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Urea Cycle Disorders Overview

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Summary

Disease characteristics. The urea cycle disorders (UCD) result from defects in the metabolism of waste nitrogen from the breakdown of protein and other nitrogen-containing molecules. Severe deficiency or total absence of activity of any of the first four enzymes (CPS1, OTC, ASS, ASL) in the urea cycle or the cofactor producer (NAGS) results in the accumulation of ammonia and other precursor metabolites during the first few days of life. Infants with a severe urea cycle disorder are normal at birth but rapidly develop cerebral edema and the related signs of lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, and coma. In milder (or partial) deficiencies of these enzymes and in arginase (ARG) deficiency, ammonia accumulation may be triggered by illness or stress at almost any time of life. In these disorders the elevations of plasma ammonia concentration and symptoms are often subtle and the first recognized clinical episode may not occur for months or decades.

Diagnosis/testing. The diagnosis of a urea cycle disorder is based on clinical suspicion and biochemical and molecular genetic testing. A plasma ammonia concentration of 150 µmol/L or higher associated with a normal anion gap and a normal plasma glucose concentration is an indication for the presence of a UCD. Plasma quantitative amino acid analysis and measurement of urinary orotic acid can distinguish between the specific UCDs. A definitive diagnosis of a urea cycle defect depends on either molecular genetic testing or measurement of enzyme activity. Molecular genetic testing is clinically available for all urea cycle defects.

Genetic counseling. Deficiencies of CPS1, ASS1, ASL, NAGS, and ARG are inherited in an autosomal recessive manner. OTC deficiency is inherited in an X-linked manner. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk using molecular genetic testing is possible for any of the urea cycle disorders if the disease-causing mutation(s) in the family are known.

Management. *Treatment of manifestations*: Acute severe hyperammonemia: Dialysis and hemofiltration to reduce plasma ammonia concentration; intravenous administration of arginine hydrochloride and nitrogen scavenger drugs to allow alternative pathway excretion of excess nitrogen; restriction of protein for 12 to 24 hours to reduce the amount of nitrogen in the diet; calories given as carbohydrates and fat; and physiologic stabilization with intravenous fluids and cardiac pressors while avoiding overhydration.

Prevention of primary manifestations: Long-term management: prevention of catabolism to avoid hyperammonemic episodes by dietary restriction of protein, use of specialized formulas, and use of oral nitrogen-scavenging drugs.

Prevention of secondary complications: Minimize risk of respiratory and gastrointestinal illnesses; routine immunizations; multivitamin and fluoride supplementation; appropriate use of antipyretics.

Surveillance: Routine monitoring by a physician experienced in the treatment of metabolic disorders.

Agents/circumstances to avoid: Valproic acid (Depakote); prolonged fasting or starvation; intravenous steroids; large boluses of protein or amino acids.

Testing of relatives at risk: Identification of affected at-risk relatives before symptoms occur allows dietary therapy and other measures to prevent hyperammonemia.

Definition

The urea cycle:

- Is the sole source of endogenous production of arginine, ornithine, and citrulline;
- Is the principal mechanism for the clearance of waste nitrogen resulting from protein turnover;
- Is the principal mechanism for the metabolism of other nitrogenous metabolic compounds like adenosine monophosphate;
- Includes enzymes that overlap with the nitric oxide production pathway (ASS and ASL).

The urea cycle comprises the following (Figure 1) [Krebs & Henseleit 1932]:

- Five catalytic enzymes:
  - Carbamoylphosphate synthetase I (CPS1)
  - Ornithine transcarbamylase (OTC)
  - Argininosuccinic acid synthetase (ASS1)
  - Argininosuccinic acid lyase (ASL)
  - Arginase (ARG)
- A cofactor producing enzyme: N-acetyl glutamate synthetase (NAGS)
- Two transporters:
  - Ornithine translocase (ORNT1)
  - Citrin

Urea cycle disorders (UCD) result from inherited deficiencies in the six enzymes of the urea cycle pathway (CPS1, OTC, ASS1, ASL, ARG, and NAGS).

Specific Urea Cycle Disorders

NAGS deficiency. Deficiency of this enzyme has been described in a number of affected individuals. Symptoms mimic those of CPS1 deficiency, as CPS1 is rendered inactive in the absence of NAGS [Caldovic et al 2003].

Carbamoylphosphate synthetase I deficiency (CPS1 deficiency) is the most severe of the urea cycle disorders. Individuals with complete CPS1 deficiency rapidly develop hyperammonemia in the newborn period. Children who are successfully rescued from crisis are chronically at risk for repeated bouts of hyperammonemia.

Ornithine transcarbamylase deficiency (OTC deficiency). Absence of OTC activity in males is as severe as CPS1 deficiency. Approximately 15% of carrier females develop hyperammonemia during their lifetime and many require chronic medical management for hyperammonemia. More recently it has been recognized that carrier females who have never had symptoms of overt hyperammonemia have deficiencies in executive function.

Citrullinemia type I (ASS1 deficiency). The hyperammonemia in this disorder can also be quite severe. Affected individuals are able to incorporate some waste nitrogen into urea cycle intermediates, which makes treatment slightly easier than in the other UCDs.

