Ammonia Levels and Hepatic Encephalopathy in Patients with Known Chronic Liver Disease

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BACKGROUND

The colonic microbiome produces ammonia from dietary nitrogen. In health, approximately 85% of it is detoxified by the liver and excreted as urea in urine, while muscle and brain tissue metabolize the remaining 15%. The process of transamination and the urea cycle prevents this metabolic product from accumulating in the body. The elevated levels of nitrogenous toxins, including ammonia, in the systemic circulation of patients with CLD occur due to hepatocellular dysfunction and/or portosystemic shunting. This hyperammonemia is compounded by reduced peripheral metabolism of ammonia by muscle as a consequence of cachexia and muscle atrophy. Astrocytes synthesize glutamine excessively in the setting of hyperammonemia, resulting in astrocyte swelling and the generation of reactive oxygen species. Astrocyte swelling, free radical generation, and increased inhibitory function of gamma-Aminobutyric Acid result in cerebral dysfunction.1-12 HE manifests as a broad spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma and was commonly graded on the West Haven Criteria (WHC) of 0 to 4 (Table).5 The Grade 0 from the previous WHC, referenced in many trials included in this article, has been replaced with minimal HE in the newly updated WHC by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver.4,5

WHY YOU MIGHT THINK AMMONIA LEVELS HELP TO GUIDE TREATMENT OF HE IN PATIENTS WITH CLD

The ammonia hypothesis posits that ammonia is key in the pathogenesis of HE.6-10 Some of the common precipitants of HE—gastrointestinal bleeding, infection, and renal failure—promote hyperammonemia.11 HE is treated with nonabsorbable disaccharides (lactulose and lactitol) and rifaximin, which reduce the serum concentration of ammonia. Given these associations between HE and ammonia, physicians have for decades tested serum ammonia levels to diagnose HE and chart its resolution. In a study conducted by the Bavarian Society of Gastroenterology,12 60% of the respondents to an anonymous questionnaire regularly performed ammonia analysis in all their patients with liver cirrhosis, believing that it efficiently diagnosed HE.

WHY SERUM AMMONIA LEVELS DO NOT HELP IN THE DIAGNOSIS OR MANAGEMENT OF HE IN CLD PATIENTS

Accuracy of Serum Ammonia

Multiple factors affect the accuracy of ammonia levels. First,
fist clenching or the use of a tourniquet during the process of phlebotomy can falsely increase ammonia levels. Second, some authors have argued that the source of the ammonia sample matters. Kramer et al. reported that partial pressure of ammonia correlated closely with the degree of clinical and electrophysiological abnormalities of HE. However, Nicolao et al. and Ong et al. showed that the blood ammonia levels, whether measured by total venous, total arterial, or partial pressure methods, were equivalent. Third, ammonia levels are dependent on the time to processing of the specimen. Inaccurate results may occur if the blood sample is not immediately placed on ice after collection or if it is not centrifuged within 15 minutes of collection.

Ammonia Levels and Diagnosis of HE

Even with proper collection and processing, ammonia levels in patients with CLD do not reliably diagnose HE. Gundling et al. determined the sensitivity and specificity of venous ammonia levels ≥ 55 µmol/L to diagnose HE to be 47.2% and 78.3%, respectively, by using a gold standard of the WHC and the critical flicker frequency test (a psychophysical test). The positive predictive and negative predictive values of ammonia were 77.3% and 48.6%, with an overall diagnostic accuracy of 59.3%. Approximately 60% of the patients with Grade 3 WHC HE had a normal ammonia level in this study. Ong et al. found that only 31% of patients with CLD and no evidence of HE had a normal ammonia level. In other words, CLD patients with normal ammonia levels may have normal cognitive functioning.

Furthermore, ammonia levels are not a valid tool to diagnose HE even with an oral glutamine challenge. Most importantly, HE is a clinical diagnosis reached following the exclusion of other likely causes of cerebral dysfunction, independent of the ammonia level.

