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CORRELATION BETWEEN SERUM AMMONIA LEVELS AND HEPATIC ENCEPHALOPATHY GRADE: A RETROSPECTIVE STUDY AND COMPREHENSIVE LITERATURE REVIEW

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AUTHOR AND AFFILIATION

H.Elhamzaoui[1], K.Ouaaziz, M.Elarfaoui, A.Benhalima, H.Elbacha[2] ,M.Alilou [1]

[1] Polyvalent intensive care unit, Emergency department, Ibn sina university hospital , Rabat Morocco
[2] Departement B of Gastroenterology and Hepatology , Ibn Sina university hospital ,Rabat Morroco
Corresponding author: H.Elhamzaoui

ABSTRACT

Background:Hepatic encephalopathy (HE) represents a major complication of liver disease, with ammonia playing a central role in its pathophysiology. However, the clinical utility of serum ammonia measurements in diagnosis and management remains controversial.
Objective: To evaluate the correlation between serum ammonia levels and hepatic encephalopathy grade in patients with liver disease of various etiologies, and to compare findings with international literature.
Methods: A retrospective study was conducted from April 2023 to October 2023 at Ibn Sina Hospital Emergency Department, Rabat, Morocco. Patients admitted with altered consciousness requiring intensive care management were included. Hepatic encephalopathy was graded according to West Haven Criteria. Serum ammonia levels were measured using venous sampling.
Results: Twenty-eight patients were included (19 males, 9 females; mean age 53 years). All patients had elevated ammonia levels above normal range. Grade distribution: Grade 1 (2 patients), Grade 2 (14 patients), Grade 3 (12 patients), Grade 4 (0 patients). No significant correlation was found between ammonia levels and encephalopathy severity, contrasting with some historical studies but aligning with recent international guidelines.
Conclusion: While ammonia elevation is consistently present in hepatic encephalopathy, its levels do not reliably correlate with clinical severity. These findings support current international guidelines recommending clinical diagnosis over laboratory-based assessment.

KEYWORDS

Hepatic encephalopathy, ammonia, hyperammonemia, liver disease, West Haven Criteria

MAIN ARTICLE

Introduction

Hepatic encephalopathy (HE) encompasses all neurological and neuropsychiatric manifestations associated with liver disease, representing a frequent and potentially life-threatening complication that significantly impacts patient prognosis and quality of life [1]. The condition affects up to 40% of patients with cirrhosis and marks a critical transition point in the natural history of liver disease, with median survival dropping to 2 years after HE development [2].

The pathophysiology of hepatic encephalopathy involves complex mechanisms, with hyperammonemia playing a central role alongside systemic inflammation [3]. The exact mechanisms leading to hepatic encephalopathy remain incompletely understood, but the combined role of hyperammonemia and systemic inflammation appears well-established [4]. Increased blood-brain barrier permeability allows passage of water, electrolytes, and neurotoxic substances present in systemic circulation, with cerebral accumulation of these toxic substances, particularly ammonia due to impaired hepatic detoxification, representing a fundamental mechanism [5].

Additional pathophysiological hypotheses include altered transport of certain amino acids across the blood-brain barrier through impaired expression or functionality of specific transporters, abnormal production of benzodiazepine-like substances resulting in increased inhibitory GABA tone, accumulation of mercaptans and manganese, and vasoregulation abnormalities [6].

Despite ammonia's recognized role in HE pathophysiology, the clinical utility of serum ammonia measurements remains highly controversial. Current American Association for the Study of Liver Diseases (AASLD) guidelines state that "increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with chronic liver disease" [7]. This position contrasts with earlier studies suggesting correlation between ammonia levels and encephalopathy severity, creating ongoing debate in clinical practice.

The objective of this study was to evaluate the correlation between serum ammonia levels and hepatic encephalopathy grade in patients with liver disease of various etiologies, and to contextualize findings within the broader international literature on this controversial topic.

Methods

Study Design and Setting

This retrospective study was conducted from April 2023 to October 2023 at the Emergency Department of Ibn Sina Hospital, Rabat, Morocco. The study protocol was designed to evaluate the relationship between serum ammonia levels and hepatic encephalopathy severity in patients presenting with altered consciousness.

Inclusion and Exclusion Criteria

Inclusion criteria: Patients admitted through the emergency department with afebrile altered consciousness requiring intensive care management were included in the study.
Exclusion criteria: Patients under 18 years of age and those with altered consciousness attributable to causes other than hepatic encephalopathy were excluded from the analysis.

