U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Lichter-Konecki U, Caldovic L, Morizono H, et al. Ornithine Transcarbamylase Deficiency. 2013 Aug 29 [Updated 2022 May 26]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Ornithine Transcarbamylase Deficiency

Synonyms: Ornithine Carbamoyltransferase Deficiency, OTC Deficiency

Uta Lichter-Konecki, MD, PhD,[1] Ljubica Caldovic, PhD,[2] Hiroki Morizono, PhD,[2] Kara Simpson, MS, CGC,[3] Nicholas Ah Mew, MD,[3] and Erin MacLeod, PhD, RD, LD[3]

Created: August 29, 2013; Revised: May 26, 2022.

Summary

Clinical characteristics

Ornithine transcarbamylase (OTC) deficiency can occur as a severe neonatal-onset disease in males (but rarely in females) and as a post-neonatal-onset (also known as "late-onset" or partial deficiency) disease in males and females.

- Males with severe neonatal-onset OTC deficiency are asymptomatic at birth but become symptomatic from hyperammonemia in the first week of life, most often on day two to three of life, and are usually catastrophically ill by the time they come to medical attention. After successful treatment of neonatal hyperammonemic coma these infants can easily become hyperammonemic again despite appropriate treatment; they typically require liver transplant to improve quality of life.
- Males and heterozygous females with post-neonatal-onset (partial) OTC deficiency can present from infancy to later childhood, adolescence, or adulthood.

No matter how mild the disease, a hyperammonemic crisis can be precipitated by stressors and become a life-threatening event at any age and in any situation in life. For all individuals with OTC deficiency, typical neuropsychological complications include developmental delay, learning disabilities, intellectual disability, attention-deficit/hyperactivity disorder, and executive function deficits.

Diagnosis/testing

The diagnosis of OTC deficiency is established in a **male proband** with suggestive clinical and laboratory findings and at least ONE of the following:

- A hemizygous pathogenic variant in *OTC* by molecular genetic testing
- A markedly abnormal increase of orotic acid excretion (≥20 umol/mmol creatinine) in a random urine collection or after an allopurinol challenge test, along with a past medical history of biochemical features

Author Affiliations: 1 Division of Genetic & Genomic Medicine UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; Email: uta.lichterkonecki@chp.edu. 2 Center for Genetic Medicine Research, Children's National Hospital, Washington, DC. 3 Division of Genetics & Metabolism Children's National Hospital, Washington, DC.

consistent with OTC deficiency (e.g., elevated ammonia, elevated glutamine and low-to-normal citrulline), as well as absence of biochemical or DNA evidence suggestive of another inborn error of metabolism
- Decreased OTC enzyme activity in liver

The diagnosis of OTC deficiency is usually established in a **female proband** with the suggestive clinical and laboratory findings and with at least ONE of the following:

- A heterozygous pathogenic variant in OTC by molecular genetic testing
- A markedly abnormal increase of orotic acid excretion (≥20 umol/mmol creatinine) in a random urine collection or after an allopurinol challenge test, along with a past medical history of biochemical features consistent with OTC deficiency (e.g., elevated ammonia, elevated glutamine and low-to-normal citrulline), as well as absence of biochemical or DNA evidence suggestive of another inborn error of metabolism

Measurement of OTC enzyme activity in liver is not a reliable means of diagnosis in females.

Management

Treatment of manifestations: Treatment is best provided by a metabolic physician / biochemical geneticist and specialist metabolic dietitian; treatment of hyperammonemic coma should be provided by a team coordinated by a metabolic specialist in a tertiary care center experienced in the management of OTC deficiency. The mainstays of treatment of the acute phase are rapid lowering of the plasma ammonia level to ≤200 µmol/L (if necessary, with renal replacement therapy); use of ammonia scavenger treatment to allow excretion of excess nitrogen via alternative pathways; reversal of catabolism; and reducing the risk of neurologic damage. The goals of long-term treatment are to promote growth and development and to prevent hyperammonemic episodes. In severe, neonatal-onset urea cycle disorders, liver transplantation is typically performed by age six months to prevent further hyperammonemic crises and neurodevelopmental deterioration. In females and males with partial OTC deficiency, liver transplant is typically considered in those who have frequent hyperammonemic episodes. Complications of OTC deficiency, including developmental delay and intellectual disability, are treated according to the standard of care for these conditions while monitoring for signs of liver disease.

Surveillance: At the start of therapy, routine measurement of plasma ammonia and plasma amino acids every two weeks with gradual extension of the intervals between testing. Laboratory analysis for vitamin and mineral deficiencies annually or as indicated by the metabolic dietician. Assess liver function (depending on symptoms) every three to six months or more often when previously abnormal. Perform neuropsychological testing at the time of expected significant developmental milestones.

Agents/circumstances to avoid: Valproate, haloperidol, fasting, systemic corticosteroids, physical and psychological stress.

Evaluation of relatives at risk: If the pathogenic variant in the family is known and if prenatal testing has not been performed, it is appropriate to perform molecular genetic testing on at-risk newborns (males and females) as soon after birth as possible so that the appropriate treatment or surveillance (for those with the family-specific pathogenic variant) can be promptly established. If the pathogenic variant in the family is NOT known, biochemical analysis (plasma amino acid analysis, ammonia level), an allopurinol challenge test (in older individuals), and/or OTC enzyme activity measurement in liver (males only) can be performed. Preventive measures should be instituted at birth and maintained until the diagnosis has been ruled out.

Pregnancy management: Heterozygous females are at risk of becoming catabolic during pregnancy and especially in the postpartum period. Those who are symptomatic need to be treated throughout pregnancy according to

pre-pregnancy protocols adapted for needs during pregnancy; those who are asymptomatic need to avoid catabolism in the peripartum and postpartum periods and should be treated accordingly.

Genetic counseling

OTC deficiency is inherited in an X-linked manner. If the mother of a proband has an *OTC* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may or may not develop clinical findings related to the disorder. Males with OTC deficiency transmit the pathogenic variant to all of their daughters and none of their sons. Molecular genetic heterozygote testing for at-risk female relatives and prenatal and preimplantation genetic testing for OTC deficiency are possible if the *OTC* pathogenic variant has been identified in the family.

Diagnosis

Diagnostic criteria for ornithine transcarbamylase (OTC) deficiency have been set forth by the Longitudinal Study of Urea Cycle Disorders (NCT00237315) conducted by the Urea Cycle Disorders Consortium of the Rare Disease Clinical Research Network [Tuchman et al 2008].

OTC deficiency is universally screened for in eight US states and territories, and likely to be detected and reported in three additional states [Vasquez-Loarte et al 2020], although infants with this disorder may present with severe illness before newborn screening results are available. For information about conditions included in newborn screening panels, search by US state/territory on the department of health website.

Scenario 1: Abnormal newborn screening (NBS) result

Currently, NBS for OTC deficiency in the US is primarily based on quantification of the analyte citrulline on dried blood spots, either alone or as a ratio with other biochemical markers, which may help to improve the accuracy of the test [Merritt et al 2018]. Messina et al [2021] recommend the use of the glutamine-to-glutamate ratio to distinguish individuals with a urea cycle disorder from healthy individuals.

Citrulline values outside the range established by the screening laboratory are considered positive and require follow-up biochemical testing, which may include plasma ammonia, plasma amino acid profile, urine organic acid profile, and urine orotic acid quantification.

If follow-up biochemical testing supports the likelihood of OTC deficiency, additional testing is required to establish the diagnosis (see Establishing the Diagnosis).

Current NBS methods of screening for OTC deficiency vary greatly in sensitivity and specificity; as a result, medical intervention in response to receipt of an abnormal NBS result is also variable. However, in any scenario, an individual with an out-of-range NBS with evidence of unexplained altered neurologic status or poor feeding requires immediate medical attention and rapid testing of plasma ammonia. Individuals with an elevated ammonia may require dietary protein restriction, alternative pathway medications, and citrulline/arginine and/or renal replacement therapy.

Scenario 2: Symptomatic individual with atypical findings or untreated neonatal-onset OTC deficiency

A symptomatic individual may have either atypical findings associated with later-onset OTC deficiency or untreated neonatal-onset OTC deficiency resulting from any of the following:

- Infant symptomatic prior to the results of NBS
- NBS not performed

- False negative NBS result
- Caregivers not adherent to recommended treatment following a positive NBS result

Supportive (but nonspecific) clinical findings and preliminary laboratory findings can include the following.

Clinical Findings

Term newborn male

- Normal at birth
- Development of reduced oral intake with poor latching and suck
- Acute neonatal encephalopathy (lethargy, somnolence) with hyperventilation and low body temperature

Child, adolescent, or adult (male or female)

- Encephalopathic or psychotic episodes (i.e., episodes of altered mental status), including erratic behavior, clouded consciousness, and delirium
- A recent stress that could be regarded as a precipitating event (e.g., significant change in diet, significant medical problem including illness or accident, delivery, systemic use of corticosteroids or valproate)
- History of recurrent vomiting
- Migraine headaches
- Reye-like syndrome
- Seizures
- History of true protein avoidance (avoidance of not only red meat but also of milk, eggs, other high-protein foods)
- Unexplained "cerebral palsy"

Preliminary Laboratory Findings

Elevated plasma ammonia concentration. During acute encephalopathy, ammonia levels are typically above 200 µmol/L and often above 500-1,000 µmol/L.

Note: The plasma ammonia concentration at which an individual becomes symptomatic varies but is generally above 100 µmol/L; in Stage 2 coma [Posner et al 2019] the plasma concentration may be between 200 and 400 µmol/L; and in Stage 3 to 4 coma, above 500 µmol/L. These levels are approximations and a wider range of elevated ammonia levels may be observed.

Abnormal plasma amino acid analysis. A high glutamine concentration (generally >800 µmol/L) and a (very) low citrulline concentration (e.g., single digits, with or without elevated plasma ammonia concentration) is suggestive of a proximal urea cycle defect, such as N-acetylglutamate synthetase (NAGS) deficiency, carbamoyl phosphate synthetase I (CPSI) deficiency, or OTC deficiency.

Elevated orotic acid on urine organic acid (UOA) analysis. Orotic acid concentration is elevated in a random urine sample (≥20 µmol/mmol creatinine if the laboratory provides quantitative values [Tuchman et al 2008]).

Blood gas findings as related to clinical state

- Respiratory alkalosis in an encephalopathic individual who is hyperventilating is pathognomonic of urea cycle disorders [Häberle et al 2012].
- In a terminally ill individual who has been in a coma for days, acidosis may develop.