Argininosuccinic aciduria (ASL deficiency) can also present with rapid-onset hyperammonemia in the newborn period. This enzyme defect is past the point in the metabolic pathway at which all the waste nitrogen has been incorporated into the cycle. Some patients develop chronic hepatic enlargement and elevation of transaminases. Biopsy of the liver shows enlarged hepatocytes, which may over time progress to fibrosis, the etiology of which is unclear. Affected individuals can also develop trichorrhexis nodosa, a node-like appearance of fragile hair that usually responds to arginine supplementation [Summar 2001, Summar & Tuchman 2001]. Affected individuals who have never had prolonged coma nevertheless have been reported to have significant developmental disabilities.

Arginase deficiency (hyperargininemia; ARG deficiency) is not typically characterized by rapid-onset hyperammonemia. Affected individuals develop progressive spasticity and can also develop tremor, ataxia, and choreoathetosis. Growth is affected [Cederbaum et al 2004].

Clinical Manifestations of Urea Cycle Disorders

Severity of the urea cycle defect is influenced by the position of the defective enzyme in the pathway and the severity of the enzyme defect.

Severe deficiency or total absence of activity of any of the first four enzymes in the pathway (CPS1, OTC, ASS1, and ASL) or the cofactor producer (NAGS) results in the accumulation of ammonia and other precursor metabolites during the first few days of life.

Because no effective secondary clearance system for ammonia exists, complete disruption of this pathway results in the rapid accumulation of ammonia and development of related symptoms. Patients with complete defects normally present in the newborn period, when the immaturity of the neonatal liver accentuates defects in the urea cycle enzymes [Pearson et al 2001, Summar 2001, Summar & Tuchman 2001]. Infants with a urea cycle disorder appear normal at birth but rapidly develop cerebral edema and the related signs of lethargy; anorexia; hyper- or hypoventilation; hypothermia; seizures; neurologic posturing; and coma.

Because newborns are usually discharged from the hospital within one to two days after birth, the symptoms of a urea cycle disorder often develop when the child is at home and may not be recognized in a timely manner by the family and primary care physician. The typical initial symptoms of a child with hyperammonemia are nonspecific: failure to feed, loss of thermoregulation with a low core temperature, and somnolence [Summar 2001].

Symptoms progress from somnolence to lethargy and coma. Abnormal posturing and encephalopathy are often related to the degree of central nervous system swelling and pressure upon the brain stem [Summar 2001]. About 50% of neonates with severe hyperammonemia may have seizures, some without overt clinical manifestations. Individuals with closed cranial sutures are at higher risk for rapid neurologic deterioration from the cerebral edema that results from ammonia elevation. Hyperventilation secondary to the effect of hyperammonemia on the brain stem, a common early finding in hyperammonemic attacks, results in respiratory alkalosis. Hypoventilation and respiratory arrest follow as pressure increases on the brain stem. Severity of neurologic sequelae is variable and correlates with duration of initial hyperammonemia.

With rapid identification and current treatment strategies, survival of neonates with hyperammonemia has improved dramatically in the last few decades [Summar 2001, Summar & Tuchman 2001, Enns et al 2007 (click Guidelines for full text), Summar et al 2008, Tuchman et al 2008, Krivitzky et al 2009].

In milder (or partial) urea cycle enzyme deficiencies, ammonia accumulation may be triggered by illness or stress at almost any time of life, resulting in multiple mild elevations of plasma ammonia concentration. The hyperammonemia is typically less severe and the symptoms more subtle than the neonatal presentation of a UCD. In individuals with partial enzyme deficiencies, the first recognized clinical episode may be delayed for months or years. Although the clinical abnormalities vary somewhat with the specific urea cycle disorder, in most the hyperammonemic episode is marked by loss of appetite, vomiting, lethargy, and behavioral abnormalities. Sleep disorders, delusions, hallucinations, and psychosis may occur. An encephalopathic (slow-wave) EEG pattern may be observed during hyperammonemia and nonspecific brain atrophy may be seen subsequently on MRI.

Defects in the final enzyme in the pathway (ARG) cause hyperargininemia, a more subtle disorder involving neurologic symptoms; however, neonatal hyperammonemia has been rarely reported. (See Arginase Deficiency.)

Neurologic aspects of UCDs. Ammonia can cause brain damage through a variety of proposed mechanisms, a major component of which is cerebral edema. The specific roles of ammonia, glutamate, and glutamine in cerebral edema are still under investigation but are thought to affect the aquaporin system and water and potassium homeostasis in brain [Lichter-Konecki 2008, Lichter-Konecki et al 2008, Albrecht et al 2010].

Damage resulting from acute hyperammonemia in infancy resembles that seen in hypoxic-ischemic events or stroke. Lacunar infarcts and white matter disruption are common findings.

Chronic hyperammonemia may disrupt ion-gradients and neurotransmitters, transport of metabolites, mitochondrial function, and the ratio of alpha-ketoglutarate/glutamate/glutamine.

Seizures are common in acute hyperammonemia and may result from cerebral damage. Recent findings suggest that subclinical seizures are common in acute hyperammonemic episodes and their effects on cerebral metabolism in an otherwise compromised state should be addressed (see Treatment of Manifestations). (Note: Valproic acid should be avoided because of its effects on CPS1 function. See Agents/Circumstances to Avoid.)

Newer neuroimaging techniques that provide information about the timing, extent, reversibility, and possible mechanism of neural injury in a noninvasive manner can be used as an adjunct to predict clinical and neurocognitive outcome [Gropman 2010].

The limitations of routine neuroimaging:

- Damage can only be detected at a macroscopic level, typically at a time when symptoms are already present.
- MRI findings may lag behind clinical changes.