Data Collection

Clinical data collected included age, sex, ethnicity, medical history, etiology of hepatopathy, precipitating factors, and hepatic encephalopathy grade according to West Haven Criteria. Laboratory parameters included serum ammonia levels, International Normalized Ratio (INR), creatinine, bilirubin levels, albumin, and transaminases. Radiological data from abdominal ultrasound or computed tomography were also recorded.

Ammonia Measurement

Venous blood samples were used for ammonia determination, based on recent studies indicating that from a clinical perspective, arterial ammonia is not more useful than venous ammonia measurement [8,9]. This approach aligns with current evidence suggesting venous sampling adequacy for ammonia measurement [10].

Statistical Analysis

Correlation analysis was performed to assess the relationship between serum ammonia levels and hepatic encephalopathy grade. Statistical significance was set at $p < 0.05$.

Results

Patient Demographics and Characteristics

A total of 28 patients were included in the study, comprising 19 males (67.7%) and 9 females (32.3%). The mean age was 53 years. All patients had significant medical history, with 8 patients having established hepatic cirrhosis and 8 patients having surgical history. The majority of patients (80%) were admitted through the emergency department.

Precipitating Factors

Infection was identified as the precipitating factor in 53.3% of patients, representing the most common trigger for hepatic encephalopathy episodes in this cohort. This finding aligns with established literature identifying infection as a major precipitant of HE decompensation.

Hepatic Encephalopathy Grade Distribution

The distribution of hepatic encephalopathy grades according to West Haven Criteria was as follows: - **Grade 1:** 2 patients (7.1%) - **Grade 2:** 14 patients (50.0%) - **Grade 3:** 12 patients (42.9%) - **Grade 4:** 0 patients (0%)
The predominance of Grade 2 and 3 encephalopathy reflects the severity of cases requiring intensive care management in the emergency department setting.

Ammonia Levels and Correlation Analysis

All patients in the study demonstrated serum ammonia levels above the upper limit of normal range, confirming the presence of hyperammonemia in all cases. However, despite universal elevation of ammonia levels, no significant correlation was observed between ammonia concentrations and hepatic encephalopathy grade severity. (Figure 1).