Unexpectedly low blood urea nitrogen (BUN). A low BUN, or a low-normal BUN under circumstances where BUN should be elevated (e.g., dehydration), may suggest reduced urea production consistent with an underlying urea cycle disorder.

Note: Because alterations of these metabolites individually are not specific for OTC deficiency, follow-up testing is required to establish or rule out the diagnosis of OTC deficiency (see Establishing the Diagnosis).

Establishing the Diagnosis

Male proband. The diagnosis of OTC deficiency **is established** in a male proband with suggestive clinical and laboratory findings and at least ONE of the following:

- A hemizygous pathogenic (or likely pathogenic) variant in *OTC* by molecular genetic testing (See Table 1.)
- A markedly abnormal increase of orotic acid excretion (≥20 umol/mmol creatinine) in a random urine collection or after an allopurinol challenge test (see Allopurinol Challenge Test), along with a past medical history of biochemical features consistent with OTC deficiency (e.g., elevated ammonia, elevated glutamine, and low-to-normal citrulline), as well as the absence of biochemical or DNA evidence suggestive of another inborn error of metabolism
- Decreased OTC enzyme activity in liver (See OTC Enzyme Activity in Liver.)

Female proband. The diagnosis of OTC deficiency **is usually established** in a female proband with the suggestive clinical and laboratory findings and at least ONE of the following:

- A heterozygous pathogenic (or likely pathogenic) variant in *OTC* identified by molecular genetic testing (see Table 1)
- A markedly abnormal increase of orotic acid excretion in a random urine sample or after an allopurinol challenge test (see Allopurinol Challenge Test) with or without a family history of OTC deficiency

Note: (1) Liver biopsy is not recommended to establish the diagnosis in females, due to the possibility of false negative results (see OTC Enzyme Activity in Liver). (2) (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *OTC* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular Genetic Testing Approaches

Scenario 1: Abnormal newborn screening (NBS) result. When NBS results and other laboratory findings suggest the diagnosis of OTC deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *OTC* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications. (2) Deep intronic *OTC* pathogenic variants (c.540+265G>A, c.867+1126A>G, and c.1005+1091C>G) have been reported [Engel et al 2008, Kumar et al 2021]; sequencing methodologies that can detect splice donor and acceptor variants should be considered.

- **A multigene panel** that includes *OTC* and other genes of interest (see Differential Diagnosis) is likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a

custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (5) Sequencing methodologies that can detect splice donor and acceptor variants should be included.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Scenario 2: A symptomatic individual who has atypical findings associated with later-onset OTC deficiency or untreated neonatal-onset OTC deficiency (resulting from NBS not performed, illness presenting before NBS results are reported, or false negative NBS result). When the diagnosis of OTC deficiency has not been considered, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Ornithine Transcarbamylase (OTC) Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2, 3] Identified by Method
OTC	Sequence analysis [4]	~80% [5, 6, 7]
	Gene-targeted deletion/duplication analysis [8]	5%-10% [5, 6]
Unknown [9]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. A number of additional individuals with contiguous gene deletions (not included in these calculations) have been reported (see Genetically Related Disorders).
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. In individuals with biochemically confirmed OTC deficiency (i.e., elevated urinary orotate, a positive allopurinol test, reduced OTC enzyme activity in liver biopsy, or a combination of these findings) [Caldovic et al 2015]
6. Data derived from Caldovic et al [2015] and publicly available databases of OTC sequence variants (ClinVar and LOVD)
7. Disease-causing variants in OTC regulatory regions [Jang et al 2018] and deep intronic regions [Kumar et al 2021] have been identified in individuals with biochemically confirmed OTC deficiency.
8. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described in Deardorff et al [2008], Di Stefano et al [2015]) and Gallant et al [2015]) may not be detected by these methods.
9. When sequence analysis was followed by deletion/duplication analysis, a molecular defect was detected in 80%-90% of affected individuals with biochemically confirmed OTC deficiency [Tuchman et al 2008, Shchelochkov et al 2009, Caldovic et al 2015]. Other loci associated with an OTC deficiency phenotype have not been identified. However, disease-causing variants located in the deep intronic region or regulator regions have been subsequently identified in individuals with negative results on previous genetic testing [Jang et al 2018, Kumar et al 2021].

Allopurinol Challenge Test

In males and females suspected of having partial OTC deficiency who have normal molecular genetic testing and normal or borderline urinary orotic acid concentration under normal conditions, an allopurinol challenge test should be performed. A markedly abnormal increase of orotic acid excretion ≥20 µmol/mmol creatinine after administering allopurinol is diagnostic [Tuchman et al 2008, Häberle et al 2012]. The test consists of taking a

single dose of allopurinol and immediately thereafter starting to collect urine during four six-hour periods for a total of 24 hours. Aliquots from each six-hour period are analyzed for orotic acid concentration.

OTC Enzyme Activity in Liver

Previously the gold standard for diagnosing OTC deficiency [Tuchman et al 1989], analysis of OTC enzyme activity in liver requires a liver biopsy, and thus is currently used only when an *OTC* pathogenic variant is not found in a male with a high clinical suspicion of OTC deficiency or if an allopurinol challenge is inconclusive.

- **Males.** In severely affected males, OTC enzyme activity is typically less than 20% of the control value. In milder OTC deficiency, enzymatic activity may be as high as 30% of the control value.
- **Females.** Results of enzyme activity analysis in a liver biopsy may not represent the true total OTC activity in a heterozygous female because of the X-chromosome inactivation pattern (previously known as lyonization) in the biopsy specimen (see Clinical Description, Heterozygous Females).

Clinical Characteristics

Clinical Description

Ornithine transcarbamylase (OTC) deficiency can occur as a severe neonatal-onset disease in males and as a post-neonatal-onset (also known as "late-onset" or partial deficiency) disease in males and females. Neonatal-onset disease in females is rare.

While neonatal-onset OTC deficiency accounted for approximately 60% of all OTC deficiency in the older literature, in its first eight years the longitudinal study of the Urea Cycle Disorders Consortium (UCDC) of the NICHD-supported Rare Disease Clinical Research Network (RDCRN) had enrolled a substantially smaller proportion of individuals with neonatal-onset OTC deficiency than with post-neonatal-onset OTC deficiency. Of 260 individuals who had symptomatic OTC deficiency, 47 (18%) had neonatal-onset disease (42 males and 5 females) and 213 (82%) had post-neonatal onset disease (154 females and 59 males) [Batshaw et al 2014]. This discrepancy may be the result of an ascertainment bias both in the older literature (in which undiagnosed individuals with milder symptoms are presumably underrepresented) as well as in the natural history study data, where individuals with very severe neonatal-onset OTC deficiency who die before study enrollment are underrepresented.

Neonatal-Onset OTC Deficiency

Males with severe OTC deficiency are asymptomatic at birth, but become symptomatic from hyperammonemia in the first week of life (most often on day 2-3) with poor suck, reduced intake, and hypotonia, followed by lethargy progressing to somnolence and coma. They hyperventilate, and may have subclinical/electroencephalographic seizures. By the time neonates with OTC deficiency come to medical attention they typically are catastrophically ill with low body temperature (hypothermia), severe encephalopathy, and respiratory alkalosis.

When clinical and laboratory findings support the diagnosis of a urea cycle disorder, rescue therapy is begun immediately (see Management, Treatment of Manifestations).

The prognosis of a newborn in hyperammonemic coma depends on the duration of elevated ammonia level, not the height of the ammonia level or the presence/absence of seizures [Msall et al 1984].

After successful rescue from neonatal hyperammonemic coma, infants with severe neonatal-onset OTC deficiency can easily become hyperammonemic again despite a low-protein diet and treatment with an oral ammonia scavenger. Even on maximum ammonia scavenger therapy a neonate with severe OTC deficiency may

only tolerate 1.5 g/kg/day of protein (the minimum amount needed to grow), and growth may be along the third percentile for length.

After neonatal rescue therapy, a child with severe neonatal-onset disease can also experience a "honeymoon" period in which the protein tolerance is so high, due to rapid growth, that the child is metabolically stable for some months before experiencing frequent hyperammonemic episodes.

Typically, a liver transplant is required to prevent life-threatening hyperammonemic episodes, avert the effect of recurrent hyperammonemia on the brain, and improve quality of life.

The overall outcome depends on the severity of brain damage during the initial hyperammonemic crisis and during subsequent hyperammonemic crises, as well as on the success of long-term treatment in maintaining metabolic balance and addressing complications of the disease.

Post-Neonatal-Onset (Partial) OTC Deficiency

Hemizygous males and heterozygous females with partial OTC deficiency can present from infancy to later childhood, adolescence, or adulthood [Ahrens et al 1996, Ausems et al 1997, McCullough et al 2000]. Often, they first become symptomatic in infancy when switched from breast milk to formula or whole milk (breast milk contains less protein than infant formulas manufactured in the US). Infants may show episodic vomiting, lethargy, irritability, failure to thrive, and developmental delay. They show true protein avoidance, which can be documented by a detailed assessment of their dietary intake. If forced to eat foods high in protein, they may become symptomatic.

When children, adolescents, or adults with post-neonatal-onset disease become encephalopathic they may reach Stage 2 coma [Posner et al 2019] with erratic behavior, combativeness, and delirium (e.g., failure to recognize family members around them, unintelligible speech). They may come to medical attention if these behavior abnormalities lead to an emergency medical or psychiatric evaluation.

A stressor can cause an individual with partial OTC deficiency to become symptomatic at any age. In general, the milder the disease, the later the onset and the stronger the stressor required to precipitate symptoms.

Adults with very mild disease have become symptomatic after crush injury, following surgery [Chiong et al 2007, Hu et al 2007], when on a high-protein diet (e.g., Atkins diet [Ben-Ari et al 2010]), during the postpartum period (see Pregnancy Management), during cancer therapy, after prolonged fasting [Marcus et al 2008], when treated with high-dose systemic corticosteroids [Lipskind et al 2011], or after a febrile illness [Panlaqui et al 2008]. Treatment with valproate [Arn et al 1990, Honeycutt et al 1992, Leão 1995, Oechsner et al 1998, Thakur et al 2006] or haloperidol [Rubenstein et al 1990] has been associated with hyperammonemic crises in persons with OTC deficiency.

Heterozygous Females

The phenotype of a heterozygous female can range from asymptomatic to significant symptoms with recurrent hyperammonemia and neurologic compromise depending on favorable vs nonfavorable X-chromosome inactivation. The amount of OTC enzyme activity in the liver of a heterozygous female depends on the pattern of X-chromosome inactivation in her liver [Yorifuji et al 1998]. Thus, a heterozygous female can manifest symptoms of OTC deficiency if X-chromosome inactivation in her liver cells is skewed such that the X chromosome with the pathogenic *OTC* variant is active in more hepatocytes than the X chromosome with the normal *OTC* allele [McCullough et al 2000, Yamaguchi et al 2006].

