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Urea Cycle Disorders Overview

[Includes: Carbamoylphosphate Synthetase I Deficiency (CPSI Deficiency, Carbamyl Phosphate Synthetase Deficiency), Citrullinemia (Argininosuccinic Acid Synthetase Deficiency, ASS Deficiency), Argininosuccinicaciduria (Argininosuccinic Acid Lysase Deficiency, ASL Deficiency), Argininemia (Arginase Deficiency, ARG Deficiency), N-acetyl Glutamate Synthetase Deficiency (NAGS Deficiency), Ornithine Transcarbamylase Deficiency (OTC Deficiency)]

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Posted: 29 April 2003

Summary

Disease characteristics. The urea cycle disorders (UCD) result from defects in the metabolism of the extra nitrogen produced by the breakdown of protein and other nitroge-containing molecules. Severe deficiency or total absence of activity of any of the first four enzymes (CPSI, 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 urea cycle disorder often initially appear normal but rapidly develop cerebral edema and the related signs of lethargy; anorexia; hyperventilation or hypoventilation; hypothermia; seizures; neurologic posturing; and coma. 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 [Bourrier et al 1988]. The hyperammonemia is less severe and the symptoms more subtle. In patients with partial enzyme deficiencies, the first recognized clinical episode may be delayed for months or years. The mainstays of treatment are 1) reducing plasma ammonia concentration, 2) pharmacologic management to allow alternative pathway excretion of excess nitrogen, 3) reducing the amount of nitrogen in the diet, 4) reducing catabolism through the introduction of calories supplied by carbohydrates and fat, and 5) reducing the risk of neurologic damage.

Diagnosis/testing. The diagnosis of a urea cycle disorder is based on evaluation of clinical, biochemical, and molecular data. A plasma ammonia concentration of 150 mmol/L or higher, associated with a normal anion gap and a normal serum glucose concentration, is a strong indication for the presence of a UCD. Plasma quantitative amino acid analysis can be used to diagnose a specific urea cycle disorder. Plasma concentration of arginine may be reduced in all urea cycle disorders, except ARG deficiency, in which it is elevated 5-7 fold. 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 CPSI) and a substrate for the distal enzymes (ASS, ASL, ARG). Urinary orotic acid is measured to distinguish CPSI deficiency and NAGS deficiency from OTC deficiency. A definitive diagnosis of CPSI deficiency, OTC deficiency, or NAGS deficiency depends on determination of enzyme activity from a liver biopsy specimen; however, the combination of family history, clinical presentation, amino acid and orotic acid testing, and, in some cases, molecular genetic testing are often sufficient for diagnostic confirmation, eliminating the risks of liver biopsy. Molecular genetic testing is clinically available for CPSI deficiency, OTC deficiency, citrullinemia, and argininosuccinicaciduria.

Genetic counseling. Deficiencies of CPSI, ASS, ASL, NAGS, and ARG are inherited in an autosomal recessive manner. OTC deficiency is inherited in an X-linked manner. Prenatal testing for CPSI deficiency is available by linkage analysis. Prenatal testing for OTC deficiency is available by either linkage analysis or direct mutation detection. Prenatal testing for ASS, ASL, and ARG deficiencies is available by biochemical analysis of fetal cells obtained by amniocentesis at 16-18 weeks' gestation or by chorionic villus sampling (CVS) at about 10-12 weeks' gestation.

