ORIGINAL ARTICLE

Ammonia Levels and the Severity of Hepatic Encephalopathy

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Abstract

Objective: To evaluate the correlation between ammonia levels with the severity of HE in patients coming to the tertiary care hospital with liver cirrhosis and hepatic encephalopathy (HE).
Study Design: Descriptive, analytical study.
Place and Duration of Study: Shifa International Hospital, Islamabad, from January 2011 to February 2012.
Methodology: A total of 135 patients with liver cirrhosis and HE had serum ammonia levels measured on admission. 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. Ammonia levels were correlated with the severity of HE using Spearman rank correlation.
Results: Out of 20 patients with normal ammonia levels, 13 (65%) were in HE I-II, 6 (30%) were in grade-III, while 1 (5%) patient was in grade-IV HE. Out of 45 patients with mild hyperammonemia, 27 (60%) were in grade I-II, 12 (26%) were in grade-III and 6 (13%) were in grade-IV HE. Out of 34 patients with moderate hyperammonemia, 9 (26%) were in grade I-II, 18 (53%) were in grade-III, and 7 (20%) were in grade-IV HE. Out of 36 patients with severe hyperammonemia, 31 (86%) patients were in grade-IV HE ($p < 0.001$).
Conclusion: Ammonia levels correlated with the severity of hepatic encephalopathy. Greater the ammonia level, severe is the grade of hepatic encephalopathy.

Key Words: *Ammonia. Hepatic encephalopathy. Cirrhosis. Hyperammonemia.*

INTRODUCTION

Hepatic encephalopathy (HE) is a broad spectrum of neuropsychiatric manifestations usually affecting individuals with end-stage liver disease.[1] Clinical manifestations include attentional deficits, alterations of sleep patterns and muscular in-co-ordination progressing to stupor and coma and may result in seizures, especially in acute liver failure.[2] It may develop in 50 to 70% of all patients with cirrhosis, including those with abnormalities demonstrable only by psychometric testing.[3] The presence of HE is a poor prognostic sign, with 1-year mortality rates of almost 60%.[1]

Hepatic encephalopathy in patients with chronic liver dysfunction is believed to be caused by failure of the liver to clear toxic products from the blood stream. The exact toxins that cause HE have not been established.[4] There is much debate about the underlying mechanisms, however, elevated plasma and central nervous system ammonia levels are considered a key factor in this syndrome's pathogenesis.[5] However, studies have shown that the correlation between serum ammonia levels and severity of HE is inconsistent.[4,6]

The value of blood ammonia measurements is limited by the fact that this is not the variable that is the most important. Ideally, one would like to know how much ammonia enters the brain, not how much is in the blood. The blood-brain barrier (BBB) is the critical and poorly understood element in this relationship.[7] Ammonia modulates the transcellular passage of low to medium-size molecules by affecting their carriers located at the BBB and by acting either directly or in synergy with liver injury-derived inflammatory cytokines also evokes subtle increases of the transcellular passage of molecules of different size (BBB leakage), which appears to be responsible for the vasogenic component of cerebral oedema associated with acute liver failure.[8]

An American study concluded that ammonia levels do correlate with the severity of HE.[9] However, many studies are inconclusive in this aspect.[4,6,10] In Pakistan, no study has been performed in this regard that may provide guidance in this regard.

The aim of this study, therefore, was to determine the correlation between ammonia levels and the severity of hepatic encephalopathy.

METHODOLOGY

This analytical study included 135 patients admitted to the Department of Gastroenterology, Shifa International Hospital, Islamabad, from January 2011 to February 2012. Sample was calculated by non-probability sampling technique by using statistical formula according to recent similar studies.[9] The sample was calculated by estimating an alpha-error of 5% and confidence interval with statistical significance of 5%, considering the strict exclusion criteria. Patients of age greater than 18 years with diagnosis of liver cirrhosis of

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any etiology and HE were included in the study. Patients who had co-morbid conditions like stroke, sepsis etc. were excluded from the study. Liver cirrhosis was confirmed by clinical, biochemical and ultrasonographic findings and diagnosis of HE was based on exclusion. Thus, HE was diagnosed after excluding infections, metabolic problems, intracranial vascular events, knowledge of existing acute or chronic liver disease, the history of precipitating factors, and/or an earlier diagnosis of HE determined by history.[11] The HE was graded according to the West Haven Classification system.[12]

Ammonia levels were checked in the serum of all patients on admission. Values less than 120 mg/dl were taken as normal. Values between 120 and 150 mg/dl were taken as mild hyperammonemia, values between 150 - 200 mg/dl as moderate hyperammonemia and values above 200 mg/dl as severe hyperammonemia.

The demographic profile of the patient and etiology of liver disease were noted. 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. The patients were assessed for ascites and were graded according to International Ascites Club.[13] All patients had complete blood counts, serum electrolytes, creatinine, LFT's, serum albumin and INR.

The data was collected in a well designed proforma and analyzed using Statistical Package for Social Sciences (SPSS) version 17. Frequency and percentage of different variables were determined. The relation between ammonia levels and the severity of hepatic encephalopathy was analyzed with the Spearman rank correlation coefficients and 95% confidence interval. All statistical tests were two-sided, and a p-value less than 0.05 was considered statistically significant. The Ethics Committee of the Hospital approved the study and informed consent was obtained from all study participants.

RESULTS

Out of 135 patients, 62 (45.9%) were males and 73 (54.07%) females. Forty-eight (35.5%) patients were of age greater than 60 years. Regarding etiology, 101 (74.8%) patients had hepatitis C, most of the patients belonged to Child class-C (n=85, 63%) and the rest to child class-B (n=50, 37%).

