CLINICAL PROBLEM-SOLVING

Too Much of a Good Thing

Mark Wijnen, M.D., Ph.D.,[1] N. Chantal Peltenburg, M.D., Ph.D.,[1] Dieuwertje Augustijn, Ph.D.,[2,3] Margreet A.E.M. Wagenmakers, M.D., Ph.D.,[1] and Janneke G. Langendonk, M.D., Ph.D.[1]

In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

Author affiliations are listed at the end of the article. Mark Wijnen can be contacted at m.wijnen.1@erasmusmc.nl or at the Department of Internal Medicine–Rg-531, Erasmus Medical Center, Dr. Molewaterplein 40, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands.

Margreet A.E.M. Wagenmakers and Janneke G. Langendonk contributed equally to this article.

N Engl J Med 2026;394:1326-32.
DOI: 10.1056/NEJMcps2510060

CME

A 57-year-old man with a 3-day history of vomiting and progressive confusion was brought to the emergency department by his wife. He had been in his usual state of health until 3 days earlier, when he had become disoriented to the day of the week. By the morning of his arrival at the emergency department, he was unable to remember the names of his medications. He reported generalized weakness and difficulty speaking and swallowing but no headache, numbness, visual disturbance, fever, recent weight loss, or other systemic symptoms. Aside from vomiting, he had no gastrointestinal symptoms.

The patient's confusion, weakness, and vomiting are consistent with acute encephalopathy. The differential diagnosis is broad and includes intoxication, intracranial hemorrhage, ischemic stroke, metabolic derangement, central nervous system (CNS) infection, neoplasm, and inflammatory disease. A detailed medical and exposure history and physical examination can help to differentiate among possible causes.

The patient's medical history included hypertension, type 2 diabetes, primary hypothyroidism, asthma, and obesity with obstructive sleep apnea. He had had a myocardial infarction 16 years earlier and a laparoscopic cholecystectomy 14 years earlier. He was followed by his primary care physician. His medications included amlodipine, metformin, levothyroxine, a formoterol–budesonide inhaler, as-needed salbutamol, clopidogrel, pantoprazole, metoprolol, and rosuvastatin (the latter four were prescribed after the myocardial infarction). He had quit smoking 4 years earlier after a 20-pack-year history, and he had never used alcohol or illicit drugs. His family history was negative for neurocognitive disorders.

His blood pressure was 164/116 mm Hg, heart rate 95 beats per minute, respiratory rate 16 breaths per minute, oxygen saturation 100% while he was breathing ambient air, temperature (tympanic) 35.8°C, and body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) 31.9. He opened his eyes to speech and obeyed commands but was confused, findings consistent with a Glasgow Coma Scale (GCS) score of 13 (on a scale from 3 to 15, with lower scores indicating less responsiveness). Neurologic examination revealed slowed cognitive processing and dysarthria. Cranial-nerve function was intact. Proximal and distal muscle strength was 4/5 in both legs, 4+/5 in the left arm, and 5/5 in other muscle groups. Sensory examination was normal. Deep tendon reflexes were intact, with flexor plantar responses. There was no nuchal rigidity. Abdominal examination revealed normal bowel sounds, tympanic percussion, no tenderness, and no palpable masses or hepatosplenomegaly. The rest of the examination was unremarkable.

The history of myocardial infarction and the presence of multiple cardiovascular risk factors arouse concern for a cerebrovascular event, particularly given the dysarthria and muscle weakness. Clopidogrel use increases the risk of intracranial hemorrhage. Antihypertensive therapy should be deferred until these possibilities have been evaluated. The history of type 2 diabetes suggests potential abnormalities in glycemia, renal function, or electrolytes. Other metabolic causes warranting consideration include severe hypothyroidism (if he is not receiving adequate levothyroxine supplementation), liver dysfunction, or hyperammonemia. Although the absence of fever and nuchal rigidity makes CNS infection less likely, its potential severity justifies diagnostic testing and empirical treatment. Despite the patient's report of no alcohol or illicit drug use, intoxication remains a possibility.

