INTRODUCTION: PATHOPHYSIOLOGY

Ammonia (NH₃) is a known potent neurotoxin commonly implicated in the development of hepatic encephalopathy (HE), a clinical marker of decompensated cirrhosis that produces a spectrum of neurological or psychiatric abnormalities. Furthermore, the development of HE is a significant predictor of mortality in patients with cirrhosis.¹

In a healthy individual with functioning hepatocytes, ammonia enters the portal circulation from the gastrointestinal tract and is subsequently converted to urea through the urea cycle (Fig. 1). Urea is then excreted physiologically via the colon or kidneys. However, in cases of severe hepatic dysfunction, or in the presence of blood shunting around the portal circulation, the burden of ammonia excretion falls on the kidneys, skeletal muscle, and brain. Under these circumstances, ammonia enters the systemic circulation, inhibits both excitatory and inhibitory postsynaptic potentials, and impairs neuronal function (Fig. 2).²⁻⁴

By penetrating the blood-brain barrier through passive diffusion or mediated transport, ammonia can produce cerebral edema by facilitating the production of glutamine, an osmolyte; this complication is known to be most severe in acute liver failure.⁴ Other factors, such as gastrointestinal bleeding, can enhance translocation of toxins from the portal to the systemic bloodstream. Cerebral edema, brain herniation, and seizures typically occur when acute hyperammonemia (i.e., in the setting of acute liver failure) leads to arterial ammonia levels greater than 200 μmol/L.⁵ As a result, arterial ammonia monitoring, which does not correlate with venous ammonia levels,⁵ is useful specifically in patients with acute liver failure.
Consulting hepatologists are commonly asked to interpret elevated serum venous ammonia levels. However, despite its implication as a neurotoxin, high serum ammonia levels alone add no diagnostic, staging, or prognostic value to patients with chronic liver disease who experience HE.\(^6,7\) Alternately, in the case of otherwise unexplained encephalopathy in a patient without a known diagnosis of cirrhosis, an elevated serum ammonia level should prompt evaluation for causes of noncirrhotic hyperammonemic encephalopathy (Table 1).

**FIG 1** The urea cycle.\(^{19}\) Reproduced with permission from *World Journal of Gastroenterology*.\(^{19}\) Copyright 2015, Baishideng Publishing Group, in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license: http://creativecommons.org/licenses/by-nc/4.0/.

**NONCIRRHTIC HYPERAMMONEMIC ENCEPHALOPATHY: DECREASED AMMONIA ELIMINATION**

**Metabolic Disorders Resulting From Inborn Errors of Metabolism**

Inborn errors of metabolism (IEMs), such as organic acidurias or carnitine deficiency, typically present during childhood, but urea cycle disorders that can affect any enzyme in the urea cycle are notorious for presenting in adults.\(^3,8\)

Ornithine transcarbamylase (OTC) deficiency, characterized by an X-linked recessive inheritance pattern, is the most common urea cycle disorder. The clinical presentation of OTC deficiency can vary from lethargy and disorientation to profound obtundation. The defect limits the liver’s ability to convert ammonia to urea, resulting in noncirrhotic hyperammonemia, and can remain asymptomatic until a precipitating event, such as infection, protein intake, or a medication, unmasks the disorder.\(^2,5\)

**Portosystemic Shunts**

Spontaneous portosystemic shunts are commonly seen in patients with cirrhosis and commonly lead to brittle HE. However, congenital shunts, which can be intrahepatic or extrahepatic and are almost always diagnosed in the neonatal period, are an obscure cause of adult-onset, noncirrhotic hyperammonemic encephalopathy.

Portal vein thrombosis (PVT) leading to a portosystemic shunt can lead to noncirrhotic hyperammonemia (shunting ammonia into the systemic circulation), although encephalopathy under these circumstances is usually mild given the patients’ preserved liver function.\(^2,8\)

**Medications**

Certain medications can disrupt the urea cycle. Valproic acid in particular is known to induce noncirrhotic
hyperammonemic encephalopathy. Valproate increases propionic acid levels, which inhibit the rate-limiting enzyme of the urea cycle, carbamyl phosphate synthetase. The reported prevalence rate of valproic acid–induced hyperammonemia is 35% to 45%, but patients are usually asymptomatic.

Hyperammonemia can also result from administration of glycine (used during transurethral resection of the prostate) and has been described, via less clear mechanisms, with the use of carbamazepine, ribavirin, and sulfadiazine.

