

Organic Acidurias

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Definition: Organic acidemias are inherited conditions that are defects in protein metabolism where an essential enzyme is absent or malfunctioning causing accumulation of organic acids in blood and urine. A person with an organic acidemia cannot properly break down certain components of protein for energy, growth, and development. Typically, these compounds are amino acids that are not completely broken down. Since the body cannot properly break down these amino acids, certain organic acids build up in the blood and urine. High levels of certain organic acids can cause serious health problems.

Outcomes without screening: Many organic acidurias present in the neonatal period as lethargy, anorexia, vomiting, dehydration, hyperammonemia, hypoglycemia, hypotonia, lactic acidosis, and ketoacidotic coma. If untreated, complications of cardiomyopathy, failure to thrive, mental retardation, movement disorders, nephritis, or pancreatitis may develop with the various disorders. The effects of the disorder will depend on the age at which symptoms occur.

Incidence: Organic acidurias are all rare disorders in the general population ranging from 1/40,000 to 1/200,000. However in some populations they may be more frequent, ie 1/2,000 for Propionic acidemia in Saudi Arabia.

Outcomes with screening: The first step of newborn screening is to identify all infants with elevated metabolite levels. The next steps are to quickly confirm the suspected disorder, assess the need for diet and cofactor therapy and begin treatment immediately. Each of these disorders is rare, and there have been only a few years of experience with children identified by a newborn screen. However, evidence is accumulating that early detection and treatment can lessen the symptoms in the classic early onset cases and protect the milder cases from the repercussions of metabolic insult.

Causes of organic acidemias: Organic acidemias are genetic conditions caused by changes in specific genes. These genes are responsible for making enzymes. These enzymes are responsible for breaking down components of protein. When there is an alteration in these genes, enzyme levels go down and organic acids build up in the blood and urine. Organic acidemias are inherited in an autosomal recessive pattern, which means two copies of a gene must be changed for a person to be affected with an organic acidemia. Most often, the parents of a child with an autosomal recessive condition are not affected because they are “carriers”, with one copy of the changed gene and one copy of the normal gene. When both parents are carriers, there is a one-in-four (or 25%) chance that both will pass a changed gene on to a child, causing the child to be born with the condition. There also is a one-in-four (or 25%) chance that they will each pass on a normal gene, and the child will be free of the condition. There is a two-in-four (or 50%) chance that a child will inherit a changed gene from one parent and a normal gene from the other, making it a carrier like its parents. These chances are the same in each pregnancy for the same parents.

Screening test and confirmation: Babies are tested (newborn screening) for organic acidemias before they leave the hospital. The baby’s heel is pricked and a few drops of blood are taken. The blood is sent to the state laboratory to find out if it has more than a normal amount of organic acids. The metabolites that are related to specific disorders are detected by tandem mass spectrometry. Due to the natural variation in the metabolic function of newborn

infants, some infants will be reported with elevated levels of metabolites that are only temporary. Thus follow-up diagnostic tests are required to identify the infants truly affected by an organic acid disorder.

There are various types of organic acidemias. The following is a list of organic acidemias that can be screened for:

- 2-Methyl-3-Hydroxybutyryl CoA Dehydrogenase deficiency (MHBD)
- 2-Methylbutyryl CoA Dehydrogenase deficiency (2-MBCD)
- 3-Hydroxy-3-Methylglutaryl CoA Lyase deficiency (HMG)
- 3-Methylcrotonyl CoA Carboxyl deficiency (3-MCC)
- 3-Methylglutaconyl CoA Hydratase deficiency (3-MGA)
- Glutaric Aciduria Type I (GA-1)
- Isobutyryl CoA Dehydrogenase deficiency (IBCD)
- Isovaleric Acidemia (IVA)
- Malonic Aciduria (MA)
- Methylmalonic Acidemia (MMA)
- Mitochondrial Acetoacetyl CoA Thiolase – (3-Ketothiolase) (BKT)
- Multiple CoA Carboxylase (MCD)
- Propionic Acidemia (PA)

Treatment: In most cases, many symptoms of an organic acidemia can be prevented by diet restrictions. Each treatment depends on the specific disorder. Children and adults with organic acidemias require follow-up care at a medical center or clinic that specializes in these types of metabolic condition. In addition, regular blood tests are used to monitor an individual's health.

Special concerns and issues: Confirmation may require analysis of urine organic acids, blood Acyl carnitine profiles and enzymatic studies.

