MGM Reports

Benefits of tailored disease management in improving tremor, white matter hyperintensities, and liver enzymes in a child with heterozygous X-linked ornithine transcarbamylase deficiency☆

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ABSTRACT

We report the case of a 19-month-old girl with late-onset ornithine transcarbamylase (OTC) deficiency initially referred to gastroenterology for intermittent vomiting lasting a year and abnormal liver enzymes (AST 730 U/L [reference range 26–55 U/L]; ALT 1213 U/L [reference range 11–30 U/L]) without hepatomegaly. While the patient was hospitalized for liver biopsy, intermittent tremors of the upper extremities with varying severity were noted. The patient was presumed to have hyperammonemia secondary to acute liver failure and was discharged after 5 days; follow-up monitoring led to readmission 7 days later. A brain MRI showed nonspecific bilateral pericallosal and bifrontal white matter FLAIR hyperintensities. These findings raised suspicion for a metabolic disease and prompted a genetics consultation. After inconclusive biochemical testing and worsening clinical status, rapid whole genome sequencing results were obtained identifying a novel, *de novo*, likely pathogenic, variant c.608C > T (p.Ser203Phe) in the *OTC* gene. The patient was promptly started on an oral nitrogen scavenger, citrulline supplementation, and protein restriction. Ammonia and glutamine levels normalized within 1 month of treatment and have stayed within the goal ranges with continued tailoring of treatment. Her parents noted resolution of vomiting and improved mood stability. Liver enzymes normalized after 2 months of treatment. The tremor, identified as asterixis, improved and a repeat brain MRI 3 months after the initial imaging showed near-complete resolution of previous white matter hyperintensities.

1. Introduction

Urea cycle disorders (UCDs) are a group of rare inherited metabolic conditions caused by enzyme deficiency within the hepatic ammonia detoxification pathway [1]. Ornithine transcarbamylase (OTC) deficiency is the most frequently occurring UCD, with an estimated incidence of 1 in 56,500 live births in the United States [2]. OTC deficiency is transmitted as an X-linked trait and is known to yield a vastly heterogeneous phenotype [3]. Infants with complete enzyme deficiency, nearly always hemizygous males, commonly present in the newborn period with hyperammonemic coma and seizures, with associated risk of developmental disabilities and death [4,5]. Individuals with partial OTC deficiency, most commonly heterozygous females, can present with late-onset disease at any time outside of the neonatal period [3,6,7]. The relative rarity and variable manifestations of late-onset OTC deficiency contribute to delayed diagnosis, which furthers significant morbidity and mortality resulting from elevated ammonia levels. Presentation can include varying degrees of protein intolerance, cyclic vomiting, headache, lethargy, tremor, acute liver failure, and behavioral and neurologic abnormalities [1,3,8–11]. Prompt diagnosis and treatment are essential in preventing subsequent cognitive impairment, which is known to correlate with the duration and severity of hyperammonemia [12]. Brain computed tomography and magnetic resonance imaging (MRI) in survivors of hyperammonemic coma have demonstrated changes persisting months later, including ventriculomegaly with increased sulcal markings, low-density white matter lesions, and diffuse

atrophy with sparing of the cerebellum. Areas of low density in the white matter have been shown to be partially reversible with treatment [5,13]. Even seemingly asymptomatic patients with OTC deficiency demonstrate a wide range of cognitive deficits compared with a normative population [5,13], including nonverbal learning disabilities and weakness in executive function, associated with white matter or subcortical dysfunction, despite average IQ scores [14,15]{FormattingCitation}. Further, chronic mildly elevated ammonia levels can cause alterations of axonal development and changes in brain amino acid and neurotransmitter levels [5].

As heterozygous OTC deficiency is an ultra-rare condition with variable manifestations, management must be tailored to the individual patient. Due to the neurotoxic consequences of untreated hyperammonemia, a high level of clinical suspicion is warranted, even among less commonly reported symptoms of OTC deficiency, such as tremor or acute liver failure, especially when paired with cyclical vomiting. Here, we describe the diagnosis and care of a patient with late-onset partial OTC deficiency who had a year-long history of cyclical vomiting but no alarming growth or development abnormalities prior to diagnosis. Initiation of tailored disease management led to improvement of hepatic, gastrointestinal, neurologic, and behavioral manifestations.

