CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3692267

Available online at: http://www.iajps.com Research Article

SERUM AMMONIA LEVELS AS A PREDICTOR FOR SEVERITY OF HEPATIC ENCEPHALOPATHY

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Article Received: December 2019 **Accepted:** January 2020 **Published:** February 2020

Abstract:

Objective: *To assess the correlation between serum ammonia levels with the severity of Hepatic Encephalopathy (HE) in patients visiting to the tertiary care hospital with advance liver disease.*

Methodology: *This is a Descriptive, analytical study conducted at Jinnah Hospital Lahore from May 2019 to November 2019. A total of 50 patients with liver cirrhosis and HE had serum ammonia levels checked at presentation of patient. The diagnosis of HE was constructed 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 15 patients with normal ammonia levels, 8 (53.3%) were in hepatic encephalopathy grade I and II, 5 (33%) were in grade-III, while 2 (13.33%) patient were in grade-IV hepatic encephalopathy. Out of 22 patients with mildly raised ammonia levels, 6 (27.27%) were having grade I-II encephalopathy, 4 (18.18%) were in grade-III and 12 (54.54%) were having grade-IV HE. Out of 4 patients with moderate hyperammonemia, 1 (25%) was in grade II, 2 (50%) were in grade-III, and 1 (25%) were in grade-IV HE. Out of 9 patients with severe hyperammonemia, 6 (66.67%) patients were in grade-IV.*

Conclusion: *Serum ammonia levels correlated with the severity of hepatic encephalopathy. Increased ammonia level, severe is the grade of hepatic encephalopathy.*

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

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Please cite this article in press Munazza Iftikhar et al, ***Serum Ammonia Levels As A Predictor For Severity Of Hepatic Encephalopathy.,*** *Indo Am. J. P. Sci, 2020; 07(02).*

INTRODUCTION:

Hepatic encephalopathy (HE) is a wide spectrum of neuropsychiatric presentations commonly affecting patients with end-stage liver disease.1 Clinical manifestations include attention deficits, alterations of sleep patterns and muscular in-co-ordination advancing to stupor, coma and may even followed by seizures, especially in acute liver failure.2 It may manifest in 50 to
70% of all the patients with advance liver disease and cirrhosis, including those with abnormalities demonstrable only by psychometric testing.3

The development of HE is a poor prognostic sign, with 1-year mortality rates of as much as of 60%.1 Hepatic encephalopathy in individuals with chronic hepatic dysfunction is considered to be lead by failure of the hepatocytes to get rid of toxic products from the blood stream. The exact toxins that cause HE is not yet known.4 There is a lot of discussion about the basic mechanisms, yet, raised plasma and central nervous system ammonia levels are viewed as a key factor in pathophysiology of HE 5. However, researches have demonstrated that the relationship between's serum ammonia levels and severity of HE is inconsistent.4,6

The estimation of blood ammonia levels is constrained by the way this is not the variable that is the most significant. Ideally, one might want to realize how much ammonia enters the brain, not what amount is in the blood. The blood-brain barrier (BBB) is the critical and inadequately comprehended component in this relationship.7 Ammonia modulates the transcellular passage of small to medium size molecules by influencing their carriers located at the BBB and by acting either directly or in synergy with liver injury-derived inflammatory cytokines likewise evokes inconspicuous increments of the transcellular section of molecules of various size (BBB leakage), which appears of being liable for the vasogenic component of cerebral edema related with acute liver failure.8

A study done in America concluded that ammonia levels do correlate with the severity of HE.9 However, othet studies are inconclusive in this aspect.4,6,10 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 50 patients admitted to the Jinnah Hospital Lahore, from May 2019 to November 2019. The sample was estimated by calculating 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 any etiology and HE were included in the study. Patients who were having co-morbid diseases like stroke, sepsis etc, were excluded from this study. Liver cirrhosis was confirmed by clinical, biochemical and ultrasonographic findings and diagnosis of HE was established on exclusion. The HE was graded according to the West Haven Classification system.12 Ammonia levels were estimated 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 levels.

