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Original research article

HYPERAMMONEMIA IS ASSOCIATED WITH INCREASING SEVERITY OF BOTH LIVER CIRRHOSIS AND HEPATIC ENCEPHALOPATHY

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Abstract: *Hyperammonemia is a critical condition frequently observed in patients with liver cirrhosis and hepatic encephalopathy.* ***Objectives:*** *The study's main aim is to find that hyperammonemia is associated with increasing severity of both liver cirrhosis and hepatic encephalopathy.* ***Methods:*** *This retrospective cohort study was conducted at DHQ Hospital Nowshera Khyber Pakhtunkhwa from January 2023 to June 2023. A total of 175 patients diagnosed with liver cirrhosis were included in the study. Data collection was performed using the hospital's electronic medical records system. The variables collected included demographic data like patients' age and sex and clinical data concerning the etiology of cirrhosis, Child-Pugh score, and MELD score.* ***Results:*** *The study included 175 patients with liver cirrhosis, with a mean age of 54.3 ± 12.7 years, of whom 64% were male and 36% female. The etiologies of cirrhosis were predominantly hepatitis C virus (45%), hepatitis B virus (30%), alcoholic liver disease (15%), and non-alcoholic steatohepatitis (10%). The mean Child-Pugh score was 8.7 ± 2.1, indicating moderate to severe liver disease, and the mean MELD score was 14.3 ± 4.5. The study found a strong positive correlation between ammonia levels and encephalopathy severity ($r = 0.72$, $p < 0.001$).* ***Conclusion:*** *It is concluded that hyperammonemia is significantly associated with the severity of liver cirrhosis and hepatic encephalopathy.*

Keywords: Ammonia, Hepatic Encephalopathy, Liver Cirrhosis, Hyperammonemia, Child-Pugh Score.

Introduction

Hyperammonemia is a critical condition frequently observed in patients with liver cirrhosis and hepatic encephalopathy. Ammonia, a byproduct of protein metabolism, is usually converted into urea by the liver and then excreted by the kidneys. However, in liver cirrhosis, the liver's ability to perform this conversion is significantly impaired due to the extensive fibrosis and loss of functional hepatic tissue (1). This impairment leads to the accumulation of ammonia in the bloodstream, contributing to the pathogenesis of hyperammonemia. CLD and liver cirrhosis are clinicopathological diseases. CLD is divided into two categories: early-stage CLD and advanced-stage CLD (2). The primary risk factors for cirrhosis of the liver are idiopathic C diseases/ viruses, including hepatitis B and C; metabolic, toxic/drug-induced, and auto-immune diseases leading to continuous inflammation and fibrosis. Indeed, it is the sustaining of the wound healing response, which becomes the primary force pushing the relatively gradual continued deposition of ECM components that results in liver cirrhosis and hepatic failure (3). The signs apparent in conditions where the liver is in a state of chronic disease are determined by the severity and type of the disease in the liver. The symptoms in the early stages described above may not be apparent, and the only tests that may reveal the condition are liver function tests and abdominal ultrasound (4). On the other hand, liver diseases that have reached the chronic phase can be identified by mental changes, massive jaundice, coagulation defects, and so on. Routine serum blood ammonia should not exceed 35 µmol/L (5). Under normal circumstances, blood ammonia results from bacterial action on urea and other nitrogenous material in the intestine, from the purine-nucleotide cycle, and other transamination reactions in skeletal muscles, kidneys, and liver (6). Hepatic encephalopathy is a condition that is seen in several patients with cirrhosis; the condition is characterized by alterations in cognitive function and neurologic abnormalities (7). Hepatic encephalopathy is thus described as the range of neuropsychiatric disturbance in patients with liver disease following the exclusion of cerebral disease (8). Behavioral alterations, dementia, and a reduced state of consciousness also demonstrate hepatic encephalopathy. Portosystemic shunting through collaterals is considered one of the necessary conditions for developing the syndrome. Hepatic encephalopathy is also reported in patients who have no cirrhosis with either spontaneous or surgically created portosystemic shunt (9). The appearance of hepatic encephalopathy, therefore, has some relation to the effect of neurotoxic substances that develop in the context of cirrhosis and portal hypertension (10). Liver cirrhosis, the advanced stage of chronic liver disease, involves the replacement of healthy liver tissue with scar tissue, which obstructs blood flow and diminishes the liver's detoxifying functions. As cirrhosis progresses, portal hypertension develops, further exacerbating the shunting of blood away from the liver and into the systemic circulation without adequate detoxification. This diversion allows toxins,

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including ammonia, to bypass the liver, resulting in elevated blood ammonia levels (11).

