Survival of a Male Infant with a Familial Xp11.4 Deletion Causing Ornithine Transcarbamylase Deficiency

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Abstract Ornithine transcarbamylase (OTC) deficiency is well known to cause severe neonatal hyperammonemia in males with absent enzyme activity. In families with large deletions of the X chromosome involving *OTC* and other contiguous genes, male infants appear to have an even more severe course. Notably, there are no published reports of these males surviving to liver transplant, even in cases where the diagnosis was known or suspected at birth. We describe two male newborns and their mother who all have a 1.5-Mb deletion of Xp11.4 encompassing the genes *TSPAN7*, *OTC*, and part of *RPGR*. The first child succumbed to his illness on his fourth day of life. His younger brother was diagnosed prenatally, and with early aggressive treatment, he survived the neonatal period. He suffered multiple life-threatening complications but stabilized and received a liver transplant at 7 months of age. This report demonstrates both the possibility of survival and the complications in caring for these patients.

Introduction

Ornithine transcarbamylase (OTC; OMIM 300461) is a proximal enzyme in the urea cycle which catalyzes the formation of citrulline from carbamoyl phosphate and ornithine. The gene *OTC* is located on the X chromosome at band Xp11.4. OTC deficiency (OMIM 311250) is the most common urea cycle disorder; in its classical form, it presents with severe neonatal hyperammonemia in affected males and has a mortality rate of 24% (Batshaw et al. 2014). This presentation typically occurs in males with null

mutations leading to absent enzyme activity in the liver (McCullough et al. 2000; Tuchman et al. 1989).

About 5–10% of cases of OTC deficiency are caused by deletions or complex rearrangements involving the *OTC* gene (Caldovic et al. 2015; Tuchman et al. 1998). Several families have been reported with large X chromosome deletions involving multiple genes, and the males described in these families seem to have a particularly poor prognosis, as described below in Table 1. Most affected males have died within days to weeks, and there are no published reports of these males receiving liver transplants. It has been proposed that the involvement of other genes in addition to *OTC* may complicate these patients' care (Balasubramaniam et al. 2010; Deardoff et al. 2008). The ratio of patients with deletions involving the *OTC* gene seems to be skewed heavily toward females, thought to be partially due to the diminished likelihood of survival in males (Shchelochkov et al. 2009).

Case 1

Patient 1 was born at 34 + 2 weeks' gestational age weighing 2,660 g. He was admitted to the neonatal intensive care unit (NICU) for prematurity following delivery and was started on standard total parenteral nutrition (TPN) and infant formula. On day 2 of life, he developed lethargy and seizures. He was loaded with phenobarbital and intubated. Labs were obtained which revealed an ammonia of 1,100 $\mu\text{mol/L}$. His IV fluids were immediately switched to dextrose 10% in water, and he was transferred to the children's hospital for further care. He was too hypotensive to safely initiate hemodialysis, so he was started on IV ammonia scavengers: sodium phenylacetate 250 mg/kg plus sodium benzoate 250 mg/kg and arginine 200 mg/kg, with one loading dose given over 2 h

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Table 1 Outcomes in male infants with OTC deficiency due to contiguous gene deletion syndromes

Reference	Deletion size, OMIM genes	Number of affected males	Positive family history?	Age at death
Gallant et al. (2015)	1.87-Mb deletion of <i>XK</i> , <i>CYBB</i> , <i>RPGR</i> , <i>OTC</i> , and <i>TSPAN7</i>	One	No	7 days old
Jain-Ghai et al. (2015)	0.74-Mb deletion of <i>RPGR</i> , <i>OTC</i> , and <i>TSPAN7</i>	One	Yes – older sister with known OTC deficiency	14 months old
Ono et al. (2010)	1-Mb deletion of <i>RPGR</i> , <i>OTC</i> , and <i>TSPAN7</i>	One	No	16 days old
Quental et al. (2009)	209-kb deletion of <i>OTC</i> and part of <i>TSPAN7</i>	One	No	Several days old
Deardoff et al. (2008)	3.9-Mb deletion of <i>XK</i> , <i>CYBB</i> , <i>RPGR</i> , and exons 1–8 of <i>OTC</i>	Two brothers	Yes – prenatal diagnosis made in second infant	5 days old (1st child) 12 weeks old (2nd child)
Arranz et al. (2007)	0.5-Mb deletion of <i>RPGR</i> , <i>OTC</i> , and <i>TSPAN7</i>	One	Yes – mother with known OTC deficiency	17 days old
Segues et al. (1995)	Both families had deletions of <i>CYBB</i> , <i>RPGR</i> , and <i>OTC</i>	Three: two brothers and one unrelated	Yes – one family had multiple male neonatal deaths	2 days old (both brothers) Several days old
Old et al. (1985)	Xp21 deletion on karyotype, spanning <i>NROB1</i> through <i>OTC</i>	One	No	36 h old

