Original Article

Co-relation of high serum ammonia levels with severity of hepatic encephalopathy in chronic liver disease patients

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Objective: To assess co-relation of high serum ammonia levels with severity of hepatic encephalopathy in chronic liver disease patients.

Methodology: This study was conducted at Department of Medicine, Civil Hospital Karachi, from April 2, 2012 to October 1, 2012. Using West Heaven Criteria mental status was assessed and serum ammonia level was determined at the time of admission. All patients of age above 18 years of either gender with chronic liver disease presenting with altered mental status were included in study. Patient age less than 18 years, had mental status changes due to cause other than hepatic encephalopathy i.e. metabolic encephalopathy, intracranial lesion, multi organ failure, previously diagnosed psychiatric illness, history of substance abuse, were excluded.

Results: There were 30 (58.8%) males and 21 (41.2%) females. Hepatitis C was the cause of CLD in 40 (78.4%), hepatitis C & B in 5 (9.8%) and alcoholic liver in 6 (11.8%) patients (p=0.088). Constipation was the precipitating factor in 24 (47.1%), upper GI bleed 14 (27.5%), infection 12 (23.5%) and SBP in one (2%) (p=0.658). Four (7.8%) had grade 1, 21 (41.2%) grade 2, 18 (35.3%) grade 3 and 08 (15.7%) had grade 4 hepatic encephalopathy (p=0.150). The mean serum ammonia level of patients with grade 1 HE was 178.3±58.9, grade two 220.9±82.6, grade three 213.2±62.9 and grade four 252.1±87.7 (p=0.389). There was weak correlation with severity of hepatic encephalopathy (rs=0.144).

Conclusion: Ammonia levels weekly correlated with the severity of hepatic encephalopathy. HE is commonly precipitated by constipation and upper GI bleed and hepatitis C virus was the commonest cause of cirrhosis in these patients. (Rawal Med J 2014;39:119-123).

Key words: Hepatic encephalopathy, CLD, Serum ammonia level,

INTRODUCTION

Hepatic encephalopathy is a significant cause of morbidity and mortality in patient with advance chronic liver disease.[1] Hepatic encephalopathy, a challenging complication of advanced liver disease, occurs in approximately 30-45% of patients with cirrhosis and 10-50% of patients with Trans jugular intrahepatic porto systemic shunt, while minimal hcpatic encephalopathy affects approximately 20-60% of patients with liver disease.[2] Serum ammonia levels increased with the severity of hepatic encephalopathy. Patient with grade 2 hepatic encephalopathy had serum ammonia levels <l50 umol/1 and patient with grade 3 and 4 hepatic encephalopathy had serum ammonia >200 umol/l.[3] About 30% of patient with cirrhosis die with hepatic coma. Cirrhosis Liver is becoming an epidemic in Pakistan due to very high prevalence of hepatitis B and C in our community.[4] Prevalence rate of 3-4% for hepatitis B and 4-6% for hepatitis C.[5] Hepatic encephalopathy is a severe Neuro psychiatric syndrome which complicate both acute and chronic liver disease.[6,7] Hepatic encephalopathy reflects a spectrum of neuropsychiatic abnormalities occurring in patient with liver dysfunction. Most cases are associated with cirrhosis and portal hypertension or portal systemic shunt and can also be seen in patient with acute liver failure.[8] A number of toxin have been implicated in the pathogeneses of hepatic encephalopathy toxin with potential to act synergistically leading to hepatic encephalopathy are ammonia, manganese, proiniflammatory cytokines (TNF-a, IL-1, IL-6), mercaptans, phenols, octanoic acid.[9] These neurotoxin substances may then contribute to morphological changes in astrocytes. In cirrhosis astrocytes may

undergo Alzheimer type II astrocytosis,although 10% of patient with significant encephalopathy have normal serum ammonia levels. Furthermore, many patient with cirrhosis have elevated ammonia levels without evidence for encephalopathy.[10] Grading of symptoms of hepatic encephalopathy is performed according to west Heaven Classification System. Over hundred years hyperammonia has been believed to be the dominant pathogenetic factors of hepatic encephalopathy in the acute and chronic liver failure.[11]

HE is not always accompanied by elevated blood ammonia level and the correlation between serum ammonia level and severity of HE remains controversial.[12] Local data depicting the relationship between grade of HE with serum ammonia level is lacking. Keeping this background in mind present study is designed to assess the co-realtion of high serum ammonia level with severity of HE in our setup.