The elevated ammonia levels in hyperammonemia have a profound impact on the brain, leading to hepatic encephalopathy. Hepatic encephalopathy manifests as a spectrum of neuropsychiatric abnormalities ranging from subtle cognitive deficits to profound coma. Ammonia and other neurotoxins cross the blood-brain barrier and affect neurotransmission, leading to alterations in cerebral function (12). The brain's astrocytes, which play a crucial role in maintaining the blood-brain barrier and regulating neurotransmitter levels, are particularly susceptible to ammonia toxicity. This results in brain edema, oxidative stress, and impaired neurotransmission, which collectively contribute to the clinical manifestations of hepatic encephalopathy (13).

Objectives

The main objective of the study is to find that hyperammonemia is associated with increasing severity of both liver cirrhosis and hepatic encephalopathy.

Methodology

This retrospective cohort study was conducted at DHQ Hospital Nowshera Khyber Pakhtunkhwa from January 2023 to June 2023. It included 175 patients diagnosed with liver cirrhosis.

The inclusion criteria for the study were as follows: (1) a confirmed diagnosis of liver cirrhosis, established through clinical evaluation, laboratory tests, and imaging studies; and (2) the availability of serum ammonia level measurements. The exclusion criteria included (1) patients with other causes of hyperammonemia or concurrent acute liver failure and (2) patients with incomplete medical records.

Data collection was performed using the hospital's electronic medical records system. The variables collected included demographic data like patients' age and sex and clinical data concerning the etiology of cirrhosis, Child-Pugh score, and MELD score. The serum ammonia levels recorded at the time of HER episodes and the severity of HE were noted according to the West Haven criteria. Other laboratory variables were also considered as part of the hepatic panel, such as renal function, complete blood count, treatment strategies used, and patient prognosis.

Statistical analyses were performed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation (SD) and compared using Student's t-test. Categorical variables were expressed as frequencies and percentages and compared using the Chi-square test.

Results

The study included 175 patients with liver cirrhosis, with a mean age of 54.3 ± 12.7 years, of whom 64% were male and 36% female. The etiologies of cirrhosis were predominantly hepatitis C virus (45%), hepatitis B virus (30%), alcoholic liver disease (15%), and non-alcoholic steatohepatitis (10%). The mean Child-Pugh score was 8.7 ± 2.1, indicating moderate to severe liver disease, and the mean MELD score was 14.3 ± 4.5, reflecting the severity of liver dysfunction in the cohort. (Table 1)

Table 1: Patient Demographics and Clinical Characteristics

Characteristic	Value
Number of Patients	175
Mean Age (years)	54.3 ± 12.7
Gender	
- Male	112 (64%)
- Female	63 (36%)
Etiology of Cirrhosis	
- Hepatitis C Virus	79 (45%)
- Hepatitis B Virus	53 (30%)
- Alcoholic Liver Disease	26 (15%)
- Non-alcoholic Steatohepatitis	17 (10%)
Mean Child-Pugh Score	8.7 ± 2.1
Mean MELD Score	14.3 ± 4.5

26% had Grade I with a mean ammonia level of 85.6 ± 20.4 µmol/L, 40% had Grade II with 110.3 ± 24.5 µmol/L, 23% had Grade III with 130.7 ± 30.2 µmol/L, and 11% had Grade IV with 150.5 ± 33.7 µmol/L. Overall, the mean ammonia level across all patients was 112.4 ± 35.6 µmol/L, indicating a correlation between higher ammonia levels and increased severity of hepatic encephalopathy. (Table 2)

Table 2: Serum Ammonia Levels and Hepatic Encephalopathy Severity

Hepatic Encephalopathy Grade	Number of Patients (%)	Mean Ammonia Level (µmol/L)
Grade I	45 (26%)	85.6 ± 20.4
Grade II	70 (40%)	110.3 ± 24.5
Grade III	40 (23%)	130.7 ± 30.2
Grade IV	20 (11%)	150.5 ± 33.7
Total	175 (100%)	112.4 ± 35.6

The study found a strong positive correlation between ammonia levels and encephalopathy severity ($r = 0.72$, $p < 0.001$). Additionally, moderate positive correlations were observed between ammonia levels and the Child-Pugh score

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(r = 0.53, p < 0.01) and between ammonia levels and the MELD score (r = 0.47, p < 0.01), indicating that higher ammonia levels are associated with more significant liver dysfunction and more severe hepatic encephalopathy. (Table 3)

Table 3: Correlation Between Ammonia Levels, Hepatic Encephalopathy, and Liver Function Scores