The patient's white-cell count was 7400 per microliter. The hemoglobin level and platelet count were normal. The glucose level was 221 mg per deciliter (reference range, 74 to 106); the rest of his basic metabolic panel was normal, as were the prothrombin time and levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, alkaline phosphatase, and C-reactive protein (CRP). A venous blood gas analysis yielded normal results. The albumin level was 2.7 g per deciliter (reference range, 3.5 to 5.0). The thyroid-stimulating hormone (TSH) level was 0.1 mIU per liter (reference range, 0.5 to 4.3). Urinalysis was positive for glucose but negative for white cells, nitrite, and ketones.

The patient was admitted to the neurology service. Computed tomography (CT) and magnetic resonance imaging (MRI) of the head showed no evidence of ischemia, hemorrhage, cerebral venous sinus thrombosis, neoplasm, or encephalitis. Blood and urine cultures were obtained. A lumbar puncture revealed a cerebrospinal fluid (CSF) leukocyte count of less than 5 cells per microliter (reference value, <5), protein level of 0.36 g per liter (reference range, 0.18 to 0.58), and glucose level of 133 mg per deciliter (reference range, 45 to 80). CSF was sent for culture and herpes simplex virus (HSV) polymerase-chain-reaction (PCR) testing, and empirical acyclovir was started. Later that day, the HSV PCR test returned negative and acyclovir was stopped.

Brain imaging rules out intracerebral ischemia, hemorrhage, and neoplasm. Blood and urine analyses argue against several potential causes. Renal function appears to be normal. Hyperglycemia is mild, and normal levels of electrolytes and venous blood gases and the absence of urine ketones rule out hyperosmolar hyperglycemic syndrome and diabetic ketoacidosis. The low TSH level is consistent with mild levothyroxine overreplacement and is unlikely to be contributory. The normal CRP level, white-cell count, and CSF analysis make CNS infection and inflammation improbable. Because hepatic function is otherwise normal, the low serum albumin level probably reflects an acute-phase response rather than a primary pathologic condition. Intoxication has not yet been ruled out, and hyperammonemia, which may occur despite normal hepatic function (i.e., noncirrhotic hyperammonemia), remains a consideration.

That afternoon, the patient became unresponsive (GCS score of 3), prompting intubation and transfer to the intensive care unit. Plasma ammonia was measured and was 344 μmol per liter (reference value, <45). Hepatic ultrasonography was performed and showed no evidence of cirrhosis or portosystemic shunting.

The plasma ammonia level is markedly elevated. Together with the normal hepatic function and absence of cirrhosis, this finding is consistent with noncirrhotic hyperammonemia as the cause of encephalopathy. The adage "time is brain" applies here: symptomatic noncirrhotic hyperammonemia warrants immediate treatment. Consultation with a specialized inherited metabolic diseases expert center should be considered. Specimens for metabolic analyses (i.e., blood for plasma amino acids and acylcarnitines and spot urine for organic acids, including orotic acid) should be obtained immediately, before initiation of treatment, to investigate the underlying cause, because treatment may normalize diagnostic markers and obscure the underlying cause.

Because of the diagnosis of noncirrhotic hyperammonemia, our specialized inherited metabolic diseases expert center was consulted and provided guidance. Blood samples were collected for plasma amino acids and acylcarnitines and urine samples for organic acids, including orotic acid, and treatment was initiated immediately. To reduce ammonia production, protein intake was stopped, and continuous infusion of 2 liters of 10% dextrose

daily was started. Several medications were started to further reduce ammonia levels, including sodium benzoate, arginine, and carnitine; these were locally unavailable but were delivered in less than 2 hours from our center by express courier. Isotonic saline was coadministered to promote diuresis and the effectiveness of sodium benzoate. Meanwhile, lactulose and rifaximin were administered by nasogastric tube, and preparations were made to initiate venovenous hemofiltration.

Cessation of protein intake, administration of nonprotein calories (e.g., 2 liters of 10% dextrose daily), and the use of lactulose and rifaximin (which reduce intestinal ammonia production and absorption) are critical in reducing ammonia levels. Nitrogen scavengers that bypass the urea cycle (i.e., sodium benzoate conjugating glycine, and sodium phenylacetate, sodium phenylbutyrate, or glycerol phenylbutyrate conjugating glutamine), as well as arginine and carnitine (which enhance urea-cycle activity), are important in facilitating ammonia clearance. If any of these agents are unavailable, treatment should be initiated with those accessible, while efforts are made to obtain others. Given the patient's plasma ammonia level exceeding 200 μmol per liter and comatose state, immediate initiation of sodium benzoate in combination with a glutamine-conjugating nitrogen scavenger — as well as continuous renal replacement therapy with a high effluent flow rate, optionally preceded by a hemodialysis session — are also appropriate.

