FACT SHEET
Healthcare Provider

Isovaleric Acidemia/ Isovaleric Aciduria (IVA)

Description:
IVA is an organic acid disorder caused by a deficiency of Isovaleryl-CoA dehydrogenase, an enzyme essential in the catabolism of the essential amino acid leucine. This genetic deficiency results in an accumulation of isovaleric acid, which is toxic to the central nervous system and leads to isovaleric acidemia. IVA occurs in both acute and chronic forms. Episodes can be triggered by infections or by excessive consumption of high-protein foods.

Incidence in General Population:
1:100,000 live births

Symptoms:
Infants with the acute neonatal form present at a few days of age 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 feet," 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.

About 50% of patients with the acute neonatal form will die in their first episode. Survivors may have neurological damage, although several patients have had complete neurological recovery. Patients with the chronic form may have neurological damage, but most have normal growth and development. Death from episodes of decompensation can occur at any age.

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. Some patients develop a natural aversion to protein-rich foods.

Diagnosis:
Newborn screening abnormality—Tandem mass spectrometry: increased C5.
A second dried blood spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

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, dehydration, 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 lethargy, apnea, or seizures. In these situations, immediate evaluation in the emergency room is necessary. In situations of metabolic decompensation, hypoglycemia can develop but 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:
- Reduced-protein diet with restricted leucine intake, in combination with glycine and carnitine supplements. Glycine and carintine allow for the nontoxic removal of excess isovaleric-CoA.
- Patients will often self-select a low-protein diet.
- The Metabolic Treatment Center will determine the patient's diet prescription that establishes the optimum percentage of fat, carbohydrate, and protein.
- The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and it should contain 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 are of particular importance.
- Care should be coordinated by the Metabolic Treatment Center.

Immunization:
- Immunizations must be kept current. Influenza vaccinations are also recommended.

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 critical 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 should be closely monitored by both the metabolic team and the primary care provider.
- Intellectual progress depends on early diagnosis and treatment and, subsequently, on compliance with the dietary and supplement plan.

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