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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 the extra nitrogen produced by the breakdown of protein and other nitrogen-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 appear normal initially 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; the hyperammonemia is less severe and the symptoms more subtle. In individuals with partial enzyme deficiencies, the first recognized clinical episode may be delayed for months or years.

Diagnosis/testing. The diagnosis of a urea cycle disorder is based on evaluation of clinical, biochemical, and molecular genetic 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 five- to sevenfold; 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 is often sufficient for diagnostic confirmation, eliminating the risks of liver biopsy. Molecular genetic testing for OTC deficiency is clinically available in the US. Molecular genetic testing for CPSI deficiency, NAGS deficiency, citrullinemia type I, arginase deficiency, and argininosuccinicaciduria is clinically available in laboratories outside the US.

Management. The mainstays of treatment for urea cycle disorders include dialysis to reduce plasma ammonia concentration, intravenous administration of arginine chloride and nitrogen scavenger drugs to allow alternative pathway excretion of excess nitrogen, restriction of protein for 24-48 hours to reduce the amount of nitrogen in the diet, providing calories as carbohydrates (intravenously as glucose) and fat (intralipid or as protein-free formula) to reduce catabolism, and physiologic stabilization with intravenous fluids and cardiac pressors (while avoiding overhydration and resulting cerebral edema) to reduce the risk of neurologic damage.

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 using molecular genetic testing is available for five of the six urea cycle disorders if the disease-causing mutations have been identified in an affected family member. For families in which the disease-causing mutations have not been identified, prenatal testing may be available by linkage analysis for families with OTC deficiency or CPSI deficiency and biochemical testing for families with ASS, ASL, or ARG deficiency.

Definition

Clinical Manifestations

The urea cycle is composed of five catalytic enzymes, a cofactor producer, and at least two transport proteins (Figure 1) [Krebs & Henseleit 1932,Jackson et al 1986]. The urea cycle is the sole source of endogenous production of arginine and it is the principal mechanism for the clearance of waste nitrogen resulting from protein turnover, the metabolism of other compounds like adenosine monophosphate, and dietary intake. This extra nitrogen is converted into ammonia (NH4) and transported to the liver where it is processed. The urea cycle disorders (UCD) result from inherited molecular defects which compromise this clearance.

The components of the pathway are:

- Carbamyl phosphate synthase I **(CPSI)**
- Ornithine transcarbamylase **(OTC)**
- Argininosuccinic acid synthetase **(ASS)**
- Argininosuccinic acid lyase **(ASL)**
- Arginase **(ARG)**
- Cofactor: N-acetyl glutamate synthetase **(NAGS)**

Severity of the disease 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 (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.

Because no effective secondary clearance system for ammonia exists, disruption of this pathway results in the rapid development of symptoms. 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, Pearson et al 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 one to two 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 nonspecific: 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. 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 cerebral edema is a common early finding in hyperammonemic attacks that results in 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. The hyperammonemia is less severe and the symptoms more subtle. 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, 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 nonspecific brain atrophy may be seen subsequently on MRI [Batshaw 1984, Brusilow 1985, Bourrier et al 1988].

Defects in the fifth enzyme in the pathway cause arginase deficiency, a more subtle disorder involving neurologic symptoms.

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 individual 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 of a UCD [Summar & Tuchman 2001]. Figure 2 highlights the use of recommended diagnostic tests.

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 such 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.

Defects in the transporter proteins for ornithine (HHH syndrome) and aspartate (citrin deficiency) are clinically different from the classic urea cycle disorders.

Citrin Deficiency —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 the ages of 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 one year of age 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; NICCD is generally not severe. Symptoms disappear by age one year with fat-soluble vitamin supplementation and lactose-free formulas or formulas containing medium-chain triglycerides. 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 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 known to be associated with citrin deficiency. Citrin deficiency is inherited in an autosomal recessive manner.

Ornithine Translocase Deficiency (HHH Syndrome)—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.

