Isovaleric Acidemia - Acute Illness Protocol

This acute illness protocol is a guideline for healthcare professionals treating the sick infant or child who is known to have isovaleric acidemia. The protocol was developed at Boston Children's Hospital under the direction of Dr. Harvey Levy, Senior Physician in Medicine/Genetics and Dr. Jonathan Picker, Fragile X Program Director, and was updated by Dr. Patroula Smpokou, Clinical Genetics Fellow.

Disclaimer
Metabolic crises in infants and children with organic acid disorders are complex medical emergencies and must be treated as such to avoid death or serious brain injury. This protocol is only a guideline and should not be used for definitive treatment without metabolic consultation. It is essential to call or page the on-call genetics/metabolism fellow, or failing this, the on-call metabolic attending at your hospital or nearest pediatric tertiary care center, as rapidly as possible. Please read our Terms of Use.

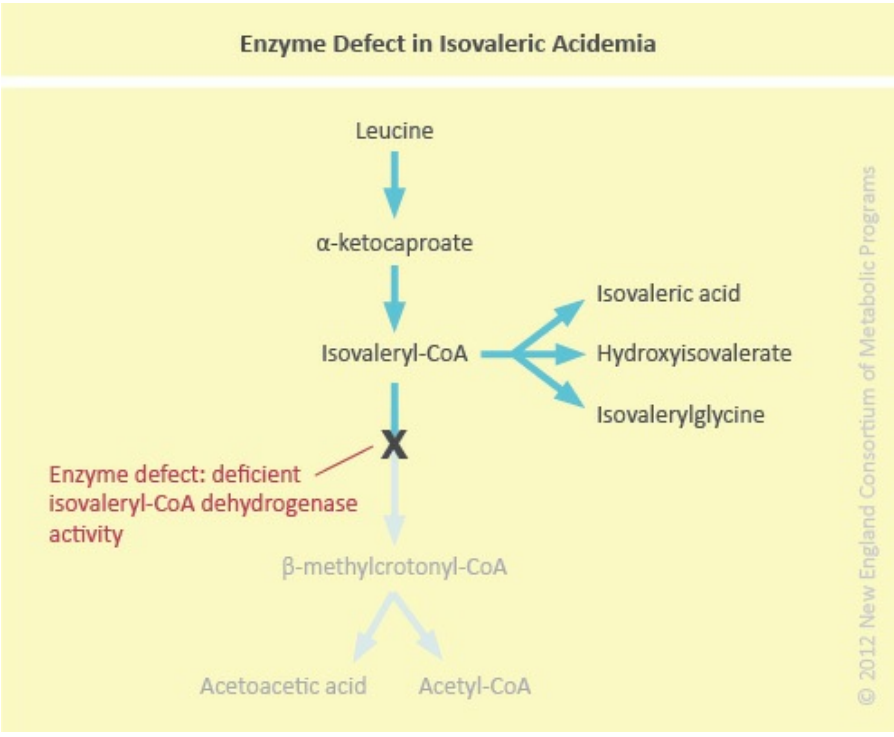
Introduction

Isovaleric acidemia (IVA,) also known as the "sweaty foot syndrome," is an autosomal recessively inherited organic acid disorder due to a defect in the mitochondrial FAD-dependent enzyme isovaleryl-CoA dehydrogenase. This enzyme catalyzes the conversion of isovaleryl-CoA to 3-methylcrotonyl-CoA. Since leucine is the amino acid precursor of isovaleryl-CoA, treatment of IVA includes control of leucine, an essential amino acid.

In acute illness in IVA, isovaleric acid and its derivatives accumulate and profound metabolic acidosis (due to ketone body production and organic acid accumulation), hypoglycemia, and hyperammonemia ensue.

Pathophysiology

The immediate metabolic precursor of isovaleryl-CoA is α-ketocaproate, which is produced from leucine. In normal metabolism, α-ketocaproate is catabolized to isovaleryl-CoA at which point isovaleryl-CoA dehydrogenase would catalyze further conversion to β-methylcrotonyl-CoA. In isovaleric acidemia, deficient activity of isovaleryl-CoA dehydrogenase prevents this conversion, as shown in this figure:



Catabolic stress such as normal perinatal catabolism or an acute illness (e.g. in the setting of infection, injury, surgery, febrile illness) produces endogenous protein breakdown leading to the liberation of amino acids, including leucine. Normal or certainly excessive protein ingestion may produce a similar increase in leucine. In IVA, the leucine leads to the accumulation of isovaleryl-CoA and then isovaleric acid, as well as the metabolites hydroxyisovalerate and isovalerylglycine, with primary and secondary consequences noted here:

Biochemical Effects in Isovaleric Acidemia

Primary abnormalities:

- Metabolic acidosis with anion gap
- Ketonuria

Secondary abnormalities:

- Hypoglycemia (inhibition of gluconeogenesis
- Hyperammonemia (inhibition of the urea cycle
- Hyperglycinemia (inhibition of glycine degradation)
- Neutropenia or pancytopenia (inhibition of blood cell precursors)

The ketoacidosis, hyperammonemia, and hypoglycemia can explain the *lethargy and obtundation* that are sometimes seen in IVA patients in acute crisis. The ketoacidosis also produces *vomiting*. Release of free fatty acids from body fat into the liver produces a *fatty liver*. Prolonged metabolic decompensation can lead to bone marrow suppression with resulting *neutropenia or pancytopenia*.