and a second dose given over the next 24 h. Labwork revealed glutamine 3,029 nmol/mL (reference range 316–1,020), citrulline 3 nmol/mL (reference range 9–38), and significantly elevated orotic acid and lactic acid in the urine. Despite treatment, his ammonia rose rapidly to 5,480 μ mol/L on day 3 of life. Treatment was stopped, and he died on day 4 of life. Molecular analysis later revealed deletion of the entire *OTC* gene.

The patient's mother presented for a clinic visit 2 months later. She gave a personal history of sleepiness after eating meat and difficulty in school. Biochemical testing was significant for ammonia 42 μ mol/L (reference range 11–35) and glutamine 1,060 nmol/mL (reference range 371–957). This information raised our suspicion that she may be a carrier of the deletion; however, confirmatory molecular testing was not done at that time due to insurance coverage. The maternal grandmother and great-grandmother both denied a history of symptoms, and there were no other males in the family who had died unexpectedly in infancy.

Genetic Testing

The patient's mother presented to prenatal diagnosis clinic when she was 25 weeks' pregnant with her second child. She opted for genetic testing via amniocentesis. Whole-genome array comparative genomic hybridization (CGH) was performed for both the fetus and the mother. The mother's report revealed a 1.5-Mb deletion at Xp11.4 and a 15-kb duplication at Xp22.33, reported as arr[hg19]

Xp22.33 (2,863,854–2,878,978)x3 and Xp11.4 (38,135,974–39,631,170)x1. The amniocentesis confirmed that the fetus was a male and carried both of these changes.

The Xp11.4 deletion encompasses *OTC* as well as three other genes: *TSPAN7* (transmembrane 4 superfamily member 2; OMIM 300096), *MID1IP1* (MID1 interacting protein 1; OMIM 300961), and part of *RPGR* (retinitis pigmentosa GTPase regulator; OMIM 312610). Both *RPGR* and *TSPAN7* have been linked to human diseases, whereas *MID1IP1* has not. Mutations in *RPGR* are a well-described cause of X-linked retinitis pigmentosa. Mutations in *TSPAN7*, also called *TM4SF2*, have been implicated in X-linked intellectual disability. The Xp22.33 duplication is classified as a variant of uncertain significance and contains part of the gene *ARSE* (arylsulfatase E; OMIM 300180). Mutations in *ARSE* can cause X-linked recessive chondrodysplasia punctata; the clinical significance of this duplication is unknown. The mother was monitored closely through the rest of her pregnancy and delivered at the academic medical center so that we could begin the baby's treatment immediately.

Case 2

Patient 2 was born at 38 + 3 weeks' gestational age weighing 3,283 g. Apgar scores were 8 and 9. He was immediately started on IV dextrose 10% in water, followed by IV ammonia scavengers started at 3 h of life. He was given a loading dose of sodium phenylacetate 250 mg/kg