Plasma ammonia, glucose, sodium, and potassium were monitored every 3 hours, as were venous blood gases. Three hours after treatment initiation, the plasma ammonia level had decreased to 265 μmol per liter; at 6 hours, it had declined to 160 μmol per liter; and by the following morning — 12 hours after treatment initiation — it had reached 110 μmol per liter. Despite persistent coma, escalation of treatment — involving initiation of a glutamine-conjugating nitrogen scavenger, venovenous hemofiltration, or both — was deferred because of the rapid reduction in the plasma ammonia level.

Neurologic recovery may lag behind biochemical normalization. Neither a glutamine-conjugating nitrogen scavenger nor renal replacement therapy is currently indicated. Escalation of treatment would have been indicated if the plasma ammonia level had not decreased within 3 hours. Renal replacement therapy is also indicated in patients with anuria or when pharmacologic agents are unavailable. After acute management, dietary protein should be gradually reintroduced within 24 hours to prevent muscle catabolism.

Meanwhile, attention is needed to potential causes of his noncirrhotic hyperammonemia. Severe malnutrition can lead to muscle catabolism and impaired urea-cycle activity through deficiencies in arginine, carnitine, and zinc. After bariatric surgery, altered gut microbiota and reduced enteral citrulline synthesis may also contribute. However, given the patient's report of no weight loss, the absence of bariatric surgery, and elevated BMI, malnutrition is unlikely. He is not taking medications associated with hyperammonemia (e.g., valproic acid and high-dose glucocorticoids) and has no history of hepatic cancer or chemotherapy. Protein overload, such as from gastrointestinal bleeding, rarely causes marked hyperammonemia without underlying liver disease or an inherited metabolic disorder; the absence of gastrointestinal symptoms other than vomiting and normal hemoglobin level argue against bleeding as a cause. Infection with urease-producing microorganisms (e.g., ureaplasma, mycoplasma, and cryptococcus species) can also raise ammonia levels, but this occurs more commonly in patients with urinary retention or after organ transplantation and is unlikely in this patient given the absence of signs of infection and the normal white-cell count and CRP level. Intrahepatic portosystemic shunts may be missed on ultrasonography and are more reliably detected on CT or MRI.

After consultation with dietary services, protein intake was increased by 0.3 g per kilogram of body weight per day, to a maximum of 1.2 g per kilogram per day over a period of 4 days. Caloric requirements were met by carbohydrates and fats. By hospital day 5 (3 days after treatment initiation), the plasma ammonia level had decreased to 29 μmol per liter. The patient regained full consciousness and was extubated and transferred to the internal medicine ward. There, intravenous medications were transitioned to oral formulations. Sodium benzoate was gradually tapered and discontinued after 6 days, together with carnitine. Rifaximin and lactulose were discontinued 2 days later. Arginine was replaced with citrulline, which

was continued pending the results regarding metabolic analytes obtained during hyperammonemia.

The patient was questioned regarding dietary changes before symptom onset; he reported no such changes and no use of protein supplements. An abdominal MRI did not reveal an intrahepatic shunt. Blood, urine, and CSF cultures that were obtained early in the admission yielded negative results. On hospital day 7, results of plasma amino acids and acylcarnitines became available. The level of glutamine was 1137 μmol per liter (reference range, 462 to 762), glutamic acid 172 μmol per liter (reference range, 0 to 48), citrulline 10 μmol per liter (reference range, 16 to 56), and arginine 22 μmol per liter (reference range, 32 to 108). Levels of other amino acids and acylcarnitines were unremarkable. Results were unavailable for urine organic acids, including orotic acid, because the specimen was lost in transit.

Plasma amino acid analysis reveals elevated levels of glutamine and glutamic acid, findings consistent with hyperammonemia during sample collection. The low levels of citrulline and arginine suggest a proximal urea-cycle defect; malnutrition could also explain these findings but would generally be associated with decreased levels of other amino acids. The normal acylcarnitine profile rules out fatty acid oxidation disorders; it also rules out certain pharmacologic causes of hyperammonemia (e.g., valproic acid). Had the result of urinary organic acids analysis, including orotic acid, been available, the presence of orotic aciduria would suggest ornithine transcarbamylase (OTC) deficiency — the most common urea-cycle disorder.