Advanced imaging sequences such as magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and functional magnetic resonance imaging (fMRI) provide additional details about the pattern and type of injury and have shed light on various neurologic problems seen in urea cycle disorders.

- **MRS.** In OTC deficiency, biochemical markers of brain injury resulting from hyperammonemia that can be measured quantitatively on 1H MRS include increased glutamine levels and depletion of myoinositol.
- **DTI**
  - In UCDs, DTI commonly shows a pattern of white matter injury affecting the cingulum, a major fiber bundle that underlies pathways involving working memory and attention.
  - In arginase deficiency, DTI demonstrates additionally decreased fiber density reflecting the predilection of corticospinal tracts to brain injury corresponding to the spastic diplegia observed in this disorder.
- **fMRI.** Persons with late onset OTC deficiency, who have traditionally been considered intellectually normal, often show altered neural circuitry by fMRI when performing tasks requiring working memory and attention.

Historically the outcome of newborns with hyperammonemia was considered poor [Brusilow 1995]. More recent data from the NIH-sponsored longitudinal study on patients treated with the more recent protocols show IQ measures within a less severe range.

Table 1. Cognitive and Adaptive Outcome in Children with UCD Age 3-16 Years

	Age 3-5		Age 6-16	
	Age at Onset			
	Neonatal [1] (n=5)	Late [2] (n=7)	Neonatal [1] (n=8)	Late [2] (n=39)
WASI/WPPSI-3 Composite Scores [3] (SD)				
Verbal IQ	81.3 (16.6)	101.7 (24.4)	72.9 (14.3)	94.3 (21.7)
Performance IQ	77.7 (15.0)	95.6 (17.4)	74.4 (11.7)	89.5 (20.4)
Full Scale IQ	77.7 (16.3)	99.6 (22.6)	71.4 (12.8)	94.1 (22.0)
ABAS-II [3] (SD)				
General adaptive composite	73.2 (31.2)	91.4 (23.6)	66.0 (17.9)	84.4 (21.6)

Adapted from Krivitzky et al [2009]

1. Clinical presentation in 1st month

2. Clinical onset after 1st month or diagnosis based on family history

3. Clinically significant difference between groups for cognitive and adaptive outcome

Establishing the Diagnosis of a Urea Cycle Disorder

The diagnosis of a urea cycle disorder in a symptomatic individual is based on clinical, biochemical, and molecular genetic data.

Family history. A three-generation family history with attention to other relatives (particularly children) with neurologic signs and symptoms suggestive of UCD should be obtained. Documentation of relevant findings in relatives can be accomplished either through direct examination of those individuals or review of their medical records including the results of biochemical testing, molecular genetic testing, and autopsy examination. A family history consistent with X-linked inheritance suggests OTC deficiency.

Physical examination. No findings on physical examination distinguish among the six types of urea cycle defect; however, trichorrhexis nodosa can be suggestive of ASL deficiency and progressive spasticity of the lower extremities of arginase deficiency.

Testing

The algorithm in Figure 2 may assist with the evaluation of a newborn with hyperammonemia. A plasma ammonia concentration of 150 µmol/L or higher associated with a normal anion gap and a normal plasma glucose concentration is a strong indication of a UCD [Summar & Tuchman 2001].

Figure 3 highlights the use of the following recommended diagnostic tests to identify the specific urea cycle disorder.

Serum ammonia concentration elevation is usually the first identified laboratory abnormality in most of the urea cycle disorders.

Quantitative plasma amino acid analysis can be used to arrive at a tentative diagnosis. (As the liver is not fully mature, affected newborns often have plasma amino acid concentrations that are quite different from those in older children and adults.)

- **Plasma concentration of citrulline** helps discriminate between the proximal and distal urea cycle defects, as citrulline is the product of the proximal enzymes (OTC and CPS1) and a substrate for the distal enzymes (ASS1, ASL, ARG).
  - Plasma citrulline is either absent or present only in trace amounts in neonatal-onset CPS1 deficiency and OTC deficiency and present in low to low-normal concentrations in late-onset disease.
  - A tenfold elevation in plasma citrulline concentration is seen in ASS deficiency.
  - A more moderate (approximately two- to fivefold) increase in plasma citrulline concentration is seen in ASL deficiency, which is also associated with high levels of argininosuccinic acid (ASA) in plasma and urine. ASA is normally absent [Summar 2001, Summar & Tuchman 2001].
- **Plasma concentration of arginine** may be reduced in all urea cycle disorders except ARG deficiency, in which it is elevated five- to sevenfold; however, in

partial enzyme defects, it may be normal.

- **Note:** Plasma concentrations of glutamine, alanine, and asparagine, which serve as storage forms of waste nitrogen, are frequently elevated.

Urinary orotic acid is measured to distinguish CPS1 deficiency from OTC deficiency. It is normal or low in CPS1 deficiency and significantly elevated in OTC deficiency. Note: Urinary orotic acid excretion can also be increased in argininemia (ARG deficiency) and citrullinemia type I (ASS1 deficiency).

Molecular genetic testing is used for diagnosis, carrier detection, and prenatal diagnosis for all six UCDs (Table 2). It has supplanted measurement of enzyme activity as the definitive diagnostic test.