METHODOLOGY

This study was conducted at Medicine OPD, Civil Hospital Karachi from April 2, 2012 till October 1, 2012. A detailed history was taken regarding alcohol. Informed written consent was taken by patient relatives as patient was unable to give consent (b/c of altered mental status). Mental status was assessed by using West Heaven Criteria and divided into Grade I-IV; serum ammonia level was collected at the time of admission and other laboratory tests were advised to patients for Hepatitis B and C. Inclusive criteria all patient of age above 18 years of either gender with chronic liver disease presenting with altered mental status were included in study. Patient age less than 18 years, have mental status changes due to cause other than hepatic encephalopathy i.e. metabolic encephalopathy, intracranial lesion, multi organ failure, previously diagnosed psychiatric illness, history of substance abuse were excluded.

RESULTS

Fifty one patients fulfilling the inclusion criteria were enrolled in this study. There were 30 (58.8%) males and 21 (41.2%) females. Mean age of male patients was 48.97 ± 10.9 years and mean age of female patients was 47.4 ± 11.1 years (p=0.702) (Table I). Mean duration of illness of males was 1.7 ± 0.84 years and mean duration of illness of females was 1.7 ± 1.2 years (p=0.183) (Table II). Mean serum ammonia level of males was 214.3 ± 76.3 and mean serum ammonia level of females was 227.5 ± 75.2 (p=0.425) (Table I).

Hepatitis C was the cause of chronic liver disease in 40 (78.4%) [21 males, 19 females], hepatitis C & B were the cause in 05 (9.8%) [3 males, 2 females] and alcoholic liver disease was the cause in 06 (11.8%) [06 males] patients (p=0.088) (Table II). 43 (84.3%) patients had the history of previous admission. On analysis of precipitating factors of hepatic encephalopathy we observed that constipation was the precipitating factor in 24 (47.1%) [14 males, 10 female], upper GI bleed 14 (27.5%) [9 males, 5 females], infection 12 (23.5%) [7 males, 5 females] and SBP was the precipitating factor in 01 (2%) [1 female] (p=0.658) (Table III).

On analysis of hepatic encephalopathy according to west heaven criteria we observed that 04 (7.8%) [2 males, 2 female] had grade 1, 21 (41.2%) [15 males, 6 females] grade 2, 18 (35.3%) [11 males, 7 females] grade 3 and 08 (15.7%) [2 males, 6 females] had grade 4 hepatic encephalopathy (p=0.150) (Table IV).

On analysis of mean serum ammonia level among the causes of CLD we observed that mean ammonia level of patients in whom cause of CLD was HCV was 219.4 ± 74.7%, HCV + HBV was 231.8 ± 96.1 and alcoholic liver disease was 212 ± 75.3 (p=0.478) (Table II).

On analysis of mean ammonia level among the precipitating factors we concluded that mean ammonia level of patients having constipation was 220.9 ± 68.1, upper GI bleed 242.9 ± 79.8 and infection 179.6 ± 68.1 (p=0.811) (Table V).

On analysis of mean serum ammonia level among the grades of hepatic encephalopathy we observed that mean serum ammonia level of patients having grade 1 HE was 178.3 ± 58.9, grade 2 HE 220.9 ± 82.6, grade 3 HE 213.2 ± 62.9 and grade IV HE 252.1 ± 87.7 (p=0.389) (Table IV). On analysis of grades of hepatic encephalopathy with serum ammonia level by spearman coefficient we observed that there was weak correlation of serum

ammonia level with severity of hepatic encephalopathy (rs=0.144).

Table 1. Descriptive statistics among the gender (n=51).

Gender	Age	Duration of illness	Serum Ammonia Level
Male	48.97 ± 10.9	1.7 ± 0.8	214.3 ± 76.3
Female	47.4 ± 11.1	1.7 ± 1.2	227.5 ± 75.2
p value	0.702	0.183	0.425

Table 2. Causes of CLD (n=51).

Cause	Gender		Serum Ammonia Level	Total
	Male	Female		
HCV	21(52.5%)	19(47.5%)	219.4 ± 74.7	40
HCV+HBV	3(60%)	2(40%)	231.8 ± 96.1	5
Alchohal liver disease	6 (100%)	0	212 ± 75.3	6

Table 3. Precipitating factors among the gender (n=51).