plus sodium benzoate 250 mg/kg and arginine 200 mg/kg given over 2 h, followed by a maintenance dose given over 24 h. His initial ammonia level at 3 h of life was 176 $\mu\text{mol/L}$ and trended downward to a low of 67 $\mu\text{mol/L}$. He was started on continuous nasogastric tube feeds of Pro-Phree formula. The following day, his ammonia started to rise, and hemodialysis was started at 36 h of life. Ammonia peaked at 276 $\mu\text{mol/L}$ before coming down to 35 $\mu\text{mol/L}$ the following morning. On day 2, Cyclinex-1 formula was added to his feeds, providing 0.25 g/kg/day of protein in the form of essential amino acids. He was taken off of dialysis on day 4 of life and transitioned to enteral ammonia scavengers on day 6 of life: sodium phenylbutyrate 550 mg/kg/day and citrulline 200 mg/kg/day, each divided into four doses and given every 6 h. The amount of Cyclinex-1 in his feeds was increased, increasing protein intake to 0.5 g/kg/day on day 5 of life and to 1 g/kg/day on day 8 of life. His ammonia remained less than 50 $\mu\text{mol/L}$ until reaching 1 g/kg/day of protein, at which time it peaked at 124 $\mu\text{mol/L}$ and protein was temporarily decreased.

On day 13 of life, the baby developed sudden respiratory failure and went into cardiac arrest. He had had a normal exam and an ammonia level of 42 $\mu\text{mol/L}$ earlier that morning. He received several rounds of CPR with epinephrine before his pulse returned. He was intubated and transferred to the pediatric intensive care unit (PICU) for postarrest care. His ammonia jumped to 778 $\mu\text{mol/L}$ and lactate to >20 mmol/L. IV scavengers were restarted and the ammonia appropriately trended downward. He received infusions of epinephrine and norepinephrine for hypotension and cryoprecipitate and packed red blood cell transfusions for anemia and disseminated intravascular coagulopathy (DIC) and was started on a hypothermia protocol for neuroprotection. Blood cultures grew *Streptococcus mitis* in multiple bottles within 24 h, consistent with bacteremia.

Over the next few days, he slowly improved, and he was transferred out of the PICU for continued care when stable. He was transitioned back to enteral sodium phenylbutyrate and citrulline at the previously described dosing. A gastrostomy tube was placed, and he was kept on continuous drip feeds as we slowly increased his protein intake. Initially we increased the ratio of Cyclinex-1 to Pro-Phree formula to increase protein by 0.25 g/kg/day. Once he reached 1 g/kg/day of protein, we added ProSobee as a source of complete protein and continued to increase protein content by 0.25 g/kg/day until reaching 1.5 g/kg/day of protein, with total caloric goal within 110–120 kcal/kg/day. Ammonia levels remained less than 100 $\mu\text{mol/L}$ during this time. His course continued to be otherwise complicated. He developed swelling and duskeness in the left foot and then the right

hand and was found to have thrombi in the left superficial femoral vein and the right jugular vein, both sites of previous central venous catheters, and was started on enoxaparin. He received several blood transfusions for anemia. He developed episodes of respiratory distress and vital sign changes consistent with sepsis around 4–5 weeks of age; blood, urine, and CSF cultures were all negative at that time. We continued to monitor him closely and determined that he was stable for discharge around 2 months of age; he was tolerating feeds, and his ammonia levels held steady around 50–60 $\mu\text{mol/L}$.

Over the next 5 months, he was followed closely in outpatient clinics. He saw either his pediatrician or his geneticist weekly for a weight check and an ammonia level. He had five admissions for ammonia levels above 100 $\mu\text{mol/L}$, typically related to viral infections. Two of these admissions required PICU-level care: the first due to an ammonia level of 282 $\mu\text{mol/L}$ treated with IV scavengers and the second due to seizures, respiratory failure, and an ammonia level of 332 $\mu\text{mol/L}$ treated with hemodialysis. During the other three admissions, he was treated conservatively with IV dextrose 10% and a brief reduction in protein intake, and he recovered quickly. Between hospitalizations, he tolerated 1.5 g/kg/day of protein in his feeds and maintained a normal weight. He was continued on enoxaparin by hematology, and workup revealed that he is heterozygous for the prothrombin 20210G>A mutation.

He was listed for liver transplant at 6 months of age, and he received a liver transplant at 7 months of age. The surgery was complicated by occlusive blood clots in the hepatic artery and portal vein which were removed in the operating room. He has been admitted several times posttransplant for respiratory illnesses and central line infections, though none have required PICU-level care. He continues to receive citrulline 200 mg/kg/day.

