Ornithine Transcarbamylase Deficiency Presenting as Encephalopathy During Adulthood Following Bariatric Surgery

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Background: Neurological complications following bariatric surgery are rare. Whereas nutritional deficiencies are the most common cause of neurological symptoms, the unmasking of previously subclinical metabolic disorders can also lead to significant morbidity.

Objective: To characterize the clinical presentation, serum biochemical fluctuations, and functional enzymatic analysis of a case of functional ornithine transcarbamylase deficiency unmasked by a dietary change following bariatric surgery.

Design: Case report.

Setting: Tertiary referral center, hospital (inpatient) setting.

Patient: A 29-year-old woman who presented with intermittent encephalopathy associated with recurrent hyperammonemia.

Interventions: Clinical, biochemical, and mutational studies.

Results: The pattern of intermittent hyperammonemia and encephalopathy following oral and parenteral nutrition suggested a urea cycle abnormality. Functional enzymatic assay results showed markedly reduced ornithine transcarbamylase activity in the absence of known coding mutations.

Conclusion: Previously asymptomatic ornithine transcarbamylase deficiency should be suspected in adult patients who develop recurrent hyperammonemia and encephalopathy following bariatric surgery.

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Obesity and overweight affect more than 60% of the adults in the United States and pose a major challenge in health care. Bariatric surgery is highly effective in reducing weight and improving the morbidity and mortality associated with obesity. Neurological complications following bariatric surgery are infrequent and may include peripheral neuropathy and encephalopathy. Deficiencies in vitamin B12 and folate represent common causes of neurological complications associated with bariatric surgery, but other neurological disorders, including stroke and central pontine myelinolysis, have been reported.

Herein we describe a patient who developed encephalopathy following bariatric surgery secondary to a previously undiagnosed urea cycle disorder. A 29-year-old right-handed white woman with morbid obesity underwent elective bariatric surgery. She had no complications in the immediate postoperative period and was placed on a high-protein, high-fat, and low-carbohydrate diet, along with an over-the-counter multivitamin formulation for nutritional supplementation. Four weeks later, she was hospitalized with proximal, painful paresthesias in her legs that spread gradually, significant extremity weakness, and confusion. Magnetic resonance imaging showed symmetrically increased T2 hyperintensities in the anterosuperior cerebellar hemispheres consistent with posterior reversible encephalopathy syndrome. Intravenous thiamine replacement was initiated because her multivitamin formulation contained insufficient thiamine, but she continued to have fluctuating symptoms of mild encephalopathy. Six months after bariatric surgery, she again became intermittently encephalopathic with symptoms of somnolence, perseveration, echolalia, and difficulties with short-term memory. Her serum ammonia level was found to be elevated at 72 µg of nitrogen per deciliter (42.3 µmol/L), with mark-
edly abnormal liver function test results showing an aspartate aminotransferase level of 467 U/L and an alanine aminotransferase level of 251 U/L. She was treated with oral lactulose, and the ammonia level gradually normalized. Repeat magnetic resonance imaging showed resolution of the cerebellar abnormalities. No clear etiology for the encephalopathy was identified, and she continued to have recurrent symptomatic hyperammonemia, which was effectively treated with lactulose and intravenous hydration. However, aggressive hydration and prolonged malnutrition also led to significant hypoalbuminemia and peripheral edema. Given her recurrent episodes of somnolence and cognitive changes, she was transferred to our institution for further evaluation. The patient's family history was unknown because she had been adopted. She had no children or history of miscarriage.

Physical examination revealed an obese, ill-appearing young woman with marked generalized edema, skin hyperpigmentation, and hyperkeratotic changes over her joints. Neurological examination showed her to be anxious but alert with no cranial nerve dysfunction. She had diffuse weakness in all extremities with marked alodynia. Limb movement was further impeded by severe peripheral edema. Deep tendon reflexes were absent throughout and plantar responses were flexor bilaterally. She was unable to stand owing to pain and weakness. Liver function test results showed mildly elevated levels of aspartate aminotransferase (58 U/L), alanine aminotransferase (44 U/L), and serum ammonia (51 µg of nitrogen per deciliter [29.9 µmol/L] [reference range, <50 µg/dL (<29.4 µmol/L)].) Other laboratory abnormalities included hypoalbuminemia of 2.1 g/dL (reference range, 3.4-4.7 g/dL), an elevated manganese level of 1.2 ng/mL (21.84 nmol/L) (reference range, 0.4-0.85 ng/mL [7.3-15.5 mmol/L]), a low serum copper level of 57 µg/dL (8.9 µmol/L) (reference range, 75-145 µg/dL [11.78-22.77 µmol/L]), and a low serum zinc level of 30 µg/dL (0.46 µmol/L) (reference range, 66-110 µg/dL [10.1-16.83 µmol/L]). Serum levels of vitamins B₁₂ and E, thiamine, and folate were all within normal limits. Intravenous thiamine hydrochloride supplementation was continued. Because the ammonia level had normalized, lactulose therapy was discontinued and a regular diet was initiated on hospital day 1.

