**Disease Name:**
CLASSIC CITRULLINEMIA
(CITRULLINEMIA, TYPE I; CTLN1; ARGININOSUCCINATE SYNTHETASE DEFICIENCY; ASS DEFICIENCY)

**Classification:**
Urea cycle defect

**Genetic Information:**
- **Inheritance:** Autosomal recessive
- **Population Incidence:** 1:57,000
- **Ethnic Incidence:** No known population at increased risk
- **Gene & Location:** ASS- 9q34
- **Common Mutation:** No known common mutations
- **OMIM #** #215700

**Symptom Onset:**
Two forms, one with neonatal onset and the other with infantile onset.

**Symptoms:**
This defect produces hyperammonemia, encephalopathy and respiratory alkalosis. 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. Milder variants, asymptomatic individuals and intra-family variability have been reported.

**Physical Findings:**
Patients with pili torti have been described, probably due to nutritional deficiency. Otherwise no dysmorphisms.

**Treatment:**
Rescue of an infant from hyperammonemic encephalopathy may be possible with aggressive hemodialysis and specialized care. Maintenance treatment consists of a protein-restricted diet, ammonia disposal drugs, arginine supplementation and aggressive intervention for recurrent bouts of hyperammonemia.

**Natural History without treatment:**
Progressive encephalopathy proceeding to coma and death if untreated. However, there are milder variants and reports of asymptomatic patients.

**Natural History with treatment:**
None of the infants with peak ammonias over 480umol/l had a normal neurological outcome. Otherwise outcome depends on amount of neurological damage and metabolic control, but theoretically normal.
**Missing Enzyme & Location:** Argininosuccinate synthetase, which catalyses the conversion of citrulline and aspartate to argininosuccinate as a rate limiting step in the urea cycle.

**MS/MS profile:**
- Citrulline- very elevated
- Arginine – low/ undetectable

**Prenatal testing:** Enzyme assay on amniocytes or CVS is possible.

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**References:**


47. Saheki T, Kobayashi K. Mitochondrial aspartate glutamate carrier (citrin) deficiency as the cause of adult-onset type II citrullinemia (CTLN2) and idiopathic neonatal hepatitis (NICCD). *J Hum Genet* 2002 47:333-341.


54. Summar M, Tuchman M. “Urea Cycle Disorders Overview”, [www.geneclinics.org](http://www.geneclinics.org)


