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Variable disease manifestations and metabolic management within a single family affected by ornithine transcarbamylase deficiency☆

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ABSTRACT

We report on a family with ornithine transcarbamylase (OTC) deficiency, an X-linked urea cycle disorder, with variable disease severity and tailored management strategies based on each family member's biochemical profile and clinical presentation. Our primary patient is a female monozygotic twin who presented to medical care at 10 months of age with acute liver failure, gastrointestinal symptoms, altered mental status, hypoglycemia, and hyperammonemia. The patient's older brother, known to have hemizygous OTC deficiency, died at 8 months of age from cardiac arrest after complications secondary to his diagnosis. Despite her family history, manifestation of symptoms of heterozygous (partial) OTC deficiency went unrecognized by multiple providers based on misconceptions regarding a female's risk for X-linked disease. Despite barriers related to the family's low socioeconomic status, follow-up care by a multidisciplinary metabolic care team, including moderate protein restriction and nitrogen scavenger therapy, led to positive outcomes for the patient. Her twin sister and mother are also heterozygous for variants in *OTC* and remain controlled on moderate protein restriction. This case illustrates the importance of genotyping all individuals with genetic risk factors for OTC deficiency and the variability in disease manifestation that necessitates tailored treatment approaches for individuals with partial OTC deficiency.

1. Introduction

The urea cycle pathway consists of 5 catalytic enzymes, 1 cofactor-producing enzyme, and 2 amino acid transporters. Deficiency in any of these enzymes or transporters results in a urea cycle disorder (UCD) [1]. Disease-causing variants in *ornithine transcarbamylase* (*OTC*) (OMIM 300461) occur in an X-linked inheritance pattern or as a result of a *de novo* variant and can cause neonatal onset of hyperammonemia with life-threatening intoxication in the male with a hemizygous variants [1,2]. Females who are heterozygous for variants in *OTC*, or males with less severe variants, have widely variable phenotypes depending on the severity of the enzyme deficiency and X-chromosome inactivation pattern [2,3]. In the early female embryo, either the maternal or paternal X chromosome in each cell is inactivated in a random pattern. Manifestation of symptoms of OTC deficiency in a female is more severe when the X chromosome harboring the pathogenic *OTC* allele is active in more hepatocytes than the wild-type *OTC* allele, leading to decreased OTC enzyme activity [2]. This has been described as partial OTC deficiency or manifesting heterozygotic OTC deficiency [2,4]. Partial OTC deficiency is challenging to diagnose as presentation can occur throughout the lifespan and includes subtle symptoms of hyperammonemia such as protein avoidance, headaches, recurrent vomiting, and mild cognitive deficits [2,5]. OTC deficiency may also present with nonspecific psychiatric symptoms, psychotic episodes, and altered mental status [2,6]. Asymptomatic or mildly symptomatic individuals remain at risk for hyperammonemic crisis during periods of physiologic

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; CVS, chorionic villus sampling; DOL, day of life; EAA, essential amino acid; GPB, glycerol phenylbutyrate; HC, head circumference; IV, intravenous; NaPB, sodium phenylbutyrate; NBS, newborn screen; NORD, National Organization for Rare Disorders; OTC, ornithine transcarbamylase; PO, *per os*, by mouth; UCD, urea cycle disorder.

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stress and increased metabolic demand [7,8]. In families of an affected neonate, genetic evaluation for OTC deficiency should be performed for all at-risk individuals, regardless of sex [2]. Female relatives of males with severe neonatal-onset OTC deficiency are at higher risk for becoming symptomatic than relatives of patients with post neonatal onset [2]. Previously, it was estimated that 15–20% of female heterozygotes become symptomatic in their lifetime; however, this estimate does not include those with subtle symptoms that may not come to medical attention [2,9,10].

2. Case presentation

2.1. Family history

The patient's family first became known to our service when their first son (Fig. 1, Sibling 3) presented at 3 days of life in cardiac arrest and severe hyperammonemic crisis, at which time confirmatory testing was sent for OTC deficiency. He died at 8 months of age due to prolonged cardiac arrest, secondary to suspected seizure activity. After his molecular confirmation, genetic testing was performed on the family's living children and mother (Fig. 1, Siblings 1, 2). Testing identified an OTC disease–causative variant only in the mother. Despite counseling on OTC deficiency in females, the mother did not return for follow-up as a patient at that time.