Prevalence

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

Causes

Carbamoylphosphate synthetase I deficiency (CPSI deficiency). Along with OTC deficiency, deficiency of CPSI is the most severe of the urea cycle disorders. Individuals with complete CPSI 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 CPSI deficiency. Approximately 15% of carrier females develop hyperammonemia during their lifetime and many require chronic medical management [Brusilow 1995].

Citrullinemia type I (ASS deficiency). The hyperammonemia in this disorder is quite severe. Affected individuals 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 affected individuals often requires only supplementation of arginine. ASL deficiency 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. Affected individuals 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]. Affected individuals who have never had prolonged coma but nevertheless have significant developmental disabilities have been reported.

Arginase deficiency (hyperargininemia; ARG deficiency). This disorder 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 1977, Cederbaum et al 1982, Cederbaum et al 2004].

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

Molecular Genetics

See Table 1 for the genes associated with each disorder and the availability of molecular genetic testing.

Table 1. Molecular Genetics of Urea Cycle Disorders

Disease Name	Gene Symbol	Chromosomal Locus	Protein Name	Molecular Genetic Test Availability
Carbamoylphosphate synthetase I deficiency	*CPS1* [1]	2q35	Carbamoyl-phosphate synthase ammonia	Clinical Testing
Ornithine transcarboxylase deficiency	*OTC*	Xp21.1	Ornithine carbamoyltransferase	Clinical Testing
Citrullinemia type I	*ASS*	9q34	Argininosuccinate synthase	Clinical Testing
Argininosuccinicaciduria	*ASL*	7cen-q11.2	Argininosuccinate lyase	Clinical Testing
Arginase deficiency	*ARG1*	6q23	Arginase 1	Clinical Testing
NAGS deficiency	*NAGS*	17q21.3	N-acetyl glutamate synthetase	Clinical Testing

1. Summar et al 2003

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, 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 defects; however, trichorrhexis nodosa can be suggestive of ASL deficiency.

Testing

- **Plasma quantitative amino acid analysis** (Figure 3) 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 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 five- to sevenfold; 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).

- Plasma citrulline is either 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.
- Individuals with citrullinemia type I have up to a 100-fold elevation in plasma citrullinemia concentration.
- Individuals with argininosuccinic aciduria (ASL deficiency) show a more moderate (approximately tenfold) increase in plasma citrulline concentration, associated with large amounts of argininosuccinic acid, which is normally 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 type I (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.** Such testing is used for diagnosis, carrier detection, and prenatal diagnosis.
  - Molecular genetic testing for OTC and NAGS deficiency is clinically available both within and outside the US.
  - Molecular genetic testing for CPSI deficiency, citrullinemia type I and II, arginase deficiency, and argininosuccinicaciduria is reported to be available in laboratories outside the US.
  - Linkage analysis is available for CPSI deficiency and citrullinemia type I in the US.

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 CPSI, ASS, 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

Biochemical methods (loading studies or stable isotope studies) may be an option for ASS, ASL, or ARG deficiency carrier testing. Molecular genetic testing is an option for carrier testing of at-risk family members for ASS, ASL, and NAGS deficiencies if both disease-causing alleles have been identified in an affected family member.

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* gene mutation, in which case the mother is not a carrier. No data are available 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 *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.

- 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 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 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 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 Detection

Carrier detection for OTC deficiency is available by molecular genetic testing if the disease-causing allele has been identified in an affected relative.

Although carrier detection can be accomplished by an allopurinol challenge test that enhances the excretion of orotic acid in the urine, such testing is rarely used because of the availability of molecular genetic testing and the recommendation that allopurinol challenge testing not be performed 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 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 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 methodology 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 particularly 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

Prenatal diagnosis is available for all six urea cycle disorders.

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 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation.

- Both disease-causing alleles of a family member with CPSI deficiency, ARG deficiency, ASS 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 can be performed for OTC deficiency.

