Open Access

Original Article

Association of Serum Ammonia Levels with Severity of Grades of Hepatic Encephalopathy in Patients Presenting to er of a Tertiary Care Hospital

Muhammad Dawood, Muhammad Nadeem Ashraf, Sonia Madad*, Andaleeb Khan, Kamil Rehman Butt, Shahana Rehman

Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan, *Federal Medical & Dental College, Islamabad Pakistan

ABSTRACT

Objective: To determine the association of serum Ammonia levels with severity of grades of hepatic encephalopathy in patients presenting to the department.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Emergency Department, Pak Emirates Military Hospital Rawalpindi Pakistan, from Dec 2020 to May 2021.

Methodology: This study was conducted on 100 patients presenting with hepatic encephalopathy at the emergency department of our hospital. Based on clinical findings and relevant investigations, a consultant gastroenterologist or emergency medicine physician diagnosed hepatic encephalopathy or the underlying cause. In addition, serum Ammonia levels were done on all the patients at the time of presentation and associated with grades of hepatic encephalopathy and other factors.

Results: Out of 100 patients included in the final analysis, 67 were males, and 33 were females. Infection (29%) was the commonest aetiology of hepatic encephalopathy, followed by Constipation (23%). In addition, 59% had normal serum ammonia levels, while 41% had raised ammonia levels in their serum. High grade of hepatic encephalopathy and raised Child-Turcotte-Pugh score were statistically significantly associated with raised ammonia levels in our study participants.

Conclusion: Raised serum ammonia levels were a common finding among patients with hepatic encephalopathy. Therefore, patients with a high grade of hepatic encephalopathy and a high Child-Turcotte-Pugh score at the time of presentation should be considered at a higher risk of having hyperammonemia.

Keywords: Ammonia**,** Hepatic encephalopathy, Liver cirrhosis.

How to Cite This Article: *Dawood M, Ashraf MN, Madad S, Khan A, Butt KR, Rehman S. Association of Serum Ammonia Levels with Severity of Grades of Hepatic Encephalopathy in Patients Presenting to er of a Tertiary Care Hospital. Pak Armed Forces Med J 2022; 72(4): 1478-1481.*

DOI: https://doi.org/10.51253/pafmj.v72i4.6853

INTRODUCTION

Liver pathologies make up a huge chunk of hospital admissions and outpatient visits in all parts of the world.[1] Impact of liver disease usually does not remain confined to one system. However, the overall physiology of the body gets affected, compromising the quality of life of the patient.[2] Once this organ has suffered from cirrhosis or has failed and stopped function, then medical remedies are usually of no use, and a liver transplant remains the only option for the patient.[3] Hepatic encephalopathy is one of the common presentations of patients suffering from acute or chronic liver failure.[4] Emergency department is usually the first place where these patients report in an acute confusional state and warrant a detailed assessment of their clinical condition.[5] Multiple biochemical changes may cause or consequence of this condition, and timely assessment of these changes may lead to better outcomes among patients suffering from hepatic encephalopathy.[6]

Correspondence: Dr Muhammad Dawood, Resident in EM, Pak Emirates Military Hospital, Rawalpindi, Pakistan

Received: 07 Jun 2021; revision received: 20 Jul 2021; accepted: 27 Jul 2021

Raised serum ammonia levels have been associated with various liver diseases in literature across the globe. Holecek *et al,* in 2015 concluded that careful monitoring of ammonia and aminoacidemia might discover important break points in the course of liver disease and indicate an appropriate therapeutic approach.[7] Hu *et al*, published a study in 2020 revealing that raised serum ammonia levels were significantly associated with organ failure, especially the liver, and poor prognosis in these patients.[8] Mallet *et al*, tried to capture this important aspect of patients with liver disease from another perspective. They tried to come up with the idea that repeated measurements could be useful in patients with chronic liver disease, but they need to perform ammonia levels that could be titrated according to the cause and presentation of the individual. It can also be used to assess the clinical response in patients after the treatment.[9]

Emergency departments across the country receive a large number of patients with hepatic encephalopathy and other problems related to liver failure. Usually, ammonia levels are not part of these investigations, but a local study by Qureshi *et al,*[10] in 2012

indicated that ammonia levels predict the severity of hepatic encephalopathy in Pakistan. We, therefore, planned this study with the rationale of looking for the association of serum Ammonia levels with severity of grades of hepatic encephalopathy in patients presenting to emergency reception of a tertiary care hospital.

