Altered Mental Status in a Teenager
Patricia M. Jones1,2*

CASE DESCRIPTION

A 13-year-old Hispanic male presented to the emergency department (ED)3 with an altered mental status (AMS) after a 4-day history of nausea and vomiting. Values for electrolytes, glucose, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, calcium, and a complete blood count were all within their reference intervals. The patient’s symptoms were treated with intravenous fluids and an antiemetic medication. He felt better and was discharged home. At home, the patient continued to vomit everything he ate or drank, even after receiving his antiemetic medication. Two hours after taking the antiemetic, he began saying things that did not make sense. He went to sleep, but he woke several hours later screaming, agitated, and in need of restraint in order not to hurt himself.

The patient was brought back to the ED 40 h after his initial presentation. He was obtunded, randomly reacting to touch, but not responsive to voice. He was admitted to the pediatric intensive care unit. He received both acyclovir for possible herpes encephalitis and cefotaxime until the cause of his symptoms was determined not to be sepsis. Tests of a sample from a lumbar puncture showed normal values for glucose, protein, and cell count, and antivirals and antibiotics were discontinued. The patient also received lorazepam for agitation and midazolam for sedation before undergoing a head computed tomography scan, the results of which were normal. A comprehensive urine drug screen showed only benzodiazepines from the midazolam.

The patient’s medical history indicated presentation at age 11 with a 3-day history of emesis and changes in mental status. At that presentation, he was sleepy, was difficult to arouse, and showed decreased muscle tone. The results of a head computed tomography scan at that time were essentially normal. The results of laboratory tests, including those for electrolytes, glucose, calcium, magnesium, phosphorus, blood gases, and a complete blood count with differential were within their respective reference intervals. A urine drug screen detected promethazine, which had been prescribed for nausea and vomiting. At the time of this first visit, the change in the patient’s mental status was attributed to an adverse reaction to promethazine. A test for ammonia was not ordered. The family history was notable in that his mother’s first child had died on day of life 8 from unknown causes.

Upon arrival in the pediatric intensive care unit for the current visit, the patient underwent testing for electrolytes and blood gases with a point-of-care instrument, which showed increases just above the reference intervals for sodium, pH, and bicarbonate, with a borderline-low value for PCO₂ (CO₂ partial pressure). The ammonia concentration was 308 μmol/L (reference interval, <50 μmol/L). We consulted Genetics, and they interviewed his parents. The interview revealed that although the patient was not strictly a vegetarian, he avoided animal protein in his diet. He ate no meat whatsoever and avoided milk and cheese. Analyses for urine organic acids and plasma amino acids were ordered.

DISCUSSION

An inborn error of metabolism (IEM) is commonly part of the differential diagnosis of an ill infant or young child, but one is not usually considered for AMS in a teenager. The differential diagnosis for a teenager with AMS includes drug intoxication, trauma, cerebrovascular events, and sepsis/infection. Urine immunoassay drugs-of-abuse screens detect classes of street drugs that could produce AMS changes, such as barbiturates and benzodiazepines. A comprehensive toxicology screen was ordered, because overdoses of pre-

QUESTIONS TO CONSIDER

1. What is the differential diagnosis for a teenager who presents with AMS?
2. What is in the differential diagnosis of hyperammonemia?
3. What is the relevance of the family history in this case?
scription medications, such as tricyclic antidepressants or antiemetics, are also common causes of AMS changes in the pediatric population. The results of the drug screens were negative except for the drugs the patient was known to be taking. Negative results in computed tomography scans and an MRI during the second admission ruled out trauma and cerebrovascular events.

With the common causes of AMS ruled out, an IEM should be considered. In addition, the death of his sibling from unknown causes suggests an indication for an IEM workup. In this case, the patient had been brought to the hospital 3 times for AMS changes before the ammonia measurement that led to his diagnosis was ordered. Because IEMs do not always present in a classic manner and because many IEMs present with increased ammonia, this test should be included as part of the initial evaluation of an AMS change in a patient in a pediatric institution. An ammonia measurement at the first ED visit might have allowed a diagnosis to be made 2 years earlier.

Ammonia is a catabolic byproduct of amino acid deamination. The urea cycle enzymes, found only in the liver, remove ammonia efficiently. When the urea cycle is not functioning correctly, however, due either to a defect in the cycle itself or to liver dysfunction, the other metabolic means of removing ammonia are insufficient to maintain normal ammonia concentrations. As blood ammonia concentrations increase, metabolism is shifted toward the production of glutamine, which allows ammonia to be held in the tissues in a relatively nontoxic amino acid form. Glutamine concentrations in children with an IEM that increases ammonia concentrations are also monitored to determine when excess ammonia in the tissues is decreasing.

Ammonia in a plasma sample can be falsely increased by contamination by atmospheric ammonia, by smoking, or by prolonged stasis during venipuncture. If the sample is not centrifuged and analyzed promptly, ammonia is formed by the continuous deamination of amino acids. The concentration increases by 20% in the first hour and by up to 100% by 2 h. Plasma samples for ammonia testing should be placed in ice water immediately and transported for analysis as soon as possible. Increased ammonia in a patient with an AMS change is a critical laboratory finding that should be addressed immediately.