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

CPSI Deficiency—Linkage analysis. Prenatal diagnosis using linkage may be available for families if both mutations have not been identified in an affected family member. Linkage must be established in the family before prenatal testing can be performed. Confirmation of the diagnosis based on enzymatic testing on hepatic tissue from the affected individual is needed prior to linkage analysis.

OTC Deficiency—Linkage analysis. Prenatal testing may be available by linkage analysis for families if the disease-causing mutation is not identified in an affected family member. Linkage must be established in the family before prenatal testing can be performed. DNA from both parents and from the affected individual is needed.

ASS Deficiency—Biochemical genetic testing. Prenatal testing may be available by linkage analysis for families if the disease-causing mutation is not identified in an affected family member. Linkage must be established in the family before prenatal testing can be performed. DNA from both parents and the proband is needed.

ASL Deficiency—Biochemical genetic testing. Prenatal testing for pregnancies at increased risk is possible by assay of argininosuccinate activity in amniotic fluid obtained by amniocentesis usually performed at about 15-18 weeks' gestation [Bachmann 2003].

ARG Deficiency—Biochemical genetic testing. Arginase is not expressed in cultured amniotic fluid cells or chorionic villus samples. Arginase is expressed in red blood cells; therefore, prenatal diagnosis is possible using PUBS (prenatal umbilical blood sampling) [Hewson et al 2003].

Management

Evaluations at Initial Diagnosis

The extent of disease 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 Manifestations

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

- **Rapidly reducing plasma 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 (HD) machine.
  - Other methods are hemofiltration (both arteriovenous and venovenous), hemodialysis, peritoneal dialysis, and continuous-drainage peritoneal dialysis. These are more likely to be available than ECMO-driven dialysis. Dialysis can usually be discontinued when plasma ammonia concentration falls below 200 µmol/L, but may vary based on clinical evaluation by an experienced metabolic disease clinician. Affected individuals often experience a "rebound" hyperammonemia that may require further dialysis.

* Does not generally apply to argininemia

- **Pharmacologic management to allow alternative pathway excretion of excess nitrogen.** 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 individual is stable. Dosing information is provided by the manufacturer for these FDA-approved drugs.
- **Reducing the amount of excess nitrogen in the diet**
  - In acutely ill individuals, calories should be provided as carboydrate and fat, either intravenously as glucose and intralipid or orally as protein-free oral formula (e.g., Mead Johnson 80056 or Ross Formula ProPhree)
  - Affected individuals 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.
  - Complete restriction of protein for more than 24-48 hours is not recommended as the individual will become protein catabolic for essential amino acids.
- **Reducing catabolism through the introduction of calories supplied by carbohydrates and fat.** Complete restriction of protein should not exceed 24-48 hours because depletion of essential amino acids results in protein catabolism and nitrogen release.

- **Reducing the risk of neurologic damage.** 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.

Prevention of Primary Manifestations

The prevention of catabolism is a key goal of treatment to prevent hyperammonemic episodes. Long-term management is focused on restriction of dietary protein through use of specialized formulas and administration of oral nitrogen scavenging drugs.

Prevention of Secondary Complications

- Efforts to minimize risk of respiratory and gastrointestinal illnesses through home care, gastrostomy tube feedings as needed
- Immunizations on the usual schedule
- Multivitamin and fluoride supplementation
- Appropriate use of antipyretics (Ibuprofen is preferred over acetaminophen.)
- Carefully monitoring for hyperammonemia following a large fracture or other trauma in which significant internal bleeding occurs

Surveillance

Affected individuals should be routinely monitored by a metabolic 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.

