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Overview

Challenges of managing ornithine transcarbamylase deficiency in female heterozygotes☆

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ABSTRACT

Urea cycle disorders (UCDs) are a group of rare inherited metabolic conditions caused by enzyme deficiency within the hepatic ammonia detoxification pathway. Ornithine transcarbamylase (OTC) deficiency, the most frequently occurring UCD, is an X-linked condition known to yield a vastly heterogeneous phenotype, with variable onset and presentation across the lifespan. Here, we introduce a series of 4 original cases, published as part of this special supplement, that illustrate learnings for the care of heterozygous females with OTC deficiency, including challenges with diagnosis, potential triggers of hyperammonemia, cognitive effects, and approaches to disease management, including peripartum care.

Ornithine transcarbamylase (OTC) deficiency is a potentially devastating genetic disease with variable onset and presentation across the lifespan [1]. This X-linked inborn error of urea cycle metabolism is caused by mutations in the gene encoding OTC (OMIM 300461), located on chromosome Xp11.4 [1]. OTC deficiency is managed with dietary protein restriction, supplemental amino acids and nitrogen-scavenging agents, or liver transplant [2]. Therapeutic options in development include liver cell transplant, protein and mRNA therapy, and gene or gene editing therapy [3]. The estimated incidence of OTC deficiency is 1 in 56,000 [4], but this is likely an underestimate due to undiagnosed oligosymptomatic cases and newborn screening that is not yet highly sensitive nor specific [4,5].

Historically, OTC deficiency was considered by many to be an X-linked dominant or partially dominant condition, as male hemizygotes typically present in the neonatal period with the most dramatic symptomatology, whereas heterozygous females, referred to as "carriers", can present with nonspecific and relatively milder manifestations of disease [1,6,7]. This contributed to the misconception that this X-linked disease only affected males and that females did not need to be monitored for disease manifestations. Over time, the field started to recognize that many females are manifesting heterozygotes. We now know that although females are more likely than males to be spared from the early-onset lethal presentation, they may instead experience variable and nonspecific chronic manifestations of disease that are often misunderstood or overlooked. In a heterozygous female, the pattern of X-chromosome inactivation in the liver determines OTC enzyme activity. If X-chromosome inactivation in liver cells is skewed toward the pathogenic *OTC* variant, a heterozygous female is more likely to manifest symptoms of OTC deficiency [1,8]. OTC deficiency is now referred to as an X-linked condition without stating recessive/dominant inheritance [1,7]. Terminology to refer to the various clinical phenotypes in hemizygous males and heterozygous females has included neonatal-onset (severe), post–neonatal-onset, or late-onset (partial) OTC deficiency [1]. Unfortunately, the use of the term "partial" may lead clinicians and patients to believe the condition is not potentially clinically dangerous. Nomenclature discussions moving forward should ensure awareness that even patients with "partial" OTC deficiency may experience a lethal acute crisis at any age.

In this issue of *Molecular Genetics and Metabolism Reports*, we illustrate these learnings and others that have contributed to advancements in understanding OTC deficiency among heterozygous females. To help address gaps in awareness, colleagues have assembled 4 patient case reports that demonstrate a variety of challenges, approaches to clinical care, and outcomes for female patients with OTC deficiency.

Andrews and colleagues describe the case of a 19-month-old girl who presented with intermittent vomiting and abnormal liver enzymes. MRI showed nondiagnostic white matter changes, and peak serum ammonia level reached 280 μmol/L (reference range 21–50 μmol/L). Ammonia is considered neurotoxic during elevations with acute metabolic crises, as well as during chronic mild elevations even in the absence of clinical symptoms [9,10]. Fortunately, prompt measurement of ammonia led to accurate diagnosis and tailored treatment in this case, but many other reported cases have had severe consequences. This case illustrates the characteristic changes in cerebral white matter seen in patients with OTC deficiency. White matter tracts are involved in working memory and executive function and have been found to be altered even in heterozygous women who were previously considered asymptomatic [11,12]. Self-reported difficulties in scholastic, professional, and social success, as well as anxiety and depression, have also been described in asymptomatic adults with OTC deficiency [13,14].