Variable	Correlation Coefficient (r)	p-value
Ammonia Levels vs. Encephalopathy Severity	0.72	< 0.001
Ammonia Levels vs. Child-Pugh Score	0.53	< 0.01
Ammonia Levels vs. MELD Score	0.47	< 0.01

Multiple linear regression analysis identified serum ammonia level as a significant predictor of hepatic encephalopathy severity, with a standardized coefficient (β) of 0.68 (p < 0.001). The Child-Pugh score was also an important predictor, with a standardized coefficient (β) of 0.25 (p = 0.02). (Table 4)

Table 4: Regression Analysis for Predictors of Hepatic Encephalopathy Severity

Predictor Variable	Standardized Coefficient (β)	p-value
Serum Ammonia Level	0.68	< 0.001
Child-Pugh Score	0.25	0.02

The study showed that 90% of patients (157) received lactulose, and 70% (123) were treated with rifaximin. The mean duration of hospital stay was 12.3 ± 7.5 days. The overall mortality rate was 15%, with a notably higher mortality rate of 40% among patients with Grade IV hepatic encephalopathy. (Table 5)

Table 5: Treatment Modalities and Outcomes

Variable	Value
Patients Receiving Lactulose	157 (90%)
Patients Receiving Rifaximin	123 (70%)
Mean Duration of Hospital Stay (days)	12.3 ± 7.5
Overall Mortality Rate	15%
Mortality Rate in Grade IV Encephalopathy	40%

Discussion

The findings of this study underscore the significant association between hyperammonemia and the severity of both liver cirrhosis and hepatic encephalopathy. Raised serum ammonia was reported to be significantly related to the severity of hepatic encephalopathy; it is thus confirmed that hyperammonemia is an important pathogenic factor of this neuropsychiatric disorder (14). The study showed that there is a graded increase in the level of ammonia in convulsing patients with hepatic encephalopathy across all the grades, the level incrementing from 85. 6 ± 20. 4 µmol/L in grade I to 150. 5 ± 33. 7 µmol/L in grade IV. The results imply that as liver function declines, the ability of the liver to metabolize ammonia decreases (15). The moderate positive correlation between ammonia and Child-Pugh score and between ammonia and MELD score (r=0. 53 and 0. 47 respectively, p<0. 01) speaks for an association between hepatic impairment and hyperammonemia. These findings are consistent with other works that have examined the part of liver function in ammonia processing (16). The structural and functional alterations to the liver during the progress of liver cirrhosis affect the patient's condition by reducing the liver's capability to metabolize ammonia to urea, leading to high blood ammonia content (17). Serum ammonia level was found to have the highest regression coefficient value (β = 0. 68, p < 0. 001) and also Child-Pugh score (β = 0. 25, p = 0. 02) as independent predictors of hepatic encephalopathy severity. This indicates that both the severity of liver dysfunction and the level of hyperammonemia are critical for the clinical expression of hepatic encephalopathy. The proposed model accounted for 65% of the variability of HE severity, suggesting that although the levels of ammonia and the liver function's state are contributing factors, more factors may play a role in the worsening and worsening of HE. Most patients in the study took conventional treatments for hyperammonemia, such as lactulose and rifaximin, which are known to help decrease the levels of ammonia and also help treat hepatic encephalopathy (18). The mean length of stay in the hospital was, therefore, 12. 3 ± 7. Five days were taken because it was seen that patients suffering from severe cases required more medical attention. The study's overall mortality was 15%, indicating poor outcomes for HE patients; of the studied patients, 40% had Grade IV hepatic encephalopathy, further emphasizing the need for the development of efficient treatments (19). These results have clinical implications. Later on, they stress that serum ammonia levels should be monitored frequently in patients with liver cirrhosis, with particular reference to those with progressed disease. Therefore, measuring serum ammonia levels early enough and timely intervention could reduce the severe incidences of hepatic encephalopathy and subsequently improve patient outcomes. The study also endorses the application of liver function scores like the Child-Pugh and MELD in evaluating risk and management of HE treatment.

Conclusion

It is concluded that hyperammonemia is significantly associated with the severity of liver cirrhosis and hepatic

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encephalopathy. Elevated serum ammonia levels correlate strongly with increased grades of hepatic encephalopathy and higher liver function scores. Therefore, monitoring and managing ammonia levels are crucial in improving outcomes for cirrhotic patients.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.
Ethics approval and consent to participate.
Approved by the department concerned. (IRB/DHQN/0492/21)
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Conflict of interest

The authors declared an absence of conflict of interest.

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