Original article

Serum ammonia level in the patient of cirrhosis with encephalopathy

Md. Ashraf-uz-zaman[1], Nasreen Sultana Lovely[2], Bilquis Ara Begum[3], Md.Masud Hasan[4]

Abstract

Objective : Cirrhosis of the liver is a common medical problem in our country. Hepatic encephalopathy is a frequent complication of cirrhosis which is a medical emergency and increases the rate of mortality.

Method : The present study was designed to detect a laboratory parameter which can early detect the encephalopathy and prompt treatment can be initiated to abort the complication. Ammonia level increases both in cirrhosis with encephalopathy and without encephalopathy. If a cut off value can be established which can differentiate these two clinical entities, the monitoring of the serum ammonia level can early detect the hepatic encephalopathy.

Results : Normal serum ammonia level is 15-33 µmol/L. In this study 30 cirrhotic patient without encephalopathy mean serum ammonia level was 44.13±31.46 and mean ammonia level in patient with encephalopathy was 83.34±34.85.

Conclusion : We can conclude that serum ammonia level is more increased in patient of cirrhosis with encephalopathy than without encephalopathy. The diagnosis of hepatic encephalopathy (HE) is based mostly on clinical criteria. It is important to assess the severity of HE quantitatively for both clinical practice and research: however, this remains a difficult and challenging problem. No single parameter or index has yet been shown to be infallible in assessing the severity of hepatic encephalopathy. Further study and research should be done in this field clinical medicine.

Key Words : Serum ammonia, cirrhosis, encephalopathy.

Introduction

Hepatic encephalopathy is characterized by neuropsychiatric manifestation ranging from slightly altered mental status to coma. This condition of chronic and acute liver disease is a result of failure of the liver to detoxify toxin originating in the intestine. The pathogenesis probably is multifactorial, although the predominant causative agent appears to be ammonia.[1] The major clinical difference from the 20th century is that, hepatic encephalopathy will be seen much less commonly because of the elimination of HBV, HDV and HCV infection. Similarly, the eradication of schistosomiasis will reduce the frequency of portal hypertension, limiting the extent of hepatic encephalopathy associated with it.[2] Continued use of the ethyl alcohol is one of the cause of cirrhosis in the civilized world.

1. Professor (CC), Department of Biochemistry, Ad-din Women's Medical College, Dhaka
2. Associate Professor, Department of Physiology, Moynamoti Medical College, Comilla.
3. Professor & Head, Department of Biochemistry, Ad-din Women's Medical College, Dhaka
4. Consultant, Gastroenterology, Comilla Diabetic Hospital,Comilla

Correspondence : Dr. Md. Ashraf-uz-zaman

E mail : apuzaman@gmail.com

As the under developed countries become overdeveloped they too; will consume this society accepted hepatotoxin. Eventually, educational programmes akin to those which are now becoming effective for tobacco abuse may gradually become valuable in reducing alcohol abuse.

Ammonia may be a primary diagnostic parameter for portosystemic encephalopathy in the absence of most important diagnostic method (EEG and psychometric test). Moreover ammonia are of great diagnositic importance in patient with coma of unknown origin and can help in prompt management. Ammonia is produced from the breakdown of protein, amino acids, purine and pyrimidine. About half of the ammonia arising from the intestine is synthesized by bacteria, remainder coming from dietary protein and glutamine. This ammonia is detoxified in the liver by synthesis of glutamine in perivenous hepatocyte and through urea cycle in periportal hepatocyte. In cirrhosis, fibrosis follows hepatocellular necrosis. The cell death followed by nodules which disturb the hepatic architecture and full blown cirrhosis develops. As a result hepatocyte cannot perform their metabolic function properly and ammonia is not detoxified fully and serum ammonia level is

increased. When the portal circulation is obstructed, a remarkable collateral circulation and hepatic encephalopathy occurs.

Several studies had been done to establish the correlation of serum ammonia level with hepatic encephalopathy. Ong et al.[3] evaluated correlation between plasma ammonia level and severity of hepatic encephalopathy. Karmar et al.[4] have done a study on relation of ammonia with hepatic encephalopathy. Marsavljivic et al.[5] have showed a prospective study on 25 cirrhotic patients with relation to serum ammonia. Jessy et al.6 have done study in the department of physiology and biophysics university on metabolic change found after the portocaval shunts. Author suggested metabolic alteration occurred due to elevated amonia level.

Methodology

It is a cross sectional study carried out in General Medical Hospital, Elephant Road, Dhaka during the period of January 2014 to December 2015. Sixty cirrhotic patients with ascites was taken. The patients were divided into two groups.