Acute Presentation

- Lethargy, altered mental status
- Nausea, vomiting
- Hepatomegaly
- Characteristic pungent (“sweaty feet”) body odor (from the accumulated isovaleric acid)

Laboratory Findings

- Metabolic acidosis with anion gap
- Hypoglycemia
- Ketonuria
- Hyperammonemia
- Hyperglycinemia

There are two types of presentation of IVA depending on the severity of the metabolic defect. The neonatal form presents within the first days of life with a life-threatening picture of severe lethargy progressing to obtundation. The infantile or late-onset form has a more insidious presentation with failure to thrive, developmental delay, and perhaps other neurologic features such as seizures and spasticity. These children can decompensate acutely during catabolic stress, usually brought on by infection. In both presentations, the characteristic pungent odor of IVA may be present on the body and in the blood. In addition, there appears to be a mild or asymptomatic form of IVA that is frequently identified through newborn screening and appears not to be associated with acute illness.

Parents of children with diagnosed metabolic disorders know the signs of decompensation in THEIR children. It is important to listen to the parents’ insight into their child’s illness.

Immediate Assessment

- dextrose stick for blood glucose
- vital signs, cardiovascular stability
- hydration status
- presence of fever; signs of infection

- hepatomegaly
- neurologic status; evidence of increased intracranial pressure
- attention to “sweaty foot” body odor

Labs

Blood

- venous blood gas for blood pH
– electrolytes, measured CO2, glucose
– blood ammonia (**draw WITHOUT tourniquet, from free-flowing blood, place on ice and transport STAT to lab to be run immediately)
– AST, ALT, AlkPO4, PT, PTT, INR
– amylase, lipase
– plasma amino acids
– plasma total and free carnitine
– CBC, differential WBC count, platelet count
– blood culture (if indicated)

Urine

- urinalysis for specific gravity and ketones
– urine for organic acids
– urine culture (if indicated)

**NOTE: organic acids and ammonia are toxic to the brain and accumulations of these may result in cerebral edema. Caution should be exercised when considering the need for a lumbar puncture.

Management

Specific management guidelines are listed here, with details below:

1. Stop all protein intake
2. Provide hydration with high caloric supplementation
3. Treat biochemical abnormalities
4. Eliminate toxic metabolites
5. Treat precipitating factor(s)
6. Prevent associated sequelae

1. Protein intake

All protein intake should be halted once it is determined that a patient with IVA is having a metabolic decompensation severe enough to need acute metabolic management.

2. Hydration/caloric supplementation

In a metabolic crisis, a patient with IVA should receive high rate intravenous fluids (either via a peripheral venous line or a central venous line) for rehydration purposes and also for provision of calories. High dextrose-containing fluids (D10) should be administered with the addition of electrolytes (half or full normal saline solution, and also potassium if urine output is adequate and renal function is sufficient) at the rate of 1.5 times the maintenance rate for the particular patient. Intravenous fluids should ideally be maintained until the patient is able to tolerate oral fluids or nutrition or until rehydration goals are reached.

Ringer’s lactate fluids should NEVER be used for fluid/electrolyte therapy in a child with a known/suspected metabolic disorder.

Any patient with IVA in metabolic crisis should receive high caloric supplementation to achieve an anabolic state since catabolism precipitated by any stressor can contribute to exacerbation of the underlying metabolic decompensation and promote worsening metabolic acidosis, ketosis, and also possibly hyperammonemia. An intravenous lipid infusion (e.g. intralipid) should be considered to provide the increased calories. Protein can be added to the nutritional regimen at a slow rate once the patient is

able to tolerate protein, depending on a combination of factors including improvement in clinical status, mental status, and laboratory results. Once the patient has stabilized, oral intake should include an amino acid preparation containing only “non-offending amino acids” (i.e., avoiding leucine) and nutritional support with minerals and vitamins.

The goal for calories during a period of decompensation, to support anabolism, would be about 20% greater than ordinary maintenance needs. One must remember that withholding natural protein from the diet also eliminates this source of calories which should be replaced by other dietary or nutritional sources.