Previously, approximately 15% of heterozygous females were thought to become symptomatic during their lifetime [Batshaw et al 1986]. Many heterozygous females exhibit mild symptoms, self-restrict protein intake, and are never diagnosed as being symptomatic. The diagnosis may only be revealed when a more severely

affected child is born, prompting molecular genetic testing in the mother. Thus, the percent of symptomatic females may be higher than previously thought. When a male has post-neonatal-onset disease, the risk for symptoms in heterozygous females in his family is much lower than in families in which a male has neonatal-onset severe disease [McCullough et al 2000].

Recent work suggests that some heterozygous females may be paucisymptomatic: while they may never have hyperammonemia or present with altered mental status, they may in fact have differences in cognitive capability, such as deficits in executive functioning and motor capability [Sprouse et al 2014, Anderson et al 2020].

Complications of Neonatal-Onset and Post-Neonatal-Onset Disease

Neuropsychological. Typical neuropsychological complications include: developmental delay; learning disabilities; intellectual disability; attention-deficit/hyperactivity disorder (ADHD); deficits in executive function, working memory, visuo-motor integration, and visual perception [Waisbren et al 2015, Buerger et al 2019]; and emotional and behavioral problems [Waisbren et al 2015]. Scores in cognitive domains were not independent; in fact, in one study they were found to closely correlate with intelligence scores [Waisbren et al 2016, Buerger et al 2019]. Intelligence scores also correlated with peak ammonia level and with number of hyperammonemic episodes [Buerger et al 2019, Posset et al 2019] which are also indicators of the severity of disease. Subjects with neonatal-onset disease have higher peak ammonia levels and lower scores on intellectual tests than those with post-neonatal-onset disease [Buerger et al 2019].

- Attention-deficit/hyperactivity disorder and executive function deficits can greatly affect (school) performance even when intellectual ability is in the normal range [Krivitzky et al 2009].
- Approximately half of school-age children with OTC deficiency were reported by their parents as having "internalizing problems" on the Child Behavior Checklist, including being withdrawn, depressed, and/or anxious, or having somatic complaints.
- Impulsivity and immaturity can lead to inappropriate behavior and problems in peer relationships especially for preteens and adolescents.
- Self-reported difficulties in social relationships, as well as anxiety and depression, have also been described in adults with OTC deficiency, including those who are "asymptomatic" [Waisbren et al 2016]. This may lead to problems in interpersonal relationships and frequent job changes.

Even heterozygous females who have never had biochemical evidence of hyperammonemia and therefore were thought to be asymptomatic, on further scrutiny have been shown to have mild cognitive impairments and deficits in executive function and fine motor tasks even when exhibiting normal IQ on neuropsychological testing. These deficits may be apparent only when these individuals are cognitively challenged [Sprouse et al 2014, Anderson et al 2020].

Neurologic. During hyperammonemic coma, electroencephalogram (EEG) shows low voltage with slow waves and may include a burst suppression pattern in which the duration of the interburst interval correlates with the height of the ammonia levels Seizures are common during hyperammonemic coma and may only be detected on EEG. They do not indicate a poor prognosis. However, persons with urea cycle disorders may also be prone to having seizures independent of hyperammonemic episodes [Zecavati et al 2008, Wiwattanadittakul et al 2018].

Neuroimaging studies show hyperintense signal in the peri-insular region; in severe disease, a progression of restricted diffusion from the peri-insular region to first frontal, then parietal, temporal, and ultimately the occipital lobes may be apparent. In extremis, restricted diffusion was also observed in the thalami [Bireley et al 2012]. Neonates who survived after prolonged coma may have ventriculomegaly, diffuse brain atrophy (not affecting the cerebellum), low-density white matter defects, and injury to the bilateral lentiform nuclei and the deep sulci of the insular and perirolandic regions [Yamanouchi et al 2002, Takanashi et al 2003].

Although metabolic strokes (involving the caudate and putamen and resulting in extrapyramidal syndromes) have been described in OTC deficiency and CPS1 deficiency [Keegan et al 2003, Takanashi et al 2003], they are not typical for urea cycle disorders.

Neuropathology in those children who died after prolonged coma included cortical atrophy with ventriculomegaly, prominent cortical neuronal loss, and spongiform changes at the gray-white interface and in the basal ganglia and thalamus [Dolman et al 1988].

Better neurologic outcomes are seen in infants with neonatal-onset disease who were treated soon after the onset of coma.

Gastrointestinal

- During a hyperammonemic crisis liver enzymes are typically moderately elevated and PT and PTT may be prolonged.
- Severe elevations of liver enzyme and coagulopathy consistent with acute liver failure are more typically seen in individuals with OTC deficiency after the neonatal period [Mustafa & Clarke 2006].
- Prolonged PT and PTT as well as mildly increased direct bilirubin are also observed in persons with a urea cycle disorder during long-term follow up when ammonia levels are normal and the individual is asymptomatic.
- Symptomatic individuals with urea cycle disorders are at risk of developing progressive growth impairment over time. Weight is not affected. Growth impairment has recently been shown to be possibly associated with reduced or borderline plasma branched-chain amino acid concentrations. Liver transplant appears to have a beneficial effect on linear growth [Posset et al 2020].

Liver cell carcinoma has been described in a few older individuals (e.g., in a symptomatic heterozygous female age 66 years [Wilson et al 2012]), suggesting that OTC deficiency may be associated with an increased risk for liver cancer. However, data are insufficient to support such a conclusion.

Genotype-Phenotype Correlations

While the following genotype-phenotype correlations do in general exist, it is well established that significant medical problems (e.g., neonatal sepsis or other causes of newborn catabolism) can cause a severe, early presentation in an individual with an *OTC* pathogenic variant typically associated with mild disease, making it appear that the pathogenic variant is associated with severe neonatal-onset disease. Likewise, individuals with pathogenic variants associated with mild, late-onset disease (including females heterozygous for a milder pathogenic variant and with skewed X-chromosome inactivation) may experience severe life-threatening hyperammonemia at any time in their life when they are exposed to strong environmental stressors.

In general:

- Pathogenic missense variants that affect residues essential for catalysis, substrate binding, and folding severely impair or completely abolish OTC enzyme activity and result in neonatal-onset disease in hemizygous males [Caldovic et al 2015].
- Pathogenic nonsense variants, insertions, and deletions that cause frameshift of the open reading frame and single-nucleotide variants in canonic intronic splice sites result in complete absence of functional OTC and neonatal-onset disease in hemizygous males [Caldovic et al 2015].
- Females heterozygous for a pathogenic variant can develop symptoms of OTC deficiency later in life if X-chromosome inactivation in their hepatocytes is skewed in favor of the X chromosome with the pathogenic variant [McCullough et al 2000, Caldovic et al 2015]. In most individuals, OTC deficiency manifests in females heterozygous for pathogenic variants that cause severe neonatal-onset disease in

hemizygous males. However, symptoms of OTC deficency were reported in females heterozygous for a hypomorphic *OTC* pathogenic variant [Luksan et al 2010, Pinner et al 2010].
- Amino acid substitutions that decrease OTC enzyme activity or stability may result in a post-neonatal-onset phenotype in hemizygous males [Caldovic et al 2015] and heterozygous females [Pinner et al 2010].

Penetrance

Penetrance for OTC deficiency is complete in hemizygous males.

The following observations, which may erroneously be interpreted as evidence of incomplete penetrance, are in fact explained by X-chromosome inactivation and environmental factors:

- Heterozygous females who become symptomatic (the result of skewed X-chromosome inactivation)
- Hemizygous males with the same mild pathogenic variant, only some of whom develop symptoms (the result of differences in environmental stressors)

Prevalence

OTC deficiency is thought to be the most common urea cycle defect (see Urea Cycle Disorders Overview).

An early estimated prevalence of OTC deficiency was 1:14,000 live births [Brusilow & Maestri 1996]. However, other surveys of incidence of OTC deficiency in Italy, Finland, and New South Wales, Australia, have revealed a lower prevalence of 1:70,000, 1:62,000, and 1:77,000 live births, respectively [Dionisi-Vici et al 2002, Keskinen et al 2008, Balasubramaniam et al 2010]. Given that males and females with partial OTC deficiency may manifest symptoms at any age, prevalence numbers are biased toward the earliest and most severe presentations.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this GeneReview are known to be associated with germline intragenic *OTC* pathogenic variants.

Contiguous gene deletions involving *OTC*. The chromosomal region that includes *OTC* is a disease-gene-rich region; therefore, individuals with a large deletion that includes *OTC* may have two life-threatening diseases – X-linked chronic granulomatous disease and OTC deficiency – as well as additional diseases with significant morbidity: retinitis pigmentosa, McLeod neuroacanthocytosis syndrome, Duchenne muscular dystrophy, and oculo-facio-cardio-dental syndrome (OMIM 300166) [Deardorff et al 2008, Di Stefano et al 2015, Gallant et al 2015]. The breakpoints of deletions and rearrangements differ in each individual and thus do NOT lead to a recurrent microdeletion syndrome.

Differential Diagnosis

Newborn male with hyperammonemia

- Neonatal-onset urea cycle disorders (UCDs) – N-acetylglutamate synthase (NAGS) deficiency, severe carbamyl phosphate synthetase I (CPSI) deficiency, argininosuccinate synthetase (ASS) deficiency (citrullinemia type I), and argininosuccinate lyase (ASL) deficiency (argininosuccinic aciduria) – show the same clinical symptoms at presentation as severe OTC deficiency (see Urea Cycle Disorders Overview).
- Fulminant hepatitis / fulminant liver failure due to neonatal herpes simplex virus infection can cause severe neonatal hyperammonemia.

Respiratory alkalosis is a typical finding in UCD and its presence clearly distinguishes a UCD from an organic acidemia presenting with hyperammonemia and ketoacidosis. However, when a child who has been in a coma for days becomes terminally ill, acidosis rather than respiratory alkalosis may be present.

