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A complex case of delayed diagnosis of ornithine transcarbamylase deficiency in an adult patient with multiple comorbidities☆

Jessica Abbott, Mia Senzatimore, Paldeep Atwal *

Atwal Clinic: Genomic & Personalized Medicine, 214 Brazilian Ave, Suite 230, Palm Beach, FL 33480, USA

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ABSTRACT

We report the case of a medically complex African American adult female with ornithine transcarbamylase (OTC) deficiency diagnosed after lifelong protein aversion and new onset of chronic vomiting and abdominal pain with intermittent lethargy and confusion. Symptomatology was crucial to diagnosis as genetic testing did not identify any pathogenic variants in *OTC*; however, the patient's diagnosis was delayed despite her having longstanding symptoms of a urea cycle disorder (UCD). Her symptoms improved after treatment with a modified protein-restricted diet, long-term nitrogen-scavenger therapy, and supplemental L-citrulline. Adherence to her UCD management regimen remained a challenge due to her underlying frailty and other medical conditions, which included primary renal impairment (further exasperated by type 2 diabetes mellitus) and decreased left-ventricular function. She passed away 3 years after her OTC deficiency diagnosis due to complications of congestive heart failure. Her OTC deficiency did not have a major impact on her final illness, and appropriate OTC deficiency management was provided until the decision was made to withdraw medical care.

1. Introduction

Ornithine transcarbamylase (OTC) deficiency (OMIM 311250) is a rare X-linked genetic disorder with an estimated prevalence of 1 in 56,000 people [1–3]. It is the most frequently observed urea cycle disorder (UCD), with common symptoms including hyperammonemia, hepatic dysfunction, and various neuropsychologic complications [2,3]. UCDs are caused by a complete or partial deficiency in any 1 of the 6 urea cycle enzymes or 2 urea cycle transporters (Fig. 1a) [1,4]. Severe neonatal-onset OTC deficiency typically only occurs in males, but a post–neonatal-onset (late-onset) presentation that varies in severity can occur in both males and females. Pathogenic variants in *OTC* are disease causing in hemizygous males but can also cause disease in heterozygous females (Fig. 1b) [5]. Late-onset OTC deficiency presents with great phenotypic variation, ranging from asymptomatic to coma and even death [6–8].

OTC deficiency may be suggested based on clinical symptom presentation and laboratory findings. Males with the severe neonatal-onset form may appear unaffected at birth but quickly develop reduced oral intake, which can progress to acute neonatal encephalopathy. In the postneonatal period, a male or female may present with a variety of symptoms including altered mental status, vomiting, headaches, seizures, protein aversion, and/or unexplained cerebral palsy (Table 1) [5]. Family history or newborn screening, plasma ammonia or amino acid analysis, urine organic acid analysis, and blood gases laboratory test results may also indicate possible OTC deficiency. A diagnosis is confirmed by molecular genetic testing or by an increase in orotic acid excretion following an allopurinol challenge test. Males may also receive a diagnosis based on decreased OTC enzyme activity in the liver [5]. Molecular testing is strongly recommended to confirm the diagnosis; however, many variants in *OTC* remain unknown. It has been previously reported that only ~80% of patients with OTC deficiency have identifiable variants in the *OTC* gene, and new variants, often family specific, continue to be reported [2,9,10].

Managing OTC deficiency is burdensome for many patients, with restrictive diet therapy and drug administration frequency and volume, tolerability, and side effects contributing to nonadherence to medical care plans [12]. For clinicians, assessing patient compliance to dietary

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; D20W, dextrose 20% in water; ED, emergency department; GPB, glycerol phenylbutyrate; IBW, ideal body weight; IV, intravenous; NAFLD, nonalcoholic fatty liver disease; NG, nasogastric; OTC, ornithine transcarbamylase; UCD, urea cycle disorder.

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* Corresponding author at: 214 Brazilian Ave, Suite 230, Palm Beach, FL 33480, USA.
E-mail address: DrA@AtwalClinic.com (P. Atwal).

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therapy for late-onset UCDs is also complicated [13]. Furthermore, managing OTC deficiency with other comorbidities, such as diabetes, cancer, or other genetic conditions, has shown to be a significant challenge [14–16]. Here, we detail a case in which comorbidities made the diagnosis and management of OTC deficiency in a female patient uniquely challenging.

