

Disease Name:

METHYLMALONIC ACIDURIA, VITAMIN B-12 NON-RESPONSIVE

(METHYLMALONIC ACIDURIA DUE TO METHYLMALONIC CoA MUTASE DEFICIENCY; METHYLMALONICACIDURIA DUE TO MCM DEFICIENCY; MMA DUE TO MCM DEFICIENCY; MCM DEFICIENCY; COMPLEMENTATION GROUP mut; METHYLMALONYL CoA MUTASE, INCLUDED; MUT, INCLUDED)

Classification:

Organic Aciduria

Genetic Information:

Inheritance:

Autosomal recessive

Population Incidence:

1:48,000 live births

Ethnic Incidence:

No known population at increased risk

Gene & Location:

Methylmalonyl Coenzyme A mutase- 6p12-q21.2

Common Mutation:

No known common mutations

OMIM #

*251000

Disease Information:

Symptom Onset:

Severe *mut*⁰ deficiency accounts for 2/3 of the mutase patients. 80% become ill during the first week of life, 90% present by end of first month. Infants with the less severe *mut*- may present later than the first month. A very few may remain asymptomatic or present much later in life depending on the residual enzyme activity and the metabolic stressors.

Symptoms:

Most common signs and symptoms are lethargy, failure to thrive, recurrent vomiting, dehydration which lead to profound metabolic acidosis, respiratory distress, hypotonia and death if not recognized. Complications of acute episodes can include metabolic stroke, extrapyramidal signs, dystonia, or bilateral lucencies of globus pallidus. Survivors may have significant neurological damage. Renal failure may appear during childhood. Clinical spectrum is wide, ranging from fatal neonatal disease to asymptomatic individuals. Patients do not have to have clinical crises in order to have neurological or other organ system compromise.

Physical Findings:

Some patients, in whom there was known consanguinity have had associated birth defects, congenital heart defects, hydronephrosis and facial dysmorphisms.

Treatment: Treatment regimens include a protein-restricted diet and OH-Cbl injections as soon as diagnosis of MMA is suspected. While mutase deficient infants are not generally responsive to OH-Cbl, this may still be beneficial. Carnitine supplementation is needed to replete intracellular and extracellular stores of free carnitine and oral antibiotic therapy may be useful as well to decrease gut production of propionate. Precursors of propionate and methylmalonate are methionine, threonine, valine, isoleucine, odd chain fatty acids and cholesterol. Unfortunately the body makes the majority of the odd chain fatty acids and cholesterol so they cannot be limited solely by manipulating the diet. However using special formulas that are deficient in these amino acids can decrease the problematic metabolic precursors. Liver transplant or combined liver/kidney transplant are options for metabolic control. The liver transplants have significant perioperative risk and there is documentation of neurological problems after transplant despite improved biochemical parameters. The renal transplants have shown good response with drop in methylmalonic acid levels. However, any type of transplant is limited because MMA enzyme is in all tissues and the transplants do not affect the levels made in the cerebral spinal fluid and brain.

Natural History without treatment: Variable, depends on the enzyme defect and the patient. Some will die as a neonate, others will survive with deficits and others will remain asymptomatic.

Natural History with treatment: About 60% of patients die within the first year of life and those of those that survive, 40% are distinctly impaired developmentally. Equal fractions of affected patients are alive and well, alive and impaired or deceased. Age of onset of symptoms can help prognosticate, those with later onset tend to have a more benign course.

Metabolic Information: **Missing Enzyme & Location:** Methylmalonyl CoA mutase catalyses methylmalonyl CoA to succinyl CoA. The designation, *mut*⁰, has little or no mutase activity while *mut-* has a structurally abnormal enzyme.

MS/MS profile: C3 (propionyl carnitine)- elevated
C3/C2 ratio >0.4

Prenatal testing: Possible via enzyme assay on amniocytes or CVS.

Miscellaneous Information:

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