Testing of Relatives at Risk

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

Agents/Circumstances to Avoid

- Valproic acid (Depakote)
- Prolonged fasting or starvation
- Intravenous steroids
- Large boluses of protein or amino acid

Therapies Under Investigation

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

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

Other

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

Genetics clinics are a source of 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.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Argininosuccinic aciduria

National Urea Cycle Disorders Foundation
4841 Hill Street
La Canada, CA 91011
Phone: 800-38NUCDF (800-386-8233)
Fax: 818-790-2460
Email: info@nucdf.org
www.nucdf.org

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
176 Nantwich Road
Crewe, CW2 6BG
United Kingdom
Phone: (+44) 0870 7700 326
Fax: (+44) 0870 7700 327
Email: steve@climb.org.uk
www.climb.org.uk

References

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

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

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Revision History

- 11 August 2005 (me) Comprehensive update posted to live Web site
- 21 June 2004 (mls) Revision: testing
- 29 April 2003 (me) Overview posted to live Web site
- 29 January 2001 (mls) Original submission

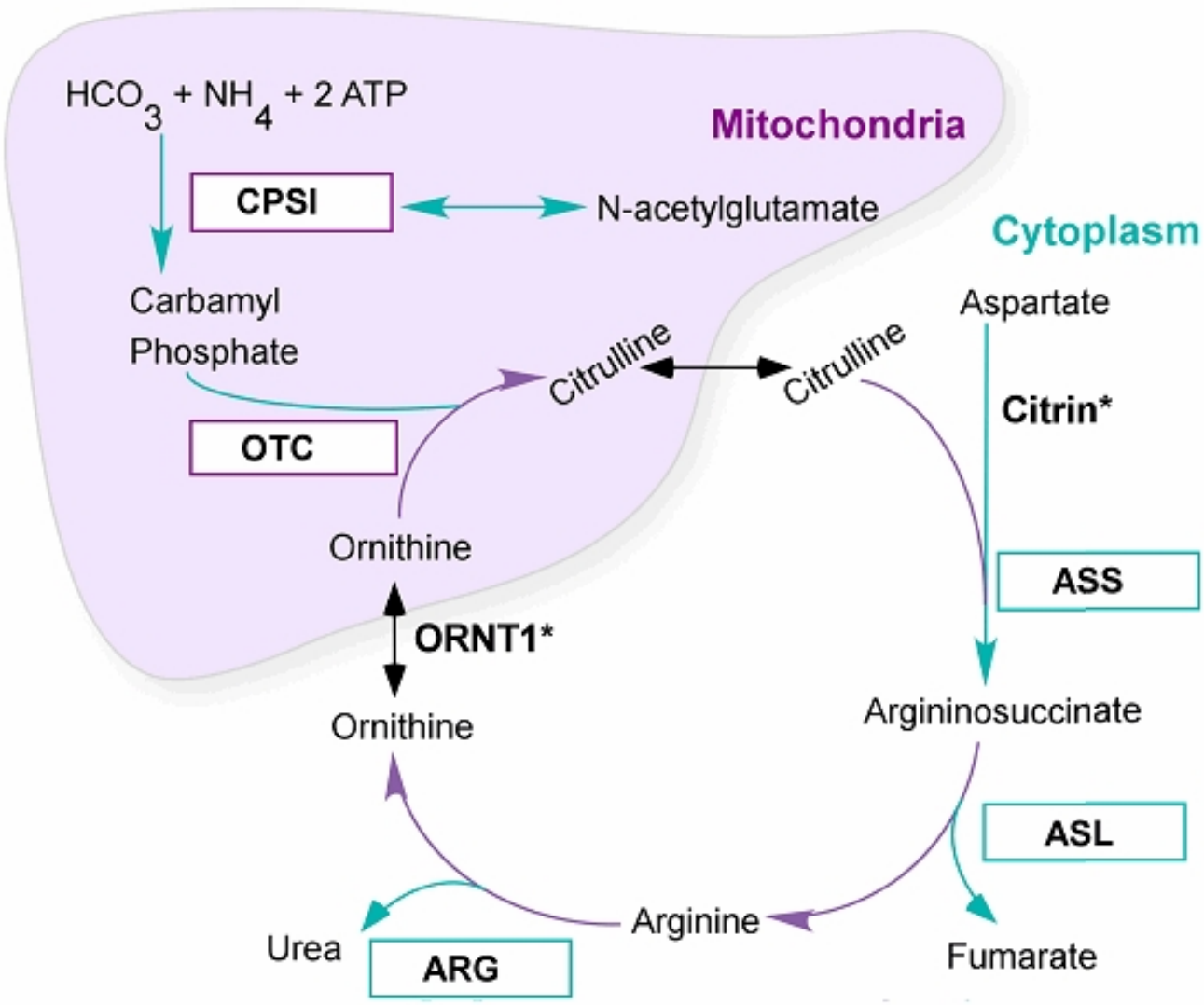

Figure 1. The Urea Cycle *See Differential Diagnosis.