2.2. Pregnancy

Subsequent pregnancies after the death of Sibling 3 were not reported to our team and the mother received prenatal care at various free clinics. A provider performed prenatal chorionic villus sampling (CVS) for the patient, a monozygotic twin (Twin A), and results were inferred for her twin sister (Twin B); however, only aneuploidy testing was completed. The family was under the impression that the *OTC* familial variant was tested for, but unfortunately this test was canceled by a different provider after the chromosomes showed 46 XX female. This was due to the provider's misunderstanding of the OTC disease process, misconception that only males are affected, and uncoordinated care.

2.3. Patient presentation

The patient, Twin A (Fig. 1), presented at 10 months of age to the emergency department with acute onset of diarrhea, vomiting, upper respiratory tract congestion, fever, hypoglycemia, and altered mental status. On admission, hypoglycemia was refractory to high glucose infusion rate, which prompted further metabolic workup. Elevated coagulation studies and significantly elevated aspartate transaminase (AST)/alanine aminotransferase (ALT) (peak AST of 3043 IU/L and ALT of 4527 IU/L) were noted. Ammonia was elevated to 174 μmol/L. Family history prompted suspicion of partial OTC deficiency. Given high clinical suspicion, the patient was transferred to the pediatric intensive care unit to initiate intravenous (IV) ammonia scavengers. After 36 h of IV scavengers, liver function began improving significantly. Biochemical and molecular testing confirmed the suspected diagnosis. She was transitioned to oral sodium phenylbutyrate (NaPB) at 450 mg/kg/d, started on 200 mg/kg/d of citrulline supplementation, and placed on a moderate protein-restricted diet. Dietary management began with protein-free PO formula (30 kcal/oz), and she was then transitioned to standard infant formula plus essential amino acid (EAA) mixture. Protein was restricted to 1.5 g/kg/d, with 30% from an EAA source and the remainder from standard formula. She was discharged in stable condition. Four days later, she was transitioned from NaPB to glycerol phenylbutyrate (GPB) at 11.2 mL/m^2/d due to poor palatability that resolved on the new medication.

Our metabolic clinic started outpatient management of Twin A 6 weeks after discharge at 12 months of age. Her parents were encouraged to start offering low-protein solids as tolerated. During subsequent clinic follow-up at 15 months of age, the patient was transitioned to lactose-free whole milk from standard infant formula. Her initial protein recommendation of 1.5 g/kg/d has been gradually weight adjusted to 1.2 g/kg/d from formula, with a simplified diet adding negligible additional protein. Dietary management continues to evolve based on biochemical control and growth parameters.

Since initiating treatment, the patient has had no additional hyperammonemic crises or hospitalizations, no clinical symptoms of hyperammonemia and liver failure has resolved. We have recommended follow-up in clinic every 2–3 months. Plasma amino acids were collected twice since her discharge and revealed normalization of glutamine and persistently low to normal citrulline levels (Table 1). Citrulline has been adjusted to maintain 200 mg/kg/d, and GPB dose has not needed adjustment. Due to continued hypotonia on examination and mild developmental delays, physical therapy was recommended and has since been initiated after insurance changes. Consistent follow-up has been complicated by socioeconomic restraints (eg, insurance limitations, transportation needs, limited access to childcare and parental time