METHODOLOGY

This comparative cross-sectional study was conducted at the Emergency Department of Pak Emirates Military Hospital Rawalpindi from December 2020 to May 2021. Ethical approval (letter no A/28/EC/298/2021) was taken from the ethical review board committee of Pak Emirates Military Hospital Rawalpindi before the start of this study. The sample was collected by using the non-probability consecutive sampling technique. The sample size was calculated using the WHO calculator and keeping the population prevalence of hyperammonemia in liver failure patients as 37.5%,[11] and the margin of error at 10%.

Inclusion Criteria: All patients between 18 and 60 years presenting to the emergency department with hepatic encephalopathy were included in the study.

Exclusion Criteria: Patients with a confusional state due to any cause other than hepatic were excluded from the study. Patients who were intoxicated, uremic, septic or under the influence of illicit drugs were also not included in the study. Patients with any cause of hyperammonemia other than hepatic cause were also excluded.

Diagnosis of liver cirrhosis and hepatic encephalopathy was made based on the consultant gastroenterologist's clinical, laboratory and radiological findings.[12] Hepatic encephalopathy was graded according to the West Haven criteria.[12] Hyperammonemia was defined as serum ammonia levels of more than 30 micromol/L.[13]

Child-Turcotte-Pugh Scoring involves total bilirubin, INR, serum albumin, presence of ascites and hepatic encephalopathy.[14]

After written informed consent from the primary caregivers of potential participants, patients presenting with hepatic encephalopathy reporting in the emergency department of Pak Emirates Military Hospital Rawalpindi Pakistan fulfilling the inclusion and exclusion were included in the study. They underwent all baseline investigations, including (Complete Blood picture, liver function test, renal function test, C-reactive protein, tumour markers etc.) and ultrasound abdomen and serum ammonia levels. In addition, a mini-mental state examination was also done to confirm hepatic encephalopathy or other causes of delirium (to exclude) in these patients.

All statistical analysis was performed using the Statistics Package for Social Sciences version 24.0 (SPSS-24.0). Mean and standard deviation was calculated for the age of patients. Frequency and percentages for gender, grades of encephalopathy and etiological causes of hepatic encephalopathy were calculated. Pearson Chi-square and Fisher's exact test were applied to look for association of age, gender, grades of hepatic encephalopathy and CTP score with raised serum ammonia levels by keeping *p*-values less than or equal to 0.05 as significant.

RESULTS

Out of 100 patients presenting with hepatic encephalopathy at the emergency department of our hospital were included in the final analysis. Of them, 67 were male, and 33 were female. The commonest aetiology of hepatic encephalopathy among our study participants was Infection (29%), followed by Constipation (23%). Table-I summarized the basic demographic data of patients included in our study. Out of 100 patients, 59 had normal serum ammonia levels, while 41% had raised ammonia levels in their serum.

Table-I: Characteristics of patients admitted with hepatic encephalopathy due to liver cirrhosis.

Characteristics	n (%)
Age (years)	
Mean ± SD	46.353 ± 6.732
Range (min-max)	19 - 59
Serum Ammonia Levels	
Normal	59 (59%)
Raised	41 (41%)
Gender	
Male	67 (67%)
Female	33 (33%)
Grade of Hepatic Encephalopathy	
I	26 (26%)
II	45 (45%)
III	19 (19%)
IV	10 (10%)
Causes of Hepatic Encephalopathy	
Infection	29 (29%)
Constipation	23 (23%)
Esophageal bleeding	21 (21%)
Hypokalemia	15 (15%)
Excessive protein in diet	09 (9%)
Others	3 (3%)

In addition, 26% had Grade I hepatic encephalopathy, 45% had Grade II, 19% had Grade III, and 10% had Grade IV encephalopathy. High grade of hepatic

encephalopathy and raised Child-Turcotte-Pugh score were statistically significantly associated (p-value <0.05) with raised levels of ammonia in our study participants (Table-II).

