ORGANIC ACIDURIAS

What are Organic Acidurias?

Organic acidurias are a group of autosomal recessive disorder caused by the deficiency or absence of any of the enzymes needed for the breakdown of some proteins. They derive their names from the substance that accumulates proximal to the block in the pathway.

Organic Acidurias includes:

- Propionic aciduria (PA) – due to a deficiency of propionyl-CoA carboxylase
- Methylmalonic aciduria (MMA) – due to a deficiency of methmalonyl-CoA mutase
- Isovaleric aciduria (IVA) – due to a deficiency of isovaleryl-CoA dehydrogenase
- 3– Methylcrotnyl CoA Carboxylase Deficiency (3-MCC)
- Beta Ketothiolase Deficiency
- Glutaric Aciduria Type 1 (GA1)
- Multiple Carboxylase Deficiency (MCD)

Untreated children with this condition may present with vomiting, irritability, drowsiness, rapid breathing and coma. Patients with propionic aciduria and isovaleric aciduria may also have hyperammonemia. As a result, untreated children may have encephalopathy, mental retardation or death.

Organic acidurias	Confirmatory Testing
Propionic aciduria (PA)	Urine organic acid and plasma acylcarnitine
Methylmalonic aciduria (MMA)	Urine organic acid and plasma acylcarnitine
Isovaleric aciduria (IVA)	Urine organic acid and plasma acylcarnitine
3– Methylcrotnyl CoA Carboxylase Deficiency (3-MCC)	Urine organic acid and plasma acylcarnitine
Beta Ketothiolase Deficiency (BKD)	Urine organic acid and plasma acylcarnitine
Glutaric Aciduria Type 1 (GA 1)	Urine organic acid and plasma acylcarnitine
Multiple Carboxylase Deficiency (MCD)	Urine organic acid and plasma acylcarnitine

Further confirmatory testing may be required after referral to a metabolic specialist.

Treatment of Organic Acidurias

Treatment is through the dietary restriction of protein. Children may be given a special milk formula that is protein free. Carnitine and/or glycine are also prescribed.

Preliminary / Initial Management During Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state and prevent essential amino acid deficiency.

ORGANIC ACIDURIAS | Isovaleric Acidemia (IVA)

What is Isovaleric Acidemia (IVA)?

Isovaleric acidemia (IVA) was the first organic acidemia to be described. It is caused by a deficiency of isovaleryl-CoA dehydrogenase, an enzyme located proximally in the catabolic pathway of the essential branched-chain amino acid leucine.[1]

CLINICAL MANIFESTATIONS

The clinical manifestation of IVA may be acute or chronic. An acute or neonatal presentation is characterized by non- specific findings of vomiting, lethargy, poor feeding, seizures that may progress to a comatose state.[2] A characteristic odor in the urine described as "sweaty feet" or "dirty socks" has been reported among patients with IVA.[1,3] It has also been found that in bone marrow cultures, isovaleric acid is an inhibitor of granulopoietic progenitor cell proliferation which accounts for the pancytopenia or thrombocytopenia found in patients.[1] A chronic form may present with developmental delay or mental retardation.[1,3] Both acute or chronic patients may suffer from metabolic crisis and are sometimes misdiagnosed as suffering from diabetic ketoacidosis because of the similarity in presentation: acidosis, hyperglycemia and ketosis.[1]

PATHOPHYSIOLOGY

At present, the specific pathophysiology of IVA is unclear. It is surmised that accumulating CoA derivative sequesters CoA, thereby disturbing the mitochondrial energy metabolism.[1]

Inheritance: autosomal recessive[1, 3]

CONFIRMATORY TESTING

There is note of increased isovalerylcarnitine and isovalerylglycine in plasma or urine. Enzymatic assaytion cultured fibroblasts or mutation analysis may also be done.[1,3]

Overview of Disease Management

Dietary management involves limiting leucine intake. Detoxification of toxic metabolites by conjugation with glycine given at 150-600mg/kg/day and carnitine at 50-100 mg/kg/day should also be instituted.[1,3]

Prognosis

In a study by Grunert et al. (2012), among patients with IVA, the mortality rate is high in association with early neonatal presentation, neurocognitive outcome is better with early diagnosis and management and age of diagnosis but not the number of catabolic episodes contribute to the neurocognitive outcome.

Preliminary / Initial Management During Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

ORGANIC ACIDURIAS

Isovaleric Acidemia (IVA)

WHAT TO DO

If unwell and cannot tolerate oral intake:

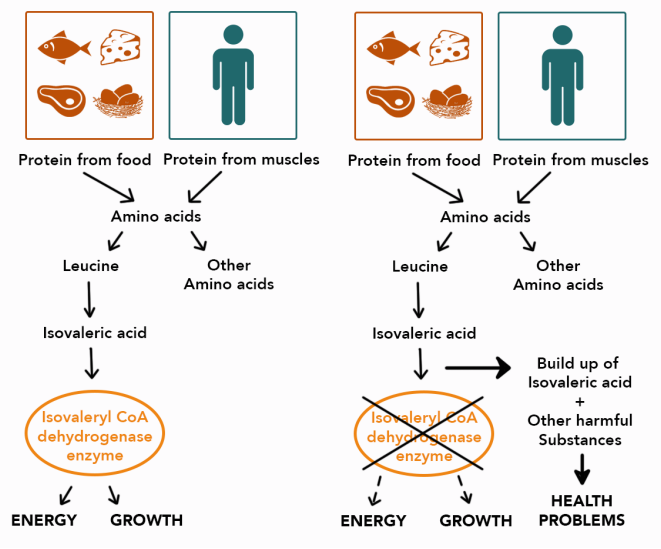
- Nothing per orem except medications
- Ensure patient's airway is secure
- Insert IV access. Collect samples for ammonia, blood gas, electrolytes and urine ketones. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if the patient requires it.
- Start D12.5% 0.3NaCl at full maintenance. Assess the patient and clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Give glycine (150mg/kg/day) q8 hours.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with protein free formula at maintenance rate
- Insert IV access. Collect samples for ammonia, blood gas, electrolytes and urine ketones. May request for investigations (i.e. CBC, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Give glycine (150mg/kg/day) q8 hours.
- Monitor input and output strictly (q6 hours)

**Monitor serum ammonia every 4 hours, if ammonia remain above 200mmol/L for three consecutive collections, medical treatment or hemodialysis may be indicated*
**Children should not be protein restricted for longer than necessary (24-48 hours)*
**Inform the metabolic doctor on call for further guidance regarding on-going management*
**If the patient is well, coordinate with a metabolic specialist regarding further management.*

Normal breakdown of protein vs IVA patient's breakdown of protein



[1] *Hoffman GF and Schulze A. Chapter 7: Organic Acidurias in Sarafoglou K, Hoffman GF and Roth KS (eds). Pediatric Endocrinology and Inborn Errors of Metabolism. New York: McGraw Hill, 2009 pp 93-94.*
[2] *Vockley J and Ensenauer R. Isovaleric academia: new aspects of genetic and phenotypic heterogeneity. Am J Med Genet C Semin Med Genet 2006;142C(2):95-103.*
[3] *Ensenauer R, Vockley J, Willard JM et al. A common mutation is associated with a mild, potentially asymptomatic phenotype in patients with isovaleric academia diagnosed by newborn screening. Am J Hum Genet 2004;75:1136-1142.*
[4] *Gurnert SC, Wendel U, Linder M et al. Clinical and neurocognitive outcome in symptomatic isovaleric academia. Orphanet J Rar Dis 2012;7:9.*