2. Materials and methods

2.1. Medical review

This retrospective chart review was approved by the University of Utah Institutional Review Board as exempt (natural history of patients with metabolic disorders, IRB_00085855). Medical records and clinical parameters were reviewed by the treating clinical team.

2.2. Rapid whole genome sequencing

After proper consent, rapid whole genome sequencing was sent to Rady Children's Clinical Genome Center through Primary Children's Hospital's Center for Personalized Medicine inpatient program. Samples from the patient's mother and father were also included for analysis. Next-generation sequencing was completed. An average genomic coverage of at least 35× was completed for the proband genome. Edico DRAGEN pipeline was used for alignment and variant calling. The patient's test included single nucleotide variants, small deletions and insertions, larger deletions and duplications, the mitochondrial genome, and *SMN1* and *SMN2* copy number analysis.

2.3. Magnetic resonance imaging

Axial T2 FLAIR brain MRI was completed on a SIGNA™ General Electric scanner, with sedation, at the local children's hospital through multiplanar 3.0 T imaging system using the routine protocol, without intravenous gadolinium contrast.

3. Clinical report/case presentation

3.1. Presentation

A 19-month-old girl was seen by gastroenterology for intermittent vomiting that had begun 1 year prior, with frequency increasing to daily episodes shortly before her evaluation. She was noted to have abnormal liver enzymes (aspartate aminotransferase [AST] 730 U/L [reference range 26–55 U/L]; alanine transaminase [ALT] 1213 U/L [reference range 11–30 U/L]). There was no hepatomegaly. Further laboratory studies found increased prothrombin time (PT) at 18.3 s (reference range 12–15.2 s) and gamma-glutamyl transferase (GGT) at 52 U/L (reference range 6–16 U/L).

3.2. Evaluation

Given the unknown cause of liver dysfunction, a liver biopsy was performed and found mild portal inflammatory infiltrate predominantly composed of lymphocytes and rare eosinophils. There was spotty necrosis with scattered Councilman bodies. Hepatocytes appeared swollen with focal cytoplasmic clearing. While the patient was hospitalized for liver biopsy, intermittent tremors of varying severity were noted. Specifically, the patient displayed tremor of her upper extremities, evidenced by an inability to steady a spoon, resulting in dropped food. Plasma ammonia was increased, with levels ranging from 74 to 280 μmol/L (reference range 21–50 μmol/L); lactulose was started but then switched to rifaximin owing to diarrhea. Plasma amino acids showed elevated glutamine (peak 1088 μmol/L; reference range 380–680 μmol/L); slightly elevated alanine (588 μmol/L; reference range 160–530 μmol/L); and normal orotic acid (2.0 mmol/mol creatinine; reference range 0.7–5.1 mmol/mol creatinine), citrulline (nadir 23 μmol/L; reference range 10–45 μmol/L), and arginine (49 μmol/L; reference range 35–125 μmol/L). Methionine and tyrosine were elevated, suggesting hepatocellular dysfunction. Family history was noncontributory, including 4 healthy older siblings. She was discharged after 5 days under the assumption that her hyperammonemia was secondary to acute liver failure. Additional liver function and coagulation monitoring was scheduled, and samples for whole genome sequencing were sent.

The patient was readmitted 7 days later with elevated ammonia (224 μmol/L; reference range 21–50 μmol/L). A neurological examination identified low-amplitude, high-frequency asterixis during sustained arm extension that resolved when the arm was relaxed. A brain MRI showed nonspecific bilateral pericallosal and bifrontal white matter fluid-attenuated inversion recovery (FLAIR) hyperintensities (Fig. 1a). These abnormal, nonspecific findings raised suspicion for a metabolic disease.

3.3. Diagnosis

Diagnosis was challenged by worsening clinical status with no prior history of metabolic decompensation, no concerning indicators of poor growth and development, and biochemical testing suggestive but inconclusive of a UCD. Results from rapid whole genome sequencing were received and identified a *de novo*, likely pathogenic, variant c.608C > T (p.Ser203Phe, NM_000531.6) in the *OTC* gene. This variant has not been previously reported in the literature and is absent from the gnomAD population database, with multiple *in silico* tools predicting a deleterious effect on protein function.