NONCIRRHOTIC HYPERAMMONEMIC ENCEPHALOPATHY: INCREASED AMMONIA PRODUCTION

Increased Muscle Catabolism

Seizures, starvation, and trauma have all been associated with hyperammonemia. These conditions can result in noncirrhotic hyperammonemic encephalopathy in patients (such as those with urea cycle disorders) whose livers cannot handle an increased nitrogen load.
Noncirrhotic Hyperammonemic Encephalopathy

Kalra and Norvell

TABLE 1. CAUSES OF NONCIRRHOTIC HYPERAMMONEMICENCEPHALOPATHY

| Decreased Ammonia Elimination | Increased Ammonia Production |
|-------------------------------|-------------------------------|
| IEMs:                         | Increased muscle catabolism:  |
| • Urea cycle defects (OTC deficiency) | • Seizures                   |
| • Organic aciduria*            | • Stavudine                   |
| • Carnitine deficiency*        | • Trauma                      |
| Spontaneous portosystemic shunt* | TPN                           |
| PVT                            | Multiple myeloma              |
| Medications:                   | Infections:                   |
| • Valproic acid                | • Proteus mirabilis           |
| • Glycine                      | • Escherichia coli            |
| • Carbamazepine                | • Klebsiella                  |
| • Ribavirin                    | • 5-Fluourouracil             |
| • Sulfadiazine                 |                               |

*Often presents during childhood.

Notably, a 2008 retrospective review of 17 cases of transient hyperammonemia found that hyperammonemia may be related to generalized seizures, and although the mechanisms require further investigation, the phenomenon may be related to persistent muscle contractions during a seizure.10 Compared with fluctuating ammonia levels in HE, patients with seizures demonstrate rapid normalization of ammonia levels.11

Total Parenteral Nutrition

The high protein load in total parenteral nutrition (TPN) can unmask previously unrecognized urea cycle disorders. The phenomenon has also been described in adults given TPN containing only essential amino acids. In these patients, the absence of ornithine (a substrate in the urea cycle) impairs ammonia detoxification.12

Malignant Myeloma

Increased amino acid metabolism by malignant cells produces excess ammonia, and plasma cell infiltration of the liver can produce portosystemic shunting, thereby bypassing the liver’s ability to metabolize ammonia.2,3,13

Infections Caused by Urease-Producing Bacteria (e.g., Proteus mirabilis, Escherichia coli, Klebsiella)

Although infections caused by urease-producing bacteria occur more commonly in children with congenital urinary tract abnormalities, they can occur in adult conditions predisposing to high urinary residuals, such as urinary retention or neurogenic bladder.2,14 These infections produce an alkaline environment, which increases the proportion of NH₃ compared with ammonium (NH₄⁺). The venous drainage of the bladder flows directly to the systemic circulation, bypassing the liver’s attempt to detoxify.8

Chemotherapy Regimens for Leukemia and Bone Marrow Transplantation

The exact mechanisms by which these hematological/oncological interventions produce hyperammonemia are likely multifactorial (increased protein catabolism, parenteral nutrition, gastrointestinal hemorrhage, sepsis, transient acquired enzyme reductions affecting urea synthesis, drug effects from chemotherapy agents). The precise mechanism remains elusive.7

Chemotherapeutic agents that have been implicated in noncirrhotic hyperammonemia include cytarabine, vincristine, amsacrine, etoposide, l-asparaginase, cyclophosphamide, and 5-fluorouracil.15

CONCLUSION

Assessing ammonia levels in a patient with known cirrhosis is unlikely to change clinical management and is therefore not recommend.16 Testing for elevated ammonia levels is appropriate in the absence of chronic liver disease to evaluate otherwise unexplained altered mental status,17 and if discovered, hyperammonemia, particularly in intensive care unit patients, should prompt urgent monitoring for complications such as brain edema and intracerebral hypertension. Hyperammonemia is associated with high morbidity and mortality in the critically ill population.5,18 In the case of noncirrhotic hyperammonemic encephalopathy, the differential diagnosis should focus on mechanisms leading to either increased ammonia production or decreased ammonia elimination.

In particular, after ruling out acute liver failure, as well as underlying chronic liver disease, the consultant should perform a careful medication/nutrition review (including TPN), an assessment for seizure activity, abdominal imaging to evaluate for a portosystemic shunt or PVT, and a comprehensive evaluation for infection. If the etiology of hyperammonemia remains obscure,
consideration of an occult urea cycle disorder, evaluating acid-base status and consideration of quantitative plasma and urine amino acids, is a reasonable next step (Table 2).

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