2. Case presentation

2.1. Presenting symptoms and diagnostic testing

We present the case of a 64-year-old African American female with a complex medical history including congestive heart failure, type 2 diabetes mellitus, impaired renal function, and obesity. She exhibited lifelong protein aversion and, in middle age, developed new-onset episodes of vomiting, abdominal pain, lethargy, and confusion of unknown etiology occurring 4 to 6 times per year. These episodes were initially dismissed as general cognitive decline by multiple specialists including a gastroenterologist, neurologist, cardiologist, and her primary care physician, and no specific interventions were recommended.

Two episodes of transient confusion resulted in visits to the emergency department (ED) and were associated with elevated ammonia (>100 μmol/L, with the highest level being 167 μmol/L; reference <30 μmol/L) and elevated alanine transaminase (ALT) and aspartate aminotransferase (AST). Head computed tomography (CT) performed at one of the ED visits was unremarkable, and no formal neurocognitive testing was performed. Nonalcoholic fatty liver disease (NAFLD) was hypothesized based on the patient's laboratory studies and history of obesity. Liver failure was considered and ruled out at the second admission, and the patient was placed on lactulose until her ammonia level normalized. Hepatology referred the patient to genetics for further investigation, with suspicion of a UCD.

Biochemical testing revealed significantly elevated urinary orotic acid (>30 mmol/mol creatinine; reference <10 mmol/mol creatinine), elevated glutamine (~1300 μmol/L; reference <950 μmol/L), and low citrulline (19 μmol/L; reference >30 μmol/L). Ammonia levels were typically ~50 μmol/L (reference <30 μmol/L). The highest ammonia level measured during an ED visit was ~150 μmol/L; however, hemofiltration was not considered for acute intervention. Analysis of 3-day diet records estimated that the patient's daily protein intake was ~0.5 g/kg at the time of her ED visits. Furthermore, our patient did not show any clinical signs of nutritional deficiencies, such as diarrhea or skin lesions. Although the patient did not have a history of developmental or intellectual impairment, her daughters expressed concern about her current cognitive functioning and repeated ED visits for altered mental status.

Targeted genetic testing using the GeneDx Hyperammonemia, Urea Cycle and Transporter Defects panel did not identify any relevant