Table 2. Molecular Genetic Test Availability in Urea Cycle Disorders

Disease Name	Gene Symbol	Protein Name	Test Availability
Carbamoylphosphate synthetase I deficiency	*CPS1* [1]	Carbamoyl-phosphate synthase	Clinical Testing
Ornithine transcarbamylase deficiency	*OTC*	Ornithine carbamoyltransferase	Clinical Testing
ASS deficiency (Citrullinemia type I)	*ASS1*	Argininosuccinate synthase	Clinical Testing
ASL deficiency (Argininosuccinicaciduria)	*ASL*	Argininosuccinate lyase	Clinical Testing
Arginase deficiency	*ARG1*	Arginase-1	Clinical Testing
NAGS deficiency	*NAGS*	N-acetylglutamate synthase	Clinical Testing

Test Availability refers to availability in the GeneTests™ Laboratory Directory. GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.
1. Summar et al [2003]

Enzyme activity. If molecular testing is uninformative, the following disorders can be diagnosed by assay of enzyme activity:

- CPS1 deficiency, OTC deficiency, or NAGS deficiency: liver biopsy
- ARG deficiency: red blood cells
- ASS1 deficiency and ASL deficiency: fibroblasts

Newborn Screening

Current extended newborn screening panels using tandem mass spectrometry detect abnormal concentrations of analytes associated with ASS1 deficiency, ASL deficiency, and arginase deficiency although the sensitivity and specificity of such screening for these disorders is unknown. In addition, some newborn screening programs are investigating methods to detect OTC deficiency and the proximal urea cycle defects.

Some caveats regarding newborn screening for urea cycle defects:

- CPS1 deficiency, OTC deficiency, and NAGS deficiency currently cannot be reliably detected.
- Although hyperargininemia (i.e., arginase deficiency) has been detected by these methods, newborn screening cannot be expected to reliably detect all cases.
- Even in UCDs detectable by newborn screening, neonates are often symptomatic prior to availability of the screening results; thus a high level of clinical suspicion by healthcare providers is necessary

Differential Diagnosis of Urea Cycle Disorders

A number of other disorders that perturb the liver can result in hyperammonemia and mimic the effects of a urea cycle disorder. The most common/significant ones are viral infection of the liver and vascular bypass of the liver.

Diseases of the liver and biliary tract

- Herpes simplex virus infection
- Vascular bypass of the liver
- Biliary atresia
- Acute liver failure

Medications

- Valproic acid
- Cyclophosphamide
- 5-pentanoic acid

Inborn errors of metabolism

- Organic acidemias (e.g., propionic acidemia and methylmalonic acidemia) (see Organic Acidemias, Methylmalonic Acidemia)
- Tyrosinemia type 1
- Galactosemia
- Mitochondrial disorders (see Mitochondrial Disorders Overview)
- Fatty acid oxidation disorders (see MCAD Deficiency)
- Citrin deficiency (see **Note**). The two phenotypes of citrin deficiency are citrullinemia type II (CTLN2) and neonatal intrahepatic cholestasis caused by citrin

deficiency (NICCD).

CTLN2 is characterized by adult-onset, recurring episodes of hyperammonemia and associated neuropsychiatric symptoms including nocturnal delirium, aggression, irritability, hyperactivity, delusions, disorientation, restlessness, drowsiness, loss of memory, flapping tremor, convulsive seizures, and coma; death can result from brain edema. Onset is sudden and usually between ages 20 and 50 years. Pathologic findings include fatty infiltration and mild fibrosis of the liver despite little or no liver dysfunction [Saheki et al 2004].

Children younger than age one year with NICCD have transient intrahepatic cholestasis, diffuse fatty liver and parenchymal cellular infiltration associated with hepatic fibrosis, low birth weight, growth retardation, hypoproteinemia, decreased coagulation factors, hemolytic anemia, hepatomegaly, variable liver dysfunction, and/or hypoglycemia. The liver dysfunction in NICCD can be severe. Symptoms disappear by age one year with fat-soluble vitamin supplementation and high-protein, low-carbohydrate, galactose-free diet. One or more decades later, some individuals develop severe CTLN2 with neuropsychiatric symptoms; the transition from NICCD to the onset of CTLN2 is gradual.

Affected individuals have the dietary peculiarity of avoiding carbohydrate rather than protein.

Citrin is an aspartate glutamate transporter across the mitochondrial membrane. Citrin deficiency leads to decreased cytoplasmic aspartate, which limits the activity of the enzyme argininosuccinic acid synthase which combines aspartate and citrulline to make argininosuccinic acid (Figure 1). The diagnosis of CTLN2 and NICCD is based on biochemical findings, including increase of blood or plasma concentration of ammonia, increased plasma or serum concentrations of citrulline and arginine, increased plasma or serum threonine-to-serine ratio, and increased serum concentration of pancreatic secretory trypsin inhibitor (PSTI).

SLC25A13 is the only gene in which mutations are known to cause citrin deficiency. Citrin deficiency is inherited in an autosomal recessive manner.

- Ornithine translocase deficiency (HHH syndrome) (see **Note**). The HHH (hyperornithinemia, hyperammonemia, homocitrullinuria) syndrome is an autosomal recessive disorder described in more than 50 individuals.

  Symptoms result from hyperammonemia and resemble those of the urea cycle disorders. Most affected individuals have intermittent hyperammonemia accompanied by vomiting, lethargy, and coma (in extreme cases). Growth is abnormal and intellectual development is affected. Spasticity and seizures are common. Adults with partial activity of the enzyme typically self-select low-protein diets.