3.4. Management

Once diagnosed with a UCD, the patient was immediately started on an oral nitrogen scavenger, citrulline supplementation (100 mg/kg/day) (Fig. 2c), and protein restriction at the recommended dietary allowance (1.0–1.2 g/kg, 11.5 g/day). Initially, sodium phenylbutyrate (900 mg TID) was prescribed; however, she refused it in all liquids. Glycerol phenylbutyrate was started at 1 mL TID (6 mL/m^2/day) and then, owing to slightly elevated ammonia and glutamine levels, increased to 1.3 mL TID (8 mL/m^2/day), which was maintained for over a year before being increased again to 2.0 mL TID (9.2 mL/m^2/day) (Fig. 2a).

Dietary management began by limiting protein to the recommended daily allowance by age at 11.5 g/day or 1.05 g/kg. Owing to low branched-chain amino acids (BCAA) (Fig. 2b), the patient's daily protein goal was then increased to 1.3 g/kg/day, with 50% from high biological value natural sources. Still, the patient's height and weight centiles stalled early in her treatment (at diagnosis: height at 14th percentile [87 cm], weight at 6th percentile [11.2 kg]). To increase caloric intake within the daily protein goal and without increasing intake volume, our team recommended increasing fat and sugar in acceptable foods. Common suggestions included butter, oils, fruits canned in syrup, nut
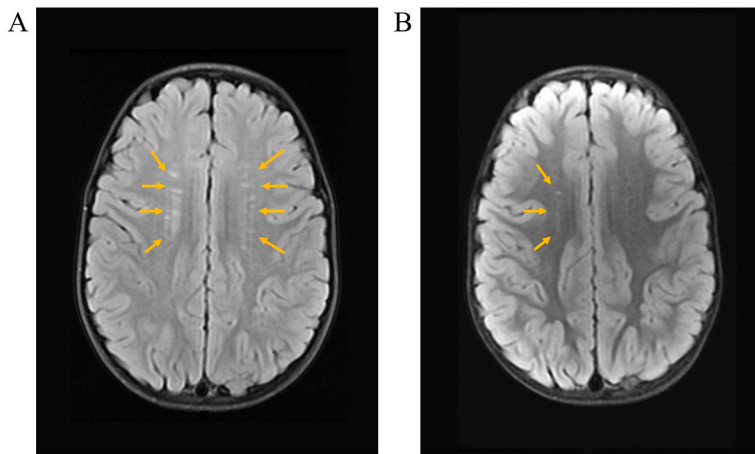
Fig. 1. Brain MRI pre- and post treatment. A. Brain MRI prior to treatment. Bilateral small linear pericallosal FLAIR hyperintensities and subtle patchy FLAIR hyperintensities in the bifrontal subcortical and deep white matter (yellow arrows). B. Brain MRI 3 months post treatment initiation. Previously seen linear pericallosal foci of FLAIR signal hyperintensity have markedly decreased since the prior examination (yellow arrows). There is otherwise no evidence for brain parenchymal signal abnormality. Midline and hypothalamic structures, pituitary, brainstem, and cerebellum all appear normal. Myelination is normal for age.

butters, and coconut flakes added to yogurt. The family was excellent at tracking intake using the MyFitnessPal application. Despite these efforts, achieving prescribed caloric intake within the daily protein goal continued to be a challenge. Duocal® was started at 45 g/day, providing 22% of the patient's total daily caloric intake.

3.5. Outcomes

No further metabolic decompensations occurred after UCD diagnosis. Ammonia and glutamine levels normalized within 1 month of treatment and have stayed within the goal ranges with continued tailoring of treatment (Fig. 2a). The patient's parents also noted resolution of vomiting and improved mood stability. Liver function tests essentially normalized after 2 months of treatment (AST 58 U/L [reference range 26–55 U/L]; ALT 26 U/L [reference range 11–30 U/L]). The tremor greatly improved but still occurs occasionally in the morning or with fine motor actions. Repeat brain MRI 3 months after the initial imaging showed near-complete resolution of previous white matter hyperintensities (Fig. 1b).