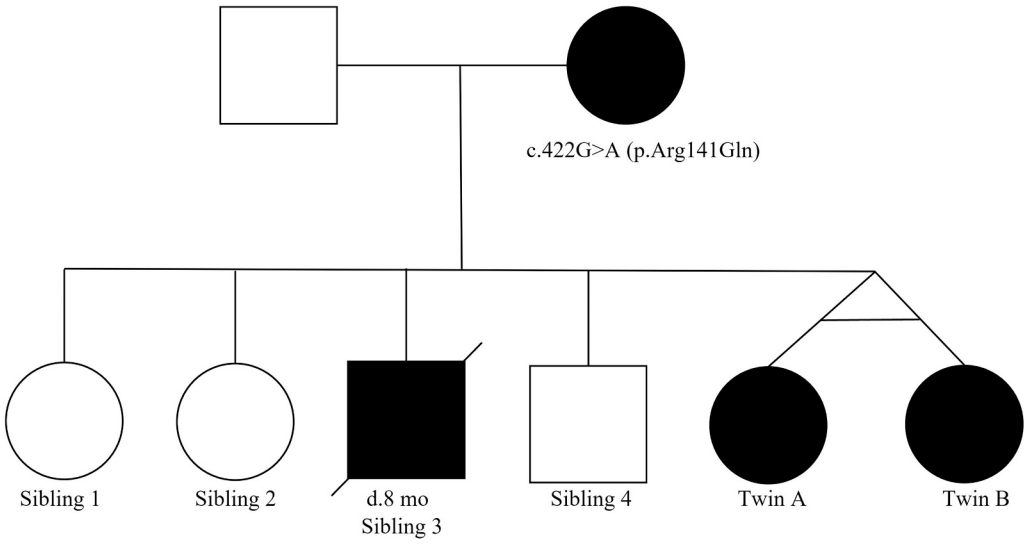

Fig. 1. Family pedigree. Genetic testing for Sibling 1, Sibling 2, and mother was performed at the time of Sibling 3's molecular confirmation. Sibling 4 was screened prenatally. *OTC* sequencing that detected the family variant was performed for Twin A and Twin B at the time of Twin A's presentation.

Table 1
Clinical and laboratory findings and differentiated management.

Size/Growth[a] [Z-Score]		Birth	10 Months (At Twin A Diagnosis)	12 Months Follow-up	15 Months Follow-up
Twin A	Weight (kg)	2.08 [−2.86]	7.6 [0.95]	7.925 [−0.94]	8.745 [−0.84]
	Length (cm)	45.1 [−2.17][b]	68.6 [−1.26]	68.7 [−1.94]	73.5 [−1.61]
	HC (cm)	31.8 [−1.76]	43.5 [−0.60]	44.0 [−0.60]	45.5 [−0.81]
	Weight-for-length (percentile)	2 [−2.00]	34 [−0.39]	51 [−0.04]	44 [−0.15]
Twin B	Weight (kg)	2.03 [−3.01]	8.305 [−0.24]	8.445 [−0.42]	9.33 [−0.31]
	Length (cm)	43.0 [−3.30]	n/a	70.4 [−1.28]	76.5 [−0.53]
	HC (cm)	31.0 [−2.43]	43.9 [−0.32]	44.5 [−0.23]	45.6 [0.10]
	Weight-for-length (percentile)	31 [−0.49]	n/a	60 [0.26]	45 [−0.11]
Liver Function, IU/L (Reference Range)					
Twin A	AST (3–44)	n/a	3043	13	16
	ALT (17–59)	n/a	4527	35	41
Twin B	AST (3–44)	n/a	17	13	19
	ALT (17–59)	n/a	44	37	46
UCD Biomarkers, μmol/L (Reference Range)					
Twin A	Ammonia (11–35)	n/a	174	n/a	n/a
	Glutamine (246–1182)	n/a	1517	590	973
	Citrulline (3–35)	n/a	5	34	5
	NBS[c] (>6)	DOL 2: 4.75, DOL 11: 9.81			
	Arginine (12−133)	n/a	18	79	20
Twin B	Ammonia (11–35)	n/a	30	n/a	n/a
	Glutamine (246–1182)	n/a	976	743	681
	Citrulline (3–35)	n/a	14	90	14
	NBS[c] (>6)	1 h: 9.8, 24 h: 8.07			
	Arginine (12–133)	n/a	69	118	35

[a]Growth assessed using WHO 2006 girls 0–24 months growth chart. [b]Noted for being small for gestational age and not meeting all developmental milestones at the same pace as Twin B. 43.2 cm at DOL 6 may reflect birth length more accurately; difficult to assess true length trajectory due to limited primary care follow-up post birth (likely due to reduced interactions during the COVID-19 pandemic). [c]NBS measured citrulline with a cut off value of >6 μmol/L; despite an initial positive test at DOL 2, Twin A's NBS results were negative for UCD at DOL 11 and no subsequent testing was performed.
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; DOL, day of life; HC, head circumference; n/a, not available; NBS, newborn screen; UCD, urea cycle disorder; WHO, World Health Organization.

off work, loss of housing) and the family's expressed emotional trauma from their previous loss of the older brother. Fortunately, various patient support services have helped maintain consistent treatment access.