3. Correct Biochemical abnormalities

a. Metabolic acidosis: this should slowly correct with rehydration and high caloric intake; if bicarbonate level less than 15 mEq/L one should consider the administration of intravenous or oral bicarbonate in the form of sodium bicarbonate or sodium acetate.

b. Hypoglycemia: if blood glucose is below 50 mg/dL, give 5-10 ml/kg bolus of D10 intravenously (alternatively may give: 1-2 ml/kg of D50 or 2-4 ml/kg of D25). This should be followed by a continuous infusion of D10 with electrolytes (potassium should be added after patient is able to void and is not hyperkalemic) at a rate of 1.5 times the maintenance rate (based on current weight).

c. Hyperammonemia: if ammonia levels are extremely elevated, there are two modes of treatment: medical treatment (ammonul infusion which provides “scavenger” medications to reduce ammonia level) and hemodialysis.

4. Eliminate toxic metabolites

a. Hemodialysis: this is indicated in cases of intractable metabolic acidosis, severe hyperammonemia, unresponsive to treatment (blood ammonia level > 600 umol/L), coma, and severe electrolyte disturbances. This mode of intervention should be instituted in consultation with a pediatric nephrology service.

b. L-carnitine (oral or intravenous) to conjugate and detoxify isovaleryl-CoA (forming isovalerylcarnitine), thus reducing isovaleric and related toxic metabolites. In addition, free carnitine levels are generally low in IVA due to increased esterification of organic acid metabolites with carnitine requiring carnitine supplementation for repletion. While carnitine supplementation is controversial, case reports have shown that it is helpful during acute metabolic decompensations. Carnitine should be mixed in 10% glucose solution and run as an infusion to provide 100 mg/kg/day divided every 8 to 12 hours (maximum dose 5 grams/day). When patient is able to tolerate oral intake, the carnitine can be given orally at a dose of 100mg/kg/day divided every 8 or 12 hours.

c. L-glycine while controversial may prove helpful during acute crises by detoxifying the accumulated acyl-CoA forming isovalerylglycine, probably a harmless metabolite that is readily excreted. Glycine may be administered orally at a dose of 150-300 mg/kg/day divided in four to eight doses.

5. Precipitating factors

An acute metabolic decompensation in a patient with IVA is almost always precipitated by a stressor, such as infection, injury, surgery, hormonal changes, or significant dietary changes (involving increased protein intake). It is of utmost importance to identify and address the precipitating factor for the patient’s metabolic decompensation. Treatment of the stressor will facilitate treatment of the metabolic derangements.

Infection: Antibiotics should be provided to treat the particular infection.

Surgery: Prevention of metabolic decompensation in association with the stress of surgery should be undertaken prior to surgery by providing adequate hydration prior to and after surgery, avoiding prolonged fasting to the extent possible, addressing pain issues, and providing adequate calories to promote fast healing.

Hormonal Changes: The particular patient situation needs to be assessed and possible dietary changes should be made in accordance with the patient’s hormonal status (e.g. puberty, growth spurt, menarche, thyroid disorder).

Change in Diet: A change in the patient’s diet, with excessive protein intake, should be assessed as this would be an easy situation to address by adjusting the protein intake.

6. Clinical sequelae associated with an acute crisis

- Acute pancreatitis: One should be aware of this sequela and check a serum amylase and lipase levels if there are any signs that indicate the possibility of acute pancreatitis. These include vomiting, abdominal pain, and feeding intolerance. In fact, pancreatitis can be the presenting illness in patients with late-onset forms of IVA. Management would include limiting protein intake.
- Stroke: Any neurologic deterioration in a patient with IVA in metabolic crisis should be addressed emergently as the risk of neurologic stroke is higher in this patient population. A brain CT or MRI should be performed in the presence of any neurologic signs that suggest the possibility of a stroke. Management of increased intracranial pressure is similar to that for any other neurologic disorder causing increased intracranial pressure, including elevation of the head of the bed, hyperventilation (if patient is mechanically ventilated), mannitol, and other diuretics.

Monitoring the Patient

Clinical parameters

- Mental status
- Hydration status/fluid balance/oral intake
- Evidence of bleeding (if thrombocytopenic)
- Symptoms of infection (if neutropenic)
- Monitor for signs/symptoms of LVH/cardiomyopathy
- Monitor for signs/symptoms of neurologic stroke
- Monitor for signs/symptoms of pancreatitis

Biochemical parameters

- Electrolytes, measured CO2, glucose, ammonia, blood gases (q 4-6 hours or as indicated)
- CBC with differential, platelets
- Urine for ketones and specific gravity with every void
- Pancreatic enzymes (as indicated)

Recovery

The patient should be kept NPO until his/her mental status is improved. Anorexia and nausea/vomiting during the acute crisis period makes a significant oral intake unlikely. If the patient is not significantly neurologically compromised, consideration should be given to providing the patient (PO or by NG tube) with a modified formula preparation containing all but the offending amino acid (i.e. leucine).

When the infant/child is able to take fluids orally/per NG/gastrostomy tube, please contact the Metabolism fellow/staff or the Metabolism nutritionists, since each patient has a unique, modified diet. Each day, the nurses caring for the patient should review the menu with the parents or the nutritionists to avoid dietary mistakes; these do happen and can be disastrous in the peri-crisis period.