  Ornithine translocase deficiency results in diminished ornithine transport into the mitochondria; reduced intramitochondrial ornithine causes orotic aciduria and impaired ureagenesis. Plasma ornithine concentrations are extremely high, but diagnosis can be complicated because plasma ornithine concentrations can normalize on a protein-restricted diet. The presence of hyperammonemia and homocitrullinuria is helpful in diagnosis. Homocitrulline is thought to originate from the transcarbamylation of lysine.

Note: Some experts, including the Urea Cycle Disorders Consortium, a Rare Disease Clinical Research Consortium, count citrin deficiency and HHH syndrome as transporter defects among the urea cycle disorders, making the total number of urea cycle disorders eight (six enzyme deficiencies and two transporter defects).

Note to clinicians: For a patient-specific 'simultaneous consult' related to the urea cycle disorders, go to SimulConsult®, an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

- NAGS deficiency
- Carbamoylphosphate synthetase I deficiency
- Ornithine transcarbamylase deficiency
- Citrullinemia type I
- Argininosuccinic aciduria
- Arginase deficiency

Prevalence of Urea Cycle Disorders

The incidence of UCDs is estimated to be at least 1:30,000 births; partial defects may make the number much higher.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Deficiencies of CPS1, ASS1, ASL, NAGS, and ARG are inherited in an autosomal recessive manner.

OTC deficiency is inherited in an X-linked manner.

Risk to Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an affected individual are obligate heterozygotes (carriers) for one mutant allele.

Carrier Detection

Molecular genetic testing is possible for at-risk family members for all five disorders if the disease-causing alleles have been identified in the family.

Risk to Family Members — X-Linked Inheritance

Parents of a male proband

- The father of a male proband is not affected and is not a carrier.
- In a family with more than one affected individual, the mother of an affected individual is an obligate carrier.
- If only one male in the family is affected, the mother may be a carrier or the affected individual may have a *de novo* mutation, in which case the mother is not a carrier. No data are available on the frequency of *de novo* mutations in OTC deficiency.

Parents of a female proband

- A female with OTC deficiency may have a *de novo* gene mutation or she may have inherited the *OTC* mutation from either her mother or her father.
- If pedigree analysis reveals that the female proband is the only affected family member, it is reasonable to offer molecular genetic testing to both of her parents.

Sibs of a male proband

- The risk to sibs of a male proband depends on the carrier status of the mother.
- If the mother is a carrier, the chance of transmitting the *OTC* mutation is 50% in each pregnancy. Males who inherit the mutation will be affected; females who inherit the mutation will be carriers and may or may not have symptoms.
- If the mother of a male proband with no known family history of OTC deficiency does not have the *OTC* mutation identified in her son, the risk to sibs is low, but greater than that of the general population because of the possibility of germline mosaicism.

Sibs of a female proband

- The risk to the sibs of a female proband depends on the genetic status of the parents.
- If the mother of a female proband has the *OTC* mutation, the chance of transmitting the mutation in each pregnancy is 50%. Males who inherit the mutation will be affected; females who inherit the mutation will be carriers and may or may not have symptoms.
- If the father of a female proband has the *OTC* mutation, all of the proband's female sibs and none of the male sibs will inherit the mutation.
- When the parents do not have the *OTC* mutation identified in the female proband, the risk to the sibs of a female proband appears to be low, but is greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a male proband

- Most affected males do not reproduce.
- Some males with late-onset and/or mild disease survive and are fertile. They will pass the disease-causing mutation to all of their daughters and none of their sons. The females will have a range of possible phenotypic expression.

Offspring of a female proband. Women with an *OTC* mutation have a 50% chance of transmitting the disease-causing mutation to each child; sons who inherit the mutation will be affected; daughters will have a range of possible phenotypic expression.

Carrier Detection

Carrier detection for OTC deficiency is possible by molecular genetic testing if the disease-causing allele has been identified in the family.

Related Genetic Counseling Issues

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

OTC deficiency

- A significant number of carrier females have hyperammonemia and neurologic compromise presumed to be secondary to skewed X-chromosome inactivation. The risk for hyperammonemia is particularly high in pregnancy and the postpartum period. Drugs such as valproic acid and corticosteroids may also trigger a hyperammonemia crisis in a carrier.
- If a male is affected with late-onset disease, the risk for symptoms in a carrier female is much lower than in families in which a male is affected with early-onset severe disease.
- Carrier females may have abnormal results on cognitive testing even in the absence of hyperammonemia.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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, are carriers, or are at risk of being affected or carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk for the six urea cycle disorders is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation.

- Both disease-causing alleles of a family member with CPS1 deficiency, ARG deficiency, ASS1 deficiency, ASL deficiency, or NAGS deficiency must be identified before prenatal testing can be performed.
- The *OTC* disease-causing allele of an affected family member must be identified before prenatal testing for OTC deficiency can be performed.
- In families in which the mutation(s) cannot be detected by molecular genetic testing, linkage analysis is an option.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Note: It is the policy of *GeneReviews* to include in *GeneReviews*™ chapters any clinical uses of testing available from laboratories listed in the GeneTests™ Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with a urea cycle defect the following evaluations are recommended:

- Neurologic evaluation to assess overall neurologic function
- MRI to assess the degree of brain damage as recognizable in imaging studies
- Serum ammonia concentration and plasma amino acid analysis to monitor therapy
- Liver function tests, including coagulation tests to assess the overall status of the liver

The extent of disease in an individual diagnosed with a urea cycle disorder can be estimated by the rapidity of onset of neurologic symptoms, the degree to which the brain is affected, and to a lesser extent the serum ammonia concentration.