A patient presenting with feature of chronic liver disease was asked for detail history and was examined for evidence of cirrhosis of liver. Presence of ascites was detected clinically on the basis of positive shifting dullness and /or positive fluid thrill examination. After taking informed consent from the patient, 5cc ascitic fluid was drawn for ascetic fluid albumin estimation. At the same time, venous blood sample was drawn to send to department of biochemistry for serum albumin estimation. After obtaining serum albumin level and ascetic fluid albumin level, serum ascitic albumin gradient was determined. Upper gastrointestinal endoscopies of the patients were done following topical anaesthesia in the department of hepatology by video endoscopies. The liver function test (serum bilirubin, SGPT) serum creatinine and chest X-ray were also done. With all aseptic precaution 3 ml venous blood was drawn from anticubital vein by using disposable syringe. Then blood was transfered into previous prepared clear and dry test tube containing, 25 ml EDTA. Plasma was separated within 15 minutes of venipuncture. Then plasma was analyzed immediately. The Vitros AMON Slide is a dry, multilayered, analytical element coated on a polyester support.

A 10µL drop of patient sample is deposited on the slide and is evently distributed by the spreading layer to the underlying layers. Water and nonproteinaceous components travel to the underlying buffered reagent layer, and the ammonium ions are converted to gaseous ammonia. The semipermeable membrane allows only ammonia to pass through and prevents buffer or hydroxyl ions from reaching the indicator layer. After a fixed incubation period, the reflection density of the dye is measured using the white background of the spreading layer as a diffuse reflector. All the data were entered into a personal computer, thoroughly checked for any possible error and then processed and analyzed by SPSS programme. Significance of the test was tested by unpaired 't' test and 'x2' test. 'P' value of <0.05 was taken as statistically significant.

Result

Table 1 : Demographic data of the study group (N=60)

Parameter		Case	Control
Sex	Male	28	25
	Female	2	5
	Total	30	30
Age	Mean	45.30	42.3

Table 2 : Serum ammonia level in study population

Parameter	Case (mean±SD)	Control (mean±SD)	p value
S. ammonia	88.34 ±34.85	44.31 ±13.46	<0.001

Table 3 : Other biochemical parameter of the study group

Parameter	Case (mean)	Control (mean)
S. Bilirubin in mmol/L	103.38	96.04
S.erum Albumin mg/dl	26.95	26.94
S. creatinine mg/dl	0.91	0.91
Prothrombin time in second	18.58	18.73
Serum ascitic albumin	1.84	1.7
gradient		

Table 4 : Serum level of ammonia in various grade of encephalopathy

Serum Ammonia	Mean±SD	P value
G-1	89.25±22.28	0.72
G-2	83.58±40.51	
G-3	97.09±36.64	
G-4	74.00±16.00	

Discussion

Hepatic encephalopathy is a neuropsychiatric syndrome occurring in patients with severe liver disesae and or portosystemic shunting. The exact pathogenesis of hepatic encephalopathy is yet not completely understood but there is a general consensus about the importance of gut derived nitrogenous substance escaping hepatic ditoxification and affecting the central nervous system function. Ammonia is one of these substances, produced both in colon and in the small bowel and extensively metabolized in the liver. In case of impaired liver function and or portal systemic shunt, blood ammonia concentration may increase and exerts its toxic activity on the brain. Although ammonia levels are almost always invariably higher in patient with acute and chronic liver failure, the correlation with severity of hepatic encephalopathy is often variable and inaccurate.

Karmar et al.[4] have done a study to test on serum ammonia level on 56 cirrhotic patient with hepatic encephalopathy. Observation was that clinical grading of hepatic encephalopathy correlated (P <0.001) with both total and partial pressure of total ammonia.

Ong et al.[3] evaluated that correlation between plasma ammonia level and the severity of hepatic encephalopathy. Diagnosis of the hepatic encephalopathty was based on clinical criteria and severity of hepatic encephalopathy was based on West Haven criteria of grading of mental state. Of 121 patients 25% had grade-0 ecenphalopathy, (22%) had grade I cncephalopathy, 19% had grade -II cncephalopathy, 23% had grade III cncephalopathy and 11% had grade IV encephalopathy.

Each of the 4 measures of ammonia increased with severity of hepatic encephalopathy. P value was (<.001). In this study, number of the total cirrhotic patients with encepphalopathy was 30. Of 30 patients, grade I were 4 in number (13%), grade II were 12 in number (42%), grade III were 11 in nuber (30%) and grade IV were 3 numbers (09%). In this study mean(±SD) of serum ammonia level in patient of grade I encephalopathy was 89.25±22.28, in patient of grade II encephalopathy was 83.58±40.51, in patient of grade III encephalopathy was 97.09±36.64 and in patient grade IV encephalopathy was 7.00±16. There was no significant difference in serum ammonia between these 4 grade of encephalopathy.