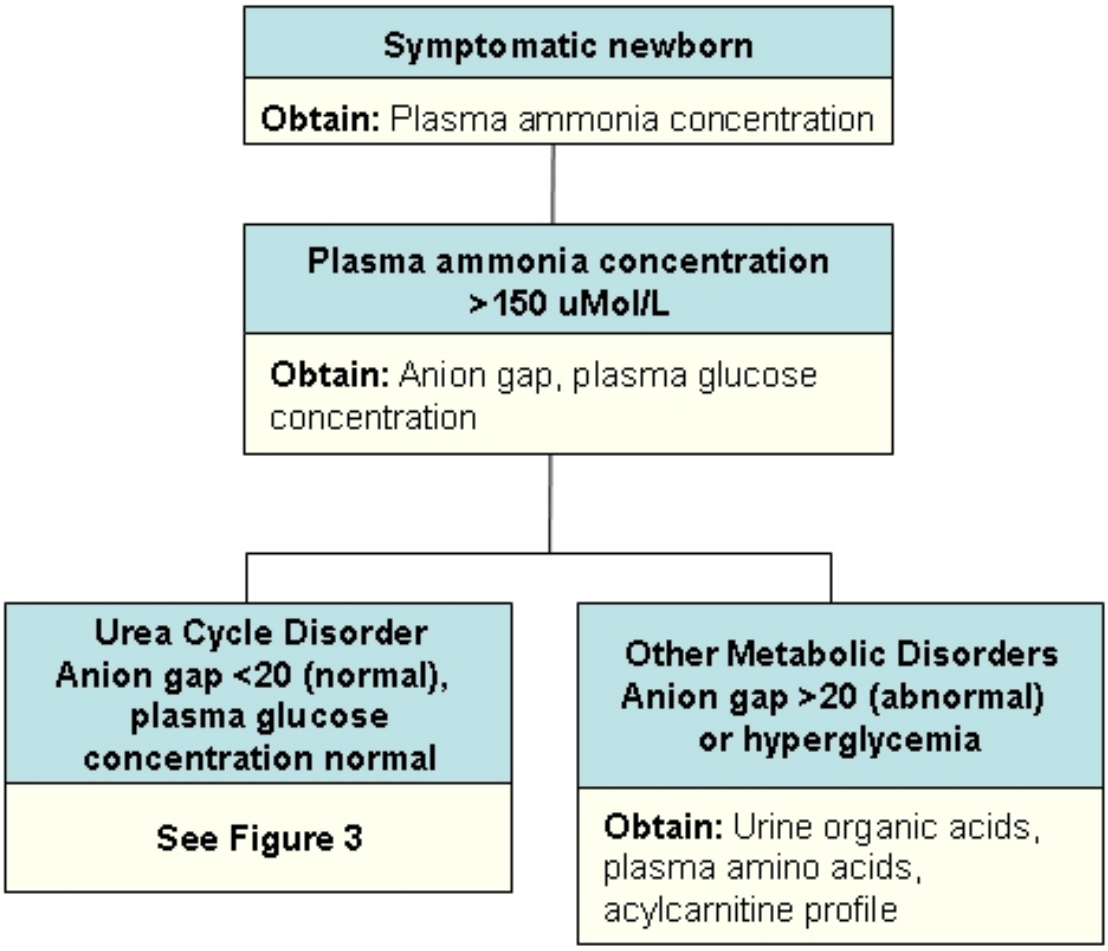

Figure 2. Steps in the Evaluation of a Newborn with Hyperammonemia