Treatment of Acute Manifestations

Once a diagnosis of a UCD is made, treatment should be tailored to the specific urea cycle disorder [Summar 2001 (click Guidelines for full text), Summar & Tuchman 2001 (click Guidelines for full text)]. Care of an infant should be provided by a team coordinated by a metabolic specialist in a tertiary care center. In the acute phase, the mainstays of treatment are the following:

1. Rapidly return plasma ammonia concentrations to normal physiologic levels. This is necessary even without a definitive diagnosis given the toxic effect of elevated plasma/serum ammonia concentration. The best way to reduce plasma ammonia concentration quickly is by dialysis. The faster the flow rate, the faster the clearance. The method employed depends on the affected individual's circumstances and available resources.

- Fastest is use of pump-driven dialysis, in which an extra corporeal membrane oxygenation (ECMO) pump is used to drive a hemodialysis machine.
- Other methods are hemofiltration (both arteriovenous and venovenous) and hemodialysis. These are more likely to be available than ECMO-driven dialysis. Note: Peritoneal dialysis is relatively ineffective for acute hyperammonemia and is generally not recommended.
- Dialysis can usually be discontinued when plasma ammonia concentration falls below 150 µmol/L, but may vary based on clinical evaluation by a clinician experienced in the treatment of metabolic disease. Affected individuals often experience a "rebound" hyperammonemia that may require further dialysis.

2. Perform pharmacologic interventions to allow alternative pathway excretion of excessive nitrogen (see Table 3)

- Nitrogen scavenger therapy (sodium phenylacetate and sodium benzoate) is available as an intravenous infusion for acute management and an oral preparation for long-term maintenance.
- Deficient urea cycle intermediates need to be replaced depending on the diagnosis; these can include arginine (IV infusion) and/or citrulline (oral preparation).

Table 3. IV Ammonia Scavenger Therapy Protocol

Deficiency	Patient Weight	Components of Infusion Solution		Dosage Provided			Administration
		Sodium phenylacetate & sodium benzoate [1, 2]	Arginine HCl injection, 10% [2]	Sodium phenyl-acetate	Sodium benzoate	Arginine HCl	
CPS & OTC	**0-20 kg**	2.5 mL/kg	2.0 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg	Loading [3] Maintenance [4]
ASS & ASL		2.5 mL/kg	6.0 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg	
CPS & OTC	**>20 kg**	55 mL/m^2	2.0 mL/kg	5.5 g/m^2	5.5 g/m^2	4000 mg/m^2	
ASS & ASL		55 mL/m^2	6.0 mL/kg	5.5 g/m^2	5.5 g/m^2	12000 mg/m^2	

1. Sodium phenylacetate/sodium benzoate must be diluted with sterile dextrose injection 10% before administration.

2. Before dilution

3. >90-120 minutes

4. >24 hours; arginine infusion not to exceed 150 mg/kg/h

- In persons with NAGS deficiency and in some with CPS1 deficiency, replacement of n-acetylglutamate with the analog molecule carbamyl glutamate (Carbaglu) can improve the clinical symptoms or in NAGS deficiency can be almost curative. This compound has recently become available in the US and should be added to the treatment regimen in a patient without a clear diagnosis at initial presentation. Dosing in adults and children is 100 mg/kg/day to 250 mg/kg/day divided into two to four doses. The only form currently available is an oral preparation; thus, administration of the medication by nasogastric/jejunal tube is necessary in the treatment of acute manifestations.

3. Treat catabolic state with calories from glucose, fats, and essential amino acids. The introduction of nutrition support in the following manner is necessary for patients on dialysis or hemofiltration in order to resolve the catabolic state while avoiding overuse of enteral feeds.

- Complete restriction of protein should not exceed 24-48 hours because depletion of essential amino acids results in protein catabolism and nitrogen release. Frequent (often daily) quantitative assessments of plasma amino acid concentrations can help optimize nutritional management by allowing the clinician to maintain adequate levels of essential amino acids without having to provide excess nitrogen. Maintenance of appropriate levels of essential amino acids is necessary to reverse the typical catabolic state because most acutely ill patients either present with essential amino acid deficiency or become deficient quickly.
- The placement of a nasogastric/jejunal tube at admission is warranted for slow drip administration of solutions of essential amino acids and infant formulas and administration of cofactors like carbamyl glutamate (analog of n-acetylglutamate).

- Multiple other strategies to combat catabolism can be used, including low dose continuous infusion of insulin with maintenance of adequate glucose delivery by high continuous delivery of carbohydrate containing fluids; however, caution is advised since patients are often exquisitely sensitive to either the glucose or insulin.

4. Reduce the risk for neurologic damage

- Use intravenous fluids (≥10% dextrose with one-quarter normal saline] for physiologic stabilization
- Use cardiac pressors as necessary while avoiding overhydration.
- Subclinical seizures which appear to be common in acute episodes may be treated and their presumed effects on cerebral metabolism in an otherwise compromised state has been addressed as follows:
  - Deep sedation (i.e., pentobarbital-induced coma) has been used to reduce brain metabolic demand; however, its utility is not proven.
  - The use of hypothermia for neuroprotection in hyperammonemia is currently under investigation.

Note: In patients with prolonged hyperammonemic coma and evidence for severe neurologic damage, the relative risks versus benefits of all the treatments discussed above should be considered.

