CLINICAL MANIFESTATIONS OF ORGANIC ACIDEMIA

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A clinical presentation of a metabolic disorder, often first seen in infants who present with poor feeding, vomiting, tachypnea, acidosis, hyperammonemia, ketosis, ketonuria, irritability, and convulsions or hypotonia and lethargy, findings that are otherwise suggestive of neonatal sepsis Diseases with OA Isovaleric and propionic acidemias, maple syrup urine disease, medium chain acyl dehydrogenase deficiency, glutaric, methylmalonic, formiminoglutamic acidurias.

Description

The term “organic acidemia” or “organic aciduria” (OA) applies to a diverse group of metabolic disorders characterized by the excretion of non-amino organic acids in urine. Most organic acidemias results from a dysfunction of a specific step in amino acid catabolism, usually due to deficient enzyme activity. This leads to the accumulation of organic acids in the biological fluids (blood and urine), which, in turn, produces disturbances in the acid-base balance and causes alterations in pathways of intermediary metabolism.

Methylmalonic acidemia occurs when the activity of Methylmalonyl CoA mutase is defective in the isoleucine, valine, methionine and threonine degradative pathway.

Propionic acidemia occurs when the activity of Propionyl CoA carboxylase is defective in the isoleucine, valine, methionine and threonine degradative pathway.

Isovaleric acidemia occurs when the activity of Isovaleryl CoA dehydrogenase is defective in the leucine degradative pathway.

Glutaric acidemia type I occurs when the activity of Glutaryl CoA dehydrogenase is defective in the lysine, hydroxylysine and tryptophan degradative pathway.

3-Hydroxy-3-methylglutaryl CoA (HMG-CoA) lyase deficiency occurs when the activity of HMG CoA lyase is defective in the leucine degradative pathway.

3-Methylcrotonyl CoA carboxylase deficiency occurs when the activity of 3-methylcrotonyl-CoA carboxylase is defective in the leucine degradative pathway.

Incidence

While each individual disorder is rare, overall incidence of organic acidemias is 1:20, 000.

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Clinical Features

A neonate affected with an organic acidemia is usually well at birth and for the first few days of life. The usual clinical symptoms of OA disorders may include vomiting, metabolic acidosis, ketosis, dehydration, coma, hyperammonemia, lactic acidosis, hypoglycemia, failure to thrive, hypotonia, global developmental delay, sepsis and hematologic disorders. The non-distinct clinical presentation may initially be attributed to sepsis, poor breast-feeding, or neonatal asphyxia.

Screening

Newborn Screening Laboratory performs a screening test for organic acidemias by tandem mass spectrometry (MS/MS). It is a screening test and not a diagnostic test.

Confirmatory Testing

A diagnosis must be confirmed using an independent analysis of urinary organic acids as well as other appropriate tests.

It is important to confirm or exclude the diagnosis of an organic acidemia in a timely fashion and with a high degree of accuracy to avoid unnecessary testing, to provide appropriate interventions, prognostic and genetic counseling, and to ensure access to specialized medical services.

Implications for Genetic Testing

The disorders included in this screening are inherited in an autosomal recessive manner. While a family history of neonatal death should prompt consideration of an organic acidemia, a negative family history does not preclude the possibility.

Interpretations/Recommendations

Mandated Disorders:

• Expected Results: No elevated markers for C3, C5, C5DC, and C5OH (Acylcarnitine Profile within acceptable limits)

• Equivocal Results: Indeterminate results Recommend: Repeat filter paper specimen within 2 days

• Presumptive-Positive Results: Elevated acylcarnitine markers indicating a possible organic acidemia or repeat equivocal results

☐ Glutaric acidemia type I – C5DC

☐ Propionic and Methylmalonic acidemia – C3

☐ Isovaleric acidemia – C5

☐ 3-Hydroxy-3-methylglutaryl CoA lyase deficiency – C5OH

☐ 3-Methylcrotonyl CoA carboxylase deficiency – C5OH

Recommend: Immediate assessment of the baby's health status and consultation with metabolic/genetic specialist strongly recommended.

Non-Mandated Disorders:

Other acylcarnitine markers detected on MS/MS

• Positive Results: An elevated acylcarnitine result that does not match a mandated organic acidemia disorder profile Recommend: Immediate assessment of the baby's health status and consultation with a metabolic/genetic specialist for appropriate urine and/or serum confirmatory/diagnostic testing and treatment Newborn screening tests are adjuncts to clinical assessment, which is paramount. An organic acidemia disorder should be considered in infants with any of the signs/symptoms regardless of newborn screening results.

Keywords: Organic Acidemia; aminoacid; tandem mass spectrometry.