The patient was discharged on hospital day 14 and referred to our adult inherited metabolic diseases outpatient clinic for further evaluation. Additional history taking revealed that 3 days before admission, he had consumed a large protein-rich meal at an all-you-can-eat restaurant. Family history was notable for the death of his brother at 12 years of age, reportedly due to meningitis. DNA sequencing of the proximal urea-cycle genes identified a pathogenic variant in *OTC*: NM_000531.6(OTC):c.119G→A, p.(Arg40His), resulting in a diagnosis of OTC deficiency.

The patient was advised not to exceed a protein intake of 1.2 g per kilogram per day, and citrulline was continued. He received a personalized plan for management during acute illness and was referred to clinical genetics services for family counseling. He reported fatigue and short-term memory loss since the hyperammonemic episode, for which he was referred for neurocognitive rehabilitation. At a 3-month follow-up, he had not had further episodes of hyperammonemia, although his fatigue and short-term memory loss persisted.

COMMENTARY

Noncirrhotic hyperammonemia is an underrecognized medical emergency requiring immediate treatment (Table 1 and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In this case, acute encephalopathy initially aroused concern for a cerebrovascular event or herpes encephalitis. Plasma ammonia was measured only after a further decline in consciousness and was found to be markedly elevated. After acute management, OTC deficiency was diagnosed.

Ammonia is a neurotoxic product of nitrogen metabolism that is converted into urea through the urea cycle (Fig. 1). In contrast to chronic hepatic encephalopathy, acute hyperammonemia rapidly increases cerebral glutamine, which acts as an osmolyte, causing cerebral edema.[3] To ensure accurate measurements, ammonia samples must be transported to the laboratory promptly. Placing the samples on ice is no longer considered to be necessary.[4]

In the absence of randomized, controlled trials, treatment guidelines for noncirrhotic hyperammonemia rely primarily on observational studies and clinical experience.[1] In an open-label uncontrolled study of the use of intravenous sodium benzoate and sodium phenylacetate with arginine and nutrition therapy in 299 patients with urea-cycle disorders presenting with one or more episodes of hyperammonemia, the percentage of patients surviving a given episode of hyperammonemia was 96%, and overall survival was 84%.[5] Similarly, a retrospective cohort study including 61 patients with urea-cycle disorders having acute hyperammonemia (95 episodes) who were treated with intravenous sodium benzoate showed 87% survival.[6] These outcomes represent a marked apparent improvement over historical survival of approximately 40% before the broader use of these guideline-recommended treatments.[7]

Renal replacement therapy is also an important treatment method for noncirrhotic hyperam-

Table 1. Pharmacologic Agents in the Acute Management of Noncirrhotic Hyperammonemia.*

Agent	Mechanism of Action	Route of Administration	Dose
Nitrogen scavengers that bypass the urea cycle†			
Sodium benzoate	Conjugates glycine to form hippurate, which is excreted renally	IV in 10% dextrose	5.5 g/m^2 bolus over 90–120 min, then 5.5 g/m^2/day continuous (maximum daily dose, 12 g)‡
Sodium phenylacetate§	Conjugates glutamine to form phenylacetylglutamine, which is excreted renally	IV in 10% dextrose	Same dose as sodium benzoate (maximum daily dose, 12 g)‡
Sodium phenylbutyrate	Same mechanism as sodium phenylacetate	IV in 10% dextrose and enteral	IV: same dose as sodium benzoate; oral: 5 g/m^2/day in four divided doses (maximum daily dose, 12 g)‡
Glycerol phenylbutyrate	Prodrug of sodium phenylbutyrate; same mechanism	Enteral	5 g/m^2/day in three divided doses (maximum daily dose, 12 g)‡
Agents that enhance the urea cycle			
Arginine	Replenishes arginine, which is essential for urea-cycle activity	IV in 10% dextrose	250 mg/kg bolus over 90–120 min, then 250 mg/kg/day continuous (maximum daily dose, 12 g)
Carnitine	Activates CPS1, neutralizes toxic metabolites, and corrects secondary carnitine deficiency	IV	100 mg/kg/day in three divided doses
N-carbamylglutamate¶	Allosterically activates CPS1	Enteral	100 mg/kg bolus, then 25–62.5 mg/kg every 6 hr
Agents that reduce intestinal ammonia production and absorption			
Lactulose	Lowers colonic pH, thereby reducing bacterial ammonia production; traps ammonia as nonabsorbable ammonium	Enteral	10 ml one to three times daily, adjusted to two or three loose stools/day
Rifaximin	Reduces ammonia-producing gut flora	Enteral	550 mg twice daily