Child, adolescent, or adult (male or female) with hyperammonemia

- Later-onset of NAGS deficiency, CPSI deficiency, ASS deficiency (citrullinemia type I), and ASL deficiency (argininosuccinic aciduria) show the same clinical symptoms at presentation as milder OTC deficiency (see Urea Cycle Disorders Overview).
- Citrin deficiency and hyperornithinemia-hyperammonemia-homocitrullinuria syndrome – both associated with urea cycle substrate transport deficiency – may also show the same clinical symptoms at presentation as milder OTC deficiency.
- Causes of generalized liver dysfunction (e.g., severe infection, multiorgan failure due to hypoxic ischemic or other injury, portal vein thrombosis) and decreased liver synthetic function (e.g., liver failure due to drug [acetaminophen] toxicity, vascular insult) resulting in hyperammonemia should also be considered in the differential diagnosis.

Management

Clinical management practices have been described in publications of the UCD Conference Group [2001] and by Häberle et al [2012].

When OTC deficiency is suspected during the diagnostic evaluation (e.g., due to hyperammonemia, elevated glutamine, low-to-normal citrulline, and/or orotic aciduria), metabolic treatment should be initiated immediately.

Development and evaluation of treatment plans, training and education of affected individuals and their families, and avoidance of side effects of dietary treatment (i.e., malnutrition, growth failure) require a multidisciplinary approach including multiple subspecialists, with oversight and expertise from a specialized metabolic center.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with OTC deficiency, the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis of Ornithine Transcarbamylase (OTC) Deficiency

Evaluation	Comment
Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian [1]	• Transfer to specialist center w/experience in mgmt of inherited metabolic diseases (strongly recommended). • Consider short hospitalization at a center of expertise for inherited metabolic conditions to provide caregivers w/detailed education (natural history, maintenance & emergency treatment, prognosis, & risks for acute encephalopathic crises).
Laboratory testing	• Plasma ammonia concentration • Plasma amino acid analysis • Laboratory values that reflect nutritional status (e.g., vitamin D level, ferritin, vitamin B_{12}) • Liver function tests (liver enzymes, bilirubin, albumin) • PT/PTT & fibrinogen • Renal function tests (BUN, creatinine)
Developmental assessment	Depending on age, referral for a developmental, neuropsychological &/or psychological eval
Neurologist	For mgmt of seizures, if present

Table 2. continued from previous page.

Evaluation	Comment
Consultation w/psychologist &/or social worker	To ensure understanding of the diagnosis & assess parental / affected person's coping skills & resources
Genetic counseling by genetics professionals [2]	To inform affected persons & families re nature, MOI, & implications of OTC deficiency in order to facilitate medical & personal decision making

MOI = mode of inheritance
1. After a new diagnosis of OTC deficiency in a child, the closest hospital and local pediatrician should also be informed.
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Treatment is best provided by a metabolic physician / biochemical geneticist and a metabolic dietitian.

In the **acute phase**, the mainstays of treatment are the following.

Table 3. Acute Inpatient Treatment of Manifestations in Individuals with Ornithine Transcarbamylase (OTC) Deficiency

Manifestation/ Concern	Treatment	Considerations/Other
Hyper-ammonemia	**Rapid lowering of plasma ammonia.** Level should be ≤200 µmol/L (even if diagnosis is not yet established) due to severely toxic effect of ↑ ammonia level on the brain. Fastest method for ↓ ammonia level: renal replacement therapy: • In the pediatric population CKRT (specifically CVVHD) is recommended for hyperammonemia. High-dose CKRT w/blood flow rate of 30-50 mL/min recommended for initial treatment of those w/ammonia level >1,000 µmol/L Intermittent HD recommended in those who require rapid ammonia clearance due to fast deterioration & signs of cerebral edema Regular CKRT can follow hemodialysis or high-dose CKRT for stabilization when blood ammonia level is <200 µmol/L [Raina et al 2020]. • An older patient can receive intermittent HD or high-dose CKRT & can also be switched to a CKRT for stabilization.	Note: Peritoneal dialysis has much lower clearance of ammonia; it is not recommended when hemodialysis is widely available.
	Ammonia scavenger therapy • Treatment utilizes an alternative pathway for excretion of excess nitrogen (see Table 4). • Nitrogen scavenger therapy is available as an IV infusion of a mixture of sodium phenylacetate & sodium benzoate for acute mgmt & as an oral preparation of phenylbutyrate or sodium benzoate for long-term maintenance therapy. • Citrulline is supplemented at 170 mg/kg/day or 3.8 g/m^2/day (enterally).	

Table 3. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Increased catabolism	**Reversal of catabolism** • Total energy provided should be 100%-120% estimated needs to ensure catabolism reversal. • Provide calories from glucose & fat; resume protein intake (in the form of natural protein & an essential amino acid mix) ≤24 hrs after protein intake was discontinued. • Use of a high glucose infusion rate supported by continuous insulin infusion to maintain high set point normoglycemia (140-180 mg/dL) as needed. Goal for a newborn in crisis: to deliver ≥100 kcal/kg/day, mostly from glucose & fat.	• Persons on hemodialysis or hemofiltration need adequate nutrition to overcome catabolism, as nutrients are removed by these procedures. • Restart protein intake after 24 hrs, as deficiency of essential amino acids → protein breakdown & uncontrolled nitrogen release. • Daily to 2x-wkly quantitative plasma amino acid analysis should guide nutritional therapy. Goal: to keep essential amino acid levels in normal range.
Risk for neurologic damage	• Intubated & sedated persons may not show clinical signs of seizures, which are prevalent in acute hyperammonemia. EEG surveillance is thus highly recommended to allow EEG detection & subsequent treatment of seizures. Note: Phenobarbital is removed by dialysis & valproic acid is contraindicated in urea cycle disorders. • No other interventions (besides ↓ ammonia level) have proven efficacy for neuroprotection in hyperammonemic coma due to a urea cycle disorder or other conditions.	

CKRT = continuous kidney replacement therapy; CVVHD = high-dose continuous venovenous hemodialysis; EEG = electroencephalogram/electroencephalographic; HD = hemodialysis; IV = intravenous

Table 4. Intravenous (IV) Ammonia Scavenger Therapy Protocol Used in OTC Deficiency and Carbamyl Phosphate Synthetase I (CPSI) Deficiency

Body Weight	Components of Infusion Solution [1]		Loading [2] and Maintenance Dose [3,4]		
	Sodium phenylacetate & sodium benzoate [5]	Arginine HCl injection, 10%	Sodium phenylacetate	Sodium benzoate	Arginine HCl [6]
<25 kg	Undiluted: 2.5 mL/kg (contains 250 mg of each) Dilute 1:10 [4]	2.0 mL/kg at 100 mg/mL	250 mg/kg	250 mg/kg	200 mg/kg

Table 4. continued from previous page.

Body Weight	Components of Infusion Solution [1]		Loading [2] and Maintenance Dose [3,4]		
	Sodium phenylacetate & sodium benzoate [5]	Arginine HCl injection, 10%	Sodium phenylacetate	Sodium benzoate	Arginine HCl [6]
≥25 kg	Undiluted: 55 mL/m^2 (contains 5,500 mg of each) Dilute 1:10 [4]	40 mL/m^2 at 100 mg/mL	5,500 mg/m^2	5,500 mg/m^2	4,000 mg/m^2

Batshaw et al [2001]

1. **Be aware of high sodium content of drug: 30.5 mg of sodium per mL of undiluted product.**

2. Loading dose given over 90 to 120 minutes

3. Maintenance dose given over 24 hours

4. If an affected person has symptomatic hyperammonemia and has not received a full dose of ammonia scavenger in the previous 12 hours, the affected person should first receive an IV bolus directly followed by maintenance infusion.

5. Sodium phenylacetate / sodium benzoate must be diluted with sterile 10% dextrose before administration. The typical dilution is 1:10 for a final concentration of 10 mg/mL.

6. Arginine infusion not to exceed 150 mg/kg/h

Long-Term Treatment

Long-term treatment (including restriction of protein intake, use of nitrogen scavengers, and liver transplantation) is aimed at promoting growth and development and preventing hyperammonemic episodes.

Table 5. Long-Term Treatment of Manifestations in Individuals with Ornithine Transcarbamylase (OTC) Deficiency

Manifestation/ Concern	Treatment	Considerations/Other
Risk for hyperammonemia	**Protein restriction** • Protein intake restricted to RDA for protein or amt necessary to allow growth & prevent catabolism depending on severity of disease (See Table 6.) • Use of an essential amino acid medical food may be needed to maintain normal essential amino acid levels in those on significant protein restriction, even those w/partial OTC deficiency. • Diet should also provide vitamins, minerals, & trace elements to meet recommended needs, either in a calorie-rich protein-free formula or in the form of supplements.	• When protein intake is too low, protein catabolism can cause chronic hyperammonemia just as high protein intake does. • Gastrostomy tube feedings help avoid malnutrition in persons who: self-restrict protein intake, object to taste of essential amino acid formulas used to treat urea cycle disorders, &/or cannot consume adequate calories for growth. • Careful monitoring of plasma amino acid concentrations is needed to detect essential amino acid deficiencies. • High glutamine concentrations are interpreted as evidence of poor metabolic control & harbinger of hyperammonemia.
	Nitrogen scavengers provide alternative routes for nitrogen disposal & allow more protein intake [Batshaw et al 2001, Berry & Steiner 2001]. • Long-term ammonia scavenger treatment may consist of 450-600 mg/kg/day sodium phenylbutyrate & 170 mg/kg/day L-citrulline in children <25 kg; & 9.9-13.0 g/m^2/day sodium phenylbutyrate & 3.8 g/m^2/day L-citrulline in persons weighing ≥25 kg. Treatment should be accompanied by an appropriate low-protein diet. • Note: (1) Citrulline offers the advantage over arginine of incorporating aspartate into the pathway thus	• Although it removes only half as much nitrogen as phenylbutyrate, oral sodium benzoate (vs phenylbutyrate) is the ammonia scavenger of choice in many European countries & Australia because it is felt to have fewer side effects. • Phenylbutyrate causes menstrual dysfunction & body odor, & appears to deplete branched chain amino acids; sodium benzoate causes hypokalemia due to ↑ renal losses of potassium [Scaglia et al 2004, Häberle et al 2012].

