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 | Propionic Acidemia (PA)

What is Propionic Acidemia (PA)?

Propionic Acidemia (PA) is an organic acidopathy also known was propionic aciduria and ketotic hyperglycinemia.[1] It is due to the defective activity of propionyl CoA which is the first step in the pathway of propionate metabolism in which propionyl CoA, the product of the metabolism of isoleucine, valine, theronine and methionine is converted to methylmalonyl CoA acid then to succinyl CoA and oxidation in the citric acid cycle.[2]

CLINICAL MANIFESTATIONS

Patients usually are healthy at birth but quickly develop overwhelming disease, which may be misinterpreted as sepsis or ventricular hemorrhage.[3] Additional symptoms include vomiting, acidosis, dehydration, lethargy to coma, recurrent ketotic episodes, hypotonia, seizures and hyperammonemia.[4] Some patients may have acute-onset neurological symptoms described as metabolic strokes, arrhythmias, cardiomyopathy and an exfoliative rash.[5]

Patients may also present with similar dysmorphic characteristics such as frontal bossing, widened nasal bridge, wide set eyes, epicanthal folds, long philtrum and upward curvature of the lips.[4]

PATHOPHYSIOLOGY

Due to an increase in propionic acid, abnormal ketogenesis occurs because propionic acid is an inhibitor of mitochondrial oxidation and succinic and alpha-ketoglutaric acid.[4] Inhibition of glycine cleavage enzyme leads to hyperglycinemia adn the inhibition of N-acetylglutamate synthase, an enzyme of the urea cycle, causes hyperammonemia.[3]

Inheritance: autosomal recessive[5]

CONFIRMATORY TESTING

Plasma acylcarnitine and urine organic acid. Further confirmatory testing may be required after referral to a metabolic specialist.

Overview of Disease Management

Long-term treatment is the lifelong dietary restriction of isoleucine, valine, threonine and methionine.[5]

Carnitine supplementation, 100 mg/kg/day in divided doses, is also given as well as metronidazole (10 days per month at 10-20mg/kg/day) to reduce the significant propionate production of the bacterial intestinal flora.[3] Initiation of management should be done in consultation with an attending physician/ metabolic specialist.

Prognosis

Despite early diagnosis and treatment, the neonatal onset form of PA is still complicated by early death in infancy or childhood while late onset forms reach adulthood but often are handicapped by severe extrapyramidal movement disorders and mental retardation; however, progress has been achieved in survival and prevention of neurologic sequelae in affected children with early diagnosis and treatment.[3]

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

Propionic Acidemia (PA)

WHAT TO DO

If unwell and cannot tolerate oral intake:

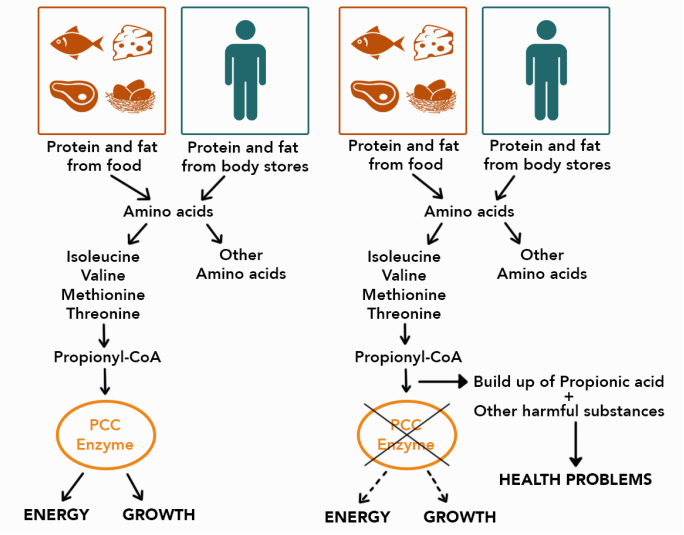
- Nothing per orem except medications
- Ensure patient's airway is secure
- Insert IV access. Collect samples for ammonia, blood gas, electrolytes and urine ketones. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if the patient requires it.
- Start D12.5% 0.3NaCl 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 carnitine (100mg/kg/day) q6 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 carnitine (100mg/kg/day) q6 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 PA patient's breakdown of protein



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[3] *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.*
[4] *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.*
[5] *Pena L, Franks J, Chapman KA et al. Natural history of propionic academia. Mol Gen Metab 2011: article under press*

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