Table-II: Prognosis of the study group and predictors

Factors	Normal Ammonia Levels	Raised Ammonia Levels	p-value
Age (years)			
<40	30 (58.2%)	21 (31.2%)	0.971
>40	29 (41.8%)	20 (68.8%)	
Gender			
Male	44 (2.8%)	23 (3.7%)	0.054
Female	15 97.2	18 (96.3%)	
CTP Score			
<9	43 (71.7%)	18 (56.1%)	0.003
>9	16 (28.3%)	23 (43.9%)	
Grade of Hepatic Encephalopathy			
I	22 (37.3%)	4 (9.7%)	0.002
II	25 (8.4%)	20 (48.7%)	
III	10 (16.9%)	09 (21.9%)	
IV	02 (3.3%)	08 (19.5%)	

DISCUSSION

Encephalopathies have always been difficult for emergency care physicians as patients present in a confusional state secondary to underlying medical and surgical conditions and warrant early intervention from the emergency care team. Liver diseases have been notorious for causing encephalopathic conditions and compromising individuals' quality of life in several ways.[15] Multiple biochemical changes may have either caused or effect the relationship with this condition which needs to be sorted out at the time of presentation and may play an important role in management. We, therefore, planned this study with the rationale of looking for the association of serum Ammonia levels with severity of grades of hepatic encephalopathy in patients presenting to emergency reception of a tertiary care hospital.

Jayakumar *et al,*[16] in 2018, conducted a study regarding the role of ammonia in the pathogenesis of hepatic encephalopathy. They further emphasized the relationship of hyperammonemia with neurological complications that occur in acute and chronic liver failure. Our results were similar in that most of the patients with hepatic encephalopathy had raised ammonia levels in our study but were also associated with high levels of encephalopathy.

Chiriac *et al,*[17] in 2021 looked for the role of ammonia in predicting the outcome of patients with acute-on-chronic liver failure. They concluded that the number of factors that predicted in-hospital mortality among patients with acute-on-chronic liver failure and venous ammonia levels was one of those factors. We did not study long-term prognosis or in-hospital mortality, as ours was an emergency department-based study, but we found that raised serum ammonia levels in our patients predicted a higher grade of hepatic encephalopathy and high CTP score.

Another recent study published in 2019 by Heidari *et al,*[18] evaluated the effect of Manganese and ammonia and their combination on mitochondrial functionality indices in isolated brain mitochondria. They revealed the additive toxicity of ammonia and Manganese in isolated brain mitochondria exposed to these neurotoxins. Their data and our study both high-light that routine baseline investigations sometimes do not cover the overall biochemical picture of patients suffering from hepatic encephalopathy, and detailed biochemical analysis may be required to understand the clinical picture completely.

Bernal *et al,*[19] studied arterial ammonia levels in this regard and looked for the relationship of these levels with encephalopathy and intracranial hypertension in acute liver failure. They revealed that ammonia levels are directly related to the development of hepatic encephalopathy and intracranial hypertension. Our study design was slightly different, and we did not study arterial ammonia levels. However, our findings supported the findings of Bernal *et al,* in the sense that serum ammonia had a strong relation-ship with hepatic encephalopathy in our study subjects.

LIMITATIONS OF STUDY

The cause and effect relationship of raised serum ammonia levels could not be established by the study design we used in our study. This is one of the main limitations of our study. More studies with better designs can generate more accurate results.

CONCLUSION

Raised serum ammonia levels were a common finding among patients with hepatic encephalopathy. Therefore, patients with a high grade of hepatic encephalopathy and a high CTP score at the time of presentation should be consi-dered at a higher risk of having hyperammonemia.

Conflict of Interest: None.

Author's Contribtution:

MD:, MNA: Substantial contributions to the conception, Drafting, Final approval, SM:, AK: Study design, Data analysis, Final approval, KRB:, SR: Conception, Data analysis, Final approval.