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
	pulling an addl nitrogen molecule into the urea cycle. (2) If sodium benzoate is being used instead of sodium phenylbutyrate recommended dose is ≤250 mg/kg/day in children <25 kg (max: 12 g/day) [Häberle et al 2012]. • Glycerol phenylbutyrate (same mechanism as sodium phenylbutyrate & significantly more palatable) is another treatment option. Dose: 5-12.3g/m^2/day.	
Risk for life-threatening hyper-ammonemic crisis	Liver transplantation. See Prevention of Primary Manifestations.	
DD/ID [1]	See Developmental Delay / Intellectual Disability Management Issues.	
Seizure disorder	Treatment w/ASM as directed by experienced neurologist. Note: Valproic acid is contraindicated for treatment of seizures in urea cycle disorders, as it can cause a hyperammonemic crisis.	Education of parents/caregivers [2]

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; RDA = required daily allowance
1. Brain damage from an initial hyperammonemic coma, frequent hyperammonemic episodes with moderate-to-severe hyperammonemia, and chronic hyperammonemia can lead to learning disabilities and intellectual disability.
2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Table 6. Recommended Protein Intake for Individuals with Ornithine Transcarbamylase (OTC) Deficiency

Age (yrs)	Total Protein (g/kg/day) [1]	Protein from Essential Amino Acid Medical Food (g/kg/day) [2]	Natural Protein (g/kg/day)
0-1	1.2-2.2	0.6-1.1	0.6-1.1
1-7	1.0-1.2	0.6-0.7	0.4-0.5
7-19	0.7-1.4	0.4-0.7	0.3-0.7
>19	0.5-1.0	0.3-0.5	0.2-0.5

1. Individuals with asymptomatic or mild presentations may not require supplementation with essential amino acid medical foods if biochemical markers (plasma ammonia, glutamine, and essential amino acids) remain normal on a diet that meets or exceeds the RDA for protein.
2. Essential amino acid supplementation, when needed, should provide 30%-50% of total protein.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability. OTC deficiency is a diagnosis of compassionate allowance per the Social Security Administration.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder (ADHD), when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Prevention of Primary Manifestations

Medical and Dietary Prevention of Hyperammonemia

In neonatal-onset OTC deficiency diagnosed prenatally, prospective intravenous (IV) treatment with ammonia scavengers at maintenance dose within a few hours of birth (before the ammonia level rises) can prevent a hyperammonemic crisis and coma.

Later on, prevention of hyperammonemic episodes is focused on restriction of dietary protein through low-protein diet and administration of oral nitrogen-scavenging drugs balanced with supplementation of essential amino acids (see Treatment of Manifestations).

Liver Transplantation

No matter how mild OTC deficiency appears to be, stressors can at any age precipitate a hyperammonemic crisis that becomes life threatening. The fear of such an event, along with the restrictions on daily living imposed by the dietary therapy, prompt many families to consider liver transplantation even if the disease has been manageable up to that point with diet and medication.

In severe, neonatal-onset urea cycle disorders, liver transplantation remains the most effective means of preventing further hyperammonemic crises and neurodevelopmental deterioration [Gerstein et al 2020]. It is typically performed by age six months.

- Females and males with partial OTC deficiency can, after diagnosis, be maintained on a low-protein diet and oral ammonia scavenger treatment for life; the need for liver transplant depends on the individual and

is typically considered when an affected individual is unstable and has frequent hyperammonemic episodes.

- Living related donor livers are often considered for partial liver transplantation in individuals with a urea cycle disorder. The suitability of a heterozygous mother as a donor has been discussed [Wong 2012]. According to Wakiya et al [2012], enzyme activity measurement in a liver biopsy sample is useful in determining the suitability of a heterozygous mother as a donor. However, this approach is problematic for several reasons:
  - A liver biopsy sample may not adequately represent the enzyme activity in the liver of a heterozygous female. It can thus not be known whether a transplanted lobe contains enough enzyme activity to prevent symptoms in the recipient.
  - After partial hepatectomy the liver of the donor mother will regenerate. Since the X-chromosome inactivation pattern in the regenerated liver in the donor cannot be predicted, it is also impossible to predict whether the overall enzyme activity in the donor mother will remain adequate to prevent symptoms in her.
  - Likewise, the lobe that is transplanted into the recipient child will undergo changes after transplantation; thus, the enzyme activity in the donated lobe cannot be accurately determined at the time of transplantation, and additional post-transplantation changes could make the final enzyme activity in the recipient even more unpredictable.

Surveillance

Table 7. Recommended Surveillance for Individuals with Ornithine Transcarbamylase (OTC) Deficiency

System/Concern	Evaluation	Frequency
Hyperammonemia	Plasma ammonia concentration	• In severe cases at least every 2 wks at start of therapy (or more often depending on stability of affected person). • Slowly extend to every month, every 2 mos, every 3 mos, then every 6 mos, as possible.
Potential for essential amino acid deficiencies (due to protein restriction)	Plasma amino acid analysis	• At least every 2 wks at start of therapy (or more often depending on stability of affected person). • Slowly extend to every month, every 2 mos, every 3 mos, then every 4 mos, as possible.
Vitamin & mineral deficiencies	Lab analysis of specific vitamins &/or minerals of concern (i.e., ferritin, 25 hydroxy vitamin D)	Annually or as indicated by dietary eval by metabolic dietitian
Severe elevations of liver enzymes & coagulopathy	Liver function tests (ALT/AST, PT/PTT, INR)	Every 3-6 mos or more often if they have been previously ↑
DD/ID	Neuropsychological testing	To be administered when significant developmental milestones are expected to be achieved (e.g., at 6-9 mos & 18 mos in infants, 4 & 8 yrs in children, 15 & 18 yrs & beyond in adolescents & adults)

DD/ID = developmental delay / intellectual disability

Agents/Circumstances to Avoid

Avoid the following:

- Valproate
- Haloperidol

- Fasting
- Stress, especially physical stress; potentially also psychological stress
- Systemic corticosteroids because they cause catabolism, which can trigger a hyperammonemic crisis

  Note: If systemic corticosteroids need to be administered as a life-saving therapy (e.g., during a severe asthma attack or an anaphylactic reaction), a metabolic specialist should be consulted; at the same time, preemptive measures (e.g., increased calorie intake) should be instituted to prevent catabolism.

Evaluation of Relatives at Risk

For Early Diagnosis and Treatment

Prenatal testing of a fetus at risk. Molecular genetic prenatal testing of both male and female fetuses at risk may be performed via amniocentesis or chorionic villus sampling to allow prompt institution of appropriate treatment/surveillance before a metabolic crisis occurs after birth (see the description of prospective treatment in Prevention of Primary Manifestations).

Newborn sib. Evaluations of a newborn sib include:

- Molecular genetic testing if the *OTC* pathogenic variant in the family is known;
- Biochemical analysis (plasma amino acid analysis, ammonia level), an allopurinol challenge test (in older individuals). If diagnosis remains unclear after the newborn period OTC enzyme activity measurement in infant liver (males only) may be considered if the *OTC* pathogenic variant in the family could not be identified.

In general, for children with neonatal-onset disease, such testing cannot be performed rapidly enough to prevent a metabolic crisis. Therefore, preventive measures at birth should be instituted until such a time as the diagnosis can be ruled out; see description of prospective treatment in Prevention of Primary Manifestations.

For Liver Donation

Any family member who is a potential liver donor should undergo molecular genetic testing to clarify the family member's genetic status so that those who do not have the *OTC* pathogenic variant are evaluated further. Note: The suitability of a heterozygous mother as a donor has been discussed; however, this approach is problematic for several reasons (see Prevention of Primary Manifestations, Liver Transplantation).

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Heterozygous females are at risk of becoming catabolic during pregnancy and especially in the postpartum period [Torkzaban et al 2019].

A symptomatic heterozygous female needs to be treated throughout pregnancy according to her pre-pregnancy protocol with adaptation for her needs during pregnancy. Care should be given to the increased protein needs in pregnancy and adjustment to intact versus essential amino acid supplementation may be needed. In the peripartum and immediate postpartum periods proactive measures to prevent catabolism include, for example, administration of a 10% dextrose solution with appropriate electrolytes at 1.5 times maintenance and addition of intralipids as needed to meet caloric requirements during these periods.

In an asymptomatic female known to be heterozygous, precautions should be taken in the peripartum and postpartum period to prevent catabolism; in addition, measurement of ammonia levels and administration of

dextrose should be considered as heterozygous females have become symptomatic for the first time in the peripartum period.

Therapies Under Investigation

For treatment of OTC deficiency, Clinical Trials NCT02991144 and NCT04442347 currently under way include gene delivery with either an adeno-associated virus (AAV) or lipid nanoparticle mRNA. AAV8-based OTC delivery has been tried in a small cohort, with some individuals showing marked improvement while others appear to show very little change. A long-term follow-up clinical trial (NCT03636438) is in place to better understand the stability of gene delivery. Several groups are planning AAV-based clinical trials (NCT05092685), although at the time of writing, recruiting has not yet started.

Other strategies to reduce blood ammonia levels include attempts to modulate the microbiome (NCT03933410); however, in another study in which Synb1020 (an engineered *E coli* Nissle strain) was introduced, ammonia levels were not sufficiently reduced to warrant continuation (NCT03447730). While microbiome modulation appears promising, the complexity of the gut microbiome introduces challenges that will need to be overcome.

In preclinical studies, genome editing holds great promise, with data showing in vivo correction of specific OTC alterations in the spf-ash mouse, as well as development of a "universal" vector which introduces an expression cassette with promoter and OTC cDNA into the OTC locus containing the mutation [Yang et al 2016, Wang et al 2020]. This latter approach nearly eliminates the need to develop multiple guide RNAs and to meet regulatory approval for each of the *OTC* pathogenic variants to be corrected. As with other gene-editing approaches, not just limited to CRISPr/Cas9, efficiency of gene conversion, concerns for off-target editing, availability of protospacer motifs, and the potential for apoptosis in response to double-stranded DNA breaks are all issues that will need to be addressed. An ex-vivo approach in which *OTC* gene correction was performed in hepatocytes from an individual with OTC deficiency that then were implanted into a mouse model showed nearly 60% correction and no off-target editing by deep sequencing [Zabulica et al 2021].

Animal models of OTC deficiency had been until recently limited to several mouse strains; however, the ease of genome editing will allow greater control and tailoring of animal models. Of particular note is the recent development of an OTC-deficient pig [Enosawa et al 2021]. Therapies such as cell transplantation as well as other surgical and medical interventions will be more readily explored in this large animal model.

For the most current information see ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe. (ClinicalTrials.gov also lists some European studies.)

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Ornithine transcarbamylase (OTC) deficiency is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of a male with an *OTC* pathogenic variant will not have OTC deficiency nor will he be hemizygous for the *OTC* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case):
  - The mother may be a heterozygote.
  - The mother may have somatic/germline mosaicism. Germline mosaicism has been reported in OTC deficiency [Komaki et al 1997, Bowling et al 1999].
  - The affected male may have a *de novo* pathogenic variant (in which case the mother is not a heterozygote). Rüegger et al [2014] reported a spontaneous mutation rate of 26% in male probands.
- If a molecular diagnosis has been established in the proband, molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

Parents of a female proband

- A female who is heterozygous for an *OTC* pathogenic variant may have inherited the pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*. Rüegger et al [2014] reported a spontaneous mutation rate of 67% in female probands.

