classified as per west haven criteria.

significant. The increase in serum ammonia levels was associated with an increasing severity, in spite of a considerable overlap in ammonia levels in different clinical grades of HE.

In Acute viral hepatitis group, grade 1 patients had a serum ammonia levels (µg/dL) ranging from 84-96 with a mean average of 90 ± 8.08, grade 2 HE ranging from 104-180 with a mean average of 144.25 ± 27.77, grade 3 HE, ranging from 146-234, with a mean average of 199 ± 38.11, grade 4 HE, ranging from 186-402, with a mean average of 271.05 ± 57.26. Serum ammonia levels were higher in the grade 4 HE (271.05 ± 57.26) and only slightly raised in grade 1 HE (90 ± 8.48). A significant difference was noted on comparing the Serum ammonia levels of Grade 1 HE (90 ± 8.48) vs Grade 4 HE (271.05 ± 57.26) (*q* = 7.19, *p* ≤ 0.001), Grade 2 HE (144.25 ±

27.77) vs Grade 4 HE (271.05 ± 57.26) (q = 8.76, p ≤ 0.001), Grade 3 HE (199 ± 38.11) vs Grade 4 HE (271.05 ± 57.26) (q = 4.52, p ≤ 0.05). In drug induced hepatitis patients, they had increased ammonia levels with increasing severity, but the difference was not significant.

Serum ammonia levels and its correlation with mortality

The distribution of serum ammonia levels in the study group shows that there were 2 patients in the serum ammonia range of 0-50, 17 patients in the serum ammonia range from 51-100, 28 patients in the serum ammonia range from 101-150, 13 patients in the serum ammonia range 151-200. There were 24 cases with serum ammonia levels > 200 µg/dL of which 20 patients had acute viral hepatitis. The overall mortality in the study population was about 40.48%. Mortality was around 21.43% in acute viral hepatitis and 14.29% in cirrhosis patients. 4.76% expired in drug induced hepatitis group.

In cirrhotic group, mortality was 100% in all 3 patients with serum ammonia levels above 200 µg /dL. In patients with serum ammonia levels in the range of 151-200, 4 out 5 expired, with an 80% mortality rate. The mortality rate approached 29.41% in patients with serum ammonia levels ranging from 101-150. No mortality was noted below this range. In viral hepatitis group, 14 out of 20 patients with

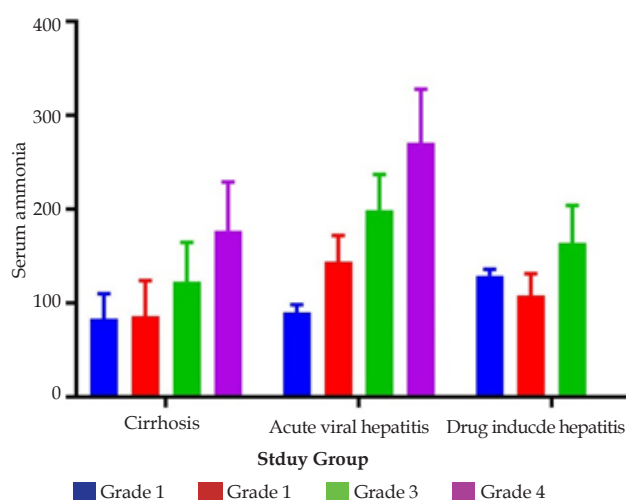


Figure 3 Correlation of Serum Ammonia levels with clinical status of HE patients.

serum ammonia levels above 200 µg/dL expired with a mortality of 70%. 2 out of 6 (33.3%) patients expired in each group with serum ammonia levels in the range of 151-200 and 100-150. The mortality is found to increase as the ammonia levels increase more than 200 µg/dL. In drug induced hepatitis group, 2 out of 4 expired had serum ammonia levels in the range of 151-200. Among the other 2 expired patients, 1 had serum ammonia in the range of 101-150 and the other in the range of > 200 (Table 6).