Growth remained slow but proportional (≈1 year post treatment: height at 31st percentile, weight at 11th percentile, body mass index at 8th percentile), with careful vigilance to achieve the caloric goal. Unfortunately, sufficient intake continues to be a challenge. Feeding therapy was recommended, and 0.5 mg/kg/day of cyproheptadine (2 mg/5 mL oral syrup) was added as an appetite stimulant to be given twice per day. Subjectively, the family reports improved intake. Two months after starting cyproheptadine, weight improved from the 11th percentile to the 34th percentile. Clinic visits have occurred every 8 months since diagnosis and include a detailed diet history, growth assessment, medication compliance history, and ongoing counseling of the treatment plan. Biochemical monitoring occurs typically every 2–3 months, depending on medication and diet changes. Neurocognitive testing, including Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV) and Behavior Assessment System for Children (BASC-3), was performed and demonstrated average or above average scores on all parameters tested.

4. Discussion

Late-onset forms of OTC deficiency are diagnostically challenging and can go unrecognized [6,14]. Hyperammonemia may be triggered by metabolic stressors such as infection, trauma, or protein consumption [1]. Before the UCD diagnosis, periods of vomiting in this patient were speculated to be due to a possible gluten intolerance. The family attempted to address this by aiming for a high-protein diet, which is the presumed trigger for the increased vomiting and crisis that ultimately led to medical intervention and diagnosis. Management of our patient's

UCD has resulted in metabolic stability and improvement of presenting symptoms, including tremor. The patient's tremor is thought to have been asterixis because it resolved as ammonia levels normalized. Her parents note occasional tremor, mostly in the morning, which may be due to fluctuations in fasting ammonia levels that have not been identified on laboratory results. Notably, asterixis is less prevalent in the pediatric population but has been previously reported in cases of acute hyperammonemia and in pediatric patients with OTC deficiency [16,17]. Tremor has also been reported in cases of OTC deficiency in adults, such as the case of a 34-year-old man who was misdiagnosed with focal epilepsy when he presented with sudden onset of abnormal behavior, lethargy, and fine tremor of his upper limbs. Continued symptoms, despite antiepileptic treatment, prompted biochemical workup indicating OTC deficiency [12,18].

Disease heterogeneity within this small patient population further contributes to diagnostic and management challenges for clinicians [19,20]. Age of onset and severity of OTC deficiency are influenced by the causative pathogenic variant, residual enzyme activity, physiological and environmental factors, as well as by the degree of X-linked inactivation of the normal allele in females [6,7,21,22]. Disease presentation can be different even within a single affected family, underscoring the importance of cascade testing [1]. In this case and others, orotic acid and citrulline were normal, which complicated an earlier conclusive biochemical diagnosis [23–25]. Rapid whole genome sequencing was recommended for this family in view of the patient's worsening clinical condition and indicated a *de novo* variant in the *OTC* gene. Even though the pathogenic variant appeared to be *de novo*, because of the possibility of germline mosaicism, the patient's older sister was then tested with a full hyperammonemia panel, which was negative. The patient's 3 older brothers, aged 5, 7, and 8 years, were not tested under the assumption that they would have presented clinically by this point.

Our patient continues to struggle with sufficient caloric intake, which is not uncommon with this condition. Aversion to foods containing high protein density and protein of high biological value (eg, animal protein) in particular has been reported in the literature [26]. Other reported behaviors include delayed introduction of solids, delayed self-feeding, and food tantrums [27].

Intellectual disabilities and chronic psychiatric problems have been described among heterozygous females with OTC deficiency [28–32]. Peak ammonia levels have been correlated with the occurrence and severity of intellectual disability. One study found that all patients with peak ammonia levels >350 μmol/L sustained severe brain damage or died, whereas patients with highest recorded ammonia levels <180 μmol/L were neurologically intact [28,33]. A study of 36 individuals with OTC deficiency showed that all patients with initial ammonia levels >300 μmol/L or maximum ammonia levels >480 μmol/L had

A

Ammonia   Glutamine

Week 20 ammonia value thought to be spurious

Ammonia (µmol/L) / Glutamine (µmol/L) vs Time Since Treatment Initiation (Weeks)

B

Isoleucine   Valine   Leucine

Peak BCAA reached at week 19

Branched-Chain Amino Acids (µmol/L) vs Time Since Treatment Initiation (Weeks)

C

Arginine   Citrulline   Methionine

Citrulline and Arginine (µmol/L) / Methionine (µmol/L) vs Time Since Treatment Initiation (Weeks)

