

Late-onset ornithine transcarbamylase deficiency: An under recognized cause of metabolic encephalopathy

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Abstract

Introduction: Ornithine transcarbamylase deficiency is the most common inherited disorder of the urea cycle, has a variable phenotype, and is caused by mutations in the *OTC* gene. We report three cases of ornithine transcarbamylase deficiency to illustrate the late-onset presentation of this disorder and provide strategies for diagnosis and treatment. The patients were maternal first cousins, presenting with hyperammonemia and obtundation. Urea cycle disorder was not initially suspected in the first patient, delaying diagnosis.

Results: Sequencing of the *OTC* gene showed a novel missense mutation, c.563G > C (p.G188A). Numerous family members were found to carry this mutation, which shows a trend toward later onset. Each urea cycle disorder has its own unique pattern of biochemical abnormalities, which differ from non-metabolic causes of critical illness.

Conclusion: Regardless of age, clinical suspicion of a urea cycle disorder is important in encephalopathic patients to ensure quick diagnosis and definitive treatment of the underlying inborn error of metabolism.

Keywords

Ornithine transcarbamylase deficiency, hyperammonemia, urea cycle disorders, inborn errors of metabolism, metabolic encephalopathy

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Introduction

Ornithine transcarbamylase (OTC) deficiency is the most common genetic disorder of the urea cycle, occurring in 1 in 14,000 people.¹ It is inherited in an X-linked fashion with variable expressivity and is caused by mutations in the *OTC* gene.² It is variable in severity ranging from asymptomatic to severe neonatal hyperammonemia. Hyperammonemia may be prompted by metabolic stressors, such as infection or protein consumption. Significant clinical heterogeneity may exist, even within families.

Later onset forms of OTC deficiency are diagnostically challenging and can go unrecognized. They often present with acute and rapidly progressive encephalopathy. We report a large extended family in which three male maternal first cousins carry a novel *OTC* mutation and developed later onset OTC deficiency. These patients underscore the need to suspect OTC deficiency in patients with unexplained hyperammonemia or encephalopathy.

Case reports

Patient 1 was a 20-year-old male who presented after being found unresponsive. He had been feeling unwell for the

previous 2 months with weight loss, nausea, and vomiting. He had been engaging in a strength-conditioning regimen for several months in preparation for football and was taking a whey-based protein supplement, creatine monohydrate, an arginine-containing supplement, and stanozolol. On admission, he had elevated serum transaminases and ammonia of 323 $\mu\text{mol/L}$ (normal: 16–60 $\mu\text{mol/L}$). He developed cerebral edema and seizures. A urea cycle disorder was suspected after consultation with a metabolist, and intravenous (IV) sodium phenylacetate/benzoate was started, after which the ammonia level normalized. Confusion persisted for 1 week after normalization of the ammonia level. Urinary orotic acid was 3.6 mmol/mol creatinine (normal: 0.4–1.2 mmol/mol

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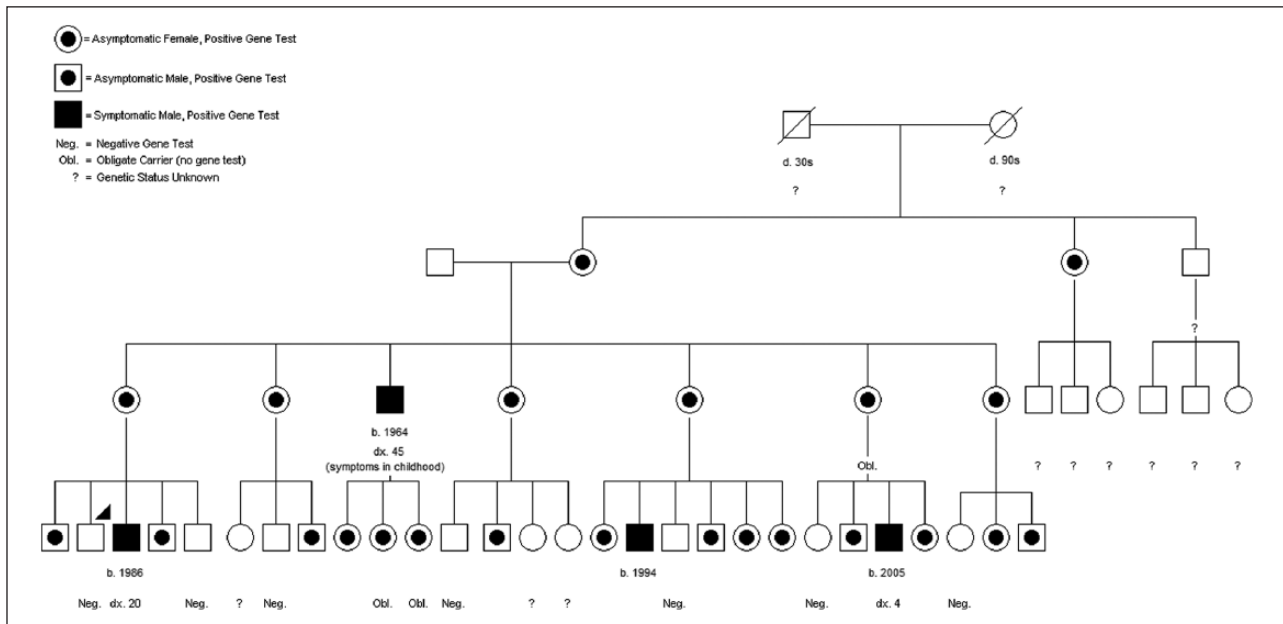


