

**The New Jersey Department of Health and Senior Services  
Newborn Screening and Genetic Services**

**The Urea Cycle Disorders  
Citrullinemia (ASD)  
Argininosuccinic Aciduria (ALD)**

**Information for Health Professionals**

**Description**

The urea cycle, consisting of five biochemical reactions, serves two primary functions: the elimination of nitrogen as urea and the synthesis of arginine. When there are defects in the urea cycle, ammonia and its precursor amino acids (glutamine, glutamic acid, aspartic acid, and glycine) accumulate. The resulting high levels of ammonia are neurotoxic.

Newborn screening in New Jersey tests for two of the five urea cycle disorders: Citrullinemia (ASD) and Argininosuccinic Aciduria (ALD), which is also known as argininosuccinic acidemia.

Citrullinemia is due to a defect in the urea cycle enzyme argininosuccinic acid synthetase. Deficiency of this enzyme results in markedly elevated blood ammonia, citrulline (40X normal), and glutamine levels, as well as urine citrulline and orotic acid, and decreased arginine production. The gene for argininosuccinic acid synthetase is located on chromosome 9 (9q34) and numerous mutations have been identified.

Argininosuccinic aciduria is due to a defect in the production of the urea cycle enzyme argininosuccinase. Deficiency of this enzyme results in markedly elevated blood ammonia, citrulline, and glutamine levels, as well as urine argininosuccinic acid. Elevations of argininosuccinic acid are not found in blood due to its efficient excretion by the kidneys. The gene for argininosuccinase has been mapped to chromosome 7.

**Incidence**

As a group, urea cycle disorders are estimated to occur 1 in 30,000 live births. All are inherited autosomal recessive traits (M:F  $\approx$  1:1) with the exception of ornithine transcarbamylase (OTC) deficiency, which is inherited as an X-linked trait.

Citrullinemia occurs in the general population with a frequency of 1 in 250,000 live births (carrier rate  $\approx$  1 in 250).

Argininosuccinic aciduria has an incidence of 1:70,000 live births (carrier rate  $\approx$  1:130), which may be an underestimation secondary to early neonatal deaths.

**Clinical Features**

The clinical course is similar for most of the urea cycle disorders, including ASD and ALD, due to hyperammonemia, a common presenting feature in four of the five deficiencies. (Most patients with arginase deficiency do not exhibit the severe episodes of acute hyperammonemic encephalopathy characteristic of the other urea cycle

disorders).The newborn appears normal at birth; clinical symptoms of citrullinemia and argininosuccinic acidemia become apparent between 1 to 3 days of age, when the infant undergoes a rapid neurological deterioration. As ammonia levels increase, infants quickly develop anorexia, vomiting, hypothermia, irritability, lethargy, seizures, apnea and cerebral edema. Without intervention, they become comatose and die.

In addition to disease with a neonatal onset, there is a late onset presentation of ASD and ALD that can occur any time from the newborn period to adulthood. Patients with partial residual activity of the defective enzyme exhibit a variety of different clinical pictures, but typically late onset presentation is characterized by vomiting, lethargy, irritability, agitation, disorientation, ataxia and occasionally coma. Episodes are frequently associated with a change in formula and/or diet or with an intercurrent illness or infection. While seizures, delayed growth, developmental delay and cerebral atrophy have all been described in patients with late onset presentation, others may have normal intelligence.

### **Screening**

The New Jersey Department of Health and Senior Services Inborn Errors of Metabolism (IEM) laboratory performs a screening test for Citrullinemia and Argininosuccinic Aciduria by tandem mass spectrometry (MS/MS). Elevations in the level of citrulline are specific for ASD and ALD; however it is a screening test and not a diagnostic test. In the newborn period, citrulline levels normally range between 10 and 20  $\mu\text{M}$ . Infants with neonatal onset ASD generally have citrulline levels greater than 1000  $\mu\text{M}$ , while infants with neonatal onset ALD have levels that range between 100 and 300  $\mu\text{M}$ .

Due to the rapid onset of symptoms, results from newborn screening are unlikely to be available in time to be therapeutically useful. A definitive diagnosis may, however, provide information for recurrence risk counseling and prenatal diagnosis in subsequent pregnancies.

Late onset cases of ASD and ALD as well as some of the other urea cycle disorders (carbamyl phosphate synthetase deficiency and ornithine transcarbamylase deficiency) are likely to be missed if blood is screened within 48 to 72 hours of life. Urine screening beyond one month of age might assist in the recognition of late onset cases and ornithine transcarbamylase deficiencies, but the sensitivity and detection rate are unknown. Diagnosis of these disorders is once again dependent on clinical recognition of signs of hyperammonemia.

Physicians need to be aware that negative screening results do not exclude the presence of a urea cycle disorder. It is important to note that, because citrulline is a product of two of the other urea cycle reactions, deficiencies in those enzymes (carbamyl phosphate synthetase and ornithine transcarbamylase) will not be detected on newborn screening, as citrulline levels will not be markedly elevated. Late onset cases of ASD and ALD have been diagnosed by screening urine at 3 to 4 weeks of age for orotic acid, citrulline, and argininosuccinic acid.

### **Confirmatory testing**

Plasma and urine amino acid analyses are the laboratory standards for confirmation of citrullinemia, and argininosuccinic aciduria.

## **Treatment**

Patients are optimally managed by a team of specialists including those from genetics, pediatric gastroenterology, and pediatric neurology. The goal of treatment in these urea cycle disorders is to provide sufficient protein and arginine, for growth, development, and energy while preventing hyperammonemia and hyperglutaminemia. This is accomplished by 1) protein restriction and caloric supplementation with protein-free powder 2) arginine supplementation to promote synthesis and excretion of citrulline in ASD and argininosuccinic acid in ALD, and 3) supplementation of sodium phenylbutyrate in ASD and ALD to promote alternate nitrogen excretion pathways.

In both neonatal and late onset, early recognition is extremely important because the ultimate prognosis depends on the duration of the initial hyperammonemic episode and the nature of recurrent episodes. Over 70% of infants with neonatal onset ASD who survive are severely or profoundly mentally retarded. The mean IQ of an ALD infant rescued from a neonatal episode is 50.

Patients with late onset presentations have a median delay in diagnosis of 16 months due to signs and symptoms being attributed to other etiologies (e.g. colic, cyclic vomiting, Reye syndrome, epilepsy, encephalitis, and postpartum encephalopathy).

## **Implications for Genetic Counseling**

Families with urea cycle disorders should receive genetic counseling, as carrier detection and prenatal diagnosis are available.

## **Interpretations/Recommendations**

**Expected Results: <100 µmol/L citrulline**

**Presumptive-Positive Results: ≥100 µmol/L citrulline**

**Recommend: Immediate assessment of baby's health status and consultation with metabolic/genetic specialist**

Additional information:

Gene Tests/Gene Clinics

<http://www.genetests.org>

Illinois Department of Public Health Newborn Screening Program

<http://www.idph.state.il/HealthWellness/fs/urea.htm>

eMedicine

<http://www.emedicine.com/ped/topic406.htm>

**For questions, contact:**

**Inborn Errors of Metabolism Laboratory at (609) 292-3090**

**Newborn Biochemical Screening Follow-Up Program at (609) 292-1582**

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