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 | 3-methylcrotonyl CoA carboxylase (3MCC)

What is 3-methylcrotonyl CoA carboxylase (3MCC)?

The deficiency of 3-methylcrotonyl CoA carboxylase (3MCC) is a disorder of leucine metabolism that was first described by Eldjarn et al. in 1970. In most instances, it has been found that neonates who test positive for this condition in expanded newborn screening do not actually have the condition but instead reflect the increased levels of the metabolites of their mothers.

CLINICAL MANIFESTATIONS

There is a broad spectrum of clinical presentation ranging from no symptoms to failure to thrive, hypotonia, and cardiomyopathy to severe metabolic decompensation with metabolic acidosis and hypoglycemia. Some patients may have a late presentation (1-3 years old) with an acute episode of Reye syndrome, massive ketosis, acidosis, lethargy, coma leading to a fatal outcome.[3,4]

PATHOPHYSIOLOGY

3-methycrotonyl CoA carboxylase is responsible for the carboxylation of 3-methylcrotonyl-CoA, the fourth step in leucine catabolism; a deficiency of which causes a disturbance in leucine catabolism.

Inheritance: autosomal recessive[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

Treatment strategies include the restriction of natural protein intake and giving of carnitine supplementation (100mg/kg).[3] Initiation of management should be done in consultation with an attending physician/metabolic specialist.

Prognosis

3-MCC is a common, mostly benign condition; whether treatment with a low-protein diet, carnitine and glycine supplementation has the potential to change the clinical course in several affected patients remains to be elucidated.[5]

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

3-methylcrotonyl CoA carboxylase (3MCC)

WHAT TO DO

If unwell and cannot tolerate oral intake:

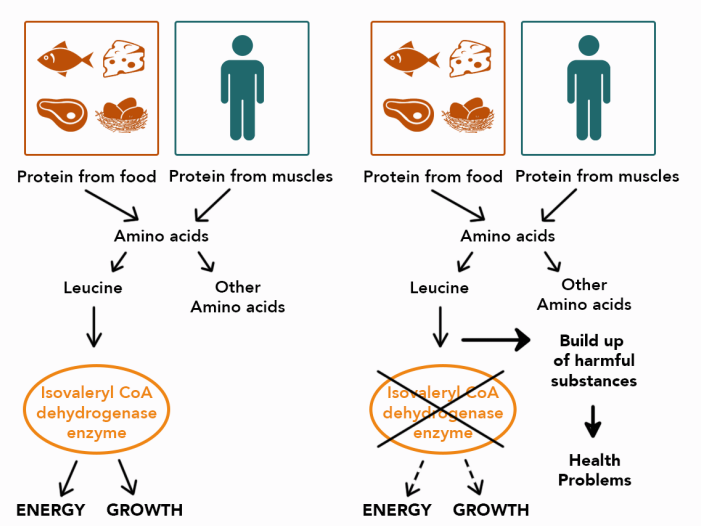
- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, blood gas, urine ketones) as needed.
- May give fluid boluses if the patient requires it.
- Start D12.5% 0.3NaCl at full maintenance. Assess the patient and clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- 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 D12.5% 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 metabolic doctor on call for further guidance regarding on-going management*
**If the baby's confirmatory test is negative, consider doing urine organic acid analysis of the patient's mother to rule out maternal 3-MCC deficiency.*
**If the patient is well, coordinate with a metabolic specialist regarding further management.*

Normal breakdown of protein vs 3MCC patient's breakdown of protein



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[2] *Nyhan WL, Barshop BA and Ozand P. Chapter 9: 3-methylcrotonyl carboxylase deficiency/3-methylcrtotonyl glycinuria. Atlas of Metabolic Diseases 2nd ed. Great Britain:Oxford University Press, 2005 pp 66-68.*
[3] *Ficicioglu MD and Payan I. 3-Methylcrotonyl-CoA carboxylase deficiency: metabolic decompensation in a noncompliant child detected through newborn screening. Pediatrics 2006;118:2555-2556.*
[4] *Baumgartner M. 3-methylcrotonyl-CoA carboxylase deficiency. Orphanet 2005. http://www.orpha.net/data/patho/GB/uk-MMC.pdf Accessed Feb. 15, 2012.*
[5] *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.*