  Note: Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.

- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. If a molecular diagnosis has been established in the proband, molecular genetic testing of the mother (and subsequently the father) can determine if the pathogenic variant was inherited.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *OTC* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected;
  - Females who inherit the pathogenic variant may or may not develop clinical findings related to the disorder. The phenotype of a heterozygous female can range from asymptomatic to significant symptoms with recurrent hyperammonemia and neurologic compromise depending on favorable vs non-favorable X-chromosome inactivation (see Clinical Description, Heterozygous Females).
- If the proband represents a simplex case and has an *OTC* pathogenic variant that cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal germline mosaicism (the general background risk of germline mosaicism is estimated to be 3%-4%).

Sibs of a female proband. The risk to sibs depends on the genetic status of the parents:

- If the mother of the proband has an *OTC* pathogenic variant, the chance of transmitting it in each pregnancy is 50% (see **Sibs of a male proband**).
- If the father of a female proband has an *OTC* pathogenic variant, he will transmit it to all of his daughters and none of his sons.
- If the proband represents a simplex case and has an *OTC* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a male proband

- Males with neonatal-onset OTC deficiency used to die before reproductive age or be too debilitated to reproduce. However, prospective treatment as soon as the child is born and improved rescue therapy followed by liver transplant now allow some such males to reach reproductive age and reproduce.
- Males with late-onset, moderate-to-mild partial OTC deficiency transmit the *OTC* pathogenic variant to:
  - All of their daughters, who will be heterozygotes and may or may not develop clinical symptoms related to the disorder (see Clinical Description, Heterozygous Females);
  - None of their sons.

Offspring of a female proband. Women with an *OTC* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child:

- Males who inherit the pathogenic variant will be affected.
- Females who inherit the pathogenic variant will be heterozygotes and may or may not develop clinical symptoms related to the disorder (see Clinical Description, Heterozygous Females).

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *OTC* pathogenic variant, members of the parent's family may be at risk.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Molecular genetic testing to identify female heterozygotes is possible if the OTC deficiency-causing pathogenic variant has been identified in the family.

Note: The phenotype of females who are heterozygous for an *OTC* pathogenic variant can range from asymptomatic to significant symptoms with recurrent hyperammonemia and neurologic compromise (see Clinical Description, Heterozygous Females).

If the OTC deficiency-causing pathogenic variant in the family cannot be identified, an allopurinol challenge may help clarify the genetic status of female family members (see Establishing the Diagnosis).

Related Genetic Counseling Issues

See Evaluating Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- Both asymptomatic and symptomatic women who are heterozygous for an *OTC* pathogenic variant may become catabolic during pregnancy and the postpartum period. They should be counseled about this risk and receive preventive treatment (see Pregnancy Management).
- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, have an OTC deficiency-causing pathogenic variant, or are at risk of having an OTC deficiency-causing pathogenic variant.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the OTC deficiency-causing pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for OTC deficiency are possible.

Because males with a neonatal presentation are more severely affected than heterozygous females, knowing the fetal sex may provide additional information helpful to families and health care providers in the newborn period.

- In a family with a history of neonatal-onset disease, it is likely (but not certain) that subsequently affected males will have a similar presentation.
- Because of the unpredictability of X-chromosome inactivation, it is not possible to predict the presentation in heterozygous females (see Genotype-Phenotype Correlations).

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)
  United Kingdom
  Ornithine transcarbamylase deficiency
- **National Urea Cycle Disorders Foundation**
  Phone: 626-578-0833
  nucdf.org
- **Connecting Families - Urea Cycle Disorders (UCD) Foundation**
  Phone: 918-490-3055
  ucdfamily.org
- **MedlinePlus**
  Ornithine transcarbamylase deficiency
- **National Organization for Rare Disorders (NORD)**
  Phone: 800-999-6673
  RareCare® Patient Assistance Programs
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state
- **Urea Cycle Disorders Consortium**
  Phone: 202-306-6489
  Email: jseminar@childrensnational.org
  ucdc.rarediseasesnetwork.org
- **European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)**
  e-imd.org/event/european-registry-and-network-intoxication-type-metabolic-diseases
- **National Urea Cycle Disorders Foundation International Patient Registry**

Email: coordinator@ucdparegistry.org
ucdparegistry.org

- **Urea Cycle Disorders Consortium Registry**
  Children's National Medical Center
  RDCRN Contact Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Ornithine Transcarbamylase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
OTC	Xp11.4	Ornithine transcarbamylase, mitochondrial	Ornithine CarbamoylTransferase (OTC) @ LOVD	OTC	OTC

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Ornithine Transcarbamylase Deficiency (View All in OMIM)

300461	ORNITHINE CARBAMOYLTRANSFERASE; OTC
311250	ORNITHINE TRANSCARBAMYLASE DEFICIENCY, HYPERAMMONEMIA DUE TO

Molecular Pathogenesis

OTC catalyzes formation of citrulline from ornithine and carbamylphosphate in the liver and small intestine [Brusilow & Horwich 2001, Yamaguchi et al 2006]. The only known function of OTC in the human body is synthesis of citrulline, either as an intermediate of the urea cycle or a precursor of arginine biosynthesis [Brusilow & Horwich 2001].

Reduced abundance or complete absence of functional OTC enzyme can result from the following types of pathogenic variants:

- Frameshift and nonsense variants that cause premature protein termination, missense variants that impair or abolish substrate binding and catalysis, and missense variants that reduce OTC enzyme stability and/or prevent its folding [Shi et al 1998]
- Variants that affect mRNA splicing result either in a defective *OTC* transcript or reduced levels of functional transcript, leading to complete absence or reduced abundance of functional OTC enzyme
- Variants in *OTC* upstream regulatory regions that result in reduced abundance of *OTC* transcript and OTC enzyme [Jang et al 2018]
- Structural variants that result in defective *OTC* transcript due to deletion, duplication or inversion of one or more *OTC* exons

Mechanism of disease causation. OTC deficiency occurs via a loss-of-function mechanism as detailed above.

Notable *OTC* variants. For a list of notable variants, see Table 8 (pdf).

Chapter Notes

Author Notes

Ljubica Caldovic, PhD and **Hiroki Morizono, PhD** have worked for decades on the molecular biology of ornithine transcarbamylase.

Ornithine Transcarbamylase Deficiency website

Dr Caldovic's web page

Dr Morizono's web page

Nicholas Ah Mew, MD is director of the Inherited Metabolic Disorders Program at Children's National Hospital and is associate professor of Pediatrics at The George Washington University. He is a clinical geneticist and clinical biochemical geneticist whose primary research interests include urea cycle disorders, organic acidemias, and other disorders of ammonia metabolism. He is the principal investigator or co-PI of several projects funded through the National Institutes of Health and Patient-Centered Outcomes Research Institute. Dr Ah Mew is the Children's National site-PI and an active member of the NIH-funded Urea Cycle Disorders Consortium (UCDC). He has authored multiple publications and book chapters on hyperammonemia and urea cycle disorders and has lectured internationally on these topics.

Dr Ah Mew's web page

Uta Lichter-Konecki, MD, PhD is the director of the Metabolism Program in the Division of Genetic and Genomics Medicine at UPMC Children's Hospital and Professor of Pediatrics at the University of Pittsburgh. As a clinician, she sees patients with inborn errors of metabolism. Her main research interest is delineating the causes of intellectual disability in patients with metabolic diseases and developing neuroprotective therapies to prevent compromise of intellectual function through translational research and improvement of treatment for all metabolic diseases but especially phenylketonuria, urea cycle disorders, and mitochondrial disorders. She is an active member of the NIH-funded Urea Cycle Disorders Consortium (UCDC) and has authored multiple publications and book chapters on hyperammonemia and urea cycle disorders.

Dr Lichter-Konecki's web page

Acknowledgments

We would like to acknowledge the support of the National Urea Cycle Disorders Foundation (NUCDF), which partners with physicians with a special focus on urea cycle disorders to further the well-being of patients with urea cycle disorders.

We would also like to acknowledge the Urea Cycle Disorders Consortium (UCDC) which has provided a platform for our work and has furthered our knowledge and understanding of OTC deficiency.

Revision History

- 26 May 2022 (ha) Revision: variants added to Molecular Genetic Testing Approaches, **Scenario 1**; Table 8 (pdf)
- 2 December 2021 (ha) Comprehensive update posted live
- 14 April 2016 (ma) Comprehensive update posted live
- 29 August 2013 (me) Review posted live
- 31 December 2012 (ul-k) Original submission

References

Literature Cited

Ahrens MJ, Berry SA, Whitley CB, Markowitz DJ, Plante RJ, Tuchman M. Clinical and biochemical heterogeneity in females of a large pedigree with ornithine transcarbamylase deficiency due to the R141Q mutation. Am J Med Genet. 1996;66:311-5. PubMed PMID: 8985493.

Anderson A, Gropman A, Le Mons C, Stratakis C, Gandjbakhche A. Evaluation of neurocognitive function of prefrontal cortex in ornithine transcarbamylase deficiency. Mol Genet Metab. 2020;129:207-12. PubMed PMID: 31952925.

Arn PH, Hauser ER, Thomas GH, Herman G, Hess D, Brusilow SW. Hyperammonemia in women with a mutation at the ornithine carbamoyltransferase locus. A cause of postpartum coma. N Engl J Med. 1990;322:1652-5. PubMed PMID: 2342525.

Ausems MG, Bakker E, Berger R, Duran M, van Diggelen OP, Keulemans JL, de Valk HW, Kneppers AL, Dorland L, Eskes PF, Beemer FA, Poll-The BT, Smeitink JA. Asymptomatic and late-onset ornithine transcarbamylase deficiency caused by a A208T mutation: clinical, biochemical and DNA analyses in a four-generation family. Am J Med Genet. 1997;68:236-9. PubMed PMID: 9028466.

Balasubramaniam S, Rudduck C, Bennetts B, Peters G, Wilcken B, Ellaway C. Contiguous gene deletion syndrome in a female with ornithine transcarbamylase deficiency. Mol Genet Metab. 2010;99:34-41. PubMed PMID: 19783189.

Batshaw ML, MacArthur RB, Tuchman M. Alternative pathway therapy for urea cycle disorders: twenty years later. J Pediatr. 2001;138:S46-54; discussion S-5. PubMed PMID: 11148549.

Batshaw ML, Msall M, Beaudet AL, Trojak J. Risk of serious illness in heterozygotes for ornithine transcarbamylase deficiency. J Pediatr. 1986;108:236-41. PubMed PMID: 3944708.