Fig. 2. Laboratory findings pre- and post treatment. Data points outside of normal range are marked with triangles (▲above normal limit, ▼below normal limit). A. Ammonia (reference range 21–50 µmol/L) and glutamine (reference range 380–680 µmol/L) levels. B. BCAA. Isoleucine (reference range 30–120 µmol/L), leucine (reference range 60–180 µmol/L), and valine (reference range 120–320 µmol/L) levels. C. Citrulline (reference range 10–45 µmol/L), methionine (reference range 15–40 µmol/L), and arginine (reference range 35–125 µmol/L) levels.

intellectual disabilities [28,34]. Studies of mildly symptomatic or asymptomatic women have shown relative deficits in fine motor skills and nonverbal domains, executive functioning (especially working memory), and cognitive flexibility when cognitive load was relatively high [15,28,35]. In this patient's case, peak ammonia reached 280 µmol/L and neurocognitive testing, including WPPSI-IV for working memory and BASC-3 for behavioral assessment, demonstrated average or above average scores on all parameters tested. Given the subtle nature and heterogeneity of cognitive impacts in females with late-onset OTC deficiency, it is possible that additional testing during increased cognitive load or assessment of fine motor skills may reveal additional information, as previously reported [13]. Regular neurocognitive monitoring is recommended at 6, 8, 12, and 18 years of age.

Anatomically, reduced fractional anisotropy has been identified in

the frontal white matter tracts of individuals with symptomatic or asymptomatic partial OTC deficiency, with symptomatic patients displaying greater differences compared with age-matched controls [14,36]. T2-weighted FLAIR MRI has shown bilateral symmetric involvement in the cerebral cortex, particularly in the peri-insular and frontoparietal cortex [13]. In this case, bilateral pericallosal and bifrontal white matter hyperintensities were seen without cortical changes. Although patients with UCDs display a characteristic pattern of white matter injury, findings may not always be apparent using standard neuroimaging or symptom assessment, particularly in cases of partial enzyme deficiency [36]. For example, diffusion tensor imaging has been used to detect areas of white matter changes in patients with partial OTC deficiency that are not apparent on T2-weighted MRI [36]. Further, Gropman et al. used single-voxel ^{1}H-MRS to examine brain metabolism

in adults with OTC deficiency, including asymptomatic heterozygotes. Findings included a depletion of myoinositol in the frontal and parietal white matter, posterior cingulate grey matter, and thalamus. Levels of myoinositol were inversely correlated with disease severity, a measure reflecting total number of hyperammonemic episodes and coma. Elevated glutamine, an indicator of inadequately detoxified ammonia, was found in posterior cingulate and frontal grey matter, as well as in the parietal and frontal white matter of asymptomatic patients [22].

The relative rarity and extreme heterogeneity of heterozygous OTC deficiency lead to limited clinical experience at any given medical center [37,38]. Although our patient presented with symptoms of liver disease with secondary hyperammonemia and noncontributory family history, consultation with the genetics specialist helped lead to identification and treatment. Furthermore, long-term management decisions are greatly aided by collaborative multidisciplinary involvement, including a nurse practitioner, metabolic geneticist, registered dietitian, and genetic counselor. The quick resolution of MRI findings and improvements in symptoms after treatment initiation highlight the importance of early treatment and lifelong metabolic control.

5. Conclusion

Patients with undiagnosed UCDs can present for care to a variety of specialists owing to their broad presentation, which can include tremors, acute liver failure, confusion, ataxia, vomiting, and protein aversion. Importantly, such symptoms can occur even with mild elevations of blood ammonia and glutamine [14]. Further, females with OTC deficiency can present with acute liver failure without orotic aciduria during times of limited intake or fasting [9]. A high index of suspicion and a low threshold for measuring ammonia levels may minimize delay of diagnosis and treatment and reduce the risk of neurologic damage [12,37]. Once diagnosed, tailored multidisciplinary management is critical to ensure optimal outcomes. This case highlights the importance of identifying cyclic vomiting, acute liver failure, or tremor as potential indicators of a metabolic condition, as well as the potential for resolution of MRI findings and symptom improvement with tailored and prompt treatment.

Consent for publication

Written informed consent was obtained from the caregiver for publication of this case report and accompanying images.

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Declaration of Competing Interest

A. Andrews has received honoraria from Horizon Therapeutics plc, Recordati, and Biomarin Therapeutics for consulting/advisory activities. S. Roberts and L. D. Botto have no competing interests to disclose. No authors received compensation for involvement with this manuscript.

Data availability

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

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