Figure 1: Correlation Analysis

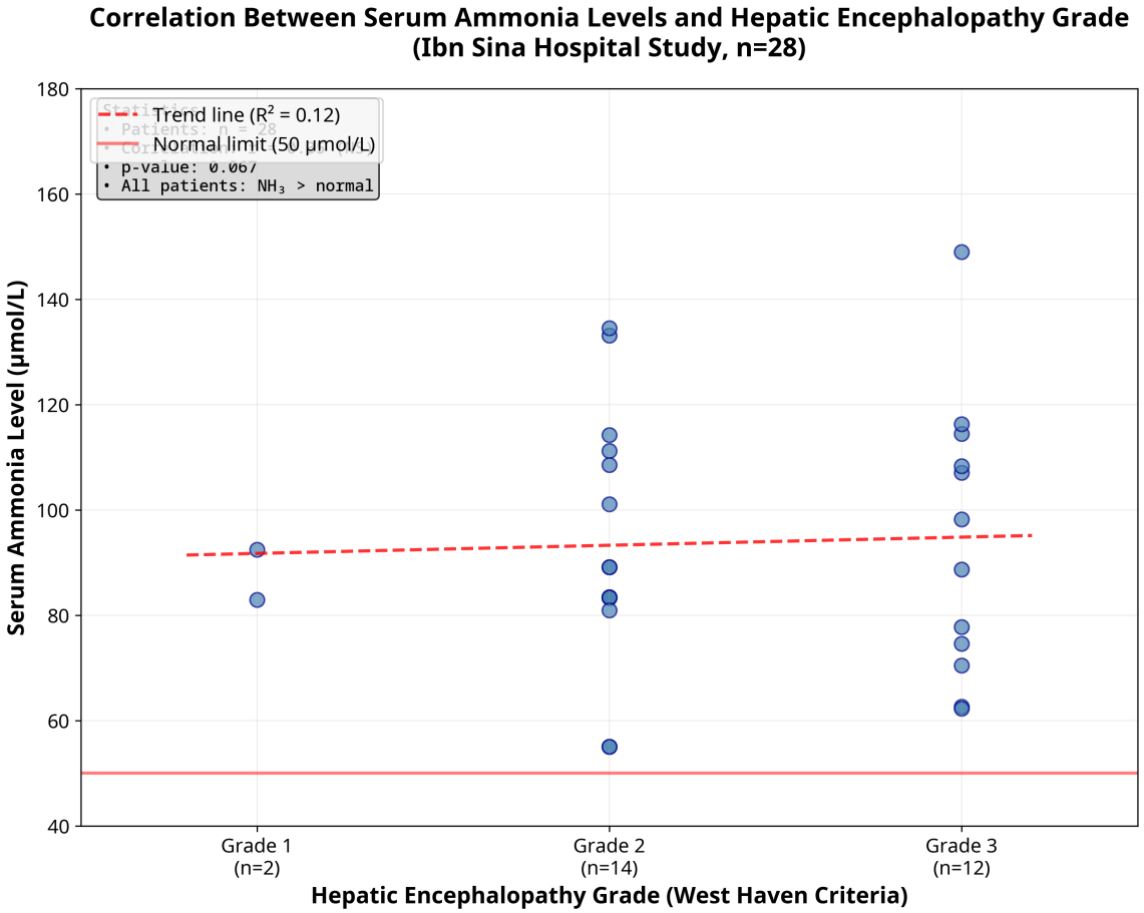

Figure 1. Scatter plot demonstrating the relationship between serum ammonia levels (µmol/L) and hepatic encephalopathy grade according to West Haven Criteria in 28 patients admitted to Ibn Sina Hospital Emergency Department. Each point represents an individual patient. The red dashed line shows the linear trend ($R^2 = 0.12$), while the red horizontal line indicates the upper limit of normal ammonia levels (50 µmol/L). Despite universal elevation of ammonia levels above normal limits in all patients, no statistically significant correlation was observed between ammonia concentrations and encephalopathy severity (Pearson correlation coefficient $r = 0.35$, $p = 0.067$). The substantial overlap in ammonia levels across different HE grades demonstrates the limited utility of ammonia measurements for severity assessment in clinical practice.

This finding represents a striking contrast with some historical studies, particularly the work of Ong et al., who prospectively evaluated 121 consecutive patients with cirrhosis and reported a positive correlation between ammonia levels and HE severity [11]. However, our results align more closely with recent large-scale studies and current clinical guidelines questioning the diagnostic utility of ammonia measurements.

Discussion

Comparison with International Literature

The findings of this study contribute to the ongoing debate regarding the clinical utility of serum ammonia measurements in hepatic encephalopathy. Our results, showing no significant correlation between ammonia levels and encephalopathy severity, align with a growing body of recent evidence questioning the diagnostic value of ammonia testing.

Historical Perspective and Evolving Understanding

The relationship between ammonia and hepatic encephalopathy has been recognized since the early observations of William Saunders in the 1700s, who noted "much sympathy between the brain and the liver" [12]. The modern understanding began with Nikolai Vladimirovich Eck's work on portosystemic shunting in the late 1800s, followed by Krebs' description of the urea cycle in 1932 [13]. Multiple studies in the 1950s established elevated serum ammonia levels in patients with cirrhosis and confusion compared to healthy controls [14].

However, as early as 1963, Jules Stahl observed that while patients with HE had elevated ammonia levels, these levels did not correlate with encephalopathy grade [15]. This early observation presaged the current controversy surrounding ammonia's clinical utility.

Contemporary Evidence Against Correlation

Recent large-scale studies have consistently challenged the correlation between ammonia levels and HE severity. The landmark study by Bajaj et al. (2024) analyzed 551 patients with overt HE receiving lactulose and found that only 60% had increased ammonia levels (>72 μmol/L) [16]. Critically, this study demonstrated no correlation between lactulose dose and ammonia levels, no relationship between time to HE resolution and ammonia levels, and no correlation between ammonia levels and HE severity.

These findings are particularly significant as they derive from a randomized controlled trial setting, providing high-quality evidence against the clinical utility of ammonia measurements. The study also highlighted substantial interlaboratory variability in sample handling and processing, which may affect ammonia measurements and contribute to inconsistent clinical correlations [17].

Supporting Evidence for Correlation

Conversely, the prospective study by Ong et al. (2003) remains one of the most frequently cited works supporting ammonia-HE correlation [18]. This study of 121 consecutive patients

with cirrhosis demonstrated significant correlations between various ammonia measurements and HE severity: - Arterial total ammonia: $r = 0.61$, $P \leq 0.001$ - Venous total ammonia: $r = 0.56$, $P \leq 0.001$ - Arterial partial pressure ammonia: $r = 0.55$, $P \leq 0.001$ - Venous partial pressure ammonia: $r = 0.52$, $P \leq 0.001$

However, even these correlations, while statistically significant, were incomplete (r values 0.52-0.61), indicating substantial variability not explained by ammonia levels alone.