Examples:

Isovaleric aciduria

Inheritance: Autosomal recessive

Population Incidence: Uncertain, 1/230,000

Ethnic Incidence: No known population at increased risk

Symptom Onset: Usually within the first 14 days of life in the acute form and later in the chronic form.

Symptoms: Infants with the acute neonatal form present after a few days of normalcy with poor feeding, vomiting, severe metabolic keto-acidosis, progressing to coma and death. Dehydration, hyperammonemia, hypocalcemia, hepatomegaly and hyper/hypoglycemia are often present. Depressed bone marrow function with neutropenia, thrombocytopenia and pancytopenia can lead to infection and/or cerebral hemorrhage. Most, but not all, will have the characteristic odor of "sweaty socks" which comes from the accumulation of isovaleryl acids. The chronic intermittent form presents later in infancy or childhood with episodes of metabolic acidosis as described above, usually associated with an intercurrent illness or increased protein load. Pancreatitis has occurred in a number of patients. The different forms can occur in the same family, so are not related to genotype.

Physical Findings: No particular dysmorphism.

Treatment: Low-protein diet with restricted leucine intake, in combination with glycine and carnitine supplements. Glycine and carnitine allow for the nontoxic removal of excess isovaleric-CoA. Patients will often self-select a low protein diet.

Propionic aciduria

Inheritance: Autosomal recessive

Population Incidence: In US the incidence is estimated to be 1:100,000

Ethnic Incidence: Saudi Arabia the frequency is 1:2000 to 1:5000; Greenland Inuit population incidence about 1:1000

Symptom Onset: Most patients present in newborn period, others have presented later in life.

Symptoms: In the newborn period, symptoms include severe metabolic acidosis manifested by refusal to feed, vomiting, lethargy, hypotonia and seizures. A few patients have presented later in life with acute encephalopathy, episodic ketoacidosis or with developmental retardation without ketosis or acidosis.

Physical Findings: Short stature and failure to thrive are common in these children as are osteoporosis and skin lesions. Pancreatitis is a complication seen in this and other organic acidurias.

Treatment: Treatment regimens are complicated with a diet restricted in protein, and use of a special formula deficient in the amino acids that feed into propionate metabolism. L-carnitine may be a useful therapeutic adjunct to replete intracellular and extracellular stores of free carnitine. Oral antibiotic therapy may be useful as well to decrease gut production of propionate. Continuous overnight feedings may be helpful in decreasing beta-oxidation and the release of odd-chain fatty acids since it theoretically will inhibit lipolysis. Liver transplant protects against acute metabolic decompensation, however the biochemical correction is incomplete and patients still have elevated metabolites.

Glutaric aciduria

Inheritance: Autosomal recessive

Population Incidence: 1:40,000 in Caucasians and 1:30,000 in Sweden

Ethnic Incidence: 1/10 carrier frequency among certain inbred populations, particularly the Old Order Amish in Pennsylvania and the Ojibway Indians in Canada.

Symptom Onset: Infancy, typically 2-37 months.

Symptoms: About 70% of patients have macrocephaly at or shortly after birth. There may be soft neurologic signs like jitteriness, irritability and truncal hypotonia in the newborn period. There are several different clinical presentations: 1). Affected infants appear normal and then suffer an acute metabolic crisis, usually 6-18 months, with subsequent neurological findings that improve slightly then remain static. Changes in the basal ganglia in particular, atrophy of the caudate and putamen develops within a few days or weeks of encephalopathic episode. Neuronal loss and fibrous gliosis occur in the caudate and putamen as part of neurotoxicity of GA1. 2). Infants have a period of normal development, acute crisis and subsequent neurological findings similar to those above, but then progress slowly with recurrent episodes of ketosis, vomiting, hepatomegaly and encephalopathy when the child develops infections. 3). Approximately 25% of infants gradually develop motor delay, hypotonia, dystonia and dyskinesia during the first few years of life without any apparent acute crisis. 4). Individuals can be completely asymptomatic without any crises and normal development. This has been documented via carrier testing and identification of 5% of affected Amish without symptoms. Some of these adults have now been diagnosed with white matter changes.

Physical Findings: Macrocephaly, cerebral palsy, dystonia.

Treatment: Prompt treatment of catabolic events with fever control, IVF, glucose, insulin and carnitine may prevent neurologic symptoms in patients without striatal damage at diagnosis. The effect of treatment with riboflavin and diet restriction of lysine and tryptophan is less clear.