State of CT
Genetics Newborn Screening Program
Health Care Provider Fact Sheet

Argininemia or Arginase 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.

Argininemia

Argininemia is a rare autosomal recessive inherited disorder characterized by complete or partial lack of the enzyme arginase which is the sixth and final enzyme of the urea cycle. Arginase deficiency is one of the least frequent of the urea cycle disorders with an incidence between 1:350,000 and 1:1,000,000. Most commonly, birth and early childhood are normal. Although a catastrophic neonatal presentation is very uncommon in arginase deficiency, dietary protein intolerance is an early sign and should not be overlooked. The typical presentation is that of an older infant whose development is delayed, has occasional episodes of vomiting and somnolence without apparent cause, is protein intolerant, and shows evidence of long-tract neurological impairment. Untreated individuals have slowing of linear growth at age one to three years, followed by development of spasticity, plateauing of cognitive development, and subsequent loss of developmental milestones. Some cases likely go undiagnosed with clinical symptomatology attributed to cerebral palsy.

Clinical Features

The clinical manifestations of arginase deficiency are strikingly different from those of Carbamyl Phosphate Synthetase, Ornithine Transcarbamylase, Argininosuccinic acid synthetase, and argininosuccinate lyase deficiencies. The major symptoms of arginase deficiency, all of which are progressive, include spastic tetraplegia with the lower limbs affected much more severely than the upper limbs, seizures, psychomotor retardation, hyperactivity, and growth failure. Symptomatic hyperammonemia progressing to encephalopathy may occur, but plasma ammonium levels are three to four times normal values, with levels rarely as high as six times normal.

Although there is phenotypic variability, with some cases presumably asymptomatic at 4 years of age, close inspection of these reported cases suggests that clinical manifestations occur early in the first

year of life; they include irritability, unconsolable crying, anorexia, vomiting, and delayed developmental milestones.

Diagnosis

Newborn screening—Tandem mass spectrometry - Arginine
Confirmation—a second sample may be requested or follow up testing will be done at the Metabolic Treatment Center at Yale or UCONN Genetics.

Situations that risk metabolic decompensation

Fasting, intercurrent illness, post vaccination, surgery

Monitoring

Clinical observation is the most important tool for monitoring patients with Arginase Deficiency. It is important for the primary care provider and the Metabolic Treatment Center to develop an on-going collaborative relationship in caring for these patients.

Treatment

The mainstay of treatment is restriction of dietary protein through use of specialized formulas and administration of oral nitrogen scavenging drugs, sodium benzoate or sodium phenylbutyrate. Because severe hyperammonemia is unusual, the need for intravenous therapy or hemodialysis is unlikely Treatment should improve neurological function, but this has not been proven. Infants and children with Arginase deficiency should have regularly scheduled visits at the Metabolic Treatment Center.

Illness

The Metabolic Treatment Center should be consulted with within 24 hours of the onset of the illness.

Immunization

Immunizations must be kept on track.

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.

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