Precipitating factors	Gender		Total
	Male	Female	
Constipation	14 (58.3%)	10 (41.7%)	24
Upper GI bleed	9 (64.3%)	5 (35.7%)	14
Infection	7 (58.3%)	5 (41.7%)	12
SBP	0	1(100%)	1

TABLE 4. Grades of hepatic encephalopathy (n=51).

West Heaven Criteria for grading Mental Status	Gender		Serum Ammonia Level	Total
	Male	Female		
Grade 1	2 (50%)	2 (50%)	178.3 ± 58.9	4
Grade 2	15 (71.4%)	6 (28.6%)	220.9 ± 82.6	21
Grade 3	11(61.1%)	7 (38.9%)	213.2 ± 62.9	18
Grade 4	2 (25%)	6 (75%)	252.1 ± 87.7	8

Table 5. Serum ammonia level and precipitating factors (n=51).

Precipitating factors	Serum Ammonia Level
Constipation	220.9 ± 68.1
Upper GI bleed	242.9 ± 79.8
Infection	179.6 ± 68

DISCUSSION

Ammonia is derived predominantly from protein degradation. Most of the ammonia in the blood comes from the intestine, where colonic bacteria use ureases to break down urea into ammonia and carbon dioxide. Fortunately, blood from the intestine is carried directly to the liver via the portal vein, where 85% of the ammonia is converted back into urea, which is less toxic and is excreted by the kidneys and colon.[13]

Ammonia levels are elevated in several conditions in which its production is increased (eg, in convulsive seizures with increased muscle production) or its clearance is impaired (eg, in hepatocellular dysfunction, portosystemic shunting, or both, with subsequent impaired hepatic detoxification of ammonia).[14]

Because the blood-brain barrier is highly permeable to ammonia, the brain is exposed to excessive concentrations of it in these circumstances. In the brain, ammonia is thought to cause both functional and structural abnormalities that could explain neuropsychiatric dysfunction, often manifested as an altered mental status of variable degree.[15]

The importance of measurements of the blood ammonia concentration in the evaluation of patients with known or suspected hepatic encephalopathy is still disputed in spite of a general acknowledgment that ammonia is important in the pathogenesis of the disorder. Several recent studies have suggested that it is not necessary to utilize arterial blood when measuring ammonia in the blood. Venous blood or a computation of the partial pressure of ammonia gas in blood samples may suffice. The value of blood ammonia measurements is limited by the fact that this is not the variable that is the most important.[16] Ideally, one would like to know how much ammonia enters the brain, not how much is in the blood. The bloodbrain barrier (BBB) is the critical and poorly understood element in this relationship. Although both ammonia in the gas and ionic forms cross the BBB, the ease with which this movement occurs is significantly higher in patients with HE.[17] In the absence of simple methods to measure the brain ammonia metabolic rate and to assess the BBB to ammonia in conjunction with measuring the blood ammonia concentration, the variables that would be

the most desirable to measure, the use of arterial and/or venous blood measurements needs to be coupled with a complete understanding of the physiology of cerebral ammonia metabolism.[18]

Mahboob.[19] in her study observed that frequency of risk factors was 47%, due to infections, 30% due to GIT bleeding, 19% due to constipation, 4% due to miscellaneous factors. Ahmed et al.[20] in their study observed that The commonest precipitating factors were, hypokalaemia 68%, Haematemesis 56%, constipation 52%, high protein intake 52%, hyponatremia 28%, diarrhea 22%, infections including spontaneous bacterial peritonitis and septicemia 28%, Benzodiazepine intake 2% surgical procedure 2%. Oesophageal varices were present in 60%.

Ong et al.[21] studied the correlation between ammonia levels and the severity of hepatic encephalopathy and found that of the 121 patients, 30 (25%) had grade 0 encephalopathy (no signs or symptoms), 27 (22%) had grade 1, 23 (19%) had grade 2, 28 (23%) had grade 3, and 13 (11%) had grade 4 (the most severe signs and symptoms). Each of the four measures of ammonia increased with the severity of hepatic encephalopathy: arterial total ammonia (r_s = 0.61, P $\leq$0.001), venous total ammonia (r_s = 0.56, P $\leq$0.001), arterial partial pressure of ammonia (r_s = 0.55, P $\leq$0.001), and venous partial pressure of ammonia (r_s = 0.52, P $\leq$0.001).

CONCLUSION

Serum ammonia was most strongly associated with grade of hepatic encephalopathy. We recommend that cirrhotic patients check the ammonia levels weekly to monitor the correlated with worsening clinical grades of hepatic encephalopathy.

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