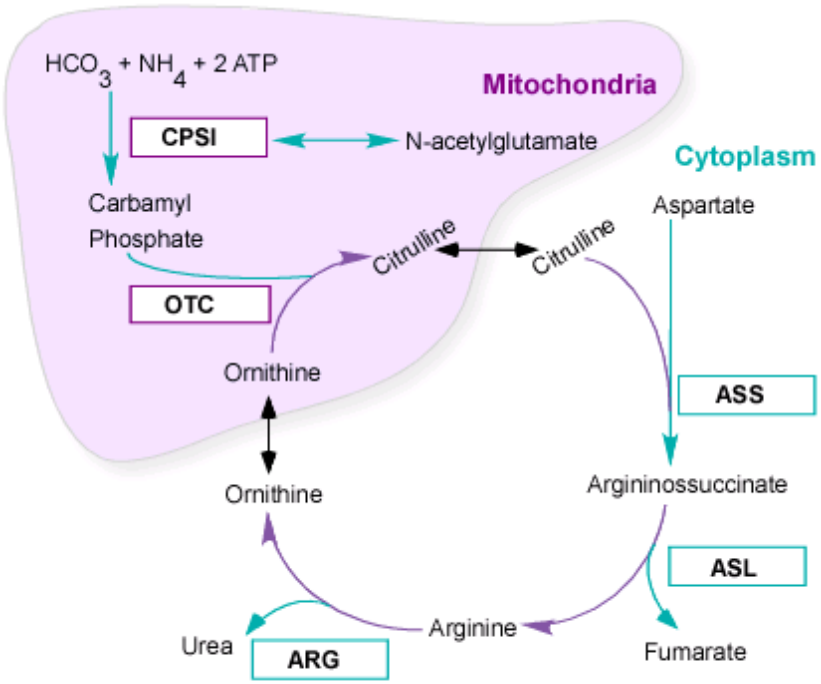
Definition

Clinical Manifestations

The urea cycle disorders (UCD) result from defects in the metabolism of the extra nitrogen produced by the breakdown of protein and other nitrogen containing molecules. This extra nitrogen is converted into ammonia (NH4) and transported to the liver where it is processed via the urea cycle, composed of five enzymes in the direct pathway and one enzyme, NAGS, which makes a necessary cofactor (Figure 1). The enzymes in order in the pathway are:

- 1: Carbamyl phosphate synthase I **(CPSI)**
- 2: Ornithine transcarbamylase **(OTC)**
- 3: Argininosuccinic acid synthetase **(ASS)**
- 4: Argininosuccinic acid lyase **(ASL)**
- 5: Arginase **(ARG)**
- Co-factor: N-acetyl glutamate synthetase **(NAGS)**

Figure 1. The Urea Cycle.



Deficiency of any of the first four enzymes (CPSI, 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. Since no effective secondary clearance system for ammonia exists, disruption of this pathway results in the rapid development of symptoms. Severity of the disease is influenced by the position of the defective enzyme in the pathway and the severity of the enzyme defect. The catabolism normally present in the newborn period combines with the immaturity of the neonatal liver to accentuate defects in these enzymes [Batshaw 1984, Summar 2001, Summar & Tuchman 2001]. Infants with a urea cycle disorder often initially appear normal but rapidly develop cerebral edema and the related signs of lethargy; anorexia; hyperventilation or hypoventilation; hypothermia; seizures; neurologic posturing; and coma.

Because newborns are usually discharged from the hospital within 1-2 days after birth, the symptoms of a urea cycle disorder are often not seen until 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 non-specific: failure to feed, loss of thermoregulation with a low core temperature, and somnolence [Brusilow 1985, Batshaw & Berry 1991, 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 [Brusilow 1985, Batshaw & Berry 1991, Summar 2001]. About 50% of neonates with severe hyperammonemia have seizures. Hyperventilation, secondary to cerebral edema, is a common early finding in a hyperammonemic attack, which causes a respiratory alkalosis. Hypoventilation and respiratory arrest follow as pressure increases on the brain stem [Batshaw 1984, Brusilow 1985, Batshaw & Berry 1991, Summar 2001, Summar & Tuchman 2001].

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 [Bourrier et al 1988]. The hyperammonemia is less severe and the symptoms more subtle. In patients 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, cyclical 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 non-specific brain atrophy may be seen subsequently on MRI [Batshaw 1984, Brusilow 1985, Bourrier et al 1988].

