Fatal Initial Adult-Onset Presentation of Urea Cycle Defect

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Background: Ornithine transcarbamylase (OTC) deficiency presents most commonly with neonatal hyperammonemic coma. The gene is on the X chromosome, but the disease may manifest as a dominant trait. Mutations that lead to later-onset presentations may lead to life-threatening disease and may be unrecognized, particularly when the first clinical disease occurs in adulthood.

Objective: To document the clinical and metabolic consequences of a mutation in the OTC gene.

Setting: A metabolic/biochemical genetic referral service.

Main Outcome Measures: Clinical and biochemical observations in 3 generations of a family.

Results: A mutation in codon 208 of exon 6 in the OTC gene was found in a family in which the proband died of hyperammonemia at 52 years of age.

Conclusions: Diagnosis of late-onset presentations of urea cycle defect in adults may be delayed. Heightened awareness could lead to effective treatment.

Ornithine transcarbamylase (OTC) deficiency is the most common of the urea cycle disorders. Defects in enzymes of the urea cycle lead to hyperammonemia, encephalopathy, and coma. Patients typically present in the neonatal period with metabolic decompensation. Some individuals, however, do not become symptomatic until much later in life. The OTC deficiency is caused by mutations in the OTC gene and is expressed in an X-linked dominant manner.

This article describes a 52-year-old man who died of hyperammonemia and cerebral edema. The diagnosis in this family was made by determining the mutation in the OTC gene in his heterozygous daughter. Prenatal diagnosis of OTC deficiency in her twin sons led to prompt and effective management.

REPORT OF CASES

CASE 1

A 20-year-old woman presented to the Metabolic Clinic of the University of California, San Diego, for evaluation for metabolic disease. Seven months earlier, her father (case 2) had suddenly become hyperammonemic and died at age 52 years. She herself had no significant medical history. Specifically, there were no times of altered consciousness, and there were no dietary preferences, such as avoidance of high-protein foods. There was otherwise no contributory family history. The patient had 2 sisters, both of whom were healthy. Neither the patient nor her sisters had had children. Second-degree relatives were also healthy. The patient’s physical examination findings were unremarkable. There was no hepatomegaly, and neurologic examination showed normal reflexes and normal muscle tone and strength.

CASE 2

The 52-year-old father of case 1 had a history of type 2 diabetes mellitus, hypertension, and hypercholesterolemia but was considered to be in good health. He had never had an episode of altered mental status, he had no special dietary habits (such as an aversion to meat), and he had been employed throughout adulthood as a crane operator. As part of a preoperative evaluation for removal of a polyp of his throat, he underwent a stress test and angiography, with normal results. He recovered well from the surgery and was discharged from the hospital. Eight days later, he awoke confused, atactic, and paranoid. He became increasingly disoriented and combative, and he was
taken to a hospital. Several tests, including transaminase enzyme measurement, yielded negative results, but his ammonia concentration was found to be greater than 4202 µg/dL. (to convert to micromoles per liter, multiply by 0.714). Three days after hospital admission he developed seizures and coma and required mechanical ventilation. Cerebral edema and cerebellar herniation had been documented by computed tomography. Brain death was diagnosed, and life support was discontinued. Autopsy findings revealed diffuse edema of the cerebral hemispheres. There was histologic evidence of cerebral edema and punctate hemorrhages of the pons. The liver was enlarged, weighing 2475 g; a 3-cm infarction was evident in the right lobe. There was histologic evidence of sinusoidal congestion but no cirrhosis or necrosis.

**CASE 3**

The patient, case 1, became pregnant with twin boys 2 years after our first encounter. Polymerase chain reaction–based DNA sequencing indicated the presence of the mother’s mutation in both fetal genomes. The mother was found to have cervical changes at 32 weeks 4 days of gestation and was admitted to the hospital, where she was given oral citrulline and a low-protein diet. Analysis of amniotic fluid obtained by amniocentesis at this time revealed a mature lung profile; labor was augmented, and the infants were delivered at 33 weeks’ gestation. Baby boy A was delivered vaginally and required intubation and cardiopulmonary resuscitation at 32 minutes of life. He was successfully stabilized and was weaned off the ventilator by the third day of life. He was initially given hyperalimentation and was eventually transitioned to a low-protein enteral diet. Intravenous arginine administration was begun at birth, and this was changed to oral citrulline once the baby was tolerating enteral feedings. His serum ammonia concentration reached a maximum of 182 µg/dL.

**CASE 4**

Baby boy B was delivered 30 minutes after baby boy A. The delivery was complicated by a compound presentation with the arm over the head and subsequent fetal bradycardia. An emergency cesarean section was performed, and the infant did well postnatally, with initial mild respiratory distress that soon resolved. He was also given hyperalimentation and intravenous arginine, and he gradually transitioned to a low-protein enteral diet and oral citrulline therapy. His maximum serum ammonia level was 265 µg/dL. Both infants were discharged from the hospital at 6 weeks of age receiving moderately low-protein diets (approximately 2 g/kg daily) and citrulline (250 mg/kg daily). They have remained healthy.