Figure 1. Pedigree of extended family, with arrowhead denoting Patient 1.

creatinine), and plasma glutamate was elevated at 871 $\mu\text{mol/L}$ (normal: 410–700 $\mu\text{mol/L}$). Aside from mild to moderate right-sided hearing loss, he made a full recovery. The patient is in good health, but does not comply with a protein-restricted diet, but has refrained from performance-enhancing substances.

Patient 2 was a 3-year 10-month old male who presented with altered mental status, seizures, and hyperammonemia. In the 3 days preceding admission, he had suffered from diarrhea and low-grade fever and had been diagnosed with viral gastroenteritis. Upon admission, he became obtunded and required intubation. Caregivers were aware of his cousin's diagnosis, so he was started on IV dextrose, sodium phenylacetate/benzoate, and arginine hydrochloride, with normalization of ammonia within 24 h. Urine organic acids showed elevated orotic acid, and plasma amino acids showed elevated glutamine. He has no sequelae from his hyperammonemic episodes and is clinically well. He receives oral sodium phenylbutyrate, complies with modest dietary protein restriction, and has had only one episode of hyperammonemia for which he was briefly hospitalized.

Patient 3 was a 16-year-old male who developed emesis, fatigue, and poor appetite several days prior to an acute episode of confusion during an athletic event, which occurred on a particularly hot day. He had been eating a normal diet and not taking any supplements. Upon admission, his ammonia was 104 $\mu\text{mol/L}$. Glutamate measured 3 days after admission was slightly elevated at 769 $\mu\text{mol/L}$. He had a good response to administration of IV glucose, sodium phenylacetate/benzoate, and arginine. He recovered fully and has been symptom free after following a protein-restricted diet and taking oral sodium phenylbutyrate.

Results and family history

After Patient 1 presented with marked hyperammonemia, OTC deficiency was suspected. Sequencing of the *OTC* gene showed a novel mutation (c.563G > C, p.G188A). This variant was not listed as a polymorphism in the dbSNP database. Two mutations at the same nucleotide position have been described in the literature in symptomatic patients^{3,4} and is highly conserved with glycine present in all vertebrate species. SIFT (Sorting Intolerant From Tolerant, located at <http://sift.jcvi.org/>) and polyphen-2 predict that the mutation will be “not tolerated” and “probably damaging,” respectively. These lines of evidence suggest that the p.G188A mutation is the cause of OTC deficiency in this family.

Patient 1's mother was found to be heterozygous for this mutation. All five of the first patient's maternal aunts are heterozygous for the mutation: four underwent testing and one is an obligate heterozygote. All are asymptomatic. Two of his brothers were hemizygous for the mutation, but had no history suggestive of hyperammonemia. The patients' maternal uncle was hospitalized as a child for several episodes of illness and disorientation of unknown cause, with diagnosis of OTC deficiency made in middle age. Refer to Figure 1 for pedigree of the extended family.

Discussion

Patients with OTC deficiency present with symptoms including confusion, lethargy, anorexia, hyperventilation, and hypothermia followed by ataxia, behavioral disturbances, and obtundation.⁵ This may mimic intoxication or central nervous system (CNS) infection. If untreated, the symptoms

Table 1. Common patterns of plasma amino acid and orotic acid disturbance by disorder.