DISCUSSION

This study defines the clinical utility of serum ammonia levels among patients, both in chronic and in acute setting. Our study is consistent with most other studies, which favor ammonia in the causation of hepatic encephalopathy. Also, our data shows that serum ammonia levels have a good correlation with clinical grades of HE and mortality of the patient, hence supporting the ammonia neuro-toxicity theories. Ammonia neurotoxicity is an important component of cerebral dysfunction in liver failure patients, but still there is much debate on the underlying mechanisms and also in understanding the better type of ammonia measurement^[21-23]. The target of ammonia toxicity in the brain appears to be the astrocyte, leading to development of Alzheimer type II astrocytosis. One proposed mechanism for ammonia-induced neurologic dysfunction is cerebral edema. Glutamine, produced by the metabolism of ammonia via glutamine synthetase within astrocytes, acts as an intracellular osmole and attracts water into the astrocytes, which leads to swelling and appears to induce oxidative dysfunction of the mitochondria. Cerebral edema is a major contributing cause of HE in ALF, and also plays a role in CLD patients, as evidenced by magnetic resonance spectroscopy^[28-29]. Although edema is more prominent in ALF patients than CLD patients, the low-grade edema seen in CLD appears to induce neurologic dysfunction directly rather than by a rise in intracranial pressure seen in ALF patients. Occasionally patients presenting with an acute exacerbation of chronic liver disease can also have intracranial hypertension in the setting of HE, which can lead to fatal cerebral herniation^[30].

We found that there is an increase in serum ammonia levels with increase in the clinical severity of HE, although there is a considerable overlap between different grades of HE. Tukey multiple comparison analysis shows that there is a significant difference

Table 4 Comparison of clinical status of HE in patients with their serum ammonia levels.

S.No	Grading Of Hepatic Encephalopathy	Serum Ammonia levels (µg/dL) in Cirrhosis Group		Serum Ammonia levels (µg/dL) in AVH† Group		Serum Ammonia levels (µg/dL) in DIH‡ Group	
		Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD
1	Grade 1	48 - 122	83.66 ± 26.42	84 - 96	90 ± 8.48	124 - 134	129 ± 7.07
2	Grade 2	52 - 160	86 ± 38.09	104 - 180	144.25 ± 27.77	86 - 140	108 ± 23.49
3	Grade 3	45 - 210	122.85 ± 41.94	146 - 234	199 ± 38.11	112 - 210	164 ± 40.23
4	Grade 4	112 - 246	177 ± 52.04	186 - 402	271.05 ± 57.26	-	-
	Total	45 - 246	118.12 ± 48.87	84 - 402	222.76 ± 74.73	86 - 210	134.6 ± 37.8

† AVH-Acute viral hepatitis,‡ DIH-Drug induced hepatitis

Table 5 Tukey-Kramer Multiple Comparisons Test comparing serum ammonia levels with clinical grades of HE.

Comparison of serum ammonia levels with grades of HE	Cirrhosis group				Acute viral hepatitis			
	Mean difference	q value	significance	P value	Mean difference	q value	significance	P value
grade 1 vs grade 2	-2.340	0.1512	NS	P > 0.05	-54.250	2.031	NS	P > 0.05
grade 1 vs grade 3	-39.190	3.270	NS	P > 0.05	-109.00	3.952	Significant	P < 0.05
grade 1 vs grade 4	-93.340	6.032	Significant	P < 0.001	-181.05	7.191	Significant	P < 0.001
grade 2 vs grade 3	-36.850	2.763	NS	P > 0.05	-54.750	3.001	NS	P > 0.05
grade 2 vs grade 4	-91.000	5.501	Significant	P < 0.01	-126.80	8.834	Significant	P < 0.001
grade 3 vs grade 4	-54.150	4.060	Significant	P < 0.05	-72.050	4.524	significant	P < 0.05

The P value is < 0.0001, considered extremely significant.

Table 6 Correlation of serum ammonia levels to mortality in HE patients.

S.No	Serum Ammonia (µg/dL)	Mean Serum Ammonia (µg/dL)	Cirrhosis		Acute Viral Hepatitis		Drug Induced Hepatitis		Total death in each distribution
			No of Patients	Death	No of Patients	Death	No of Patients	Death	
1	0-50	46.5±2.12	2	-	-	-	-	-	0
2	51-100	85.46±14.27	13	-	2	-	2	-	0
3	101-150	127.29±9.5	17	5	6	2	5	1	8(9.52%)
4	151-200	179.7±9.77	5	4	6	2	2	2	8(9.52%)
5	>200	233.06±24.60	3	3	20	14	1	1	18(21.43%)
	TOTAL	134.40±43.64	40	12 (14.29%)	34	18 (21.43%)	10	4(4.76%)	34(40.48%)