On hospital day 5, she became acutely obtunded without any new focal neurological deficits. The serum ammonia level was elevated at 156 µg of nitrogen per deciliter (91.6 µmol/L), with an elevated γ-glutamyltransferase level of 351 U/L. Lactulose therapy was reinitiated and her serum ammonia level started to decrease (Figure, open arrow). On hospital day 7, total parenteral nutrition was begun to improve her caloric intake. This led to another elevation of her serum ammonia level despite continued lactulose treatment (Figure, black arrow). Because of recurrent hyperammonemia after protein loading, an inborn error of metabolism was suspected. The urine level of orotic acid was found to be mildly elevated at 3.2 mmol per mole of creatinine (reference range, 0.4-1.2 mmol per mole of creatinine). Quantitative plasma amino acid analysis showed an elevated glutamine level at 29.5 mg/dL (20.18 µmol/L) (reference range, 3.0-11.0 mg/dL [205-753 µmol/L]), a low normal citrulline level of 0.25 mg/dL (17 µmol/L) (reference range, 0.21-0.96 mg/dL [12.55 µmol/L]), and a normal arginine level of 1.78 mg/dL (102 µmol/L) (reference range, 0.26-2.18 mg/dL [15-128 µmol/L]). The elevated glutamine level was thought to reflect the persistent increase in her serum ammonia level. Other biochemical studies, including urinary organic acid, plasma acylcarnitine, lactate, creatine kinase, biotinidase, and urine porphyrin profiles, were normal. A liver biopsy specimen showed moderate steatohepatitis. The serum analysis suggested a biochemical diagnosis of ornithine transcarbamylase (OTC) deficiency. Genetic testing for OTC mutations was negative for known coding mutations, but functional testing using fresh frozen liver tissue from the biopsy revealed less than 1% of normal enzymatic activity. Modified low-protein total parenteral nutrition with carnitine supplementation was begun. The patient's serum ammonia level and mental status normalized and remained stable during the remainder of the hospitalization even after discontinuation of lactulose therapy and institution of an oral limited-protein diet. Further inquiry revealed that, since childhood, the patient had routinely felt nauseated after eating meat, leading to avoidance of such products; however, she had increased her intake of protein and fat after the bariatric surgery. In a follow-up visit 1 year later, her cognitive function continued to be stable without any further episodes of encephalopathy.

**Comment**

Bariatric surgery remains the most effective therapy for weight reduction in extent and duration, and the number of bariatric surgical procedures performed in the United States has more than tripled from 1997 to 2002. Neurological complications of bariatric surgery include polyneuropathy, encephalopathy, rhabdomyolysis, stroke, and Guillain-Barré syndrome. Among patients who develop encephalopathy, thiamine deficiency accounts for
nearly 90% of all cases. Although thiamine deficiency could have initially contributed to this patient’s encephalopathy, her recurrent episodic cognitive decline was clearly temporally associated with hyperammonemia following oral or parenteral feedings with a high protein content (Figure). Posterior reversible encephalopathy syndrome was considered an alternate cause of her early encephalopathy because the syndrome is associated with mental status changes in addition to headache, vomiting, and seizures. However, her encephalopathy persisted on resolution of brain magnetic resonance imaging abnormalities, and she had a rapid recovery after the correction of hyperammonemia. Thus, her cyclical encephalopathy was most likely the result of the underlying urea cycle abnormality. Before the diagnosis of functional OTC deficiency, intravenous hydration and lactulose therapy resulted in reduction of the serum ammonia concentration and resolution of the associated encephalopathy. In the absence of severe liver disease, clinical suspicion for a metabolic cause of hyperammonemic encephalopathy led to the correct diagnosis. Allopurinol loading as an alternative diagnostic test was not performed in our patient because the diagnosis was attempted through genetic and enzymatic activity assays. Additional DNA and enzymatic studies in family members were not possible because she had been adopted.

Ornithine transcarbamylase deficiency is an X-linked disorder of the urea cycle and has an incidence of 1 in 80,000 live births. Female carriers have variable clinical symptoms and age at onset, possibly as a consequence of random X-chromosome inactivation. Approximately 85% of female carriers will remain asymptomatic during their lifetime, but serious neurological complications, including coma, have been reported in previously healthy female carriers. Healthy carriers may voluntarily restrict their daily protein intake, reflected in a decreased amount of excreted urea nitrogen and total nitrogen. Mutational analysis of OTC will detect 70% to 80% of coding mutations, and a mutation in the non-coding regions or a larger gene deletion that alters the level of enzyme expression may explain the low level of OTC activity in our patient. It is surprising that this very low enzyme activity was associated with symptomatic onset after childhood. However, there is substantial nitrogen incorporation into urea even in patients with very low in-vitro OTC activity and late-onset OTC deficiency. Hence, our patient’s lifelong dietary pattern may reflect subclinical disease that manifested fully only after her bariatric surgery. She is at increased risk for postpartum encephalopathy with future pregnancies and for metabolic decompensation with future stressors such as surgery or catabolic states.

In summary, we present a woman with functional OTC deficiency who developed recurrent encephalopathy after bariatric surgery temporally associated with hyperammonemia. Her lifelong pattern of meat avoidance was a possible clue to her subclinical disease, and the postsurgical diet pattern change and total parenteral nutrition for malnutrition likely served as provocative protein loads. In adult patients who develop ammonia-related encephalopathy after bariatric surgery, OTC deficiency and other urea cycle abnormalities should be strongly considered.

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