2.4. Differentiated treatment within single family

During Twin A's initial hospitalization, *OTC* gene sequencing and biochemical laboratory tests were performed for Twin B, revealing a mild partial OTC biochemical profile with reduced citrulline and elevated glutamine (Table 1). Protein restriction and citrulline supplementation were initiated similarly to Twin A; however, the medical team chose to hold on nitrogen scavenger therapy. At a follow-up visit 5 months after Twin A's diagnosis, the parents reported they were not restricting protein from solids for Twin B as cautiously as Twin A because they felt her symptoms have never been as severe. In alignment with this observation, her biochemical profile suggests she is able to tolerate a larger protein load than Twin A.

The patient's mother was recommended to start moderate protein restriction (0.8 g/kg/d) and citrulline supplementation (200 mg/kg/d) 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. Follow-up biochemical monitoring for Twin B and the mother was significantly delayed due to lapsed insurance coverage and the significant out-of-pocket cost; however, the family has worked with our clinical social worker to establish coverage with Medicare and obtain further support through National Organization for Rare Disorders (NORD). Biochemical monitoring for Twin B and mother has now been repeated and remains stable. All family members appear to remain in good metabolic control with individualized treatment plans.

3. Materials and methods

3.1. Medical review

Medical records and clinical parameters were reviewed by the treating clinical team. Informed consent was obtained from the patient's parents for publication of this case.

3.2. Gene sequencing

Genetic testing was conducted through the UCD Genetic Testing Program sponsored by Horizon Therapeutics and performed by Invitae. Sequence analysis included clinically relevant regions of genes associated with enzymes and transporter proteins responsible for the production and detoxification of ammonia, including coding exons and 10–20 base pairs of adjacent intronic sequence on either side of the coding exons. In addition, the analysis covered select noncoding variants. Based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15 bp in length and exon-level deletions and duplications.

3.3. Monitoring

Biochemical monitoring includes complete metabolic profile (including liver enzymes), plasma amino acids, ammonia levels, and coagulation profile. Medication and diet are monitored and altered for age, weight, and laboratory values. All patients have been closely monitored on growth charts to evaluate for appropriate physical development on protein-restricted diets [11,12].

4. Discussion

This case study highlights the clinical heterogeneity of OTC deficiency, namely in 3 females in the same family carrying the same pathogenic variant and exhibiting differing clinical presentations. Although our patient presented at a young age in acute liver failure and hyperammonemic crisis during intercurrent illness, her identical twin sister appears to have remained clinically asymptomatic with mild biochemical abnormalities despite experiencing the same viral illnesses as her twin sister. Their mother has reported mild symptoms and notes improvements in headaches and executive functioning skills with citrulline supplementation. To the best of our knowledge, this degree of phenotypic variation between monozygotic twins has not been previously reported in the literature [13]; however, variability within families and among female patients with OTC deficiency has been well documented [3]. Neuroimaging findings indicate that even patients who appear to be asymptomatic may exhibit neuronal changes underlying neurocognitive deficits in specific domains [14,15].

OTC gene sequencing revealed a previously reported pathogenic missense variant c.422G > A (p.Arg141Gln, NM_000531) in this family, thought to account for 3–10% of OTC deficiency cases [10,16]. This variant affects the active site of the enzyme with complete loss of activity *in vitro*, resulting in neonatal onset in male patients and variable expression in females [17–19]. Considering the monozygotic twins in this case received an identical diet prior to Twin A's presentation, it is likely that variable disease manifestations are mostly related to differential X-chromosome inactivation in the hepatocytes, with a potentially higher number of hepatocytes containing the active pathogenic *OTC* variant in Twin A's liver [2].

Consensus-driven guidance regarding metabolic care for female heterozygotes is sparse [6,20], leaving metabolic providers to use their best clinical judgment regarding risks of hyperammonemia, metabolic crisis, and disease sequelae compared with the risks and benefits of lifelong daily medication and/or dietary adjustments. In addition, treatment adherence and long-term follow-up are inconsistent in asymptomatic females, particularly if they feel well overall.