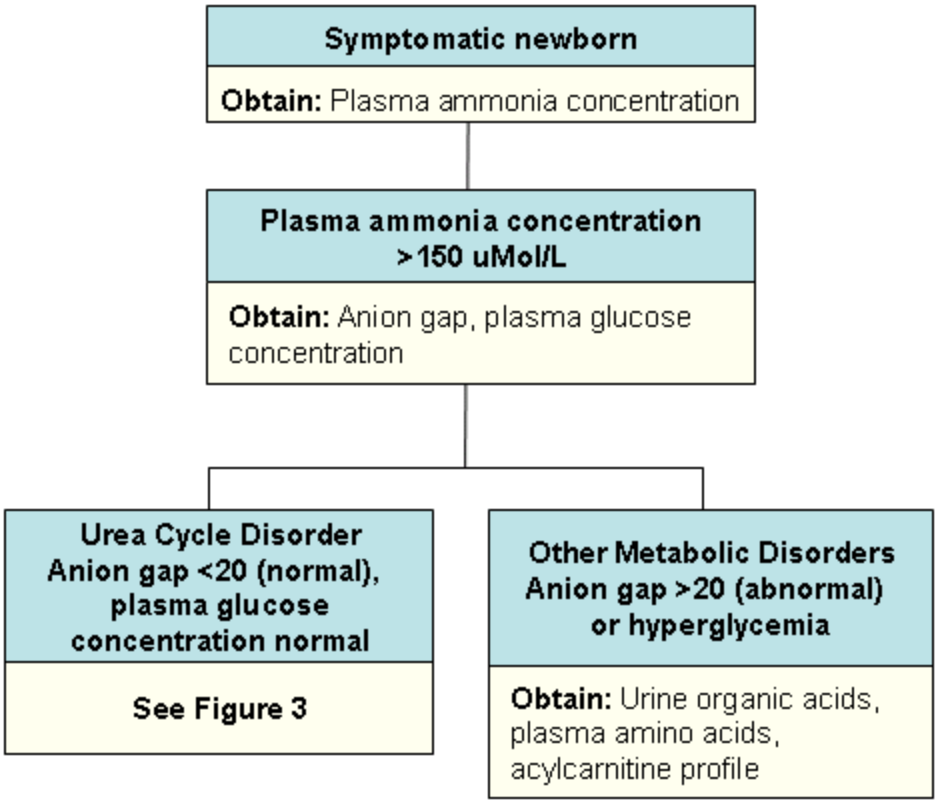
Deficiency of the fifth enzyme, arginase, results in a chronic debilitating disease affecting primarily the nervous system [Batshaw 1984].

Establishing the Diagnosis

Symptomatic individual. The diagnosis of a urea cycle disorder is based on evaluation of clinical, biochemical, and molecular data. The algorithm in Figure 2 may assist with the evaluation of a newborn with hyperammonemia, but other factors such as the overall health of the liver, the duration of hyperammonemia, and pharmacologic agents already given to the patient need to be considered.

Laboratory data useful in the diagnosis of UCDs include plasma ammonia concentration, pH, CO2, the anion gap, quantitative plasma amino acids analysis, and analysis of urine organic acids and urine orotic acid. A plasma ammonia concentration of 150 mmol/L or higher, associated with a normal anion gap and a normal serum glucose concentration, is a strong indication for the presence of a UCD [Summar & Tuchman 2001]. Figure 2 highlights the use of recommended diagnostic tests.

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



Newborn screening. Current extended newborn screening panels using tandem mass spectrometry detect abnormal concentrations of analytes associated with ASS deficiency and ASL deficiency, although the sensitivity and specificity of this screening for these disorders is unknown. CPSI deficiency, OTC deficiency, and NAGS deficiency cannot be detected using tandem mass spectrometry. Although argininemia has been detected by these methods, newborn screening cannot be expected to reliably detect all cases.

Differential Diagnosis

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.

Prevalence

The overall incidence of urea cycle disorders is considered to be around 1:30,000 live births; however, no population studies have been performed.

Causes

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

Ornithine transcarbamylase deficiency (OTC deficiency). Absence of its activity in males is as severe as CPSI deficiency. Approximately 15% of carrier females develop hyperammonemia during their lifetime and many require chronic medical management [Brusilow 1995].