when lower grades of HE are compared with higher grades of HE (grade 1 vs grade 4), (grade 2 vs grade 4), (grade 1 vs grade 3) but the difference is not significant when adjacent grades of HE (grade 1 vs grade 2), (grade 2 vs grade 3) are compared. This observation illustrates that serum ammonia levels can be useful in differentiating patients as low grade HE and high grade HE, but ascertaining certain range of ammonia levels to each clinical grade is not possible. Ammonia is a single element studied in pathogenesis of hepatic encephalopathy, other causative agents that are implicated in HE, include manganese^[31], mercaptans, phenols, aromatic amino acids^[32], pro-inflammatory cytokines, and medications administered in patients suffering from liver failure. These agents accumulate in the brain and induce neurotoxic actions, derailing normal brain function and can act as confounding factors in study^[33]. Impairment in neurotransmission involving changes in central neurotransmitters such as melatonin, glutamate, catecholamine, serotonin and histamine has also been proposed, but they are not proved sufficiently^[34]. There is variability in ammonia levels throughout the day which can also lead to a high degree of overlap in ammonia levels in different clinical grades of hepatic encephalopathy.

Thomsen *et al*^[35] did a study in a group of 106 cirrhosis patients. They classified patients as having no HE, minimal HE and Grade I HE and reported that ammonia levels were similar in patients with minimal HE and grade I HE but were significantly lower in the no HE group. Further, he demonstrated significantly higher baseline levels of HE grade and ammonia in patients who died compared to those who survived. Grade 3 and Grade 4 HE patients were not considered as part of its study design. Even though the information was limited for low grades of HE, the inference that there was no significant difference in serum ammonia levels between adjacent grades of HE was similar to our report. Bhatia *et al*^[24] reported that acute liver failure patients with grade 3 or 4 encephalopathy had higher median ammonia levels than patients with grade 1 or 2 encephalopathy. Moreover, patients with clinical cerebral edema at presentation had higher median ammonia levels than patients without overt cerebral edema. Ong *et al*^[22] demonstrated that serum ammonia levels correlate with the severity of hepatic encephalopathy. Further, they reported venous sampling is adequate for ammonia measurement and there appears to be no additional advantage of measuring the partial pressure of ammonia over total ammonia levels. Patients with grade 3 or 4 encephalopathy had higher total ammonia levels, arterial or venous. Patients with grade 1 or 2 encephalopathy usually had ammonia levels < 150 mmol/L. Qureshi *et al*^[20] measured serum ammonia levels in 135 patients with liver cirrhosis with HE and reported that ammonia levels correlated with the severity of hepatic encephalopathy, but this study did not evaluate the variation in serum ammonia levels between the clinical grades of HE. Serum ammonia levels in acute viral hepatitis group were found to be much higher than cirrhosis and drug induced hepatitis group. The mean serum ammonia levels in cirrhosis patients were increasing with increase in clinical grades. In contrast, Kundra *et al*^[36] studied in a group of 40 patients, comprising 20 patients with ALF (Group A) and

8 patients of CLD with HE (Group B1) and 12 patients without HE (group B2). They reported that patients with acute liver failure had a good correlation with plasma ammonia levels but among patients with CLD, plasma ammonia levels were not significantly different between those with and without HE. Moreover, the mean ammonia levels for patients graded 3 and 4 were actually less than the mean ammonia levels of grade 2 HE. The poor correlation of serum ammonia levels in CLD patients may be due to small sampling size in their study population. Mean serum ammonia levels in this study are lower than our mean serum ammonia levels in each group.

The overall mortality in the study population was about 40.48%. Mortality was around 21.43% in acute viral hepatitis and 14.29% in cirrhosis group. As, liver transplantation facilities were not available at our center, acute liver failure patients were managed conservatively, which can considerably affect mortality in our data. Further, we did patient assessment, clinical grading, serum ammonia level estimation on the first day of admission. Patient subsequently developing secondary complications such as renal failure, respiratory failure and sepsis can have considerable impact on the mortality of patient. This limits us from defining a particular level of serum ammonia levels relating to mortality. However Clemmesen *et al* found ammonia levels of > 146 mmol/L within first 24 hours to be predictive of subsequent cerebral herniation in patients with ALF^[25]. Bhatia *et al*^[24] demonstrated an arterial ammonia level of > 124 mmol/L was found to be 78.6% sensitive and 76.3% specific for predicting mortality.

CONCLUSION

Hepatic encephalopathy is mainly a disease of exclusion and diagnosis is based on clinical decision. Serum ammonia levels correlate well with clinical severity of HE, both in acute and chronic setting. Serum ammonia estimation could be useful additive as a diagnostic test. They can be useful to identify patients with higher grade HE and to start early detoxification measures.

CONFLICT OF INTEREST

All authors declared no potential conflicts of interest.

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