

Disease Name:

**METHYLMALONIC ACIDURIA, VITAMIN B-12
RESPONSIVE**

(METHYLMALONICACIDURIA, VITAMIN B12-RESPONSIVE, DUE TO DEFECT IN SYNTHESIS OF ADENOSYLCOBALAMIN, cb1A COMPLEMENTATION TYPE; METHYLMALONICACIDURIA, cb1A TYPE; MMAA; METHYLMALONICACIDURIA, VITAMIN B12-RESPONSIVE, DUE TO DEFECT IN SYNTHESIS OF ADENOSYLCOBALAMIN, cb1B COMPLEMENTATION TYPE)

Classification:

Organic Aciduria

**Genetic
Information:**

Inheritance:

Autosomal recessive

Population Incidence:

Unknown

Ethnic Incidence:

No known population at increased risk

Gene & Location:

Cobalamin A disease- MMAA gene - [4q31.1-q31.2](#)
Cobalamin B disease- MMAB gene - [12q24](#)

Common Mutation:

No known common mutations

OMIM #

#251100; #251110

**Disease
Information:**

Symptom Onset:

Ranges from presentation in the first week of life to completely asymptomatic.

Symptoms:

Episodic ketoacidosis accompanied by lethargy and coma can lead to death. In survivors, developmental and growth retardation, spastic quadriparesis, dystonia and seizures are common. Neutropenia, thrombocytopenia and osteoporosis are common complications.

Physical Findings:

No dysmorphisms

Treatment:	<p>Treatment regimens include a diet restricted in protein and OH-Cbl injections. L-carnitine may be useful therapeutic adjunct to replete intracellular and extracellular stores of free carnitine since these patients usually have low levels. 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.</p> <p>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.</p>
Natural History without treatment:	Variable depends on the enzyme defect and the patient. Some will die as a neonate; other will survive with deficits and others will be asymptomatic.
Natural History with treatment:	<p><i>cblA</i>- They have the best prognosis because the biochemical and clinical abnormalities reverse in about 90% of patients when they are provided pharmacological doses of hydroxy-cobalamin (OH-cbl) injections.</p> <p><i>cblB</i>- 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. About 40% of these patients will respond with a drop in MMA level when given pharmacological doses of OH-cbl injections.</p>
<u>Metabolic Information:</u>	<p>Missing Enzyme & Location:</p> <p>Cobalamin A (<i>cblA</i>) deficiency: defect in the mitochondrial cobalamin reductase. These patients are unable to make adenosylcobalamin.</p> <p>Cobalamin B (<i>cblB</i>) deficiency: defect of mitochondrial cob(I)alamin adenosyltransferase and the patients are unable to make adenosylcobalamin.</p>
MS/MS profile:	C3 (propionyl carnitine)- elevated C3/C2 ratio >0.4
Prenatal testing:	Possible via enzyme assay on amniocytes or CVS.

Miscellaneous
Information:

Prepared for the NW Regional Newborn Screening Program by Sara Copeland MD, Judith Tuerck RN MS and Lorinda Paradise at OHSU in Portland, OR.

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