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 | Beta-Ketothiolase Deficiency (BKD)

What is Beta-Ketothiolase Deficiency?

Beta ketothiolase deficiency is a defect of mitochondrial acetoacetyl-CoA thiolase involving ketone body metabolism and isoleucine catabolism.[1]

CLINICAL MANIFESTATIONS

This rare disorder is characterized by normal early development followed by progressive loss of mental and motor skills, it is clinically characterized by intermittent ketoacidotic episodes with no clinical symptoms in between. Some patients may present with vomiting, hypotonia, lethargy, coma, hyperventilation and dehydration. Ketoacidotic crises may occur following a bout of infection or mild illness.[2]

PATHOPHYSIOLOGY

Mitochondrial acetoacetyl CoA thiolase is responsible for the cleavage of 2-methylacetoacetyl CoA in isoleucine metabolism, acetoacetyl CoA formation in ketogenesis and acetoacetyl CoA cleavage in ketolysis.[2]

Inheritance: autosomal recessive[2, 3]

CONFIRMATORY TESTING

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

Overview of Disease Management

Due to the heterogeneity in the severity of clinical presentation, there should be individual treatment programs; general guidelines for treatment include dietary isoleucine restriction and to avoid fasting.[3] Initiation of management should be done in consultation with an attending physician/ metabolic specialist.

Prognosis

The frequency of ketoacidotic attacks decreases with age.[3] Clinical consequences can be avoided by early diagnosis and appropriate management of ketoacidosis.[2]

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

Beta-Ketothiolase Deficiency (BKD)

WHAT TO DO

If unwell and cannot tolerate oral intake:

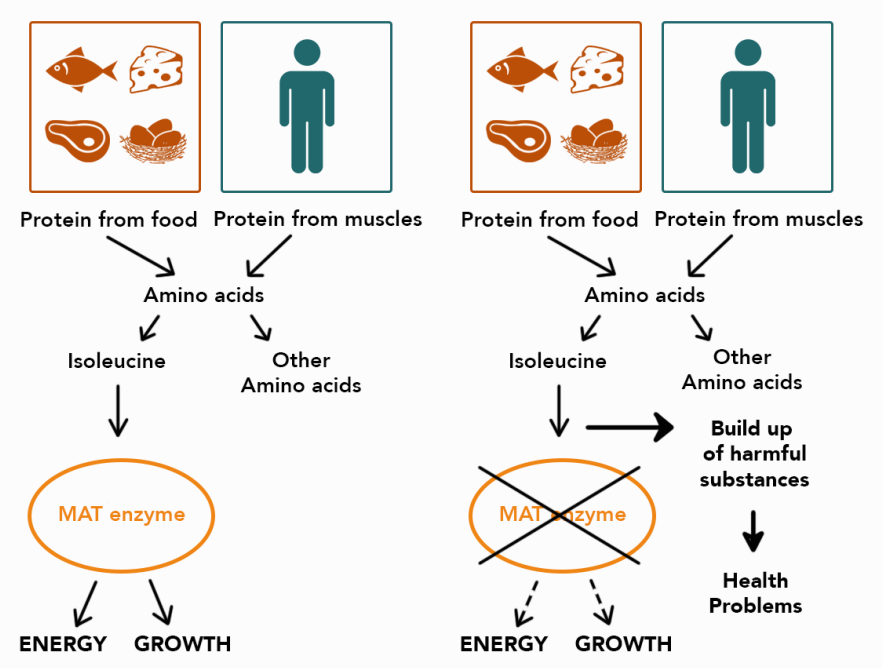
- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, blood gas, urine ketones) as needed.
- May give fluid boluses if the patient requires it.
- Start D10% 0.3NaCl at full maintenance. Assess the patient and clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- 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. Monitor glucose levels. May request for investigations (i.e. CBC, blood gas, urine ketones) as needed.
- Start D10% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours)

**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 BKD patient's breakdown of protein



[1] *Fukao T. Beta kethothiolase deficiency. Orphanet 2001 http://www.orpha.net/data/patho/GB/uk-T2.pdf Accessed Feb 15, 2012.*
[2] *Nyhan WL, Barshop BA and Ozand P. Chapter 17: Mitochondrial acetoacetyl CoA thiolase (3-oxothiolase) deficiency. Atlas of Metabolic Diseases 2nd ed. Great Britain:Oxford University Press, 2005 pp 102-106.*
[3] *Strauss AW, Andersen BS and Bennett MJ. Chapter 5: Mitochondrial Fatty Acid Oxida on Defects in Sarafoglou K, Hoffman GF and Roth KS (eds). Pediatric Endocrinology and Inborn Errors of Metabolism. New York:McGraw Hill, 2009 pp 60-62.*