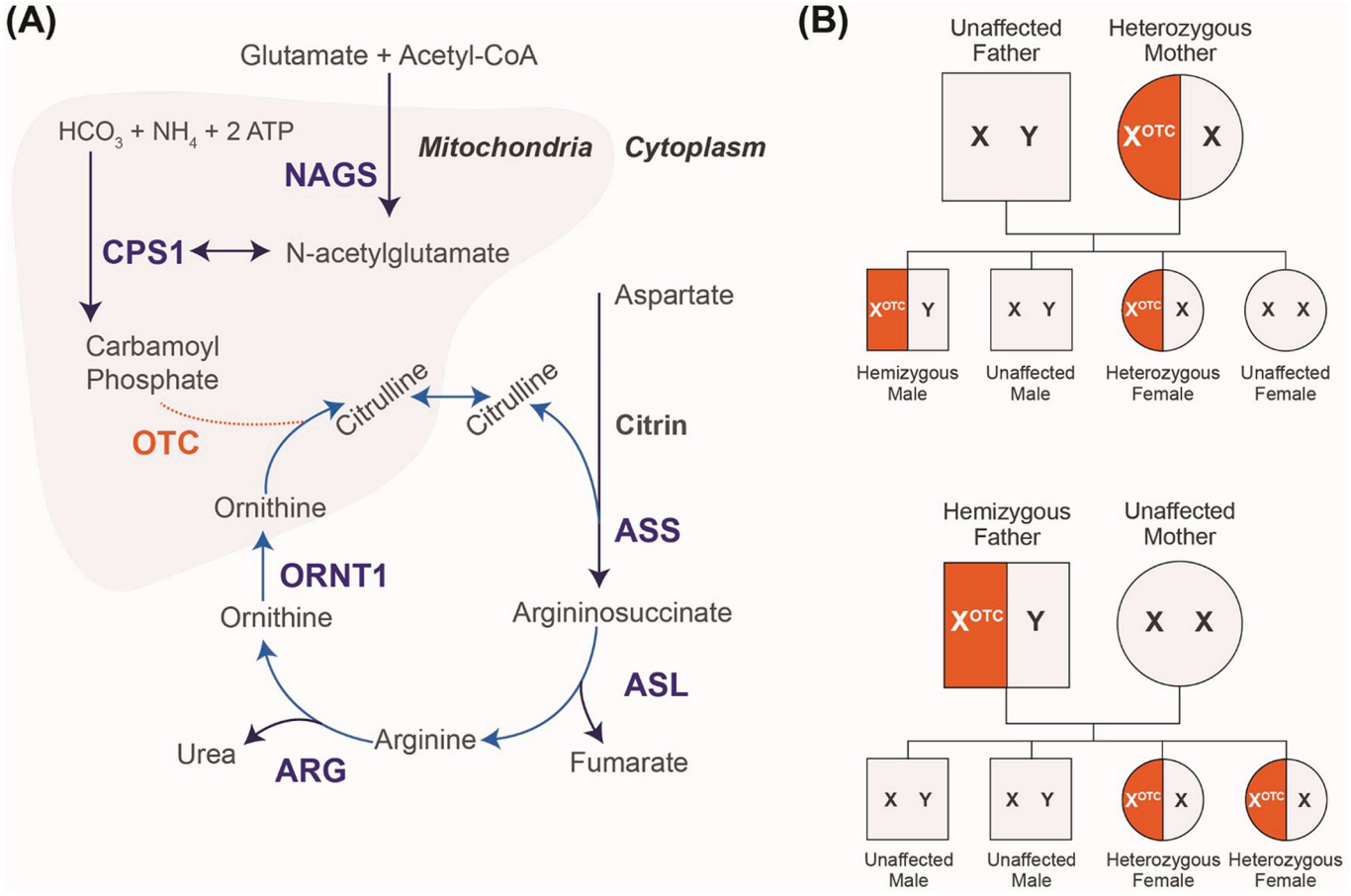

Fig. 1. Enzymatic defect and X-linked inheritance pattern of OTC deficiency. (A) The urea cycle is composed of 6 enzymes that metabolize waste nitrogen from the breakdown of protein-containing molecules. Deficiency of any of these enzymes or the 2 transporter proteins causes a UCD and can lead to hyperammonemia. OTC (in orange) catalyzes the formation of citrulline from ornithine and carbamoyl phosphate. A deficiency of OTC reduces citrulline formation and impairs urea cycle function [1,5]. Abbreviations: ARG, arginase; ASL, argininosuccinic acid lyase; ASS, argininosuccinic acid synthetase; CPS1, carbamoyl phosphate synthetase I; NAGS, *N*-acetyl glutamate synthetase; ORNT1, ornithine translocase; OTC, ornithine transcarbamylase; UCD, urea cycle disorder. (B) OTC deficiency follows a pattern of X-linked inheritance. Female heterozygotes have a 50% chance with every pregnancy of passing the pathogenic variant to their child. All daughters of males with OTC deficiency will inherit the pathogenic variant. Sons of hemizygous males will not inherit the pathogenic variant. Female heterozygotes are often referred to as carriers; however, this terminology is potentially misleading as female heterozygotes may demonstrate symptoms of OTC deficiency [5].

genetic variants. Testing for OTC enzyme activity was considered but not completed due to the invasive nature of the testing and low reliability of results in heterozygous females. We ultimately diagnosed the patient with late-onset OTC deficiency based on her biochemical testing and clinical history, which were consistent with this diagnosis.

2.2. Family and obstetric history

Family history was significant for a maternal uncle who died of unknown causes shortly after birth. The patient's obstetric history included 3 successful live births (all female) and no history of pregnancy loss. She did not report any changes in cognitive function, aversion to high-protein foods, or postpartum psychosis related to her pregnancies. Family genetic testing was not recommended because the patient's *OTC* variant could not be identified on genetic testing. The patient's daughters received genetic counseling and were recommended to have amino acid and urine orotic testing completed, but it has not yet been performed.

