MEDICAL MYTHOLOGY

Myth: Interpretation of a single ammonia level in patients with chronic liver disease can confirm or rule out hepatic encephalopathy

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Introduction

Although the exact pathophysiology of hepatic encephalopathy (HE) is not fully understood, for more than a century ammonia has been thought to play a critical role.[1] However, the interpretation and utility of ammonia levels in patients with chronic liver disease (CLD) presenting with HE has been a long-standing source of confusion. It is a common belief in the emergency department and on the wards that a single elevated ammonia level in a patient with CLD can confirm the diagnosis of HE, and a normal level essentially rules it out. This confusion stems from the fact that early studies showed a correlation between degree of encephalopathy and the ammonia level, but numerous subsequent studies have shown that severely encephalopathic patients often have normal ammonia levels. This paper reviews the published literature on ammonia levels in patients with CLD in an attempt to clarify its value as a clinical decision-making tool in patients with suspected HE.

Methods

A MEDLINE search of the literature from 1966 to July 2006 was performed with the headings "ammonia" (focused on the subheading "blood") and "hepatic encephalopathy" (all subheadings included). In addition, an ancestral search of the most cited articles was performed to ensure no significant papers had been omitted. The results were then limited to English language and human studies, identifying 46 articles in total. All abstracts were reviewed, and articles pertaining to the ammonia level and how it relates to the degree of HE in patients with CLD were selected and evaluated.

The literature

In 1963, Stahl published one of the first studies looking at ammonia levels in patients with liver disease and HE.[2] The study examined arterial and venous ammonia levels in 178 patients with hepatic coma. Although the study did show a loose correlation, the article states "it has been difficult to establish a quantitative correlation between intensity of the nervous symptoms and the arterial or venous blood ammonia levels." It further remarked that "considerable overlap still persists among the ammonia values of the different degrees of coma."

In 2003, Ong and colleagues published a prospective study of 121 consecutive patients with CLD with cirrhosis, regardless of initial mental status, admitted to hospi-

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Received: Aug. 9, 2006; accepted: Aug. 11, 2006

Can J Emerg Med 2006;8(6):433-5

tal between September 1998 and December 1999.[3] The mental status of each patient was graded from 0 to 4 using the West Haven Criteria (WHC), and their total ammonia level and partial pressure of ammonia were analyzed in both arterial and venous samples. The authors concluded that each of the 4 measured samples increased to a significant degree with increasing levels of clinically graded HE, with the highest correlation coefficient seen in the arterial sample ($r = 0.61$). Note that correlation coefficients from 0.5 to 0.75 are considered to represent moderate to good relationships. Although this seems to suggest that a statistical correlation exists, it is a poor one and not useful clinically. In the group assessed to be grade 0 (no HE), 69% (20/29) had an elevated ammonia level, meaning only 31% did not. There were a significant number of patients with grades 3 and 4 encephalopathy with normal to mildly elevated ammonia levels. These facts lead the authors to later admit that "because of the substantial overlap in total ammonia levels and partial pressures between cirrhotic patients with and without hepatic encephalopathy, a single level has little clinical utility in the diagnosis of hepatic encephalopathy."

Nicolao and coworkers in 2003 also published a prospective study, which included 27 cirrhotic patients with HE (graded by WHC), 15 cirrhotic patients without HE, and 9 controls who were having arterial blood drawn at the same time, for respiratory issues.[4] They assessed ammonia levels on all patients at admission, and repeated levels in the 17 patients with HE who returned to normal mental status upon resolution of symptoms and again at 48 hours post-resolution. They found ammonia levels to be higher in patients with HE than in either controls or patients with CLD and no HE, with mean levels as follows: (mean ± SD): grade 0 = 75.1 ± 52.1, grade 1–2 = 173.6 ± 66.5, grade 3–4 = 234 ± 94.4. The calculated correlation coefficient between groups was 0.76, a stronger correlation than that found by Ong and colleagues, although they used broader categories, grouping grade 1 with 2 and grade 3 with 4. Again a correlation was seen due to the extraordinarily large amount of overlap between the groups, thus the clinical utility of the test is extremely limited.

Examination of serial ammonia levels is even more illuminating. Of the 17 patients who had resolution of encephalopathy, several had little or no decline in ammonia levels at the time of resolution and 48 hours post-resolution, and 3 actually had an increase in ammonia levels. This compelling information caused the authors to state that ammonia levels are "limited both for the diagnosis of hepatic encephalopathy and for the clinical management of the patients."

Kundra and associates[5] evaluated ammonia levels in 40 patients, 20 of whom had CLD. Mental status was evaluated by a system similar to the WHC, designating 4 stages of encephalopathy. For analysis, the 20 CLD patients were divided into 2 subgroups: 8 patients with clinically evident HE and 12 patients without. The patients with HE had a mean venous total ammonia level of 58.75 ± 29.38, with only 37.5% (3/8) having levels above the normal range. Patients without HE had a mean venous total ammonia level of 42.17 ± 18.19, with 33.3% (4/12) having levels above the upper limit of normal. When further broken down by the grade of HE, the mean ammonia levels for patients graded 3 and 4 (58.67 and 42, respectively), were actually less than the mean ammonia level for patients graded 2 (72.34). The correlation coefficient calculated for CLD patients ($r = 0.30$) in this study shows no significant correlation between grade of HE and total venous ammonia levels. Although admittedly limited by a small sample size, authors commented "elevated ammonia values may neither confirm nor exclude the diagnosis of HE in these [CLD] patients."

Uncertainty regarding the use of serum ammonia levels as a diagnostic test for HE is in part due to the lack of understanding of the pathogenesis of HE. If elevated ammonia levels do cause encephalopathy, their impact on central nervous system function is nonlinear because of the blood–brain barrier's modifying effect. This makes clinical correlation with a single level significantly less useful.[6] In addition, other factors, including phlebotomy technique when the specimen is drawn, can artificially elevate ammonia values,[7] further limiting the clinical utility of this test.

Conclusion

The degree of the correlation between ammonia levels and the severity of HE continues to be controversial. What is evident from the literature is that a single normal ammonia level does not rule out HE in a patient with CLD, and serial levels may not correlate with the evolving clinical picture. An ammonia level is merely a data point among the constellation of variables that may contribute to the development of HE and, for now, the final diagnosis remains a clinical one. Reliance on ammonia levels to make the diagnosis of HE is inappropriate and perhaps dangerous if it results in failure to seek other causes of altered mentation in ED patients with CLD.

https://doi.org/10.1017/S148180350001424X Published online by Cambridge University Press

Competing interests: None declared.

Key words: ammonia levels; chronic liver disease; hepatic encephalopathy

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