The ammonia concentration often does not correlate with the neurologic symptoms observed. In general, patients with values <100 μmol/L are asymptomatic. Values between 100 and 500 μmol/L are associated with a variety of symptoms, including loss of appetite, vomiting, ataxia, irritability, lethargy, combative ness, sleep disorders, delusions, and hallucinations. Ammonia concentrations >500 μmol/L are associated with cerebral edema, coma, and cytotoxic changes in the brain. The neurotoxic effects of ammonia include reduced cerebral blood flow, reduction in cellular energy metabolism, inhibited neurotransmitter systems, alterations in membrane potential and mitochondrial function, and astrocyte swelling. Formation of glutamine inside astrocytes is believed to play a role in this last effect [1].

The differential diagnosis of hyperammonemia in the pediatric population includes transient hyperammonemia of the neonate and a large number of IEMs, including organic acidopathies, urea cycle defects, congenital lactic acidosis, and some aminoacidopathies [2]. The immature liver in the newborn period with concomitant immature urea cycle enzymes or a generalized liver dysfunction may also contribute. Hyperammonemia accompanied by ketosis and anion-gap acidosis suggests organic acid disorders. When the glucose status and the acid/base status are normal, as in this patient, urea cycle disorders are the most likely cause. Organic acid and amino acid analyses can be used to sort out the differential diagnosis.

CASE RESOLUTION/SUMMARY

An organic acid analysis of the patient’s urine showed massive excretion of orotic acid and uracil, and an amino acid analysis showed a glutamine concentration >1500 μmol/L. These biochemical findings were consistent with ornithine transcarbamylase (OTC) deficiency.

OTC deficiency is the most common urea cycle disorder, occurring at an incidence of approximately 1 in 30,000 individuals. The disorder is not detected in newborn screens, because the biochemical abnormalities are detected in urine and blood samples are used for newborn screening. OTC deficiency is the only X-linked urea cycle disorder [3]. Heterozygous females often show a mild presentation, or they may be asymptomatic. Males tend to experience a severe disease course and often do not survive the first hyperammonemnic episode, which usually occurs when protein is introduced into the diet. Ammonia concentrations may reach as high as 1000–3000 μmol/L. A teenage male presenting with OTC is rare. Diagnosis is often delayed in late-onset cases because the most common symptoms (AMS or behavior changes and cyclical vomiting) are very nonspecific.

The primary treatments for urea cycle disorders are to reduce ammonia concentrations, adjust the diet to keep the dietary nitrogen low, and induce alternative pathways of nitrogen excretion [4]. Fig. 1 is a schematic of the urea cycle and the common interventions, including driving the urea cycle with supplements of arginine or citrulline and by administering compounds.
such as sodium benzoate or sodium phenylacetate to form complexes with ammonia that can be excreted in the urine. Keeping dietary nitrogen low will help reduce the formation of ammonia.

This patient’s ammonia concentrations varied in the 3 days before the organic acid and amino acid results indicating OTC deficiency came back from testing (Fig. 2). Ammonia concentrations increased whenever the patient was not completely without food. After diagnosis, he was treated with sodium phenylbutyrate (which is metabolized to phenylacetyl-CoA) to complex and remove glutamine. L-Citrulline was added 2 days later in an effort to further drive the urea cycle. Despite these treatments, the patient’s ammonia concentration continued to increase whenever he consumed solid foods. On hospital day 6, he was placed on continuous venovenous hemofiltration (CVVH) to remove the ammonia from his body. After 4 days of the patient on CVVH and after slowly adding solid food back to his diet, the ammonia concentration remained low, and the patient was removed from CVVH. He was discharged home on citrulline supplementation and sodium phenylbutyrate. Gene sequencing to confirm the diagnosis showed a hemizygous mutation, c.392A>T (p.L131S), which has been reported in an OTC-deficient patient with late-onset disease (5).

**Author Contributions:** All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

**Authors’ Disclosures or Potential Conflicts of Interest:** No authors declared any potential conflicts of interest.

**References**


**Fig. 1.** Diagram of the urea cycle (double-line arrows) showing treatment options (boldface boxes) for removing ammonia from the system.

**Fig. 2.** The patient’s serial ammonia concentrations during his hospital stay. Points of treatment are shown.

**POINTS TO REMEMBER**

- An IEM may be exposed by the catabolic state induced by a concurrent infection or illness; thus, IEM should be considered even in the presence of such illnesses to prevent a delay in diagnosis.
- An AMS can indicate high ammonia concentrations.
- Not all IEMs present in the classic manner. In pediatric patients, an IEM should always be part of the differential.
- Ammonia analysis should be part of a standard blood workup in a pediatric ED, especially when an IEM is suspected and for cases with AMS changes.