Citrullinemia type I (CTLN1) is a rare inherited disorder caused by a deficiency or lack of the enzyme argininosuccinate synthetase (ASS). Argininosuccinate synthetase is one of six enzymes that play a role in the urea cycle. The lack of this enzyme results in excessive accumulation of nitrogen, in the form of ammonia (hyperammonemia), in the blood.

Elevated citrulline is a marker for several urea cycle disorders including citrullinemia I [ASAS deficiency], citrullinemia II [citrin deficiency] and argininosuccinic aciduria [ASA lyase deficiency].

- **Clinical Symptoms**

There are two forms of citrullinemia type I; the common “classic/neonatal” form and a milder form. High ammonia levels in the blood cause symptoms to begin within the first few days of life in infants with the classic form. Symptoms include: feeding problems, lethargy, and irritability. If untreated, high ammonia levels can cause hypotonia, breathing problems, problems regulating body temperature, seizures, swelling of the brain, poor growth, enlarged liver, learning delays or intellectual disabilities, and coma. Death typically occurs within the first few weeks of life if untreated.

In the milder form, symptoms begin in late infancy or childhood and include poor growth, hyperactivity, spasticity, learning problems or intellectual disabilities, hair shaft abnormalities, and episodes of high levels of ammonia in the blood (often after periods of fasting, illness, or after high-protein meals). High blood ammonia levels in children can cause poor appetite, headaches, slurred speech, lethargy, ataxia, and vomiting. If untreated, high ammonia levels may lead to breathing problems, seizures, swelling of the brain, coma, and possible death.

Citrin deficiency is associated with neonatal intrahepatic cholestasis (NICCD) and citrullinemia type II (CTLN2). 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.

- **Incidence**

Citrullinemia occurs in less than 1 out of every 100,000 births.

- **Genetics of citrullinemia**

Mutations in the ASS1 gene cause citrullinemia type I. Mutations in this gene reduce or eliminate the activity of the enzyme argininosuccinate synthetase 1. This enzyme is necessary in the urea cycle and the mutations prevent processing of nitrogen. By products of the urea cycle, particularly ammonia, accumulate in the blood causing the symptoms of this condition.

- **How do people inherit citrullinemia?**

Citrullinemia is inherited in an autosomal recessive manner. Parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs or symptoms of the condition. Carrier parents have a 25% recurrence risk with each pregnancy to have an affected offspring.

- **Treatment**

Immediate diagnosis and treatment of citrullinemia, especially the classic form, in the neonatal period is critical to normal development and survival. Treatment is usually effective if started before ammonia levels are excessive. Individuals should follow a lifelong low-protein diet, which may require medical formulas and foods. Certain medications, such as sodium benzoate and/or phenylbutyrate/phenylacetate, as well as supplementation of arginine may help prevent ammonia build-up. Episodes of high ammonia levels may require medications via IV or dialysis.
Screening Methodology

Primary newborn screening for citrullinemia utilizes tandem mass spectrometry to determine the level of citrulline. Individuals with a positive screen will have very elevated levels of citrulline. False positive and false negative results are possible with this screening.

What to do After Receiving Presumptive Positive Citrullinemia Screening Results

1) The clinician should immediately check on the clinical status of the baby.
2) Consultation with a metabolic specialist is essential.
3) The specialist may request blood or urine amino acid analysis on baby.
4) Call KS Newborn Screening Program at 785-291-3363 with questions about results.
5) Report Clinical Findings to Newborn Screening Program at 785-291-3363.
6) Same birth siblings (twins, triplets) of infant diagnosed with citrullinemia should be re-screened; additional testing of these siblings may be indicated.
7) Consider testing older siblings of affected individuals. Some people with mild or no symptoms may go undiagnosed.

Confirmation of Diagnosis

The diagnosis can be confirmed by performing quantitative plasma ammonia and amino acid analysis and urine amino acid analysis. Patients with citrullinemia will have greatly elevated blood citrulline levels, and may have elevated orotic acid levels in urine. Symptomatic individuals will have elevated blood ammonia levels.

Communication of Results to Parents

If a baby has a presumptive positive citrullinemia newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If the baby is diagnosed with citrullinemia, the following points should be conveyed to parents:

- Parents should understand that treatment for citrullinemia will be lifelong.
- Parents should understand that treatment is not curative and that all morbidity cannot necessarily be prevented. Long-term management, monitoring, and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended and should include the following specialties: pediatrics, metabolic disease specialists, and dieticians. Regular blood analysis is needed.
- Genetic counseling services may be indicated. A list of counselors and geneticists, whose services are available in Kansas, should be given to the parents if they have not already seen a geneticist.

For consultation contact:

Bryce Heese, MD
Biochemical Genetics
Children's Mercy Hospital- Kansas City, MO
Clinic phone: 816-234-3771
Hospital Operator: 816-234-3000
Office Fax: 816-302-9963