



## Genetics Newborn Screening Program Health Professional Fact Sheet

### Citrullinemia or Argininosuccinic Acid Synthetase Deficiency

#### Introduction - Urea Cycle Disorders

The urea cycle disorders (UCD) result from defects in the metabolism of the extra nitrogen produced by the breakdown of protein. Severe deficiency or total absence of activity of any of the first four enzymes - Carbamyl phosphate synthase (CPSI), Ornithine transcarbamylase( OTC), Argininosuccinic acid synthetase (ASS), and Argininosuccinic acid lyase (ASL) in the urea cycle or the cofactor producer N-acetyl glutamate synthetase (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. 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. However, 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.

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. The overall incidence of urea cycle disorders is considered to be around 1:30,000 live births.

#### Citrullinemia

Citrullinemia I, the acute neonatal form or classic form, is a rare autosomal recessive inherited disorder caused by deficiency or lack of the enzyme argininosuccinate synthetase. Patients with complete argininosuccinate synthetase deficiency present with severe hyperammonemia in the newborn period. Infants are generally well for the first 24-72 hours but then demonstrate lethargy, poor feeding, vomiting, grunting respirations, tachypnea, hypothermia, progressing to opisthotonus, seizures, cerebral edema, coma, apnea and death if not treated. Children who are treated promptly may survive but usually with significant neurological deficit. The use of arginine in these patients allows some nitrogen (ammonia) to be incorporated into the urea cycle which makes treatment somewhat easier than other defects in the cycle. Citrulline levels in these patients can be 100's of times the normal values. Unlike CPSI, NAGS, and OTC, this enzyme is distributed throughout the body. Diagnosis is by enzymatic assay of fibroblasts.

#### Diagnosis

Newborn screening—Tandem mass spectrometry - Citrulline (CPSI, OTC, and NAGS deficiency cannot be detected using tandem mass spectrometry.)

Confirmation— a second sample may be requested or follow up testing will be done at the Metabolic Treatment Center at Yale or UCONN Genetics.

#### Monitoring

Frequent monitoring of growth and biochemical parameters, along with indicated adjustments to the diet and medications, are essential in managing individuals with urea cycle disorders. During infancy, patients are evaluated at least weekly to evaluate ammonia status and to detect under or over

restriction of protein intake. It is also important for the primary care provider and the Metabolic Treatment Center to develop an on-going collaborative relationship in caring for these patients.

### **Treatment**

Initial treatment of the disorder often requires dialysis and/or intravenous combined sodium benzoate and sodium phenylacetate, along with L-arginine, to control hyperammonemia. The intravenous fluids usually contain 10% dextrose to help prevent catabolism and the release of stored body protein. Once vital signs are stable and emesis has ceased, non-protein enteral feedings should be started.

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

Infants and children with Citrullinemia should have regularly scheduled visits at the Metabolic Treatment Center. The Metabolic Treatment Center will set a patient's diet prescription and provide the family with an emergency protocol which contains basic information about the disorder, necessary diagnostic investigations, and guidelines for treatment.

### **Illness**

- Parents should be warned that if infant shows symptoms, such as vomiting or lethargy, they should seek immediate medical attention.
- Prevention and/or early intervention is of particular importance
- Consult with the Metabolic Treatment Center within 24 hours of the onset of the illness

### **Immunization**

- Immunizations must be kept current.

### **Surgical/surgical procedures**

- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- Any procedure requiring anesthesia should be done at a hospital with a metabolic service.

### **Growth and development**

- It is crucial to closely monitor all growth, development, and biochemical parameters on a regular basis.
- The child should be referred to an early intervention program and developmental progress closely monitored by both the metabolic team and the primary care provider.



860-509-8081

The information provided is offered for general informational and educational purposes only. It is not offered as and does not constitute medical advice. In no way are any of the materials presented meant to be a substitute for professional medical care or attention by a qualified practitioner, nor should they be construed as such. Contact your physician if there are any concerns or questions.