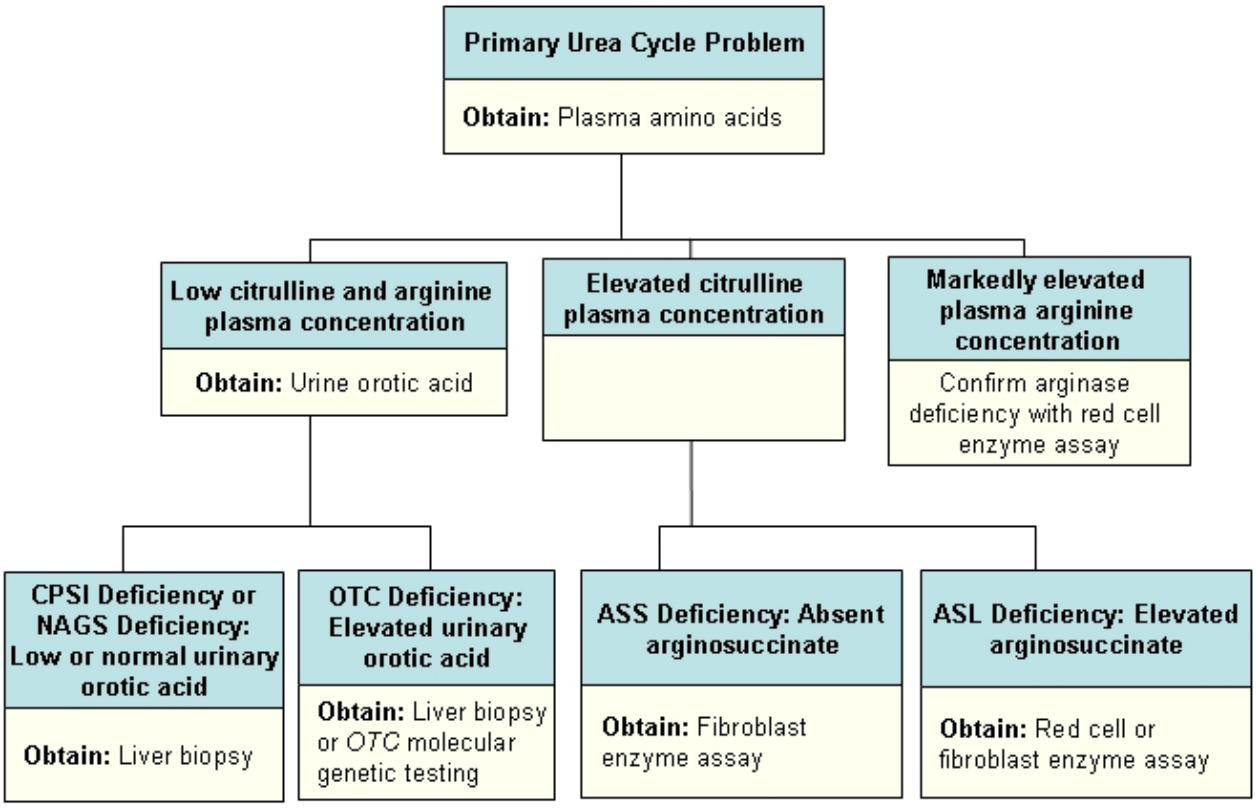

Figure 3. Testing Used in the Diagnosis of a Specific Urea Cycle Disorder