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 | Multiple Carboxylase Deficiency (MCD)

What is Multiple Carboxylase Deficiency (MCD)?

Multiple carboxylase deficiency, also known as holocarboxylase synthase leads to a failure of synthesis of all carboxylases.

CLINICAL MANIFESTATIONS

Most patients present acutely in the first few hours of life.[1] Patients may have dehydration, go into deep coma leading to death, ketosis, high anion gap metabolic acidosis, failure to thrive, alopecia and a characteristic erythematous eruption on the skin that can be bright, red, scaly or desquamative.

PATHOPHYSIOLOGY

Holocarboxylase synthase binds biotin, an essential cofactor in gluconeogenesis, fatty acid synthesis and the catabolism of several amino acids.[1] This in turn, leads to a failure of the synthesis of the active holocarboxylases which is the body's main source of biotin.[1]

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 is through giving biotin 10mg/kg/day.[1,3] The clinical response to treatment is dramatic, ketosis and acidosis disappear along with hyperammonemia; lethargy, hypotonia and ataxia disappear and dermatological effects of the disorder are reversed.[3] Initiation of management should be done in consultation with an attending physician/metabolic specialist.

Prognosis

Prognosis is good if treatment is initiated immediately and the clinical course is followed carefully by close monitoring of biochemical abnormalities.[1]

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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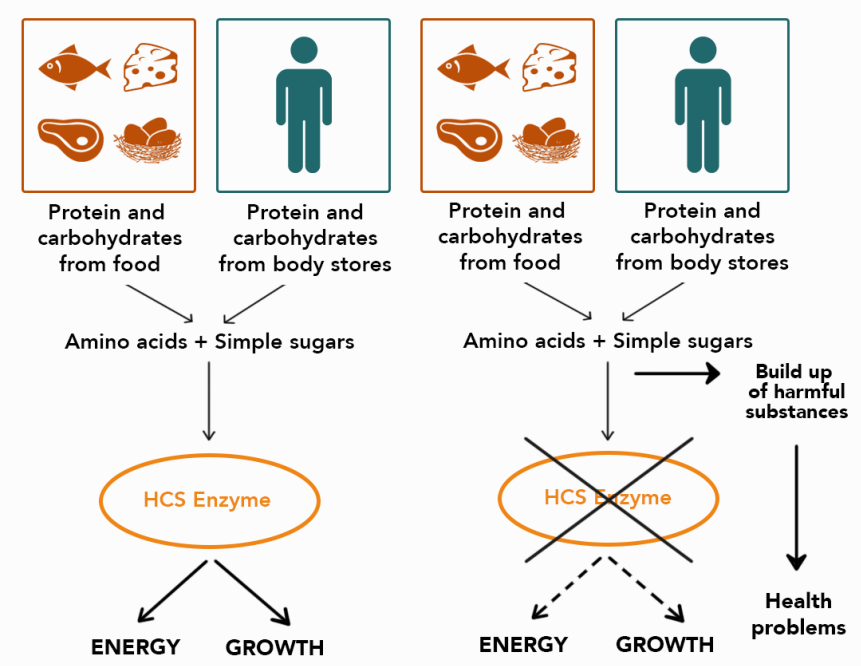
Multiple Carboxylase Deficiency (MCD)

WHAT TO DO IF UNWELL

- Ensure patient's airway is secure
- Insert IV access. Collect samples for serum ammonia and blood gas. May request for investigations (i.e. CBC, etc.) 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.

*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 MCD 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] Nyhan WL, Barshop BA and Ozand P. Chapter 6: Multiple carboxylase deficiency/biotinidase deficiency. Atlas of Metabolic Diseases 2nd ed. Great Britain:Oxford University Press, 2005 pp 42-48.
[3] Nyhan WL, Barshop BA and Ozand P. Chapter 5: Multiple carboxylase deficiency/holocarboxylase deficiency. Atlas of Metabolic Diseases 2nd ed. Great Britain:Oxford University Press, 2005 pp 36-39.