CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will distinguish the situations in which measuring the serum ammonia level is or is not useful

ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What is the utility of measuring the serum ammonia level in patients with altered mental status?

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A normal ammonia level does not rule out hepatic encephalopathy

A: If you already know that the patient with altered mental status has decompensated liver disease, measuring the arterial or venous ammonia level has little utility. In these patients, one's clinical suspicion is the main guide to diagnosing hepatic encephalopathy, and a normal or modestly elevated blood ammonia level does not rule out the diagnosis.

On the other hand, provided that it is appropriately performed, blood ammonia testing may be helpful if there is no clear evidence of underlying chronic liver disease. In these cases, an elevated blood ammonia level may have significant prognostic value (as in acute liver failure) or may prompt you to initiate further evaluation for uncommon but significant meta bolic disorders such as urea cycle disorders.

WHEN AMMONIA LEVELS RISE

Ammonia is derived predominantly from protein degradation. Most of the ammonia in the blood comes from the intestine, where colonic bacteria use ureases to break down urea into ammonia and carbon dioxide. Fortunately, blood from the intestine is carried directly to the liver via the portal vein, where 85% of the ammonia is converted back into urea, which is less toxic and is excreted by the kidneys and colon. **TABLE 1** summarizes ammonia metabolism and the organs involved.

Ammonia levels are elevated in several conditions in which its production is increased (eg, in convulsive seizures with increased muscle production) or its clearance is impaired (eg, in hepatocellular dysfunction, portosystemic shunting, or both, with subsequent impaired hepatic detoxification of ammonia).

Because the blood-brain barrier is highly permeable to ammonia, the brain is exposed to excessive concentrations of it in these circumstances. In the brain, ammonia is thought to cause both functional and structural abnormalities that could explain neuropsychiatric dysfunction, often manifested as an altered mental status of variable degree.[1–3]

DOES THE PATIENT HAVE DECOMPENSATED LIVER DISEASE?

Physicians often measure the venous (and less often, the arterial) ammonia level while evaluating patients presenting with altered mental status. However, in many cases, this test result may be of uncertain utility—it may not have a significant impact on a specific patient's management and, worse, it can confuse the physician regarding diagnosis. Also, the test itself is a needless expense. Therefore, we need to carefully consider whether to obtain a blood ammonia test and how to interpret the results in patients with altered mental status.

The key initial question in such patients is whether the patient is known to have decompensated liver disease with a typical clinical picture of hepatic encephalopathy.

*Dr. O'Shea has disclosed that he has received research support from the Celgene Corporation.

doi:10.3949/ccjm.76a.08072

TABLE 1

Organs involved in ammonia metabolism

	SMALL BOWEL	COLON	LIVER	KIDNEY	MUSCLE
Produces ammonia	Yes [a]	Yes [b]	No	Yes [a]	Yes (with moderate-strenuous exercise) [a]
Consumes ammonia	No	No	Yes [c,d]	Yes (urinary excretion)	Yes (at rest) [d]

[a] Through deamination of glutamine
[b] By urease of colonic bacteria that split urea into ammonia and carbon dioxide
[c] Through converting ammonia into urea in the periportal hepatocytes (major part)
[d] Through amination of ammonia to form glutamine

If the patient is known to have chronic liver disease

Hepatic encephalopathy is a common complication of end-stage liver disease and is also one of the diagnostic markers of acute liver failure. An accepted factor in its pathophysiology is that the liver fails to clear toxic products of bacterial metabolism brought via the portal venous system from the gut, owing to low detoxifying capacity, portosystemic shunts, or both.[4] Although the exact neurotoxins involved remain poorly defined, ammonia is thought to play a central role.[5–7]

If the patient is known to have chronic liver disease, we usually do not need to measure the blood ammonia level because normal levels in these patients do not rule out hepatic encephalopathy. Multiple studies have shown that the ammonia level correlates to some extent with the severity of hepatic encephalopathy,[8] but ammonia levels substantially overlap among patients with differing clinical grades of hepatic encephalopathy. Moreover, 69% of patients with no evidence of encephalopathy had ammonia levels higher than normal in a study by Ong et al.[8]

Therefore, hyperammonemia is neither sensitive nor specific for the presence or the degree of hepatic encephalopathy. In this respect, three related issues should be emphasized:

Altered mental status in cirrhotic patients does not always equal hepatic encephalopathy. Regardless of the degree of blood ammonia elevation, other relevant causes of altered mental status should be excluded on the basis of the clinical presentation.