Patient 2 is currently 16 months old. He is behind in meeting developmental milestones but is making consistent progress. He is sitting unassisted and rolling over and working on putting pressure on his feet when held in a standing position. He transfers objects between his hands, waves, and drinks thickened liquids through a sippy cup. He is interactive, babbles, and says “hi” and “dada.” His weight has never been below the second percentile. He appears to have some difficulty fixing visually as well as persistent nystagmus. Dilated eye exam does not show any retinal anomalies yet; electroretinography (ERG) may be considered in the future. His mother was advised to follow a protein-restricted diet and receives citrulline supplementation due to intermittently elevated glutamine levels,

maximum of 1,150 nmol/mL (reference range 371–957). She has poor vision and endorses worsening vision at night. She is currently pregnant with an unaffected female.

Discussion

Deletions at Xp11.4 involving *OTC* and surrounding genes are expected to produce the most severe form of *OTC* deficiency. We saw this in our personal experience in taking care of this family, and this is reflected in prior literature which describes survival of weeks to months in most affected males. Males with absence of the entire gene are unable to make any amount of even truncated or minimally active enzyme. It has been previously proposed that the deletion of additional genes adds complexity (Deardoff et al. 2008), and we agree with this theory. *RPGR* is a protein involved in ciliary function and is expressed in the retina, respiratory tract epithelium, cochlea, and multiple other cell lines. Absence of this gene may have contributed to patient 2's multiple respiratory infections. *TSPAN7* is less well-described, and it is difficult to predict how this deletion is contributing to his developmental delays and hypotonia, especially in the setting of a previous cardiac arrest and multiple episodes of moderate hyperammonemia.

We attribute patient 2's survival, while his older brother had died, to prenatal diagnosis allowing for immediate treatment following delivery. His deletion was also smaller in size than some of the other male neonates who died, and notably did not contain *CYBB*, responsible for X-linked chronic granulomatous disease and thought to contribute to complications in other patients (Deardoff et al. 2008). Characterization of the deletion on cytogenetic testing allowed for us to have a realistic estimate of prognosis and to be prepared for a severe course. We recommend molecular testing in all those with a biochemical diagnosis of *OTC* deficiency and prenatal testing for at-risk fetuses for this reason. Another benefit of prenatal diagnosis is that it would allow for perinatal treatment. A recent paper describes the administration of IV sodium phenylacetate/sodium benzoate and arginine to mothers during labor and delivery of male infants with severe defects in the *OTC* gene, and both infants had good neurodevelopmental outcomes (Wilnai et al. 2018). We agree that this is a reasonable approach in severe cases and may portend the best chance for survival.

Patient 2's long-term management was even more conservative than what we typically do for males with *OTC* deficiency. He was discharged from the NICU with both a gastrostomy tube and a tunneled central line for emergency management. Feeds were initially advanced slowly: we increased protein content by 0.25 g/kg/day, and we kept him on continuous rather than bolus feeds during that time to avoid giving him a large protein load at

any one time. We also insisted that he was seen by a physician for an exam, weight check, and ammonia level test weekly. We admitted him for observation whenever his ammonia level rose above 100 μ mol/L. He was ultimately listed for liver transplant by age 6 months. We would recommend a similar time frame in other males with severe neonatal disease to allow for the best chance of survival and a good neurocognitive outcome.

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Synopsis

OTC deficiency resulting from contiguous Xp11.4 gene deletion is typically fatal in male neonates, but with early and conservative management, survival to transplant is possible.

General Information

Author Contributions

- Molly McPherson: participated in patient care, researched pertinent literature, designed the outline of the report, wrote initial draft of the work, made corrections and revisions, approved final draft
- Melissa Lah: primary attending caring for the patients described, researched pertinent literature, involved in the design and planning of the paper, consulted during writing, revised the work, approved final draft

Conflicts of Interest

- Molly McPherson declares that she has no conflict of interest.
- Melissa Lah declares that she has no conflict of interest.