Clinicians need to be aware that UCD management for families and patients will require frequent follow-up and ongoing education. For this family, education was provided regarding OTC deficiency in females at the time of the initial diagnosis for their affected son, and appropriate testing was performed on a subsequent male sibling. However, the family had many misconceptions regarding the true risk of disease presentation in OTC-deficient females, and this twin pregnancy was not disclosed to their metabolic providers. Additionally, incorrect information was provided to the family during prenatal genetic counseling. Misconceptions regarding genetic aspects of OTC deficiency are unfortunately common, particularly outside of genetic specialists, given the rarity of OTC deficiency and lack of provider familiarity with rare metabolic disorders. Although the family elected to have CVS performed during this pregnancy, they were unaware that the provider ordered testing would not detect their familial *OTC* variant. In addition, citrulline results below the test cutoff noted on initial NBS (Table 1) were not well-communicated to the family by their primary care physician, further highlighting the need for greater awareness of OTC deficiency among healthcare providers.

Patients with lower socioeconomic status may experience lack of a consistent and specialized care team, leading to delays in diagnosis and treatment, as was the case with this patient's family [21]. Challenges with insurance (public or private), difficulty accessing specialists, and insufficient financial assistance have been cited as common barriers interfering with accurate diagnosis and proper care for rare disease [22,23]. The overall impact of socioeconomic barriers on care for rare diseases is not well studied in the United States and is a potential area for increased attention and advocacy [24].

Ongoing management of OTC deficiency requires a multidisciplinary approach. Collaboration among clinicians is necessary to address the dietary adjustments, laboratory test monitoring, medication adjustments, sick day protocols, and emergency care [25]. Genetics team members involved in the ongoing care of this family include a biochemical geneticist, metabolic advanced practice nurse, metabolic dietitian, metabolic nurses, and social worker. When available, a genetic counselor can also provide dedicated support around family planning that emphasizes the potential risks to all family members, regardless of sex.

The patient's family has expressed the difficulty of receiving a diagnosis of OTC deficiency for 2 children after the death of their son with the same diagnosis. They struggle to return to the hospital where their infant son died and suffer from anxiety with restarting medications and dietary regimens that remind them of their son. However, the parents have remained compliant with protein restriction and administration of citrulline and GPB for Twin A overall. After insurance changes and establishment with NORD for UCD patient financial assistance, Twin A has been followed closely in the metabolic clinic.

The phenotype of females heterozygous for variants in *OTC* is highly variable, ranging from asymptomatic to severe symptoms, such as recurrent hyperammonemia, coma, and death. A single test does not exist to accurately gauge the exact degree of medical intervention needed to prevent a hyperammonemic crisis. Variables such as X-inactivation, environmental triggers, and sufficiency of long-term compensatory measures can all play a role in the manifestation of disease. Further, subclinical signs and symptoms such headaches or protein self-restriction [2,6,10] may delay diagnosis and adequate treatment; meanwhile even mild elevations in ammonia can have long-term neurotoxic effects [26]. The ongoing management of females with OTC deficiency therefore needs to be continuously adjusted to both biochemical findings and clinical presentations.

Consent for publication

Informed consent was obtained from the patient's parents for this work.

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Declaration of Competing Interest

Joshua Baker, Lauren Hitchins, Erika Vucko, and Katherine Arduini have participated in advisory boards and received honoraria from Horizon Therapeutics plc. Joshua Baker is PI for a clinical trial sponsored by Ultragenyx. He has received consulting fees/honoraria from Biomarin, Horizon, Takeda, and Ultragenyx. Lauren Hitchins has received consulting fees/honoraria from Amicus and Acer Therapeutics. Erika Vucko has received consulting fees/honoraria from Takeda, BioMarin, and Sanofi Genzyme. Katherine Arduini has been involved in clinical trials sponsored by Ultragenyx, and has received consulting fees/honoraria from Acer Therapeutics. Kirsten Havens and Karen Becker have no conflicts to disclose. No authors received compensation for involvement with this manuscript. The authors confirm independence from the sponsor; the content of the article has not been influenced by the sponsor.

Data availability

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

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