Citrullinemia (ASS deficiency). The hyperammonemia in this disorder is quite severe. These patients are able to incorporate some waste nitrogen into urea cycle intermediates, which makes treatment slightly easier.

Argininosuccinic aciduria (ASL deficiency). This disorder also presents 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. Treatment of these patients often only requires supplementation of arginine. This disorder is marked by 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. These patients can also develop trichorrhexis nodosa, a node-like appearance of fragile hair, which usually responds to arginine supplementation [Batshaw 1984, Brusilow 1985, Batshaw & Berry 1991, Summar 2001, Summar & Tuchman 2001]. Reports exist of affected patients who have never had prolonged coma, but nevertheless have significant developmental disabilities.

Argininemia (ARG deficiency). This disorder is not typically characterized by rapid-onset hyperammonemia. These patients develop progressive spasticity. They can also develop tremor, ataxia, and choreoathetosis. Growth is also affected [Cederbaum et al 1977, Cederbaum et al 1982].

NAGS deficiency. Deficiency of this enzyme has been described in a number of patients. Symptoms mimic those of CPSI deficiency, since CPSI is rendered inactive in the absence of NAG. Mutation in the gene *NAGS* encoding the protein N-acetyl glutamate synthetase are causative [Caldovic et al 2003].

Molecular Genetics

Table 1. Molecular Genetics of Urea Cycle Disorders

Disease Name	Gene	Locus	Protein	Molecular Genetic Test Availability
Carbamoylphosphate synthetase I deficiency	*CPS1*	2q35	Carbamoyl-phosphate synthase ammonia	Clinical Testing
Ornithine transcarboxylase deficiency	*OTC*	Xp21.1	Ornithine carbamoyltransferase	Clinical Testing
Citrullinemia	*ASS*	9q34	Argininosuccinate synthase	Clinical Testing
Argininosuccinicaciduria	*ASL*	7cen-q11.2	Argininosuccinate lyase	Research
Argininemia	*ARG1*	6q23	Arginase 1	

NAGS deficiency	*NAGS*	17q21.3	N-acetyl glutamate synthetase	

Evaluation Strategy

The following information is used to distinguish the specific urea cycle defect in an individual meeting the diagnostic criteria for a urea cycle defect.

