Hyperammonemic Coma Due to Parenteral Nutrition in a Woman With Heterozygous Ornithine Transcarbamylase Deficiency

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Ornithine transcarbamylase deficiency is an X-linked disorder of the urea cycle that can cause hyperammonemic encephalopathy in hemizygous males and heterozygous females. Affected females typically limit protein intake in their diet. This case report describes a 36-year-old woman with ulcerative colitis who went into hyperammonemic coma after administration of total parenteral nutrition. A similar episode of coma had occurred 7 years earlier after she delivered a normal boy. Heterozygous ornithine transcarbamylase deficiency was diagnosed based on a positive allopurinol tolerance test result after elevated levels of plasma glutamine and low plasma citruline were detected. The protein load associated with parenteral alimentation resulted in symptomatic expression of this partial enzyme deficiency in this unique case. Partial ornithine transcarbamylase deficiency must always be considered in adult women and men with hyperammonemia who have normal liver function test results.

Inborn errors of metabolism, such as urea cycle defects, previously diagnosed primarily in pediatric patients, are now being recognized more frequently in adults.1,2 Ornithine transcarbamylase (OTC) deficiency is an X-linked urea cycle disorder that can cause fatal hyperammonemia in male newborns.4 Increasingly, milder phenotypes are being recognized in adult men.5,6 Females who have a mutation at the OTC locus of one of their X chromosomes are usually asymptomatic carriers and are identified only after giving birth to affected male newborns.6 Females who are heterozygous for OTC deficiency, however, can have a variety of symptoms, including protein avoidance, episodic irritability, lethargy and ataxia,7 and postpartum coma.8 The variability in presentation of OTC deficiency is probably a result of different mutations at the OTC locus. The presentation of this X-linked disorder in females is also related to the proportion of hepatocytes and enterocytes in which the active X chromosome bears the mutation.2

We report a case of heterozygous OTC deficiency in a 36-year-old woman who had maintained a vegetarian diet since childhood and who had experienced two episodes of coma, the first after delivering a healthy boy and the second while receiving total parenteral nutrition for an exacerbation of ulcerative colitis.

Case Report

A 36-year-old woman with ulcerative colitis and no history of liver disease was evaluated for unexplained hyperammonemia. In 1986, when the patient was 29 years old, ulcerative colitis was diagnosed after she had bloody diarrhea. She was treated briefly with sulfasalazine and corticosteroids; her disease was subsequently in remission. In 1988, she had a normal full-term pregnancy and delivered a healthy boy. Four days after delivery, she became increasingly confused and lethargic. Computerized tomography of the head and cerebral angiography showed no abnormalities. Plasma ammonia level was not measured, and she recovered from the episode without a diagnosis being made. In 1990, the patient had another normal full-term pregnancy and delivered a healthy girl without postpartum complications.

In July 1993, the patient had a relapse of her ulcerative colitis, characterized by rectal bleeding. Flexible sigmoidoscopy to 25 cm showed erythema and ulcerations. She was treated at home for 1 week with 20 mg methylprednisolone intravenously every 8 hours. Her diet was limited to Vivonex T.E.N. (250 mL every 6 hours; Sandoz, Basel, Switzerland). This elemental diet contains 38.2 g free amino acids per liter (approximately 0.7 g/kg). Her colitic symptoms persisted, and she was hospitalized.

On admission to the hospital, administration of methylprednisolone was continued. On the second hospital day, total parenteral nutrition including 63.75 g amino acids per 24 hours (approximately 1.16 g/kg) was initiated. The next day, the patient's stool was positive for Clostridium difficile toxin, and metronidazole was administered. Later that day, she was noted to be confused and combative. Computerized tomography of the head showed no abnormalities. A neurological consultation was performed, and a diagnosis of steroid psychosis or a conversion reaction was made.

Abbreviations used in this paper: OTC, ornithine transcarbamylase.
The following day, the patient was in a coma and unarousable. Blood test results were remarkable for a plasma ammonia level of 275 μmol/L (normal < 35). Further evaluations showed normal aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, albumin, glucose, iron, ceruloplasmin, and α-fetoprotein levels; normal prothrombin time; normal platelet count; and normal total iron-binding capacity. Hepatitis A, B, and C serologies were negative. A lumbar puncture showed no abnormalities. A toxicology screen was negative. Urine orotate was not measured.

Total parenteral nutrition was discontinued. Two days later, the patient was more alert and the plasma ammonia level had decreased to 175 μmol/L. By the ninth hospital day, she was fully alert and plasma ammonia level was 40 μmol/L. She was discharged on the twelfth hospital day.