Long-Term Treatment of Manifestations

Decrease nitrogen load with dietary restriction of protein.

- In general infants require 1.2 to 2 g of protein/kg body weight. Typically half of the required protein is provided as essential amino acids and half as natural protein.
- Adolescents and adults have requirements that are typically lower than those of younger children.
- Although restriction is the mainstay of therapy, excessively low protein diets which induce catabolism are as bad as high protein loads in these patients. Careful monitoring by amino acid profile is warranted.

Use nitrogen scavengers to provide alternative routes for nitrogen disposal.

- Sodium phenylbutyrate is converted in the gut to sodium phenylacetate, which is conjugated in the liver with glutamine to form phenylacetylglutamine, which is excreted by the kidneys.

  Note: Glycerol phenylbutyrate, which is significantly more palatable than sodium phenylbutyrate, may be added to the treatment regimen when it becomes available (possibly in the near future).
- Sodium benzoate is conjugated in the liver with glycine to make hippuric acid, which is excreted by the kidneys.

Prompt replacement of citrulline or arginine may be necessary depending on whether the defect is in a proximal or distal urea cycle disorder. Dosing of IV arginine in proximal urea cycle disorders begins at 200 mg/kg (see Table 3) but may be adjusted to maintain plasma arginine concentration around the 75th percentile. Note: Following liver transplantation supplementation with either arginine or citrulline may still be necessary since the gut is considered the primary exporter of these compounds.

- Citrulline (for proximal urea cycle defects) offers the advantage of incorporating aspartate into the pathway thus pulling one additional nitrogen molecule into the cycle.
- Overdosing of arginine with very high plasma concentrations is thought to be associated with long-term neurologic problems similar to those seen in ARG deficiency.

Carbamyl glutamate (Carbaglu) may be used to promote normal or near-normal function of the CPS1 enzyme in NAGS deficiency and in individuals with CPS1 deficiency who are responsive to therapy.

Liver transplantation

- In patients with severe types of urea cycle disorders, liver transplantation remains the most effective means of preventing further hyperammonemic crises. Factors affecting the decision for liver transplantation include the extent of neurologic damage and the extent of liver damage (in ASL deficiency).
- Following liver transplantation for ASS deficiency or ASL deficiency, hyperammonemia and tolerance of dietary protein improve; however, it is not clear at this time if other long-term physiologic problems may result from interactions in other pathways such as the nitric oxide production system, because the enzymes ASS and ASL are ubiquitously expressed.

Prevention of Primary Manifestations

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

Prevention of Secondary Complications

Over-restriction of protein/amino acids is one of the most common causes for reaccumulation of ammonia and poor growth [Author, personal observation]. Gastrostomy tube feedings help avoid malnutrition in patients who self-restrict protein intake.

Other

- Minimize risk of respiratory and gastrointestinal illnesses through home care.
- Immunize on the usual schedule.
- Provide multivitamin and fluoride supplementation.
- Use antipyretics appropriately. Note: Ibuprofen is preferred over acetaminophen.

Surveillance

The following measures are appropriate:

- Routine monitoring of all patients by a physician experienced in the care of urea cycle disorders:
  - The age of the individual and the severity of the UCD determine the frequency of clinic visits and monitoring.
  - Long-term developmental evaluation should be considered in all patients in order to judge the efficacy of treatment and nutritional support.

- Monitoring for hyperammonemia following a large fracture or other trauma in which significant internal bleeding occurs

Agents/Circumstances to Avoid

The following should be avoided or regarded as cause for alert:

- Valproic acid (Depakote) because of its effects on function of the enzyme CPS1
- Prolonged fasting or starvation
- Intravenous steroids
- Large boluses of protein or amino acid
- Excessive protein restriction
- Illness
- Bone fractures or excessive bruising
- Dehydration
- Any physiologic or psychological stress (e.g., birthdays, prom, weddings, examinations)

Evaluation of Relatives at Risk

Molecular genetic testing (in those families in which the disease-causing mutations are known) can identify affected at-risk relatives before symptoms occur, allowing prompt intervention with dietary therapy and other measures to prevent hyperammonemia.

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

Registries

Contact information for voluntary patient registries is provided by *GeneReviews* staff.

Urea Cycle Disorders Consortium Registry
Phone: 815-333-4014
Email: jseminar@cnmc.org
rarediseasesnetwork.epi.usf.edu/ucdc

Therapies Under Investigation

The NIH-funded Urea Cycle Disorders Consortium provides expert diagnosis and treatment of urea cycle disorders as well as clinical and therapeutic studies.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Mannitol is thought to be ineffective in treating the hyperammonemia-related cerebral edema of the UCDs.