Batshaw ML, Tuchman M, Summar M, Seminara J. A longitudinal study of urea cycle disorders. Mol Genet Metab. 2014;113:127-30. PubMed PMID: 25135652.

Ben-Ari Z, Dalal A, Morry A, Pitlik S, Zinger P, Cohen J, Fattal I, Galili-Mosberg R, Tessler D, Baruch RG, Nuoffer JM, Largiader CR, Mandel H. Adult-onset ornithine transcarbamylase (OTC) deficiency unmasked by the Atkins' diet. J Hepatol. 2010;52:292-5. PubMed PMID: 20031247.

Berry GT, Steiner RD. Long-term management of patients with urea cycle disorders. J Pediatr. 2001;138:S56-60; discussion S-1. PubMed PMID: 11148550.

Bireley WR, Van Hove JL, Gallagher RC, Fenton LZ. Urea cycle disorders: brain MRI and neurological outcome. Pediatr Radiol. 2012;42:455-62. PubMed PMID: 21989980.

Bowling F, McGown I, McGill J, Cowley D, Tuchman M. Maternal gonadal mosaicism causing ornithine transcarbamylase deficiency. Am J Med Genet. 1999;85:452-4. PubMed PMID: 10405441.

Brusilow SW, Horwich AL. Urea cycle enzymes. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. *The Metabolic & Molecular Bases of Inherited Disease*. 8 ed. McGraw-Hill; 2001:1909-63.

Brusilow SW, Maestri NE. Urea cycle disorders: diagnosis, pathophysiology, and therapy. Adv Pediatr. 1996;43:127-70. PubMed PMID: 8794176.

Buerger C, Garbade SF, Dietrich Alber F, Waisbren SE, McCarter R, Kolker S, Burgard P, Urea Cycle Disorders C. Impairment of cognitive function in ornithine transcarbamylase deficiency is global rather than domain-specific and is associated with disease onset, sex, maximum ammonium, and number of hyperammonemic events. J Inherit Metab Dis. 2019;42:243-53. PubMed PMID: 30671983.

Caldovic L, Abdikarim I, Narain S, Tuchman M, Morizono H. Genotype-Phenotype Correlations in Ornithine Transcarbamylase Deficiency: A Mutation Update. J Genet Genomics. 2015;42:181-94. PubMed PMID: 26059767.

Chiong MA, Bennetts BH, Strasser SI, Wilcken B. Fatal late-onset ornithine transcarbamylase deficiency after coronary artery bypass surgery. Med J Aust. 2007;186:418-9. PubMed PMID: 17437397.

Deardorff MA, Gaddipati H, Kaplan P, Sanchez-Lara PA, Sondheimer N, Spinner NB, Hakonarson H, Ficicioglu C, Ganesh J, Markello T, Loechelt B, Zand DJ, Yudkoff M, Lichter-Konecki U. Complex management of a patient with a contiguous Xp11.4 gene deletion involving ornithine transcarbamylase: a role for detailed molecular analysis in complex presentations of classical diseases. Mol Genet Metab. 2008;94:498-502. PubMed PMID: 18524659.

Di Stefano C, Lombardo B, Fabbricatore C, Munno C, Caliendo I, Gallo F, Pastore L. Oculo-facio-cardio-dental (OFCD) syndrome: the first Italian case of BCOR and co-occurring OTC gene deletion. Gene. 2015;559:203-6. PubMed PMID: 25620158.

Dionisi-Vici C, Rizzo C, Burlina AB, Caruso U, Sabetta G, Uziel G, Abeni D. Inborn errors of metabolism in the Italian pediatric population: a national retrospective survey. J Pediatr. 2002;140:321-7. PubMed PMID: 11953730.

Dolman CL, Clasen RA, Dorovini-Zis K. Severe cerebral damage in ornithine transcarbamylase deficiency. Clin Neuropathol. 1988;7:10-5. PubMed PMID: 3370859.

Engel K, Nuoffer JM, Mühlhausen C, Klaus V, Largiadèr CR, Tsiakas K, Santer R, Wermuth B, Häberle J. Analysis of mRNA transcripts improves the success rate of molecular genetic testing in OTC deficiency. Mol Genet Metab. 2008;94:292-7. PubMed PMID: 18440262.

Enosawa S, Hsu HC, Yanagi Y, Matsunari H, Uchikura A, Nagashima H. Characterization and treatment responsiveness of genetically engineered ornithine transcarbamylase-deficient pig. J Clin Med. 2021;10:3226. PubMed PMID: 34362010.

Gallant NM, Gui D, Lassman CR, Yong WH, Teitell M, Mandelker D, Lorey F, Martinez-Agosto JA, Quintero-Rivera F. Novel liver findings in ornithine transcarbamylase deficiency due to Xp11.4-p21.1 microdeletion. Gene. 2015;556:249-53. PubMed PMID: 25434494.

Gerstein MT, Markus AR, Gianattasio KZ, Le Mons C, Bartos J, Stevens DM, Mew NA. Choosing between medical management and liver transplant in urea cycle disorders: A conceptual framework for parental treatment decision-making in rare disease. J Inherit Metab Dis. 2020;43:438-58. PubMed PMID: 31883128.

Häberle J, Boddaert N, Burlina A, Chakrapani A, Dixon M, Huemer M, Karall D, Martinelli D, Sanjurjo Crespo P, Santer R, Servais A, Valayannopoulos V, Lindner M, Rubio V, Dionisi-Vici C. Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis. 2012;7:32. PubMed PMID: 22642880.

Honeycutt D, Callahan K, Rutledge L, Evans B. Heterozygote ornithine transcarbamylase deficiency presenting as symptomatic hyperammonemia during initiation of valproate therapy. Neurology. 1992;42:666-8. PubMed PMID: 1549234.

Hu WT, Kantarci OH, Merritt JL, 2nd, McGrann P, Dyck PJ, Lucchinetti CF, Tippmann-Peikert M. Ornithine transcarbamylase deficiency presenting as encephalopathy during adulthood following bariatric surgery. Arch Neurol. 2007;64:126-8. PubMed PMID: 17210820.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Jang YJ, LaBella AL, Feeney TP, Braverman N, Tuchman M, Morizono H, Ah Mew N, Caldovic L. Disease-causing mutations in the promoter and enhancer of the ornithine transcarbamylase gene. Hum Mutat. 2018;39:527-36. PubMed PMID: 29282796.

Keegan CE, Martin DM, Quint DJ, Gorski JL. Acute extrapyramidal syndrome in mild ornithine transcarbamylase deficiency: metabolic stroke involving the caudate and putamen without metabolic decompensation. Eur J Pediatr. 2003;162:259-63. PubMed PMID: 12647200.

Keskinen P, Siitonen A, Salo M. Hereditary urea cycle diseases in Finland. Acta Paediatr. 2008;97:1412-9. PubMed PMID: 18616627.

Komaki S, Matsuura T, Oyanagi K, Hoshide R, Kiwaki K, Endo F, Shimadzu M, Matsuda I. Familial lethal inheritance of a mutated paternal gene in females causing X-linked ornithine transcarbamylase (OTC) deficiency. Am J Med Genet. 1997;69:177-81. PubMed PMID: 9056557.

Krivitzky L, Babikian T, Lee HS, Thomas NH, Burk-Paull KL, Batshaw ML. Intellectual, adaptive, and behavioral functioning in children with urea cycle disorders. Pediatr Res. 2009;66:96-101. PubMed PMID: 19287347.

Kumar RD, Burrage LC, Bartos J, Ali S, Schmitt E, Nagamani SCS, LeMons C. A deep intronic variant is a common cause of OTC deficiency in individuals with previously negative genetic testing. Mol Genet Metab Rep. 2021;26:100706. PubMed PMID: 33489762.

Leão M. Valproate as a cause of hyperammonemia in heterozygotes with ornithine-transcarbamylase deficiency. Neurology. 1995;45:593-4. PubMed PMID: 7898728.

Lipskind S, Loanzon S, Simi E, Ouyang DW. Hyperammonemic coma in an ornithine transcarbamylase mutation carrier following antepartum corticosteroids. J Perinatol. 2011;31:682-4. PubMed PMID: 21956151.

Luksan O, Jirsa M, Eberova J, Minks J, Treslova H, Bouckova M, Storkanova G, Vlaskova H, Hrebicek M, Dvorakova L. Disruption of OTC promoter-enhancer interaction in a patient with symptoms of ornithine carbamoyltransferase deficiency. Hum Mutat. 2010;31:E1294-303. PubMed PMID: 20127982.

Marcus N, Scheuerman O, Hoffer V, Zilbershot-Fink E, Reiter J, Garty BZ. Stupor in an adolescent following Yom Kippur fast, due to late-onset ornithine transcarbamylase deficiency. Isr Med Assoc J. 2008;10:395-6. PubMed PMID: 18605371.

McCullough BA, Yudkoff M, Batshaw ML, Wilson JM, Raper SE, Tuchman M. Genotype spectrum of ornithine transcarbamylase deficiency: correlation with the clinical and biochemical phenotype. Am J Med Genet. 2000;93:313-9. PubMed PMID: 10946359.

Merritt JL 2nd, Brody LL, Pino G, Rinaldo P. Newborn screening for proximal urea cycle disorders: Current evidence supporting recommendations for newborn screening. Mol Genet Metab. 2018;124:109-13. PubMed PMID: 29703588.

Messina M, Raudino F, Iacobacci R, Meli C, Fiumara A. New ratio as a useful marker for early diagnosis of proximal urea cycle disorders. Clin Chim Acta. 2021;520:154-9. PubMed PMID: 34116006.

Msall M, Batshaw ML, Suss R, Brusilow SW, Mellits ED. Neurologic outcome in children with inborn errors of urea synthesis. Outcome of urea-cycle enzymopathies. N Engl J Med. 1984;310:1500-5. PubMed PMID: 6717540.

Mustafa A, Clarke JT. Ornithine transcarbamoylase deficiency presenting with acute liver failure. J Inherit Metab Dis. 2006;29:586. PubMed PMID: 16802108.

Oechsner M, Steen C, Sturenburg HJ, Kohlschutter A. Hyperammonaemic encephalopathy after initiation of valproate therapy in unrecognised ornithine transcarbamylase deficiency. J Neurol Neurosurg Psychiatry. 1998;64:680-2. PubMed PMID: 9598692.

Panlaqui OM, Tran K, Johns A, McGill J, White H. Acute hyperammonemic encephalopathy in adult onset ornithine transcarbamylase deficiency. Intensive Care Med. 2008;34:1922-4. PubMed PMID: 18651132.