Disorder	Amino acid abnormalities	Urine orotic acid
Ornithine transcarbamylase deficiency	Decreased citrulline, elevated glutamine, elevated alanine, decreased arginine ^{10,11}	Markedly elevated
N-acetylglutamate synthetase deficiency	Decreased citrulline, elevated glutamine, elevated alanine ¹¹	Normal
Carbamoyl phosphate synthetase deficiency	Decreased citrulline, elevated glutamine, elevated alanine, decreased arginine ^{10,11}	Normal
Arginosuccinic acid synthetase deficiency	Markedly elevated citrulline, decreased arginine ¹⁰⁻¹²	Elevated
Arginosuccinic acid lyase deficiency	Elevated citrulline, elevated arginosuccinic acid, decreased arginine ^{11,13}	Elevated
Arginase deficiency	Elevated arginine ¹¹	Elevated
Sepsis	Elevated aromatic and sulfur containing amino acids, decreased branched-chain amino acids ¹⁴	Normal
Hepatic dysfunction	Elevated tyrosine and methionine, decreased branched-chain amino acids ¹⁵	Normal

can progress to seizures, cerebral edema, and potentially death.⁶ Between episodes, patients are often completely asymptomatic, but can show symptoms such as nausea, vomiting, and anorexia. Patients who recover from critical illness caused by OTC deficiency can have residual neurological deficits, and there is an increased risk of cognitive impairment. The severity and number of hyperammonemic episodes is associated with the degree of deficit.⁷

Hyperammonemic episodes can be brought on by a number of factors. Our first patient was consuming excessive amounts of protein and engaging in strenuous exercise, both of which likely contributed to his hyperammonemia. Interestingly, his arginine supplement may have partially protected him. Our second patient likely had a viral gastroenteritis, which would increase his catabolism and also cause dehydration, both predisposing to hyperammonemic episodes. Our third patient presented after strenuous activity on a hot day, suggesting again that metabolic stress and dehydration contributed to his hyperammonemia.

Urea cycle disorders have a predictable pattern of laboratory abnormalities which can greatly assist in diagnosis. Hyperammonemia caused by other types of critical illness is frequently associated with additional laboratory abnormalities such as elevated lactic acid⁸ and prominent acidosis. In contrast, hyperammonemia without acidosis should prompt consideration of a urea cycle disorder. Patients will typically present with respiratory alkalosis caused by ammonia stimulating the respiratory center in the brain,⁹ and an inappropriately low serum blood urea nitrogen (BUN), which is a reflection of the impaired ureagenesis.

The biochemical evaluation of a urea cycle disorder includes plasma amino acids, urine orotic acid, and urine organic acids. Each of the urea cycle disorders has a unique pattern of biochemical abnormalities, which are summarized in Table 1. The pattern is decidedly different from that

observed in patients with acute illness from sepsis¹¹ or hepatic failure.¹²

Treatment for a presumptive urea cycle disorder should not wait for definitive diagnosis to be made. Consultation with a metabolic specialist should occur as early as possible in the patient's clinical course. Protein intake should be discontinued temporarily and protein catabolism suppressed by dextrose-containing fluid replenishment. Protein intake should be restarted within 24–48 h to avoid further catabolism. Patients should be monitored for the cerebral edema. For severe hyperammonemia, hemodialysis to remove ammonia can be life-saving.¹⁶ IV 10% arginine supplementation should be initiated. IV sodium benzoate/phenylacetate is effective in lowering hyperammonemia by conjugating and eliminating two non-essential amino acids, glycine and glutamine, that otherwise contribute ammonia to the urea cycle.

Conclusion

Urea cycle disorders should be considered in the differential diagnosis of patients who present with symptoms of acute hyperammonemia. If a urea cycle disorder is being considered, treatment should be started prior to confirmation of the diagnosis. Only by clinical suspicion and careful investigation will inborn errors of metabolism be uncovered and treated in a timely manner.

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Declaration of conflicting interests

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Research ethics

This research was approved as exempt by the University of Nebraska Medical Center Institutional Review Board and has been assigned IRB# 561-13-EX. Per local guidelines, written consent was not required, but verbal consent was obtained from patients and their families for inclusion of their case information and pedigree in this article.

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