Family History

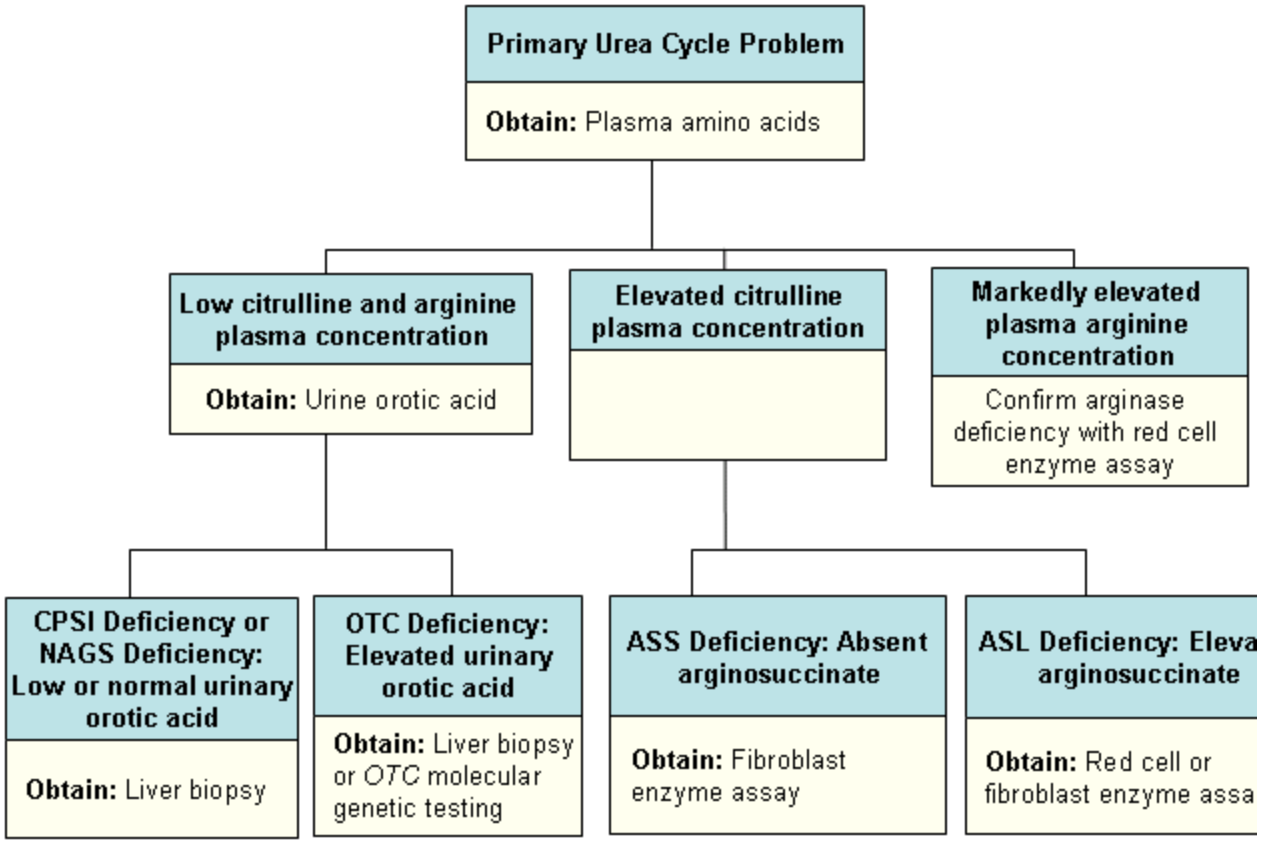
A three-generation family history with attention to other relatives (particularly children) with neurologic signs and symptoms suggestive of UCD should be obtained. Documentation of relevant findings in relatives can be accomplished either through direct examination of those individuals or review of their medical records including the results of biochemical testing, DNA-based 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 defects; however, trichorrhexis nodesa can be suggestive of ASA deficiency.

Testing

Figure 3. Testing used in the diagnosis of a specific urea cycle disorder.



- **Plasma quantitative amino acid analysis** can be used to arrive at a tentative diagnosis. Since the liver is not fully mature, sick newborns have plasma amino-acid concentrations that are often quite different from those in children and adults.
    - **Plasma concentrations of glutamine, alanine, and asparagine,** which serve as storage forms of waste nitrogen, are frequently elevated.
    - **Plasma concentration of arginine** may be reduced in all urea cycle disorders, except ARG deficiency, in which it is elevated 5-7 fold; however, in partial defects, it is frequently normal.
    - **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 CPSI) and a substrate for the distal enzymes (ASS, ASL, ARG). Consequently, plasma citrulline is absent or present only in trace amounts in neonatal-onset CPSI deficiency and OTC deficiency and present in low to low-normal concentrations in late-onset disease. Plasma concentration of citrulline is markedly elevated in citrullinemia and argininosuccinic acidemia. Patients with citrullinemia have up to a 100-fold elevation in plasma citrullinemia concentration. Patients with argininosuccinic aciduria (ASL deficiency) show a more moderate increase in plasma citrulline concentration of about 10-fold, associated with large amounts of argininosuccinic acid, which normally is absent [Batshaw 1984, Brusilow 1985, Batshaw & Berry 1991, Summar 2001, Summar & Tuchman 2001].
- **Urinary orotic acid is measured** to distinguish CPSI deficiency from OTC deficiency. It

is significantly elevated in OTC deficiency and normal or low in CPSI deficiency. Urinary orotic acid excretion can also be increased in argininemia (ARG deficiency) and citrullinemia (ASS deficiency) [Batshaw 1984].