Pinner JR, Freckmann ML, Kirk EP, Yoshino M. Female heterozygotes for the hypomorphic R40H mutation can have ornithine transcarbamylase deficiency and present in early adolescence: a case report and review of the literature. J Med Case Rep. 2010;4:361. PubMed PMID: 21070677.

Posner JB, Saper CB, Schiff ND, Claasen J. *Plum and Posner's Diagnosis and Treatment of Stupor and Coma*. 5 ed. Oxford, UK: Oxford University Press; 2019.

Posset R, Garbade SF, Gleich F, Gropman AL, de Lonlay P, Hoffmann GF, Garcia-Cazorla A, Nagamani SCS, Baumgartner MR, Schulze A, Dobbelaere D, Yudkoff M, Kolker S, Zielonka M, et al. Long-term effects of medical management on growth and weight in individuals with urea cycle disorders. Sci Rep. 2020;10:11948. PubMed PMID: 32686765.

Posset R, Gropman AL, Nagamani SCS, Burrage LC, Bedoyan JK, Wong D, Berry GT, Baumgartner MR, Yudkoff M, Zielonka M, Hoffmann GF, Burgard P, Schulze A, McCandless SE, Garcia-Cazorla A, Seminara J, Garbade SF, Kolker S, et al. Impact of diagnosis and therapy on cognitive function in urea cycle disorders. Ann Neurol. 2019;86:116-28. PubMed PMID: 31018246.

Raina R, Bedoyan JK, Lichter-Konecki U, Jouvet P, Picca S, Mew NA, Machado MC, Chakraborty R, Vemuganti M, Grewal MK, Bunchman T, Sethi SK, Krishnappa V, McCulloch M, Alhasan K, Bagga A, Basu RK, Schaefer F, Filler G, Warady BA. Consensus guidelines for management of hyperammonaemia in paediatric patients receiving continuous kidney replacement therapy. Nat Rev Nephrol. 2020;16:471-82. PubMed PMID: 32269302.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Rubenstein JL, Johnston K, Elliott GR, Brusilow SW. Haloperidol-induced hyperammonaemia in a child with citrullinaemia. J Inherit Metab Dis. 1990;13:754-5. PubMed PMID: 2246861.

Rüegger CM, Lindner M, Ballhausen D, Baumgartner MR, Beblo S, Das A, Gautschi M, Glahn EM, Grünert SC, Hennermann J, Hochuli M, Huemer M, Karall D, Kölker S, Lachmann RH, Lotz-Havla A, Möslinger D, Nuoffer JM, Plecko B, Rutsch F, Santer R, Spiekerkoetter U, Staufner C, Stricker T, Wijburg FA, Williams M, Burgard P, Häberle J. Cross-sectional observational study of 208 patients with non-classical urea cycle disorders. J Inherit Metab Dis. 2014;37:21-30. PubMed PMID: 23780642.

Scaglia F, Brunetti-Pierri N, Kleppe S, Marini J, Carter S, Garlick P, Jahoor F, O'Brien W, Lee B. Clinical consequences of urea cycle enzyme deficiencies and potential links to arginine and nitric oxide metabolism. J Nutr. 2004;134:2775S-82S. PubMed PMID: 15465784.

Shchelochkov OA, Li FY, Geraghty MT, Gallagher RC, Van Hove JL, Lichter-Konecki U, Fernhoff PM, Copeland S, Reimschisel T, Cederbaum S, Lee B, Chinault AC, Wong LJ. High-frequency detection of deletions and variable rearrangements at the ornithine transcarbamylase (OTC) locus by oligonucleotide array CGH. Mol Genet Metab. 2009;96:97-105. PubMed PMID: 19138872.

Shi D, Morizono H, Ha Y, Aoyagi M, Tuchman M, Allewell NM. 1.85-A resolution crystal structure of human ornithine transcarbamoylase complexed with N-phosphonacetyl-L-ornithine. Catalytic mechanism and correlation with inherited deficiency. J Biol Chem. 1998;273:34247-54. PubMed PMID: 9852088.

Sprouse C, King J, Helman G, Pacheco-Colon I, Shattuck K, Breeden A, Seltzer R, VanMeter JW, Gropman AL. Investigating neurological deficits in carriers and affected patients with ornithine transcarbamylase deficiency. Mol Genet Metab. 2014;113:136-41. PubMed PMID: 24881970.

Takanashi J, Barkovich AJ, Cheng SF, Weisiger K, Zlatunich CO, Mudge C, Rosenthal P, Tuchman M, Packman S. Brain MR imaging in neonatal hyperammonemic encephalopathy resulting from proximal urea cycle disorders. Am J Neuroradiol. 2003;24:1184-7. PubMed PMID: 12812952.

Thakur V, Rupar CA, Ramsay DA, Singh R, Fraser DD. Fatal cerebral edema from late-onset ornithine transcarbamylase deficiency in a juvenile male patient receiving valproic acid. Pediatr Crit Care Med. 2006;7:273-6. PubMed PMID: 16575347.

Torkzaban M, Haddad A, Baxter JK, Berghella V, Gahl WA, Al-Kouatly HB. Maternal ornithine transcarbamylase deficiency, a genetic condition associated with high maternal and neonatal mortality every clinician should know: A systematic review. Am J Med Genet A. 2019;179:2091-100. PubMed PMID: 31441224.

Tuchman M, Lee B, Lichter-Konecki U, Summar ML, Yudkoff M, Cederbaum SD, Kerr DS, Diaz GA, Seashore MR, Lee HS, McCarter RJ, Krischer JP, Batshaw ML. Cross-sectional multicenter study of patients with urea cycle disorders in the United States. Mol Genet Metab. 2008;94:397-402. PubMed PMID: 18562231.

Tuchman M, Tsai MY, Holzknecht RA, Brusilow SW. Carbamyl phosphate synthetase and ornithine transcarbamylase activities in enzyme-deficient human liver measured by radiochromatography and correlated with outcome. Pediatr Res. 1989;26:77-82. PubMed PMID: 2771513.

UCD Conference Group. Consensus statement from a conference for the management of patients with urea cycle disorders. J Pediatr. 2001;138:S1-5. PubMed PMID: 11148543.

Vasquez-Loarte T, Thompson JD, Merritt JL 2nd. Considering proximal urea cycle disorders in expanded newborn screening. Int J Neonatal Screen. 2020;6:6. PubMed PMID: 33073005.

Waisbren SE, Gropman AL, Batshaw ML, et al. Improving long term outcomes in urea cycle disorders-report from the Urea Cycle Disorders Consortium. J Inherit Metab Dis. 2016;39:573-84. PubMed PMID: 27215558.

Waisbren SE, He J, McCarter R. Assessing psychological functioning in metabolic disorders: validation of the Adaptive Behavior Assessment System, Second Edition (ABAS-II), and the Behavior Rating Inventory of Executive Function (BRIEF) for identification of individuals at risk. JIMD Rep. 2015;21:35-43.

Wakiya T, Sanada Y, Urahashi T, Ihara Y, Yamada N, Okada N, Ushijima K, Otomo S, Sakamoto K, Murayama K, Takayanagi M, Hakamada K, Yasuda Y, Mizuta K. Impact of enzyme activity assay on indication in liver transplantation for ornithine transcarbamylase deficiency. Mol Genet Metab. 2012;105:404-7. PubMed PMID: 22264779.

Wang L, Yang Y, Breton C, Bell P, Li M, Zhang J, Che Y, Saveliev A, He Z, White J, Latshaw C, Xu C, McMenamin D, Yu H, Morizono H, Batshaw ML, Wilson JM. A mutation-independent CRISPR-Cas9-mediated gene targeting approach to treat a murine model of ornithine transcarbamylase deficiency. Sci Adv. 2020;6:eaax5701. PubMed PMID: 32095520.

Wilson JM, Shchelochkov OA, Gallagher RC, Batshaw ML. Hepatocellular carcinoma in a research subject with ornithine transcarbamylase deficiency. Mol Genet Metab. 2012;105:263-5. PubMed PMID: 22129577.

Wiwattanadittakul N, Prust M, Gaillard WD, Massaro A, Vezina G, Tsuchida TN, Gropman AL. The utility of EEG monitoring in neonates with hyperammonemia due to inborn errors of metabolism. Mol Genet Metab. 2018;125:235-40. PubMed PMID: 30197275.

Wong DA. Ornithine transcarbamylase deficiency: are carrier females suitable donors? Pediatr Transplant. 2012;16:525-7. PubMed PMID: 22672071.

Yamaguchi S, Brailey LL, Morizono H, Bale AE, Tuchman M. Mutations and polymorphisms in the human ornithine transcarbamylase (OTC) gene. Hum Mutat. 2006;27:626-32. PubMed PMID: 16786505.

Yamanouchi H, Yokoo H, Yuhara Y, Maruyama K, Sasaki A, Hirato J, Nakazato Y. An autopsy case of ornithine transcarbamylase deficiency. Brain Dev. 2002;24:91-4. PubMed PMID: 11891099.

Yang Y, Wang L, Bell P, McMenamin D, He Z, White J, Yu H, Xu C, Morizono H, Musunuru K, Batshaw ML, Wilson JM. A dual AAV system enables the Cas9-mediated correction of a metabolic liver disease in newborn mice. Nat Biotechnol. 2016;34:334-8. PubMed PMID: 26829317.

Yorifuji T, Muroi J, Uematsu A, Tanaka K, Kiwaki K, Endo F, Matsuda I, Nagasaka H, Furusho K. X-inactivation pattern in the liver of a manifesting female with ornithine transcarbamylase (OTC) deficiency. Clin Genet. 1998;54:349-53. PubMed PMID: 9831349.

Zabulica M, Srinivasan RC, Akcakaya P, Allegri G, Bestas B, Firth M, Hammarstedt C, Jakobsson T, Jakobsson T, Ellis E, Jorns C, Makris G, Scherer T, Rimann N, van Zuydam NR, Gramignoli R, Forslow A, Engberg S, Maresca M, Rooyackers O, Thony B, Haberle J, Rosen B, Strom SC. Correction of a urea cycle defect after ex vivo gene editing of human hepatocytes. Mol Ther. 2021;29:1903-17. PubMed PMID: 33484963.

Zecavati N, Lichter-Konecki U, Singh R, Crawford J, Seltzer R, Gropman AL, editors. Seizures in urea cycle disorders (UCDs): An under-recognized symptom in patients outside of the acute metabolic phase. American Society of Human Genetics 58th Annual Meeting; 2008; Philadelphia, PA.

License