JAMA Diagnostic Test Interpretation

Serum Ammonia Level for the Evaluation of Hepatic Encephalopathy

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A 31-year-old Asian man with hepatitis C cirrhosis complicated by variceal hemorrhage and ascites underwent an inpatient evaluation for orthotopic liver transplantation. He was a graduate student who was doing well until he developed decompensated cirrhosis with variceal hemorrhage. When he first presented, he had hypovolemic shock from acute blood loss related to variceal hemorrhage that was treated with many blood transfusions and variceal banding procedures. When he was transferred to the liver unit on hospital day 25, his liver test abnormalities had mostly recovered and he had no further gastrointestinal bleeding. He had a serum ammonia level measured as part of the routine liver transplant evaluation. He did not have any confusion, insomnia, or decreased mental alertness. Jaundice was noted on the physical examination but he was alert and oriented with normal cognitive function. No tenderness was noted on his abdominal examination and he had mild ascites. During the inpatient liver transplant evaluation, his cognitive capacity and mental status remained stable and he had no symptoms of encephalopathy. He received oral diuretics for the management of his ascites. The **Table** lists results of laboratory analyses performed at admission and on hospital days 25 and 38.

HOW DO YOU INTERPRET THESE TEST RESULTS?

A. The patient has hepatic encephalopathy and should be treated.

B. The patient has subclinical hepatic encephalopathy and should be treated.

C. The patient is at high risk for developing hepatic encephalopathy and should be prophylactically treated.

D. The patient does not have hepatic encephalopathy so no treatment is necessary.

Table. Laboratory Test Results in a Patient With Hepatitis C Cirrhosis

	Day 1 (Hospital Admission)	Day 25 (Transfer to Liver Unit)	Day 38	Reference Range
White blood cell count, $\times 10^3/\mu L$	60.42	15.45	14.68	4.16-9.95
Hemoglobin, g/dL	10.9	9.9	8.1	13.5-17.1
Platelet count, $\times 10^3/\mu L$	70	319	123	143-398
Creatinine, mg/dL	1.0	1.6	0.9	0.5-1.3
Serum ammonia, µg/dL	NA	55	221	39-90
Total bilirubin, mg/dL	6.2	10.9	3.3	0.2-1.1
AST, U/L	1215	34	33	7-36
ALT, U/L	1364	28	17	4-45
Alkaline phosphatase, U/L	82	114	144	31-103
Total protein, g/dL	3.4	5.2	6.0	6.2-8.6
Serum albumin, g/dL	2.2	2.6	2.3	3.7-5.1
INR	1.9	1.2	1.2	0.8-1.2

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; NA, not applicable.

Answer

D. The patient does not have hepatic encephalopathy so no treatment is necessary.

Test Characteristics

Measuring serum ammonia is useful under certain conditions. In acute liver failure, ammonia levels have prognostic significance. In one study, an arterial ammonia level of 124 µmol/L (211 µg/dL) or higher predicted mortality with 78.6% sensitivity, 76.3% specificity, and 77.5% diagnostic accuracy.[1] In another study, arterial ammonia level higher than 100 µmol/L (170 µg/dL) predicted the onset of hepatic encephalopathy and intracerebral hypertension with 59% sensitivity, 78% specificity, and 70% diagnostic accuracy. The combination of MELD score higher than 32 and ammonia level higher than 100 µmol/L (170 µg/dL) improved specificity to 94% and diagnostic accuracy to 74%.[2] An additional study demonstrated correlation between plasma ammonia levels and severity of encephalopathy.[3] The 2013 Medicare midpoint reimbursement for a serum ammonia assay is $27.07 (http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/index.html).

Ammonia is mostly cleared by the liver and there is some extrahepatic metabolism in muscle tissue. Hepatic encephalopathy is thought to be caused by accumulation of unmetabolized ammonia resulting in neuropsychiatric toxicity and encephalopathy. However, elevated ammonia levels also occur in urea cycle disorders, portosystemic shunting, urinary tract infection from urease-producing organisms, gastrointestinal bleeding, shock, ureterosigmoidostomy, renal disease, heavy exercise, smoking, parenteral nutrition, salicylate intoxication, medications (high-dose chemotherapy, valproic acid, bar-

biturates, narcotics, diuretics), and alcohol.[4] The accuracy of venous ammonia measurement is influenced by fist clenching, tourniquet use, and whether the sample is placed on ice.

Application of Test Result to This Patient

It is common for ammonia levels to be obtained during the evaluation of chronic liver disease. However, the evidence does not support ammonia measurement under these circumstances.[3,5,6] When patients have chronic liver disease, hepatic encephalopathy is diagnosed by the overall clinical presentation and not on ammonia levels.[7] A normal ammonia level does not exclude a diagnosis of hepatic encephalopathy, nor does an elevated ammonia level establish a diagnosis of hepatic encephalopathy.[5] In patients with chronic liver disease, the measurement of ammonia can be misleading, causing additional unnecessary testing and treatment. Even in patients with established hepatic encephalopathy, serial monitoring of ammonia is not as useful as serial bedside clinical assessment for establishing the degree of encephalopathy. Blood ammonia levels correlate poorly with the grade of hepatic encephalopathy.[6]

This patient had an elevated serum ammonia level found incidentally during his inpatient liver transplant evaluation. The patient had a normal mental status, normal cognitive function, and no evidence of overt or subclinical hepatic encephalopathy. Given the lack of objective signs of encephalopathy, measurement of serum ammonia was not necessary. The patient's elevated ammonia level was probably from diuretic use. Because there was no clinically important encephalopathy, treatment based on ammonia levels is not indicated. Given the patient's chronic liver disease, elevated serum ammonia levels do not predict any additional risk for developing hepatic encephalopathy.

What Are Alternative Diagnostic Testing Approaches?

The diagnosis of hepatic encephalopathy relies on history and physical examination, exclusion of alternative causes of altered mental status, and evaluation of precipitating causes such as gastrointestinal bleeding, infections, renal failure, hypovolemia, and metabolic disturbances. Psychometric tests including the Reitan number-connection test and the psychometric hepatic encephalopathy score allow for objective measurement of cognitive impairment and have been validated for the diagnosis and monitoring of hepatic encephalopathy.[8,9] Patients without hepatic encephalopathy should finish the timed number-connection test in the number of seconds less than or equal to their age in years.[10]

Patient Outcome

Although the patient had an elevated serum ammonia level, he demonstrated no clinical evidence of encephalopathy and was preparing his doctoral thesis without difficulty. As a result of the ammonia findings he received lactulose, which caused him considerable discomfort and frustration, without clinical benefit or improvement to his serum ammonia levels. The treatment was discontinued. Currently, 9 months following this hospitalization, the patient is waiting for a liver transplant. He is also scheduled to start non–interferon-based treatment for hepatitis C while completing his graduate studies and preparing to defend his thesis. He continues to be without hepatic encephalopathy.

Clinical Bottom Line: Serum Ammonia Level

- Measurement of serum ammonia level is not intended and not useful for the evaluation or screening of hepatic encephalopathy in patients with chronic liver disease because it can neither rule in nor rule out hepatic encephalopathy, and levels do not correlate with the degree of encephalopathy.
- Measurement of serum ammonia level is an important diagnostic step in the evaluation of acute liver failure because levels correlate with the severity of encephalopathy and elevated levels are predictive of severe encephalopathy and cerebral edema.

ARTICLE INFORMATION

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