



# Argininosuccinic Aciduria (ASA LYASE)/Citrullinemia (ASA Synthase)

## Background

The finding of elevated Citrulline in a newborn screen dried blood spot suggests one of two metabolic defects: Argininosuccinic Acid Synthetase Deficiency or Arginino-succinate Lyase Deficiency. Both are disorders of the Urea Cycle and are associated with severe, episodic hyperammonemia. Argininosuccinic Acid Synthetase Deficiency (commonly called Citrullinemia) occurs in 1:57,000 births and causes a dramatic elevation of plasma Citrulline. Argininosuccinate Lyase Deficiency causes a less dramatic increase of plasma Citrulline, but is no less clinically devastating. It is found in 1:70,000 births.

## Clinical

Both forms of Citrullinemia have a similar clinical presentation. With an early onset presentation, the newborn appears normal for the first 24 hours. Symptoms develop in association with worsening hyperammonemia. By 72 hours, lethargy, feeding difficulties and vomiting usually appear. The patient develops hypothermia, respiratory alkalosis and often requires ventilation. Seizures progressing to coma and death are typical in untreated patients. Physical examination reveals encephalopathy, which is due to brain edema and swollen astrocytes from glutamine accumulation and the resulting water retention. Patients with Argininosuccinate Lyase Deficiency may exhibit hepatomegaly. These patients are frequently mistaken for a case of sepsis. A key laboratory abnormality suggesting a Urea Cycle defect is low blood urea nitrogen, which should dictate measurement of ammonia. Patients who survive the newborn period may have a neurologic impairment. These neonatal onset patients have recurrent episodes of hyperammonemia associated with viral infections or increased dietary protein intake. Some patients with either disorder have a later onset with a less severe course making diagnosis difficult.

## Testing

Newborn screening by tandem mass spectrometry using a dried blood spot can detect elevated levels of Citrulline with either disorder. The levels of Citrulline in Arginino-succinic Acid Synthetase Deficiency range up to 100 times the normal limit. Arginino-succinate Lyase Deficiency patients have measurable levels of Argininosuccinic acid in plasma, which is not normally detected. The activity of either enzyme can be measured from a liver biopsy. Both genes have been isolated and mutations identified. DNA studies can be performed for prenatal diagnosis when the mutation is known from both parents. Biochemical studies of cultured amniocytes and chorionic villus tissue are also informative. The presence of Argininosuccinic acid in the amniotic fluid of Arginino-succinate Lyase Deficiency patients has been used for prenatal diagnosis.

## Treatment

The symptoms of Citrullinemia seem to originate from the hyperammonemia rather than Citrulline accumulation. Acute hyperammonemia may necessitate hemodialysis, which is more effective for lowering ammonia than peritoneal dialysis or arterio-venous hemofiltration. Sodium benzoate is given to conjugate Glycine, a major amino acid that contributes ammonia to the urea cycle, forming hippurate, which is subsequently excreted in the urine. Intravenous Arginine results in ammonia clearance by enhancing formation of Citrulline in Argininosuccinic Acid Synthetase Deficiency or Argininosuccinate in Argininosuccinate Lyase Deficiency. Both of these metabolites are excreted in the urine and draw off excess nitrogen from ammonia. Patients who survive the initial presentation are placed on protein restriction. Patients with either defect having onset in the newborn period face a poor outcome and significant risk of neurological damage or demise.

Because the diagnosis and therapy of these metabolic disorders is complex, the pediatrician is strongly advised to manage the patient in close collaboration with a consulting pediatric metabolic disease specialist. It is recommended that parents travel with a letter of treatment guidelines from the patient's physician.

## Inheritance

These disorders most often follow an autosomal recessive inheritance pattern. With recessive disorders affected patients usually have two copies of a disease gene (or mutation) in order to show symptoms. People with only one copy of the disease gene (called carriers) generally do not show signs or symptoms of the condition but can pass the disease gene to their children. When both parents are carriers of the disease gene for a particular disorder, there is a 25% chance with each pregnancy that they will have a child affected with the disorder.

## References

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