2.3. UCD management

The patient's UCD management was overseen by a metabolic geneticist and dietitian. The patient was prescribed a low-protein diet (~0.6 g/kg/d of protein), glycerol phenylbutyrate (GPB; 17 mL daily, divided into 3 doses), and L-citrulline (3 g/m^2/d). Her confusion, abdominal pain, and headaches improved significantly after starting treatment. Plasma amino acids and ammonia levels were monitored every 3 months and trended toward normalization.

Despite a long history of vegetarianism due to previously unexplained stomach pain with high-protein foods, the patient had variable adherence to the modified low-protein diet prescribed for OTC deficiency. Her food habits were long established, and her daughters reported frequent difficulties in their ability to keep her on the prescribed OTC deficiency diet. A complicating factor was the need for a heart-healthy diet (in which lean protein, whole grains, fruits, and vegetables are typically encouraged, and *trans* and saturated fats are restricted) [17] and her diabetes status (limiting simple carbohydrates).

2.4. Outcome

The patient remained in stable metabolic control on her low-protein diet, oral nitrogen-scavenger therapy, and L-citrulline. Her daughters and husband noted an improvement in her general cognitive function, although no formal assessments were conducted. She experienced only one known hyperammonemic episode approximately 2 years after starting treatment for OTC deficiency; however, she unfortunately required multiple hospital admissions for peripheral and pulmonary edema related to heart failure, during which she required additional management to maintain her baseline metabolic control.

During her final hospital admission, she was initiated on lactulose and nasogastric (NG) feeds, with 50% of protein from essential amino acids and her remaining nutrition needs met from standard enteral formula and a protein-free modular. She received GPB (home regimen of 5.5 mL, 3 times daily) via NG tube. After 2 days, the adult intensivist initiated IV (intravenous) dextrose 20% in water (D20W) at 50 mL/h to maximize anabolism in the setting of rising ammonia levels (77 to 91 μmol/L) and high stool output causing concern for enteral feed malabsorption due to lactulose. L-citrulline (prescribed at 2.774 g, 3 times daily) was ordered but delayed due to hospital supply issues.

Due to her rising ammonia levels, the decision was made to discontinue standard enteral formula and provide protein solely from essential amino acids. Total parenteral nutrition was also considered if concern for malabsorption due to lactulose continued; however, it was not initiated. Metabolic control improved in due course on a regimen of D20W IV fluids and enteral feeds, providing a combined daily total of 59 kcal/kg ideal body weight (IBW) and 0.5 g/kg IBW protein (50% from essential amino acids). Unfortunately, her cardiac dysfunction continued to worsen, and she ultimately passed away at age 67 due to complications of heart failure.

3. Discussion

Late-onset UCDs are challenging to diagnose due to their clinical heterogeneity, nonspecific symptomatology, and relative rarity [5,11,13,18]. The most important step in diagnosing a UCD is the clinical suspicion of hyperammonemia [4]. Our patient was initially dismissed as having general cognitive decline until hyperammonemia was biochemically identified, prompting treatment first for hyperammonemia and possible liver disease, and then eventually for OTC deficiency. Transient neurologic changes associated with protein aversion or vomiting should immediately prompt ammonia testing to rule out a UCD, though it is important to note that ammonia levels may be normal during asymptomatic periods [13]. In these cases, plasma amino acids may reveal abnormalities (eg, elevated glutamine and low citrulline suggestive of a proximal UCD) even in the setting of normal ammonia levels [5]. Additionally, an understanding of the broad spectrum of UCD presentations is helpful to evaluate clinical histories of headaches, abdominal pain, psychiatric episodes, and other ongoing, nonspecific symptoms that may suggest a late-onset UCD [2]. Approximately 10% of all individuals with a UCD are diagnosed after 16 years of age; though OTC deficiency is the most commonly identified UCD outside the neonatal period, other UCD variants should not be ruled out in children, teens, and adults [19].

Because many pathogenic variants of *OTC* remain unaccounted for

Table 1
Common findings of late-onset urea cycle disorders [2,4,5,11].

