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 | Methylmalonic Acidemia (MMA)

What is Methylmalonic Academia (MMA)?

Methylmalonic academia (MMA) is due to a defect in metholmalonyl CoA mutase or a defect in the enzyme's vitamin B12 derived co-factor 5'-deoxyadenosylcobalamin.[1] Among patients with a defect of methylmalonyl CoA mutase, two subgroups exist: Mut^0 patients have no enzyme activity while Mut- patients have a spectrum of residual activity.[2]

CLINICAL MANIFESTATIONS

Patients present with severe metabolic crisis in the first months of life, progressive failure to thrive, feeding problems, recurrent vomiting, dehydration, hepatomegaly, lethargy, seizures and developmental delay.[2] Some affected children may also have failure of linear growth, anorexia and developmental failure.[3] Patients may have metabolic decompensations following bouts of acute illness or minor infections.[2,3] They are prone to episodes of metabolic strokes that primarily affect the basal ganglia.[3]

Neonates affected with MMA share similar physical characteristics such as high forehead, broad nasal bridge, epicanthal folds, long smooth philtrum and triangular mouth.[3] Unique to this disorder is the development of chronic renal failure in the second decade in 20-60% of patients.[2]

PATHOPHYSIOLOGY

Methylmalonyl CoA-mutase catalyzes the conversion of methylmalonyl CoA to succinyl CoA which can enter the tricarboxylic acid cycle. This causes the accumulation of methylmalonate in the body which may be toxic to the brain and the kidneys.

Inheritance: autosomal recessive[2]
Screening: increase in propionylcarnitine on MSMS[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

Vitamin B12 responsive MMA will benefit from the supplementation of the cofactor.[3] For patients with the absence or decreased activity of methylmalonyl CoA mutase are advised to limit natural protein intake and supplementation with an Amino Acid Mixture that is free of isoleucine, valine, methionine and threonine.[2] Carnitine supplementation is considered an adjunct to therapy.[3]

Intestinal bacteria can be a source of propionate and methylmalonate that is naturally produced in the gut, this can be reduced by giving metronidazole 10 days per month at 10-20mg/kg/day, colistin or neomycin.[2,3]

Initiation of management should be done in consultation with an attending physician/metabolic specialist.

Prognosis

The long-term outcome of in MMA is influenced by the underlying defect.[4] Mut^0 patients have the worst prognosis, most of the patients may have very early onset signs and symptoms that occur even before the results of NBS are available, and die immediately or survive with significant neurodevelopmental disability.[3] Vitamin B12 responsive methylmalonic acidurias have a reasonable outcome.[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.

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ORGANIC ACIDURIAS

Methylmalonic Acidemia (MMA)

WHAT TO DO

If unwell and cannot tolerate oral intake:

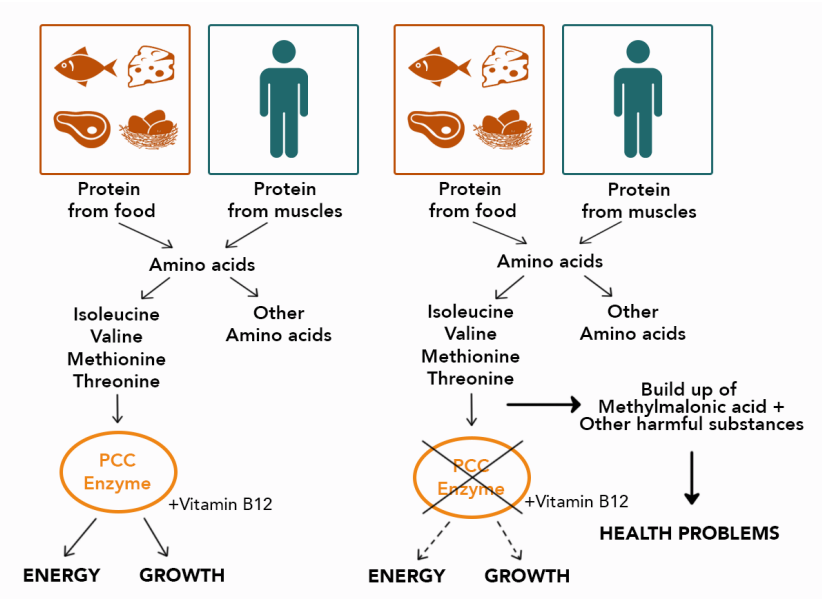
- Nothing per orem except medications
- Ensure patient's airway is secure
- Insert IV access. Collect samples for ammonia, blood gas, electrolytes and urine ketones. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D12.5% 0.3NaCl at full maintenance. Assess patient 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)

**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 MMA patient's breakdown of protein



[1] *Nyhan WL, Barshop BA and Ozand P. Chapter 3: Methylmalonic Acidemia. Atlas of Metabolic Diseases 2nd ed. Great Britain:Oxford University Press, 2005 pp 18-26.*
[2] *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.*
[3] *http://www.e-imd.org/rc/e-imd/htm/Ar cle/2011/e-imd-20110728-195831-072/src/htm_fullText/fr/MethylmalonicAciduria.pdf Accessed Feb 25, 2012.*
[4] *Cheng KH, Lie MY, Kao CH et al. Newborn screening for methylmalonic aciduria by tandem mass spectrometry: 7 years' experience from two centers in Taiwan. J Chin Med Assoc 2010;73(6)314-319.*