* Recommended doses are based on the guidelines for urea-cycle disorders by Häberle et al.[1] Oral formulations of sodium benzoate, sodium phenylbutyrate, arginine, and carnitine exist, but intravenous administration is preferred in acute management. The availability of nitrogen scavengers and agents that enhance the urea cycle varies across countries.[2] CPS1 denotes carbamoyl-phosphate synthetase type 1, and IV intravenous.

† Sodium benzoate is recommended as the initial nitrogen scavenger. The addition of sodium phenylacetate, sodium phenylbutyrate, or glycerol phenylbutyrate can be considered in cases of hyperammonemia exceeding 200 μmol per liter or if sodium benzoate is ineffective within 3 hours. Nitrogen scavengers are less effective in persons with hepatic or renal failure and may cause hypokalemia and carnitine depletion.

‡ Higher doses are frequently used on the basis of expert opinion.

§ Sodium phenylacetate is available only as a fixed-dose combination with sodium benzoate, which is approved by the Food and Drug Administration and can be obtained in Europe on a named-patient basis.

¶ *N*-carbamylglutamate is not typically used for noncirrhotic hyperammonemia in the United States.

monemia. Continuous techniques with a high effluent flow rate — such as venovenous hemofiltration or hemodiafiltration — are preferred because they provide sustained clearance and prevent rebound hyperammonemia, a complication associated with intermittent hemodialysis.[8] An initial hemodialysis session, however, can achieve rapid reduction in the ammonia level and may be considered in clinical practice,[9] although studies are lacking to evaluate whether this approach results in better outcomes than continuous therapy alone. Peritoneal dialysis is less effective and therefore is not recommended unless continuous renal replacement therapy or intermittent hemodialysis is unavailable and the patient cannot be rapidly transferred.[8]