In September 1993, the patient was seen in consultation in the Yale Liver Clinic. She was feeling well and had returned to her job at an insurance agency. Her history was otherwise notable for being a vegetarian, having discovered that she “did not like” meat when she started eating solid food as a child. There was no family history of any inherited diseases. There was no history in the pedigree of any neonatal male deaths or unexplained episodes of coma. Her two children were both healthy. Her physical examination showed no abnormalities, and there were no stigmata of chronic liver disease.

Further laboratory evaluation confirmed that liver function test results were normal. However, plasma amino acids were remarkable for an elevated glutamine level (1341.2 μmol/L; normal, 493–835 μmol/L) and low citrulline level (14.3; normal, 17–40 μmol/L). Plasma arginine, lysine, and ornithine levels were within the normal range. Urine screened for organic acids by gas chromatography–mass spectrometry was normal, and urine amino acid levels including lysine were normal. An allopurinol tolerance test was performed as described by Hauser et al. to establish the carrier status of women who are at risk for having a mutation at the OTC locus. The patient was administered 300 mg allopurinol orally, and urinary orotidine excretion was measured in four fractional urine samples over 24 hours afterward. The urine orotidine levels (micromoles per millimolars of creatinine) after allopurinol administration were abnormally high in the fractional urine samples, varying from 3.1 to 8.1-fold greater than normal levels. These results are consistent with the diagnosis of heterozygous OTC deficiency.

Since the episode of hyperammonemic coma in July 1993, the patient has been asymptomatic. She has continued to voluntarily limit protein intake in her diet. In November 1994, her plasma ammonia level was slightly elevated at 60 μmol/L.

Discussion

Women who are heterozygous for OTC deficiency often avoid protein. The patient reported is typical. Although she was unaware she was a carrier for a urea cycle defect, she “did not like” meat and had maintained a vegetarian diet since first taking solid food as a child.

This inability to tolerate oral protein by carriers for OTC deficiency has enabled the protein loading test to be used for diagnostic purposes. The protein loading test involves giving women who are suspected to be heterozygous for OTC deficiency 1 g/kg of oral protein and then measuring urinary orotic acid levels for the next 6–12 hours. Affected women will have significant increases in urinary orotic acid levels. However, there are potential problems with this test, including the development of symptomatic hyperammonemia in affected women and reports of false negative test results. Therefore, we chose to confirm the diagnosis of heterozygous OTC deficiency in our patient with the allopurinol tolerance test. This test is 95% sensitive and 100% specific for the detection of female carriers of OTC deficiency when an OTC-deficient proband has been identified in the pedigree. Our patient has no other known OTC-deficient individuals in her pedigree. However, there are only a few other conditions that could give a positive allopurinol tolerance test result, including other urea cycle disorders, the hyperammonemia, hyperornithinemia, and homocitrullinemia syndrome, and lysinuric protein intolerance. These disorders were all excluded by measuring plasma and urine amino acid levels.

Our patient represents the first reported instance of total parenteral nutrition causing an episode of hyperammonemic coma in a woman who is heterozygous for OTC deficiency. We presume that total parenteral nutrition precipitated the hyperammonemia in our patient because of the temporal relationship between the administration of 63.75 g intravenous amino acids per day (approximately 1.16 g·kg⁻¹·day⁻¹), the development of coma, and the improvement that occurred as soon as total parenteral nutrition was discontinued. Methylprednisolone might also have played a role because of the proteolytic effects of steroids.

Total parenteral nutrition has been reported to cause hyperammonemia in two clinical situations. One is in infants given total parenteral nutrition; in these cases, hyperammonemia has been attributed to hepatic immaturity. The second situation is when total parenteral nutrition containing only essential amino acids has been given to adults. The absence of ornithine in essential amino acid solutions has been postulated to impair ammonia detoxification.

A diagnosis of OTC deficiency should be considered in all adults who develop hyperammonemia but have normal liver test results, particularly if they have a history of protein avoidance. The development of altered mental status after an intravenous protein load, such as total parenteral nutrition, as in the present case, should also raise this suspicion. The disease can be misdiagnosed for years in men who are hemizygous and women who are...
heterozygous for OTC deficiency, or the patients can be suspected of having a psychiatric disorder, as was the case in our patient.

It is important not to miss the diagnosis of OTC deficiency because the treatment of hyperammonemia in OTC deficiency is different than the treatment of porto-systemic encephalopathy and involves administering intravenous arginine hydrochloride, sodium benzoate, and sodium phenylacetate. In addition, once the diagnosis is made, genetic counseling can be offered.

References