The data was collected in a well designed proforma and analyzed using SPSSv25. 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 were considered statistically significant.

RESULTS:

Out of 50 patients, 23 (46%) were males and 27 (54%) females. 47 (94%) patients were of age greater than 60 years. Regarding etiology, 38 (76%) patients had hepatitis C, most of the patients belonged to Child class-C (n=22, 57.8%) and the rest to child class-B (n=16, 42.1%). Out of 15 patients with normal serum ammonia levels, 8 (53.3%) patients were in hepatic encephalopathy grade I-II, 5(33%) were in grade-III, while 2 (13.33%) patient was in grade-IV HE. Out of 22 patients with mildly raised serum ammonia levels, 6 (27.27%) patients were in grade I-II, 4 (18.18%) were in grade-III and 12 (54.54%) were in grade-IV HE. Spearman rank correlation showing strong correlation between ammonia levels and severity of hepatic encephalopathy ($r = 0.644$, $p < 0.001$).

Out of 4 patients with moderate hyperammonemia, 1 (25%) was in grade II, 2 (50%) were in grade-III, and 1 (25%) were in grade-IV HE. Out of 9 patients with severe hyperammonemia, 3 (33.33%) were in grade-III while 6 (66.67 %) patients were in grade-IV HE ($p < 0.001$).

DISCUSSION:

Hepatic encephalopathy, the neuropsychiatric presentation of liver disease, incorporates a spectrum of presentations ranging from minor derangements in neuropsychological function to confused and coma state. Over the past 10 years, different studies have established the strong correlation between higher levels of ammonia in serum 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 existence of chronic liver dysfunction, urea metabolism is impaired and the brain acts as an alternative significant ammonia detoxification pathway. Astrocytes have the function to eliminate ammonia by the production of glutamine, however, increased ammonia levels leads to the storage of glutamine within astrocytes, which causes an osmotic stress that leads astrocytes to take in water and swell.16 Low-grade brain edema has been shown in patients with minimal HE undergoing liver transplantation using MRI.6 A decrease in magnetization transfer ratio suggestive of enhanced brain water correlated with abnormalities in neuropsychological function and was reversed by liver transplantation.17 Further aid 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 enhancement in brain glutamine, decrease in magnetization transfer ratio, and remarkable deterioration in neuropsychological function was indicative of rise in brain water.18

There are various possible precipitants of HE including gastrointestinal bleeding, infection, and dehydration secondary to diuretic use, diarrhea, or vomiting. All of these precipitants have the potential to increase ammonia production/absorption, increase inflammation, or decrease cognitive reserve.9 Episodes are usually caused by factors that ascend inflammation or ammonia production. There is agreement that ammonia is the basic toxin involved in the disease process.19

The determination of plasma ammonia levels is often done 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 Various conditions not related to liver disease can result in increased ammonia levels. Plasma ammonia levels are commonly raised 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. Few recent studies that have shown small or no correlation between ammonia concentration and severity of hepatic encephalopathy, 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 research of 20 patients with chronic liver failure, Kundra et al. found no statistically significant correlation in the patients with increased ammonia levels and the presence of HE.22 In another study, Nicalao et al. measured ammonia levels in 27 cirrhotic patients recovering from HE and highlighted the utility of ammonia levels in the treatment of HE. These studies suggested that there are variations in the results. Because of these variations in results and no data in the setup, this study was carried out. Our results showed a strong correlation between ammonia levels and the severity of HE in the study population. 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 demonstrated that ammonia levels correlated with the severity of hepatic encephalopathy in our given population. Also, predominantly patients visiting to the study hospital with hepatic encephalopathy were aged more than 50 years, HCV as the major cause of their disease, with majority of patients in child class-C. Hence, there is a need to focus on such populace more ardently and ammonia level is a useful tool in this regard.

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