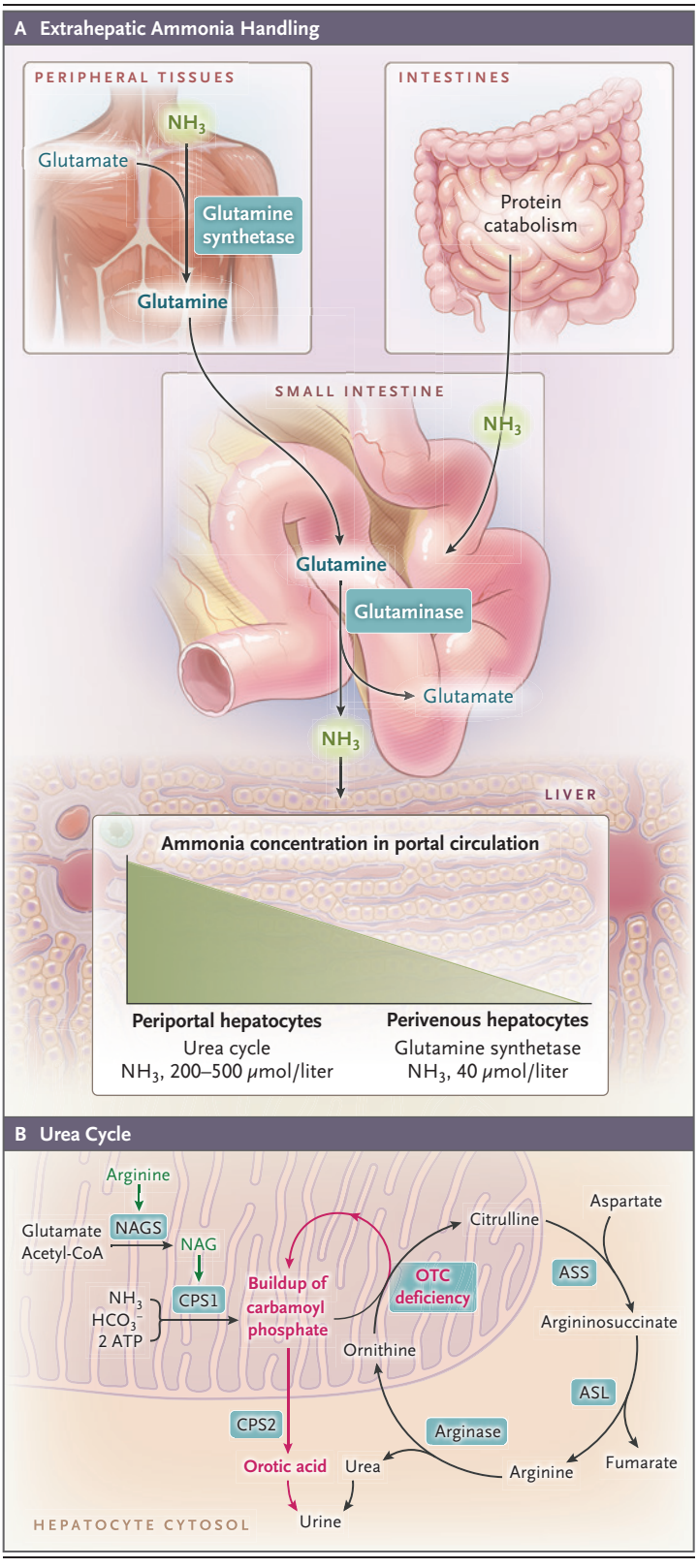

Figure 1. Extrahepatic Ammonia Handling and the Urea Cycle.

As shown in Panel A, ammonia (NH_3) is produced during protein catabolism and in the intestines. In peripheral tissues, ammonia is incorporated with glutamate into glutamine by glutamine synthetase. In the small intestine, glutaminase releases ammonia and glutamate from glutamine. Ammonia enters the liver through the portal circulation, where periportal hepatocytes convert ammonia into urea through the urea cycle. Residual ammonia is taken up by perivenous hepatocytes and incorporated into glutamine again. As shown in Panel B, the urea cycle consists of five catalytic enzymes and one cofactor-producing enzyme. It incorporates two nitrogen atoms (one from ammonia and one from aspartate) into a single urea molecule. Deficiency of ornithine transcarbamylase (OTC), the second enzyme of the cycle, is the most common urea-cycle disorder. OTC deficiency results in accumulation of carbamoyl phosphate and overflow into the cytosol, where carbamoyl phosphate synthetase 2 (CPS2) converts it into orotic acid, which is detectable in the urine. ASL denotes argininosuccinate lyase, ASS argininosuccinate synthase, CoA coenzyme A, CPS1 carbamoyl phosphate synthetase 1, HCO_3^- bicarbonate, NAG *N*-acetylglutamate, and NAGS *N*-acetylglutamate synthase.

The current patient reported persistent fatigue and short-term memory loss after having hyperammonemia. In a retrospective cohort of adults with urea-cycle disorders, 26% had persistent neurologic deficits after their first hyperammonemic episode.[10]

After treatment is initiated, the cause of hyperammonemia should be evaluated (Table S1). In a retrospective cohort of 167 adults admitted to the intensive care unit, noncirrhotic hyperammonemia was most commonly attributed to malnutrition, medications, cancer, gastrointestinal bleeding, and inherited metabolic diseases.[11] In clinical practice, multiple contributing factors are often present. In this patient, DNA sequencing identified a pathogenic variant in *OTC*, which was diagnostic of OTC deficiency as the cause of noncirrhotic hyperammonemia.

OTC deficiency is the most common urea-cycle disorder manifesting in adulthood[10] and has an X-linked inheritance pattern.[12] Boys typically present in the neonatal period; fewer than 5% of men present as adults.[13] Female patients may present at any age; approximately 20% become symptomatic owing to skewed X-chromosome inactivation.[14]

Recognized triggers include catabolic conditions (e.g., infection or surgery), medications, pregnancy, and protein overload (e.g., postpartum uterine involution or excessive protein intake).[10,15] Management of OTC deficiency includes dietary protein restriction and pharmacotherapy with nitrogen scavengers and citrulline or arginine. Liver transplantation may be considered for severe disease.[1] In vivo gene therapies (ClinicalTrials.gov numbers, NCT05345171 and NCT06255782) and messenger RNA therapy (NCT06488313), aimed at restoring liver-enzyme function, are currently under investigation.