Computed tomography of the head is usually obtained in cirrhotic patients:

- Who have changes in mental status but whose presentation is not typical of hepatic encephalopathy (such as those with focal neurologic signs);
- In cases of severe hepatic encephalopathy, suspected head trauma (especially given the commonly associated coagulopathy in cirrhotic patients), and hepatic encephalopathy resistant to standard therapy; and
- Without clear precipitating factors for hepatic encephalopathy, such as infection (eg, spontaneous bacterial peritonitis) and renal insufficiency.

Similarly, in alcoholic patients who present with altered mental status, we should always consider Wernicke encephalopathy.

In alcoholic patients with altered mental status, consider Wernicke encephalopathy

In patients with established hepatic encephalopathy, monitoring the ammonia level during therapy is not as useful as ongoing clinical assessment.

In patients with acute liver failure, a blood ammonia level may have a special prognostic value. In hyperammonemic states that subsequently lead to elevated ammonia in the brain, astrocytes convert ammonia to glutamine. Glutamine is not toxic, but it is osmotically active, and as it accumulates, it leads to astrocyte swelling and brain edema. This pathologic process is very prominent in acute hyperammonemic states in which astrocytes do not have time to adapt osmotically by pumping in myoinositol.[9] Clemmesen et

al[10] have shown that arterial ammonia levels higher than 200 µg/dL are strongly associated with cerebral herniation in patients with acute liver failure.

If the patient is not known to have chronic liver disease

Occasionally, the blood ammonia level is found to be high in a patient who presents with altered mental status but who does not have known liver disease. In these patients, undiagnosed or new-onset decompensated cirrhosis is still possible, and the possibility should be explored. Acute liver failure is another possibility, but it is usually obvious, with associated coagulopathy, hyperbilirubinemia, and other clinical and laboratory features.

The main diagnostic challenge is in patients who have altered mental status and hyperammonemia but no features to suggest the above possibilities. In this setting, three tasks should be approached simultaneously:

- **Look for and aggressively manage cerebral edema and increased intracranial pressure** with ammonia-lowering measures such as lactulose, renal replacement therapy, and other specific therapeutic agents if a urea cycle disorder is suspected.[11]
- **Search for causes of elevated ammonia other than hepatic dysfunction.** These causes can be classified into two major categories[11]: 1) causes of increased ammonia production such as total parenteral nutrition, gastrointestinal hemorrhage, and steroid use, and 2) causes of decreased ammonia excretion such as portosystemic shunts, medications that decrease ammonia metabolism, and inborn errors of metabolism such as urea cycle disorders. Portosystemic shunts have been well documented in patients with no underlying liver disease.[12]

Several drugs, such as glycine (used during transurethral prostate resection), salicylates, and valproate raise the ammonia level by altering the urea cycle.[11] Although most severe inborn errors of metabolism become evident early in childhood, certain urea cycle disorders, especially ornithine transcarbamylase deficiency, may manifest later during adulthood when a precipitating event occurs, such as an increase in protein intake (eg, with total parenteral nutrition), use of certain medications, or infection.

- **Explore concomitant or alternative causes of altered mental status** based on the clinical setting, such as a cerebrovascular accident, infectious meningoencephalitis, drug intoxication, or other metabolic or systemic disorders.

IN AMMONIA TESTING, TECHNIQUE MATTERS

Prolonged tourniquet application can falsely raise the blood ammonia level

To obtain an accurate measurement, the blood sample for ammonia testing must be obtained and handled properly. Prolonged application of a tourniquet or fist-clenching while obtaining the blood sample or improper specimen handling can result in a falsely elevated blood ammonia level, which can lead you down the wrong diagnostic pathway.

Venous blood, if appropriately collected, transported in ice, and handled quickly for analysis, has been shown to be as useful as arterial blood in ammonia measurement.[8]

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