**RESULTS**

The abrupt onset of severe hyperammonemia in case 2 suggested a defect of the urea cycle. Disorders of fatty acid oxidation or organic acidemias were other possibilities. Results of analysis of the plasma for amino acids were normal. The concentration of glutamine was 9.3 mg/dL. (to convert to micromoles per liter, multiply by 68.423); alanine, 9.3 µmol/L (to convert to micromoles per liter, multiply by 68.423); ala-

**COMMENT**

The importance of these observations for practice is that late-onset presentations of urea cycle disease are often unrecognized and, as evidenced by case 2, may be fatal, despite as many as 52 symptom-free years. Early symptoms suggestive of a psychiatric disorder, such as confusion or combativeness, or neurologic manifestations, such as ataxia, may be followed by cerebral edema and herniation. Prompt recognition can avert such an outcome because there are effective treatments, including hemodialysis, intravenous arginine, and sodium benzoate/phenylacetate. Intuitively, one would expect that patients with late-onset disease had mutations that determined an enzyme with appreciable residual activity, and, therefore, would be relatively easy to treat once a diagnosis was made. This has been our experience. For example, in a boy with OTC deficiency who presented at 12½ years of age, normal levels of ammonia were achieved with intravenous arginine administration alone, and he has not had a further episode of hyperammonemia in 15 years of follow-up treatment with oral citrulline and only modest restriction of protein. The twins (cases 3 and 4) have not been restricted to a protein intake lower than 2 g/kg daily, have also received oral citrulline, and have had no episodes of hyperammonemic metabolic imbalance.

Ornithine transcarbamylase deficiency presents most commonly in male hemizygotes in the first days of life with overwhelming hyperammonemic coma. These infants are difficult to rescue and, of those who survive the initial episode, most die in infancy or become severely neurologically impaired. The gene is on the X chromosome, at band p21.1, and female heterozygotes manifest a variety of severities and onsets of clinical disease. A few females with neonatal presentations are indistinguishable from the classic neonatal male in severity of disease, but most females...
present later, and some remain asymptomatic. Many females have presentations similar to those of males with late-onset variants. Nevertheless, many of these patients die of the disease.3 Episodes are usually triggered by catabolism, usually after infection but in some after surgery, as in case 2. Pregnancy is an additional risk; initial symptoms have been reported to appear in pregnancy.6,7 and fatality has been reported.7 On the other hand, the patient in case 1 went through pregnancy and delivery of twins with no evidence of metabolic imbalance, further evidence that this mutation should be treatable. Fatal late-onset presentation of OTC deficiency has previously been reported in a 62-year-old man.8 In that family, a grandson, the son of a daughter, had been previously diagnosed as having OTC deficiency and a V337L mutation in the gene. Nevertheless, the grandfather underwent magnetic resonance imaging on hospital admission, and the findings were normal, but he did not have a blood ammonia measurement until 3 days later, which was 1800 µg/dL. Autopsy findings revealed cerebral edema and uncal herniation.

Other families have been described in whom the A208T mutation has been found. In one 5-generation family,9 the 59-year-old great-grandfather was homozygous for the mutation, but he has never had hyperammonemia or dietary restriction; nevertheless, 8 males had died suddenly at 4 months to 23 years of age. In another 4-generation family,10 there was an asymptomatic 97-year-old hemizygous man, whereas the proband was his 10-year-old grandson, who had a fatal episode of hyperammonemia as his initial presentation. These observations are consistent with our experience of the capricious nature of mutations in this gene.

In both of these kindreds,9,10 all of the female heterozygotes were asymptomatic, as was the patient in case 1 in this report. We expect that the 2 sisters of case 1 will remain asymptomatic. They have had no children. They were advised to be tested. In view of the variability within families with this mutation, it would not be inconceivable for the twin infants to exhibit symptoms after the stress of parturition, but the relatively mild degree of plasma ammonia elevation they developed might easily be missed, and their symptoms were minimal to nil. Nevertheless, their prognosis might be expected to be markedly improved with expectant management.

The progression from confusion to delirium, coma, and cerebral edema may occur in any disorder of the urea cycle. An initial presentation with headache progressing to hyperammonemic coma has been reported in the hyperornithinemia, hyperammonemia, homocitrullinuria syndrome.11 Hyperammonemic citrin deficiency or citrinullinuria type II usually presents first in adulthood and, in patients who lacked the neonatal intrahepatic cholestasis presentation, diagnosis may be delayed and the end result may be death.12 In an adult in a coma, it may be expected that a magnetic resonance image might be ordered before blood ammonia measurement. The magnetic resonance image may lead to the diagnosis of hyperammonemia.13 Magnetic resonance spectroscopy may provide evidence of increased glutamine levels.12

The OTC gene has been found to exhibit enormous variation. More than 340 mutations have been identified in families in which there was clinical OTC deficiency.13 The diagnosis is usually initially suspected because of the presence of hyperammonemia and its attendant clinical manifestations. Analysis of the amino acids of the plasma may reveal elevated glutamine or alanine levels and sometimes aspartic acid levels, all consequences of hyperammonemia. Citrulline levels may be low. Analysis of organic acids of the urine reveals elevated orotic acid and uracil levels. Enzyme assay requires biopsy of the liver but, because 80% of patients with confirmed enzyme deficiency have a demonstrable mutation,13 the diagnosis is now most commonly made using sequence analysis of the DNA, as was done in this family.

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