Isovaleric Acidemia (IVA)

Introduction
Isovaleryl-CoA dehydrogenase (IVD) is a mitochondrial matrix enzyme that catalyzes the third step in leucine catabolism. The genetic deficiency of IVD results in an accumulation of isovaleric acid, which is toxic to the central nervous system and leads to isovaleric acidemia. With onset between birth and one year, IVA occurs in both acute and chronic forms. Episodes can be triggered by upper respiratory infections or by excessive consumption of high-protein foods. Treatment involves a protein-restrictive diet and carnitine supplementation. Oral administration of glycine is life-saving and may permit normal growth and development. Untreated, a child suffers from irreversible brain damage.

Infants with the acute neonatal form present after a few days of normalcy with poor feeding, vomiting, severe metabolic keto-acidosis, progressing to coma and death. The infants are listless and lethargic and may be hypothermic. Tremors or twitching and convulsions may be seen. Dehydration, hyperammonemia, hypocalcemia, hepatomegaly and hyper/hypoglycemia are often present. Depressed bone marrow function with neutropenia, thrombocytopenia and pancytopenia can lead to infection and/or cerebral hemorrhage. Most, but not all, will have the characteristic odor of "sweaty socks" which comes from the accumulation of isovaleric acid.

The chronic intermittent form presents later in infancy or childhood with episodes of metabolic acidosis as described above, usually associated with an intercurrent illness or increased protein load. The recurrent episodes typically involve vomiting, lethargy progressing to coma, acidosis with ketonuria and the characteristic odor of "sweaty feet". The episodes resolve with protein restriction and infusion of glucose. The different forms can occur in the same family, so are not related to genotype. The biochemical defect is the same in both forms. Infants who survive the acute episode go on to exhibit the chronic form.

As in most of the organic acidemias, the frequency of episodes is highest during infancy and subsequently decreases because of fewer infections and decreased protein intake, which naturally occurs with normal growth. Many patients develop a natural aversion to protein-rich foods.

Diagnosis
Newborn screening—Tandem mass spectrometry: C5
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 IVA. They should be observed and assessed for neurological status, recurrent vomiting, refusal to eat, increased

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lethargy, apnea or seizures. In these situations, immediate evaluation in the emergency room is necessary. In situations of metabolic decompensation hypoglycemia can develop, but a normal blood glucose does not rule out metabolic instability and should never be a reason to delay therapy. It is also important for the primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.

**Treatment**
- Low-protein diet with restricted leucine intake, in combination with glycine and carnitine supplements. Glycine and carnitine allow for the nontoxic removal of excess isovaleric-CoA.
- Patients will often self select a low protein diet.
- The Metabolic Treatment Center will set a patient’s diet prescription that determines the optimum percentage of fat, carbohydrate, and protein.
- The parents should have an emergency protocol with them at all times. This protocol, provided by the Metabolic Treatment Center, contains basic information about the disorder, necessary diagnostic investigations and guidelines for treatment.
- Infants and children with IVA should have regularly scheduled visits at the Metabolic Treatment Center.

**Illness**
- Any illness can potentially lead to metabolic decompensation
- Prevention and/or early intervention is of particular importance
- Care should be coordinated by the Metabolic Treatment Center

**Immunization**
- Immunizations must be kept current.

**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**
- It is crucial to closely monitor all growth parameters on a regular basis.
- In cases with neurological deficits, 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.
- Intellectual prognosis depends on early diagnosis and treatment and, subsequently, on compliance with the dietary and supplement plan.