The argininosuccinate chromatographic peak may co-elute with leucine or isoleucine, resulting in an apparent increase in one of these amino acids, but its anhydrides eluting later in the run should allow the correct identification of argininosuccinate. Deficiencies of ASS, ASL, and ARG can be diagnosed on the basis of the amino acid pattern.

- **Enzyme activity.** Although a definitive diagnosis of CPSI deficiency, OTC deficiency, or NAGS deficiency depends on determination of enzyme activity from a liver biopsy specimen [Summar & Tuchman 2001], often the combination of family history, clinical presentation, amino acid and orotic acid testing, and in some cases, molecular genetic testing are often sufficient for diagnostic confirmation, eliminating the risks of liver biopsy.

- **Molecular genetic testing** is clinically available for:

  - **CPSI Deficiency.** Linkage analysis is used for carrier detection and prenatal diagnosis. Linkage studies are based upon accurate clinical diagnosis of CPSI deficiency in the affected family member and accurate understanding of the genetic relationships in the family. Linkage analysis is dependent on the availability and willingness of family members to be tested. The markers used for CPSI deficiency linkage are highly informative and very tightly linked (or intragenic) to the CPS1 locus; thus, they can be used in more than 95% of families with greater than 98% accuracy.

  - **OTC Deficiency.** Seventy-five to eighty percent of patients have an *OTC* mutation, identifiable by mutation scanning. Molecular genetic testing is used for diagnosis, carrier detection, and prenatal diagnosis.

  - **Citrullinemia.** Linkage analysis is used for carrier detection and prenatal diagnosis.

  Molecular genetic testing for the other disorders is available on a research basis only.

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 or cultural issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Deficiencies of CPSI, ASS, ASL, NAGS, and ARG are inherited in an autosomal recessive manner. OTC deficiency is inherited in an X-linked manner.

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, the sibs of an affected individual have a 25% chance of being affected, a 50% chance of being unaffected and a 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 testing. Biochemical methods (loading studies or stable isotope studies) may be an option for ASS, ASL, or ARG deficiency carrier testing. Molecular genetic methods may be an option for ASS, ASL, NAGS, or CPSI deficiency carrier testing in 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* gene mutation and thus the mother is not a carrier. No data are available, however, on the frequency of *de novo* gene mutations [Tuchman et al 1995].

Parents of a female proband

- A female with OTC deficiency may have a new 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, there is a 50% chance of transmitting the *OTC* mutation in each pregnancy.
  - Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and may or may not have symptoms.
- If the mother of an isolated male proband does not have in her leukocytes the *OTC* mutation identified in her son, the risk to sibs is low, but is greater than that of the general population, since the possibility of germline mosaicism exists.

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 gene mutation, the chance of transmitting the *OTC* mutation in each pregnancy is 50%.
  - Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and may or may not have symptoms.
- If the father of a female proband has the gene mutation, all of the proband's female sibs, but none of the male sibs, will inherit the mutation.
- When the parents do not have in leukocytes 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, since the possibility of germline mosaicism exists.

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* gene 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 testing. Carrier detection for OTC deficiency can be accomplished by an allopurinol challenge test that enhances the excretion of orotic acid in the urine. This carrier test is not recommended for pregnant at-risk individuals. The indication for such testing is diminishing because of the availability and utility of molecular genetic testing and the increased variability of biochemical testing during pregnancy.

Related Genetic Counseling Issues

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 post-partum 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 cases in which a male is affected with early-onset severe disease.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methods and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particulately relevant in situations in which molecular genetic testing is available on a research basis only or by linkage analysis, or if the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Testing for prenatal diagnosis is available for all of these disorders.

CPSI deficiency. Prenatal testing for CPSI deficiency is available by linkage analysis in families with confirmation of the diagnosis based on enzymatic testing on hepatic tissue from the affected individual and known to have informative markers. DNA can be extracted from fetal cells obtained by amniocentesis at 16-18 weeks' gestation* or chorionic villus sampling (CVS) at about 10-12 weeks' gestation.