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Ethics Approval

This paper is exempt from IRB approval, as it is a case report and therefore does not qualify as human subject research.

Consent

The family gave their consent for us to write this case report. There is no identifying information included in this article. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study. Proof that informed consent was obtained can be provided on request.

Animal Rights

This article does not contain any studies with animal subjects performed by any of the authors.

References

- Arranz JA, Madrigal I, Ruidor E, Armengol L, Mila M (2007) Complete deletion of ornithine transcarbamylase gene confirmed by CGH array of X chromosome. *J Inherit Metab Dis* 30:813
- Balasubramaniam S, Rudduck C, Bennetts B, Peters G, Wilcken B, Ellaway C (2010) Contiguous gene deletion syndrome in a female with ornithine transcarbamylase deficiency. *Mol Genet Metab* 99:34–41
- Batshaw M, Tuchman M, Summar M, Seminara J (2014) A longitudinal study of urea cycle disorders. *Mol Genet Metab* 113:127–130
- Caldovic L, Abdikarim I, Narain S, Tuchman M, Morizono H (2015) Genotype-phenotype correlations in ornithine transcarbamylase deficiency: a mutation update. *J Genet Genomics* 42(5):181–194
- Deardoff MA, Gaddipati H, Kaplan P et al (2008) Complex management of a patient with a contiguous gene deletion involving ornithine transcarbamylase: a role for detailed molecular analysis in complex presentations of classical diseases. *Mol Genet Metab* 94:498–502
- Gallant NM, Gui D, Lassman C et al (2015) Novel liver findings in ornithine transcarbamylase deficiency due to Xp11.4-p21.1 microdeletion. *Gene* 556:249–253
- Jain-Ghai S, Skinner S, Hartley J, Fox S, Buhas D, Rockman-Greenberg C, Chan A (2015) Contiguous gene deletion of chromosome Xp in three families encompassing OTC, RPGR, and TSPAN 7 genes. *J Rare Disord* 1:1
- McCullough BA, Yudkoff M, Batshaw ML, Wilson JM, Raper SE, Tuchman M (2000) Genotype spectrum of ornithine transcarbamylase deficiency: correlation with the clinical and biochemical phenotype. *Am J Med Genet* 93:313–319
- Old JM, Purvis-Smith S, Wilcken B et al (1985) Prenatal exclusion of ornithine transcarbamylase deficiency by direct gene analysis. *Lancet* 325(8420):73–75
- Ono M, Tsuda J, Mouri Y, Arai J, Arinami T, Noguchi E (2010) Contiguous Xp11.4 gene deletion leading to ornithine transcarbamylase deficiency detected by high-density single-nucleotide array. *Clin Pediatr Endocrinol* 19(2):25–30
- Quental R, Azevedo L, Rubio V, Diogo L, Amorim A (2009) Molecular mechanisms underlying large genomic deletions in ornithine transcarbamylase (OTC) gene. *Clin Genet* 75:457–464
- Segues B, Rozet JM, Gilbert B et al (1995) Apparent segregation of null alleles ascribed to deletions of the ornithine transcarbamylase gene in congenital hyperammonemia. *Prenat Diagn* 15:757–761
- Shchelochkov OA, Li FY, Geraghty MT et al (2009) High-frequency deletions and variable rearrangements at the ornithine transcarbamylase (OTC) locus by oligonucleotide array CGH. *Mol Genet Metab* 96:97–105
- Tuchman M, Tsai MY, Holzknecht RA, Brusilow SW (1989) Carbamyl phosphate synthetase and ornithine transcarbamylase activities in enzyme-deficiency human liver measured by radiochromatography and correlated with outcome. *Pediatr Res* 26(1):77–82
- Tuchman M, Morizono H, Rajagopal BS, Plante RJ, Allewell NM (1998) The biochemical and molecular spectrum of ornithine transcarbamylase deficiency. *J Inherit Metab Dis* 21(Suppl 1):40–58
- Wilnai Y, Blumenfeld YJ, Cusmano K et al (2018) Prenatal treatment of ornithine transcarbamylase deficiency. *Mol Genet Metab* 123(3):297–300