The present case underscores the importance of evaluating for hyperammonemia as a cause of acute encephalopathy, regardless of the presence of cirrhosis, and the need for rapid treatment initiation. The patient's diagnosis at 57 years of age also highlights the potential for late manifestations of inherited metabolic disease.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patient for providing written informed consent for publication; the physicians who provided acute care under our supervision; our metabolic dieticians, metabolic laboratory specialists, and intensive care unit physicians for their ongoing collaboration in the management of noncirrhotic hyperammonemia; and Walter Bruins (Department of Internal Medicine, Erasmus Medical Center) for editorial assistance with an earlier version of the manuscript.

AUTHOR INFORMATION

[1] Department of Internal Medicine, Center for Lysosomal and Metabolic Diseases, Erasmus Medical Center, Rotterdam, the Netherlands; [2] Laboratory of Clinical Genetics, Center for Lysosomal and Metabolic Diseases, Erasmus Medical Center, Rotterdam, the Netherlands; [3] Department of Clinical Chemistry, Erasmus Medical Center, Rotterdam, the Netherlands.

REFERENCES

1. Häberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision. J Inherit Metab Dis 2019;42:1192-230.
2. Stolwijk NN, Häberle J, Huidekoper HH, et al. Mapping challenges in the accessibility of treatment products for urea cycle disorders: a survey of European healthcare professionals. J Inherit Metab Dis 2025;48(1):e12815.
3. Walker V. Ammonia metabolism and hyperammonemic disorders. Adv Clin Chem 2014;67:73-150.
4. Mercer-Smith GW, Appleton M, Hanon ÉA, Bowron A. Blood samples for ammonia analysis do not require transport to the laboratory on ice: a study of ammonia stability and cause of *in vitro* ammonia increase in samples from patients with hyperammonaemia. Clin Chem Lab Med 2025;63:1132-8.
5. Enns GM, Berry SA, Berry GT, Rhead WJ, Brusilow SW, Hamosh A. Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. N Engl J Med 2007;356:2282-92.
6. Husson M-C, Schiff M, Fouilhoux A, et al. Efficacy and safety of i.v. sodium benzoate in urea cycle disorders: a multicentre retrospective study. Orphanet J Rare Dis 2016;11:127.
7. Nassogne MC, Héron B, Touati G, Rabier D, Saudubray JM. Urea cycle defects: management and outcome. J Inherit Metab Dis 2005;28:407-14.
8. Gupta S, Fenves AZ, Hootkins R. The role of RRT in hyperammonemic patients. Clin J Am Soc Nephrol 2016;11:1872-8.
9. Boer DP, Mourik SL, van den Hoogen MWF, Langendonk JG, de Geus HRH. Successful treatment of severe hyperammonaemia with ultra-high dose continuous veno-venous haemodiafiltration. Blood Purif 2019;48:283-5.
10. Toquet S, Spodenkiewicz M, Douillard C, et al. Adult-onset diagnosis of urea cycle disorders: results of a French cohort of 71 patients. J Inherit Metab Dis 2021;44:1199-214.
11. Sakusic A, Sabov M, McCambridge AJ, et al. Features of adult hyperammonemia not due to liver failure in the ICU. Crit Care Med 2018;46(9):e897-e903.
12. Simpson KL, MacLeod EL, Kakajiwala A, Gropman AL, Ah Mew N. Urea cycle disorders overview. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews. Seattle: University of Washington, 1993-2026.
13. Summar ML, Dobbelaere D, Brusilow S, Lee B. Diagnosis, symptoms, frequency and mortality of 260 patients with urea cycle disorders from a 21-year, multicentre study of acute hyperammonaemic episodes. Acta Paediatr 2008;97:1420-5.
14. Ibrahim MS, Gold JI, Woodall A, Yilmaz BS, Gissen P, Stepien KM. Diagnostic and management issues in patients with late-onset ornithine transcarbamylase deficiency. Children (Basel) 2023;10:1368.
15. Stepien KM, Langendonk JG, Dao M, et al. The management and clinical outcomes of pregnancies in women with urea cycle disorders: a review of the literature and results of an international survey. J Inherit Metab Dis 2024;47:1239-59.