REFERNCES

1. Butt AS. Epidemiology of Viral Hepatitis and Liver Diseases in Pakistan. Euroasian J Hepatogastroenterol 2015; 5(1): 43-48.

2. Wang FS, Fan JG, Zhang Z, Gao B, Wang HY. The global burden of liver disease: the major impact of China. Hepatology 2014; 60(6): 2099-108.
3. Perri GA, Khosravani H. Complications of end-stage liver disease. Can Fam Physician 2016; 62(1): 44-50.
4. Elsaid MI, Rustgi VK. Epidemiology of Hepatic Encephalopathy. Clin Liver Dis 2020; 24(2): 157-174.
5. Chuang CJ, Wu YF, Wu KH, Chen YC. Patients with Liver Cirrhosis as Frequent Attenders of Emergency Departments. Emerg Med Int 2020; 2020(1): 8289275.
6. Kerbert AJC, Jalan R. Recent advances in understanding and managing hepatic encephalopathy in chronic liver disease. F1000 Res 2020; 9(3): F1000
7. Holecek M. Ammonia and amino acid profiles in liver cirrhosis: effects of variables leading to hepatic encephalopathy. Nutrition 2015; 31(1): 14-20.
8. Hu C, Huang K, Zhao L, Zhang F, Wu Z, Li L. Serum ammonia is a strong prognostic factor for patients with acute-on-chronic liver failure. Sci Rep 2020; 10(1): 16970.
9. Mallet M, Weiss N, Thabut D, Rudler M. Why and when to measure ammonemia in cirrhosis? Clin Res Hepatol Gastroenterol 2018; 42(6): 505-511.
10. Qureshi MO, Khokhar N, Shafqat F. Ammonia levels and the severity of hepatic encephalopathy. J Coll Physicians Surg Pak 2014; 24(3): 160-163.
11. Kundra A, Jain A, Banga A, Bajaj G, Kar P. Evaluation of plasma ammonia levels in patients with acute liver failure and chronic liver disease and its correlation with the severity of hepatic encephalopathy and clinical features of raised intracranial tension. Clin Biochems 2005; 38(8): 696-699.
12. Swaminathan M, Ellul MA. Hepatic encephalopathy: current challenges and future prospects. Hepat Med 2018; 10(1): 1-11.
13. Ali R, Nagalli S. Hyperammonemia. StatPearls Treasure Island (FL): StatPearls Publishing; 2021. [Internet] availiable at: Available from: https://www.ncbi.nlm.nih.gov/books/NBK5/.
14. Tsoris A, Marlar CA. Use Of The Child Pugh Score In Liver Disease. StatPearls. Treasure Island (FL): StatPearls Publishing; 2021. [Internet] availiable at: Available from: https://www.ncbi.nlm.nih.gov/books/NBK542308/.
15. Patidar KR, Thacker LR, Wade JB, Sterling RK, Sanyal AJ, Siddiqui MS, et al. Covert hepatic encephalopathy is independently associated with poor survival and increased risk of hospitalization. Am J Gastroenterol 2014; 109(11): 1757-1763.
16. Jayakumar AR, Norenberg MD. Hyperammonemia in Hepatic Encephalopathy. J Clin Exp Hepatol 2018; 8(3): 272-280.
17. Chiriac S, Stanciu C, Cojocariu C, Singeap AM, Sfarti C. Role of ammonia in predicting the outcome of patients with acute-on-chronic liver failure. World J Clin Casess 2021; 9(3): 552-564.
18. Heidari R, Jamshidzadeh A, Ommati MM, Rashidi E, Khodaei F, Sadeghi A, et al. Ammonia-induced mitochondrial impairment is intensified by manganese co-exposure: relevance to the management of subclinical hepatic encephalopathy and cirrhosis-associated brain injury. Clin Exp Hepatols 2019; 5(2): 109-117.
19. Bernal W, Karvellas CJ, Auzinger G. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatologys 2007; 46(6): 1844-1852.