OTC deficiency. Prenatal testing is available by either linkage analysis or direct mutation detection. DNA can be extracted from fetal cells obtained by amniocentesis at 16-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The *OTC* disease-causing allele of an affected family member must be identified or linkage established in the family before prenatal testing can be performed. In either method, DNA from the affected patient or the carrier mother is needed; in linkage analysis, DNA from both parents and patient is needed.

ASL deficiency. In ASL deficiency, the amniotic fluid can be assayed for argininosuccinate activity [Blau et al 2003]. Analysis of ASA in the amniotic fluid is reliable.

ASS, ARG deficiency. Because these enzymes are ubiquitously expressed, prenatal testing is available by biochemical analysis of fetal cells obtained by amniocentesis at 16-18 weeks' gestation* or chorionic villus sampling (CVS) at about 10-12 weeks' gestation.

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

Management

Care of an infant should be provided by a team coordinated by a metabolic specialist in a specialized center. In the acute phase, the mainstays of treatment are 1) rapidly reducing plasma ammonia concentration,* 2) pharmacologic management to allow alternative pathway excretion of excess nitrogen, 3) reducing the amount of excess nitrogen in the diet, 4) reducing catabolism through the introduction of calories supplied by carbohydrates and fat, and 5) reducing the risk of neurologic damage.

* Does not generally apply to argininemia.

- The best way to reduce plasma ammonia quickly is by dialysis; the faster the flow rate, the faster the clearance. The method employed depends on the patient's circumstances and available resources. Fastest is use of pump-driven dialysis, in which an extra corporeal membrane oxygenation (ECMD) pump is used to drive a hemodialysis (HD) machine. Other methods are hemofiltration (both arteriovenous and venovenous), hemodialysis, peritoneal dialysis, and continuous-drainage peritoneal dialysis. Dialysis can usually be discontinued when plasma ammonia concentration falls below 200 µmol/l. Patients will often experience a "rebound" hyperammonemia that may require further dialysis.
- Blocking the production of ammonia is accomplished by the intravenous administration of arginine chloride and a combination of the nitrogen scavenger drugs sodium phenylacetate and sodium benzoate. A loading dose is followed by maintenance administration, which is initially intravenous and converted to oral when the patient is stable.
- In acutely ill patients, calories should be provided as carboydrate and fat, either intravenously as glucose, and intralipid or orally as protein-free oral formula, such as Mead Johnson 80056 or Ross Formula ProPhree; however, complete restriction of protein

should not exceed 24-48 hours, because depletion of essential amino acids results in protein catabolism and nitrogen release. Patients should be transitioned from parenteral to enteral feeds as soon as possible. In early treatment, feeding 1.0 to 1.5g of protein/kg body weight with 50% as essential amino acids is advised.
- Cautionary measures are physiologic stabilization with intravenous fluids (10% dextrose with one quarter normal saline) and cardiac pressors as necessary while avoiding overhydration and resulting cerebral edema, the duration of which correlates with poor neurologic outcome.

Long-term management is focused on restriction of dietary protein through use of specialized formulas and administration of oral nitrogen scavenging drugs. Home care is recommended with gastrostomy tube feedings as necessary, and minimizing risk of intercurrent respiration and gastrointestinal illness is recommended.

Immunizations can be provided on the usual schedule. Mutivitamin and fluoride supplementation and appropriate use of antipyretics are indicated. Ibuprofen is preferred over acetaminophen.

Once a diagnosis is made, treatment should be tailored to the specific urea cycle disorder [Summar 2001].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. -ED.

- **National Urea Cycle Disorders Foundation**
  4841 Hill Street
  La Canada, CA 91011
  Phone: 800-38NUCDF
  Fax: 818-790-2460
  Email: info@nucdf.org
  www.nucdf.org

- **Climb (Children Living with Inherited Metabolic Diseases)**
  Climb Building
  176 Nantwich Road
  Crewe, CW2 6BG
  United Kingdom
  Phone: 0870 7700 326
  Fax: 0870 7700 327
  Email: info@climb.org.uk
  www.climb.org.uk

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