Nolte et al.[7] have done a study on hepatic encephalopathy and determination of arterial ammonia level was performed in 55 cirrhotic patients treated consecutively by transjugular intraheptic porto systemic shunt. Arterial ammonia increased from a mean of 94±26 µg/dl to 140±28 µg/dl at 3 months after TIPS (P<0.001). In this study mean serum ammonia level without encephalopathy was 44.31±13.46 in cirrhotic patient and mean serum ammonia level in patient with encephalopathy was 88.34±34.85. Serum ammonia level was significantly higher in patient with encephalopathy group (P< 0.001) than patient without encephaloapathy.

Marisavjivic et al.[5] showed one year prospective study on 25 cirrhotic patients with portal systemic encephaloapthy admitted to emergency care centre in Belgrade to investigate the significance of clinical biochemical, electroencephalographic parameter and blood ammonia in the diagnosis, differential diagnosis and prognosis of PSE. Fifteen cirrhotic patients without PSE constituted the control group.

Ammonia levels correlated with the severity of protosystemic encphalopathy (P<0.05) but not with other biochemical parameter (Prothombine time albumin and creatinine). In this study the mean (±SD) level of serum bilirubin. albumin, creatinine, prothombin time and SAAG in the patient with hepatic encephalopathy were 103.38±88.67, 26.29± 8.05, 0.91±0.30, 88.34±34.85 18.58±5.44, 1.84±0.67 respectively. The mean (±SD) of those serum bilirubin, albumin, creatinine, prothombin time and SAAG were 96.04±115.41, 26.94 ±8.26, 0.91±.33, 18.73±4.66 and 1.7±0.55, in cirrhotic patient without encephalopathy respectively. The present study had not showed any, significant difference of serum bilirubin, albumin, prothombin time, SAAG and creatinine in between two groups (P>0.05). But in this study the serum ammonia (mean±SD) were 88.34±34.85 in study group and 44.31±13.46 in control group. The patient with hepatic encephalopathy had higher level of serum ammonia than the patient without encephalopathy. The difference in the means of serum ammonia between study group and control was statistically significant (P<0.001). Nicolao et al.[8] studied to compare the venous, arterial and partial pressure of amonia in 27 consecutive cirrhotic patients with hepatic encephalopathy and 15 cirrhotic patients without encephalopathy. In patients with encephalopathy, ammonia was higher than in patient without encephalopathy. Mean serum ammonia levels was 39.42±44.7 in patient without encephalopathy which was significantly lower than the patient with encephalopathy. In this study, mean serum ammonia level in cirrhotic patient with encephalopathy was 88.34±34.85 and in patient without encephalopathy was

44.31 ± 13.46. Value was higher and statistically significant in patient of cirrhosis with encephalopathy (P<0.001).

Conclusion

We can conclude that serum ammonia level is more increased in patient of cirrhosis with encephalopathy than without encephalopathy. The diagnosis of hepatic encephalopathy (HE) is based mostly on clinical criteria. It is important to assess the severity of HE quantitatively for both clinical practice and research: however, this remains a difficult and challenging problem. No single parameter or index has yet been shown to be infallible in assessing the severity of hepatic encephalopathy. Further study and research should be done in this field clinical medicine.

Reference

1. AssaiSA,VlahcevicZR.2005,'Hepaticencephalopathy', http//www. postgradmed.com/ issue/ 2001/ 02_01/ assi.htm.
2. Sheila D, 1994, ' Hepatic encephalopathy in 21st century', in Conn H & Bircher J (eds.) Hepatao Encepholopathy syndrome and treatment 1st ed. Med Ed Press Bloomington P-414.
3. Ong JP, Aggarwal A, Krieger D, Easley KA, Karafa MT, Van Lente F, Arroliga AC, Mullen KD 2003, 'Correlation between ammonia level and the severity of hepatic encephalopathy', Am J Med 114:188-193.
4. Kramer L, Tribl B, Gendo A, Zauner C, Schneider B, Ferenci P, Madl C. 'Partial pressure of ammonia versus ammonia in hepatic encephalopathy', Hepatology. 2000, 31(1):30-34.
5. Marsavljivic A, Golubovic M, Tomic D, Krstic M. 1990, 'Ammoniemia in portosystemic encepholopathy-diagnostic, differential diagnosis and prognostic significance', Srp Arh Celok Lek.118(5-6): 185-191
6. Jessy J, Mans AM, DeJoseph MR, Hawkins RA. 1990, 'Hypermmonaemia causes many of the changes found after portacaval shunting', Biochem J 27(2):311-317.
7. Nolte W, Wiltfang J, Schindler C, Munke H, Unterberg K, Zumhasch U, Figulla HR, Werner G, Hartmann H, Ramadori G. 1998, 'Portosystemic hepatic encephalopathy after transjugular intrahepatic porstosystemic shunt in patients with cirrhosis: clinical, laboratory, pschyometric and electroencephalographic investigations', Hepatology 28(5):1215-1225.
8. Nicolas C and Worth RB, 2004, 'Effect of liver failure on inter organ trafficking of ammonia Journal of Gastroenterology and hepatology', 19:S219-S222