Ammonia Levels and Staging HE

The grading of HE was introduced to assess the response to an intervention in patients with HE enrolled in clinical trials. Tools like the WHC (Table) categorize the severity of HE. Nicolao et al. noted significant overlap in the levels of ammonia between patients with HE Grades 1 and 2 when compared with patients with Grades 3 and 4. This considerable overlap in levels of ammonia was more evident among patients with Grades 0 to 2 per Ong’s study. Most importantly, hospitalists do not need ammonia levels to determine that a patient has HE Grade 3 or HE Grade 4 symptoms, as the stage is graded on clinical grounds only. Once other causes for cerebral dysfunction have been ruled out, the ammonia level does not add to the clinical picture.

Serial Ammonia Levels and Resolution of HE

If the ammonia hypothesis is the sole explanation for the pathogenesis of HE, then the resolution of HE symptoms should be associated with normalization of ammonia levels. Physicians have commonly followed ammonia levels serially throughout a hospital stay. Nicolao et al. evaluated the association of ammonia with HE. They noted that some of the CLD patients

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<thead>
<tr>
<th>WHC per 2001 ACG practice guidelines</th>
<th>WHC per 2014 AASLD/EASL guidelines</th>
<th>ISHEN</th>
<th>Description</th>
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<tbody>
<tr>
<td>Stage 0</td>
<td>Minimal HE</td>
<td>Covert</td>
<td>Abnormal results of established psychometric or neuropsychological tests without clinical manifestations</td>
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<td>Stage 1*</td>
<td>Grade 1</td>
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<td>Trivial lack of awareness</td>
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<td>Euphoria or anxiety</td>
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<td>Shortened attention span</td>
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<td>Impairment of addition or subtraction</td>
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<td>Altered sleep rhythm</td>
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<td>Stage 2</td>
<td>Grade 2</td>
<td>Overt</td>
<td>Lethargy or apathy</td>
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<td>Disorientation for time</td>
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<td>Obvious personality change</td>
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<td>Inappropriate behavior</td>
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<td>Dyspraxia</td>
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<td>Asterixis</td>
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<td>Stage 3</td>
<td>Grade 3</td>
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<td>Somnolence to semistupor</td>
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<td>Responsive to stimuli</td>
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<td>Confused</td>
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<td>Gross disorientation</td>
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<td>Bizarre behavior</td>
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<td>Stage 4</td>
<td>Grade 4</td>
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<td>Coma</td>
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</tbody>
</table>

* Asterix can be detected.

NOTE: Abbreviations: AASLD, American Association for the Study of Liver Disease; ACG, American College of Gastroenterology; EASL, European Association for the Study of the Liver; HE, hepatic encephalopathy; ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; WHC, West Haven Criteria.
had unchanged or increasing levels of ammonia despite overt neurological improvement from their HE. Some have argued that the normalization of ammonia levels lag behind the clinical improvement by 48 hours after resolution of symptoms. In the Nicolao et al. study, ammonia levels for almost all of the patients did not normalize 48 hours after resolution of neurologic symptoms. These data underscore why serial measurements of ammonia in patients with CLD are not useful. For patients with overt symptoms, clinicians can determine improvement based on serial exams.

RECOMMENDATIONS

• HE is a diagnosis of exclusion and is made on clinical grounds.
• Do not check serum ammonia levels in patients with CLD to diagnose HE, to assess the severity of HE, or to determine whether HE is resolving.
• Use your clinical evaluation to determine the severity and course of HE.
• Treatment should be tailored according to clinical findings, not ammonia levels.

CONCLUSION

The attraction of the ammonia theory to explain HE continues to lead physicians to check and follow blood ammonia levels in patients with CLD and suspected HE. However, ammonia measurement, as in the clinical vignette, should be replaced by a thorough clinical evaluation to rule out other causes for altered mental status. Serial exams of the patient should guide management, not ammonia levels.

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References