Argininosuccinic aciduria (argininosuccinate 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.

Argininosuccinic aciduria (Argininosuccinate Lyase Deficiency)—ASA or ALD
ASA is an autosomal recessive inherited urea cycle disorder with an incidence of about 1:70,000. Neonatal onset presents in the first 2-3 days of life with vomiting, lethargy, respiratory alkalosis, and hypothermia progressing to hyperammonemic encephalopathy, cerebral edema, hepatomegaly, and death. There is a high mortality rate. Hyperammonemia is not severe and symptoms are non-specific. The missing enzyme is argininosuccinic lyase; it cleaves argininosuccinate to arginine and fumarate as part of the urea cycle.

Clinical features in the neonatal period are: lethargy, poor feeding, hypotonia, apnea/tachypnea, Hepatomegaly, seizures, and death. In infancy and childhood, the clinical features are: episodic vomiting, lethargy, hepatomegaly, developmental delay, dry, brittle hair (trichorrhexis nodosa), and ataxia.

Diagnosis
Newborn screening—Tandem mass spectrometry—Citrulline
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
Metabolic decompensation can be triggered by the catabolic processes that occur in the course of infections, after an immunization, increased physical activity or with a prolonged period of fasting.
Monitoring
Clinical observation is the most important tool for monitoring patients with Argininosuccinic aciduria. It is important for the primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.

Treatment
Treatment consists of a low protein diet, arginine supplementation to help complete the urea cycle, ammonia scavenging drugs in some cases and supplement carnitine if the patients have a secondary deficiency. Liver transplant offers a partial correction of the enzyme deficiency and improved metabolic status. Patients must avoid fasting and during stressors, like illness, need to supplement with high carbohydrates, non-protein calories to avoid catabolism. While early diagnosis and treatment may be lifesaving, neurologic damage is not usually prevented.

Illness And Immunization
Prevention and/or early intervention are of particular importance. For this and other reasons immunizations must be kept on track.

Surgical/surgical procedures
- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- A surgical procedure constitutes a potentially catabolic situation and preoperative fasting should be avoided with 10% dextrose being started preoperatively and continuing postoperatively until the child is eating and drinking well. Any procedure requiring anesthesia should be done at a hospital with a metabolic service.

Growth and development
As with any child on a special dietary regime, regular monitoring of growth parameters becomes particularly important. There is a direct correlation between the length of time a patient is in hyperammonemic coma as a neonate and IQ. An early intervention program should assess any neurological/behavioral problems early. It is hoped that pre-symptomatic identification of ASA by expanded newborn screening and early treatment will prevent, or at least improve, long-term neurological problems that have been a major problem, particularly in the neonatal onset cases.

860-509-8081

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