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

Resources

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page PubMed

Published Guidelines/Consensus Statements

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Chapter Notes

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- 1 September 2011 (me) Comprehensive update posted live
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- 29 January 2001 (mls) Original submission

Figures

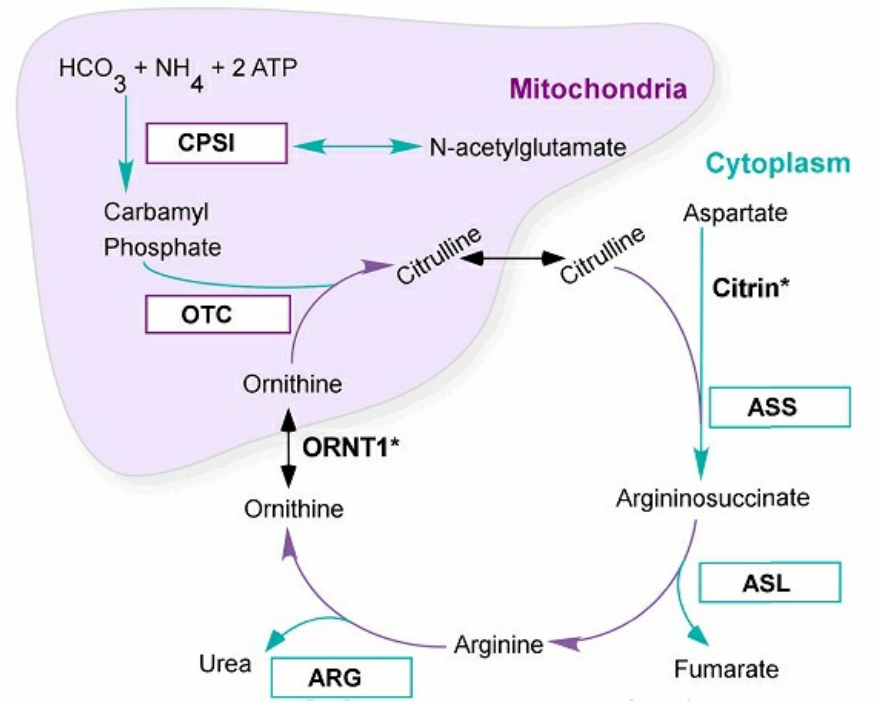

Figure 1. The urea cycle (see Differential Diagnosis)

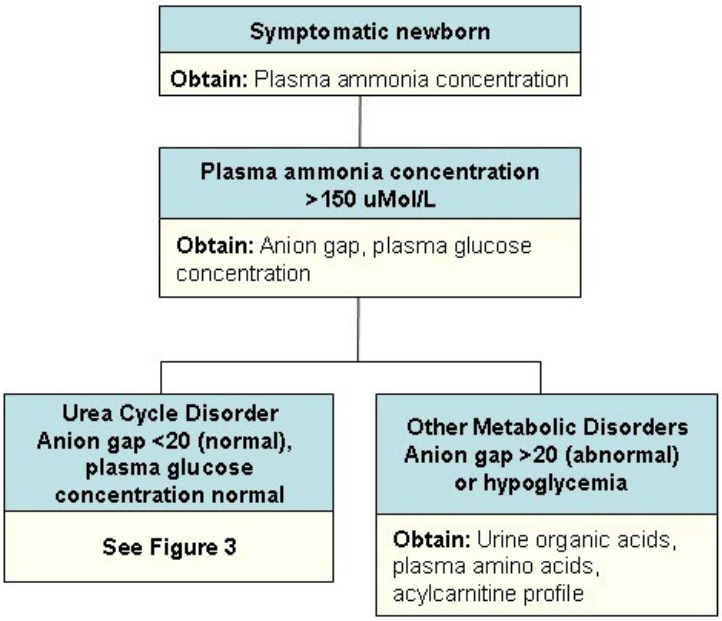

Figure 2. Steps in the evaluation of a newborn with hyperammonemia

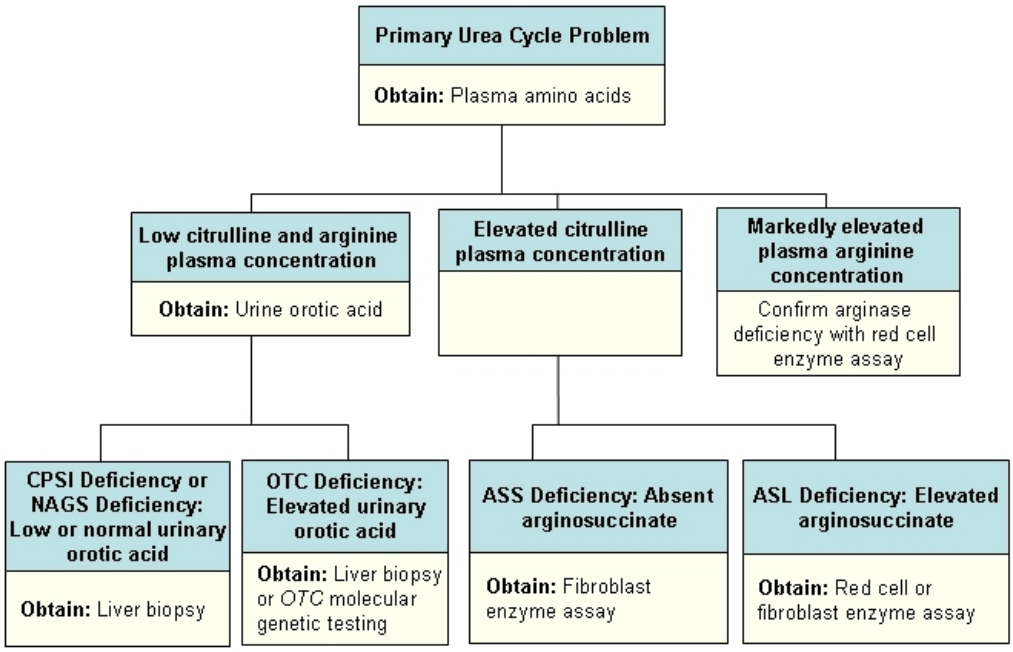

Figure 3. Testing used in the diagnosis of urea cycle disorders