Neurologic	Biochemical	Gastrointestinal	Situational Triggers
Headaches	Elevated plasma ammonia	Aversion to dietary protein	Catabolic events such as rapid weight loss, infection, surgery, trauma, or labor and delivery
Confusion	Elevated glutamine and low citrulline on plasma amino acids	Loss of appetite	Administration of IV steroids
Behavioral abnormalities	Elevated urine orotic acid	Nausea and/or vomiting	Elevated dietary protein load
Sleep disorders	Elevated liver enzymes	Abdominal pain	
Psychiatric symptoms	Respiratory alkalosis		
Deteriorating mental status			
Lethargy			
Seizures			
Nonspecific brain atrophy on MRI			
Cerebral edema			
Severe encephalopathy			

Abbreviations: IV, intravenous; MRI, magnetic resonance imaging.

[10], genetic sequencing alone may not suffice for confirmation of diagnosis. Patient symptomatology and biomarkers (Table 1) are crucial in establishing early and accurate diagnoses of OTC deficiency [4,5]. It has been reported that ~20% of individuals with OTC deficiency do not have identifiable pathogenic variants in the coding regions or exon-intron boundaries of the *OTC* gene [10]. This is corroborated by a recent study in which ~18% of patients with OTC deficiency did not have an identifiable variant in *OTC* on gene sequencing [20]. Continued genetic sequencing of patients with OTC deficiency is, therefore, very important to build the database of disease-causing variants.

Adults suffering from hyperammonemia may be unable to accurately communicate relevant information about their medical history and symptoms. Family members become significant advocates and informants who can provide information that can help lead to a UCD diagnosis [21]. Our patient's daughters were instrumental in seeking further investigations of the patient's episodes of confusion to reach the diagnosis of OTC deficiency. After the proband is identified and treatment is initiated, family members should be offered genetic counseling to help identify other at-risk family members who could be proactively managed to prevent onset of symptoms or hyperammonemia and to facilitate discussions about future family planning and prenatal testing for OTC deficiency, if relevant [5,22]. If the proband's genetic variant cannot be identified, or if genetic testing is financially or otherwise unavailable, biochemical screening of family members is recommended [5].

OTC deficiency can manifest at any age and can be difficult to detect and treat in adulthood [13]. Our patient's multiple comorbidities presented numerous clinical and practical challenges. She struggled to adapt to UCD management (particularly dietary therapy) and relied heavily upon family members for support to manage her multiple medical conditions. Other case studies have highlighted difficulties of managing patients with UCDs who also require chemotherapy for breast cancer and who experience comorbid epilepsy after liver transplantation [15,23]. It is also possible that the standard treatment for a comorbidity may conflict with UCD management strategies, such as in a reported case of concurrent type 1 diabetes mellitus and OTC deficiency in which dietary management complications led to persistent obesity that could only be mediated by physical activity [14]. This dilemma may become increasingly relevant as our ability to diagnose and treat inherited metabolic disorders (such as OTC deficiency) improves and patients experience longer lifespans, contributing to age-related comorbidities [24].

Comorbidities may also play a role in masking or unveiling a UCD diagnosis [18,23]. Although our patient experienced at least one known lifelong symptom of OTC deficiency (protein aversion), significant cardiac dysfunction and possible NAFLD may have contributed to the exacerbation of the more striking symptoms that led to her OTC deficiency diagnosis (eg, lethargy, confusion). Both clinical and experimental models of NAFLD and nonalcoholic steatohepatitis have shown downregulation of urea cycle enzymes without the presence of a diagnosed UCD [25], suggesting this as a potential precipitating factor that more fully unmasked our patient's OTC deficiency. However, hyperammonemia and cognitive changes are also symptoms of NAFLD [26], and it is fortunate that the hepatology team recommended a genetics consultation for our patient despite her liver complications unrelated to OTC deficiency.

Early diagnosis of OTC deficiency is crucial as even asymptomatic patients are at risk for life-threatening hyperammonemic crisis and can benefit from a tailored UCD management plan [5,13]. We stress a high level of clinical suspicion for late-onset UCD in patients with symptoms like those seen in this patient case, including unexplained vomiting, abdominal pain, aversion to high-protein foods, and intermittent lethargy or disorientation, and recommend initiating therapy promptly to support metabolic control and minimize the risk of hyperammonemia.

Consent for publication

Informed consent was obtained from the patient's husband and daughter for this work.

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Declaration of Competing Interest

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Data availability

No data was used for the research described in the article.

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