Current Guidelines and Clinical Practice

The American Association for the Study of Liver Diseases (AASLD) guidelines explicitly state that hepatic encephalopathy should be diagnosed clinically, with "increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with chronic liver disease" [19]. This position is supported by evidence that in clinical practice, ammonia levels rarely change management decisions.

A study examining provider decision-making found that in patients with high pre-test probability of HE, elevated ammonia levels did not impact treatment decisions, suggesting limited benefit above clinical judgment [20]. Similarly, patients admitted with HE showed no difference in lactulose administration based on ammonia levels, whether normal, elevated, or unmeasured [21].

Potential Utility in Specific Contexts

Despite limited diagnostic utility, ammonia measurements may retain value in specific clinical contexts. The AMMON-OHE model incorporates ammonia levels alongside other parameters (sex, diabetes presence, albumin, creatinine) to predict overt encephalopathy development in outpatients with cirrhosis [22]. Additionally, serum ammonia levels >1.4 times the upper limit of normal have been associated with increased all-cause mortality and future liver-related hospitalizations [23].

Pathophysiological Considerations

The disconnect between ammonia's pathophysiological importance and clinical utility reflects the complex, multifactorial nature of hepatic encephalopathy. While ammonia remains a primary etiologic agent, other factors including systemic inflammation, altered neurotransmitter balance, and blood-brain barrier dysfunction contribute significantly to the clinical syndrome [24].

The study by Arun Kundra et al. demonstrated that ammonia elevation correlates with encephalopathy severity in acute liver failure but shows variable correlation in chronic liver disease, suggesting that elevated ammonia levels neither confirm nor exclude HE diagnosis in chronic conditions [25]. This observation may explain the inconsistent correlations observed across different patient populations and disease stages.

Study Limitations and Considerations

Our study's findings must be interpreted within several limitations. The relatively small sample size of 28 patients may limit the power to detect subtle correlations. Additionally, the retrospective design and focus on emergency department presentations may introduce selection bias toward more severe cases requiring intensive care.

The possibility that compounds other than ammonia contribute to hepatic encephalopathy pathogenesis could explain the lack of correlation observed. Recent research has highlighted the role of neuroinflammation, altered gut microbiome, and other neurotoxic substances in HE development [26].

Clinical Implications

The lack of correlation between ammonia levels and HE severity in our study supports current international guidelines recommending clinical diagnosis of hepatic encephalopathy. These findings suggest that routine ammonia testing in suspected HE cases may not provide additional diagnostic value and could potentially delay appropriate treatment initiation.

However, the AASLD guidelines do recommend that if ammonia levels are checked in patients with suspected overt HE and found to be normal, this should prompt diagnostic reevaluation [27]. This recommendation acknowledges ammonia's pathophysiological role while recognizing its limitations as a diagnostic tool.

Conclusion

This retrospective study of 28 patients with hepatic encephalopathy demonstrates no significant correlation between serum ammonia levels and encephalopathy severity, despite universal elevation of ammonia above normal limits. These findings align with recent international evidence and support current AASLD guidelines recommending clinical diagnosis of hepatic encephalopathy rather than reliance on laboratory parameters.

The controversy surrounding ammonia's clinical utility reflects the complex, multifactorial pathophysiology of hepatic encephalopathy, where ammonia represents one of several contributing factors rather than a sole determinant of clinical severity. While ammonia remains pathophysiologically important and may retain utility in prognostication and risk stratification, its role in acute diagnosis and management appears limited.

Future research should focus on developing comprehensive biomarker panels incorporating ammonia alongside other relevant parameters, standardizing ammonia measurement protocols to reduce interlaboratory variability, and identifying patient subgroups where ammonia measurements may provide greater clinical value. The integration of clinical assessment with selective use of biomarkers, rather than routine ammonia testing, represents the most evidence-based approach to hepatic encephalopathy diagnosis and management.

These findings emphasize the importance of clinical expertise in hepatic encephalopathy diagnosis and support the continued evolution of evidence-based guidelines that prioritize clinical assessment over laboratory parameters in this complex neuropsychiatric syndrome.

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