Abbreviations: IV, intravenous; MRI, magnetic resonance imaging; OTC, ornithine transcarbamylase; UCD, urea cycle disorder.

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The case by Feigenbaum et al. builds on challenges with peripartum triggers of disease. This patient was very knowledgeable about her condition and remained adherent to her management plan after diagnosis at 12 years old. She achieved successful pregnancy and intrapartum management that required close collaboration and discussion with non–urea cycle disorder (UCD) specialties, including anesthesia, obstetrics, prenatal genetics, and the high-risk obstetric unit. Despite this, she still experienced a hyperammonemic crisis related to poor enteral nutrition after successful childbirth and discharge, which may have been prevented with on-site access to a biochemical geneticist or metabolic dietitian with an understanding of the rapidly changing postpartum physiology. Few comprehensive published protocols are available to guide clinical decision-making for patients with inborn errors of metabolism during pregnancy [9,15,16]. Full team discussions are needed to address labor and delivery decisions, anesthesia options, and anticipated need for oral and IV nutrition and nitrogen scavenger therapy throughout labor, delivery, and the postpartum period. In this case, communication and counseling, along with continued disease education, were key in reaching positive outcomes for the patient and her son.

Baker et al. further underscore the variability in disease manifestations and need for individualized treatment with the case of a female monozygotic twin who presented to medical care at 10 months of age with acute liver failure and hyperammonemia, while her twin sister and mother (also heterozygous for OTC deficiency) do not restrict protein and have not experienced a crisis. Current biochemical monitoring suggests that the patient's twin sister is able to tolerate a larger protein load. Moderate protein restriction and citrulline supplementation were recommended for the patient's mother given reports of possible symptoms, including headache and brain fog. Over the course of several months, she reported less frequent headaches while taking citrulline supplementation. To our knowledge, she has not altered her intact protein intake, a step that ideally would be explored to evaluate effects on her reported cognitive symptoms. The patient's older brother, known to have hemizygous OTC deficiency, died at 8 months of age from complications secondary to his diagnosis. Despite the patient's family history, the patient was not diagnosed prenatally or in the neonatal period, and manifestations of heterozygous OTC deficiency went unrecognized by multiple providers.

To further highlight variable disease manifestations, Abbott et al. report the case of a medically complex adult woman with OTC deficiency who was 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*, which is the case for approximately 20% of patients with OTC deficiency [17,18]. Sequence analysis of *OTC* has detected missense, nonsense, and splice site variants, small intragenic deletions/insertions, single-exon, multiexon, or whole-gene deletions/duplications, promotor and enhancer mutations and more recently a deep intronic pathogenic variant [1,18]. In this case, diagnosis and management were complicated by multiple comorbidities. The patient struggled to adapt to dietary therapy as an adult and relied heavily upon family members for support. The risks associated with OTC deficiency can be particularly difficult to appreciate when a patient receives a diagnosis in adulthood and has been unaware of their condition aside from an acute crisis. A triggering event to unmask OTC deficiency can occur at any time, such as during infection, fever, fasting, surgery (eg, bariatric surgery), or the increased metabolic demands of the pregnancy and peripartum periods [15,19–24]. Adults suffering from hyperammonemia may also be unable to accurately communicate relevant information about their medical history and symptoms, delaying diagnosis.

In summary, this overview summarizes a compilation of 4 original case reports that collectively illustrate that female patients with OTC deficiency require unique clinical care, including prevention and treatment of acute illnesses, continued disease state education, connections to social support, and clarification on the genetic risks of the condition. It is our hope that through these cases, we can share with the clinical community our experiences and successes with tailored treatment plans, patient-centric approaches for improving adherence and disease state understanding, and management throughout pregnancy and the postpartum period.

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Declaration of competing interest

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