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 | Glutaric Acidemia 1 (GA1)

What is Glutaric Acidemia 1 (GA1)?

Glutaric Acidemia 1 (GA1) was first described by Goodman and colleagues in 1975. [1] It is caused by a deficiency of glutaryl- CoA dehydrogenase which catalyzes the oxidative decarboxylation of glutaryl-CoA, an intermediate in the degradation of the amino acids lysine and tryptophan. [2] This causes an increase in glutaric, 3-hydroxyglutaric, glutaconic and glutarylcarnitine.[1]

CLINICAL MANIFESTATIONS

Two subsets of patients are characterized based on the levels of glutaric acid excreted in the urine: the low (<100 mmol/mmol creatinine) and high excretors (>100 mmol/mmol creatinine). However, the risk of developing striatal injury resulting in neurologic dysfunction is the same regardless of excretion status.[3]

Patients with GA1 may present with hypotonia with head lag, feeding diffculties, irritability.[1] Macrocephaly is seen in about 75% of infants, but this is non-specific.3 If left untreated, 90% of patients develop neurologic disease presenting as dystonic-dyskinetic posturing, athetoid movements, opisthotonus, spastic, rigidity, clenched fists, tongue thrust and profuse sweating.[1,3] The encephalopathic crises precipitated by immunization, infection, surgery and fasting results in the affectation of the basal ganglia and exaggerates the neurologic manifestations occur frequently until the 4th year of life.[1]

PATHOPHYSIOLOGY

It was found that 3-hydroxglutaric and glutaric acid share structural similarities with glutamate which causes excitatory cell damage; further, the accumulation of these metabolites modulate glutamatergic and GABAergic neurotransmission resulting in an imbalance of excitatory and inhibitory neurotransmitters.[1]

Inheritance: autosomal recessive[1, 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

The main goal of treatment is to prevent encephalopathic crises and neurological deterioration and this can be achieved through dietary management.[1,2] This includes lysine intake restriction, giving carnitine 100mg/kg/day, riboflavin 100mg/day and the use of neuropharmacologic drugs to control neurologic symptoms.[1,3] Initiation of management should be done in consultation with an attending physician/metabolic specialist.

Prognosis

The early diagnosis and treatment intervention in patients with GA1 prevents striatal degeneration in 80-90% of infants.1 However, study by Beauchamp et al. (2009) showed that despite early treatment, patients with GA1 may have mild fine motor and articulation problems and raise the question of prenatal damage or subtle post-natal ongoing neurotoxic effects of glutaric and hydroxyglutaric acids or both.

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

Glutaric Acidemia 1 (GA1)

WHAT TO DO

If unwell and cannot tolerate oral intake:

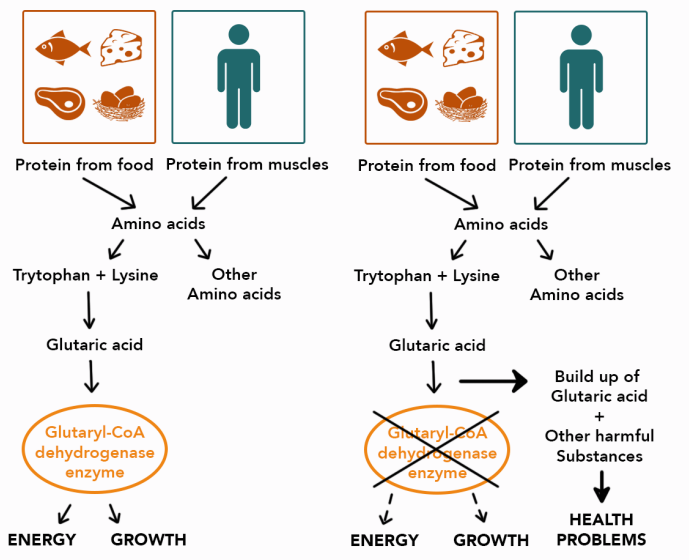
- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, blood gas, urine ketones) as needed.
- May give fluid boluses if the patient requires it.
- Start D12.5% 0.3NaCl at full maintenance. Assess the patient and clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Start IV 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 GA1 milk formula or 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
- Start IV 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)
Co-management with a neurologist is indicated to control the dystonia
**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 GA1 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] *Keyser B, Muhlhause C, Dickmanns A et al. Disease-causing missense mutations affect enzymatic activity, stability and oligomerization of glutaryl-CoA dehydrogenase (GCDH). Hum Mol Gen 2008;17(24):3854-3863.*
[3] *Kolker S, Christensen E and Leonard JV. Guideline for the diagnosis and management of glutaryl-CoA dehydrogenase deficiency. J Inherit Metab Dis 2007;30:5-22*
[4] *Beauchamp MH, Boneh A and Anderson V. Cognitive, behavioural and adaptive profiles of children with glutaric aciduria type I detected through newborn screening. J Inherit Metab Dis 2009;169:1-7. .*