Out of 20 patients with normal ammonia levels, 13 (65%) patients were in HE grade I-II, 6 (30%) were in grade-III, while 1 (5%) patient was in grade-IV HE. Out of 45 patients with mild hyperammonemia, 27 (60%) patients were in grade I-II, 12 (26%) were in grade-III and 6 (13%) were in grade-IV HE. Spearman rank correlation showing strong correlation between ammonia levels and severity of hepatic encephalopathy ($r = 0.644$, $p < 0.001$).

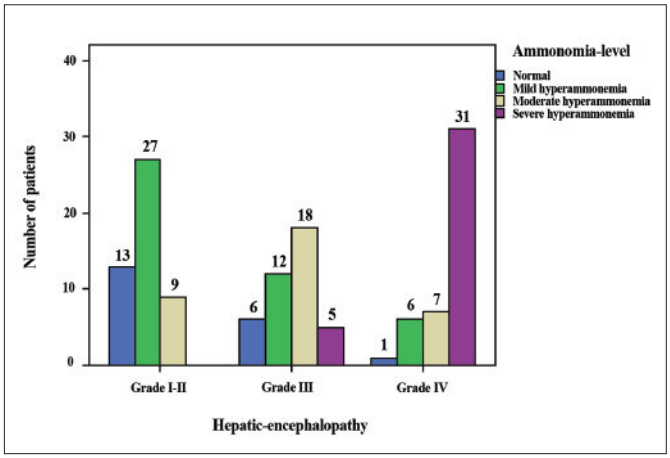

Figure 1: Correlation between ammonia level and severity of encephalopathy.

For moderate hyperammonemia, 9 (26%) were in grade I-II, 18 (53%) were in grade-III, and 7 (20%) were in grade-IV HE. Out of 36 patients with severe hyperammonemia, 31 (86 %) patients were in grade-IV HE ($p < 0.001$, Figure 1).

DISCUSSION

Hepatic encephalopathy, the neuropsychiatric manifestation of liver disease, incorporates a spectrum of manifestations ranging from minimal derangements in neuropsychological function to confusion and coma. Over the past 10 years, studies have confirmed the strong association between hyperammonemia due to liver dysfunction and infection/inflammation in the pathogenesis of HE, in acute liver failure,[13] cirrhosis,[14] and more recently in acute-on-chronic liver failure.[15]

In the presence of chronic liver dysfunction, urea synthesis is impaired and the brain acts as an alternative major ammonia detoxification pathway. Astrocytes have the ability to eliminate ammonia by the synthesis of glutamine, however, hyperammonemia leads to the accumulation of glutamine within astrocytes, which exerts an osmotic stress that causes astrocytes to take in water and swell.[16] Low-grade brain oedema has been demonstrated in patients with minimal HE undergoing liver transplantation using magnetic resonance imaging.[6] A decrease in magnetization transfer ratio indicative of increased brain water correlated with abnormalities in neuropsychological function and was reversed by liver transplantation.[17] Further support for the ammonia-glutamine-brain water hypothesis has been provided by inducing hyperammonemia in patients with cirrhosis through the oral administration of an amino-acid solution mimicking the composition of haemoglobin (upper gastrointestinal bleeding being a common precipitant of HE).[18] An increase in brain glutamine, reduction in magnetization transfer ratio, and significant deterioration in neuropsychological function was suggestive of an increase in brain water.[18]

There are many possible precipitants of HE including gastrointestinal bleeding, infection, and dehydration secondary to diuretic use, diarrhea, or vomiting. Each of these precipitants has the potential to increase ammonia production/absorption, increase inflammation, or reduce cognitive reserve.[9] Episodes are usually precipitated by factors that increase inflammation or ammonia production. There is agreement that ammonia is a key toxin involved in the disease process.[19]

The determination of plasma ammonia levels is often performed in the clinical setting to support the diagnosis of HE. However, this practice has been scrutinized over the past decade with poor correlation between ammonia levels and HE.[20] Many conditions unrelated to liver disease can result in elevated ammonia levels. Plasma ammonia levels are generally higher in patients with liver disease; however, the use of plasma ammonia levels as a diagnostic marker for HE presents many challenges.[21] There are variations in the previous studies in correlation of ammonia levels with HE. Some recent studies that have shown little or no correlation between ammonia concentration and severity of HE, while few showed correlation between these two. Ong *et al*. compared four different measurements of ammonia concentration (arterial and venous total, arterial and venous partial pressure) in 121 patients with cirrhosis and grade 0 - 4 hepatic encephalopathy and showed a moderate correlation between all four measurements and grade of HE.[9] In a smaller study of 20 patients with chronic liver failure, Kundra *et al*. found no statistically significant correlation in the patients with elevated ammonia levels and the presence of HE.[22] In another study, Nicalao *et al*. measured ammonia levels in 27 cirrhotics recovering from HE and highlighted the utility of ammonia levels in the management of HE. These studies suggested that there are variations in the results.

Due to these variations in results and no data in the setup, this study was carried out. Results showed a strong correlation between ammonia levels and the severity of HE in the study population (86% patients with severe hyperammonemia were in grade-IV HE, while only 5% with normal ammonia levels were in grade-IV HE). This is in contrast to some already reported studies but is in accordance to other studies including an American study which showed moderate correlation between ammonia levels and degree of HE.[9]

CONCLUSION

This prospective study showed that ammonia levels correlated with the severity of hepatic encephalopathy in the study population. Also, majority of patients coming to the study hospital with hepatic encephalopathy were aged above 50 years, HCV as the major cause of their disease, with majority of patients in child class-C. Therefore, there is a need to focus on such population more vigilantly and ammonia level is a helpful tool in this regard.

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