

<b>Disease Name</b>	
<b>METHYLMALONIC ACIDURIA, VITAMIN B-12 RESPONSIVE (MMA Cbl A &amp; B)</b>	
<i>(METHYLMALONICACIDURIA, VITAMIN B12-RESPONSIVE, DUE TO DEFECT IN SYNTHESIS OF ADENOSYLCOBALAMIN, cblA COMPLEMENTATION TYPE; METHYLMALONICACIDURIA, cblA TYPE; MMAA; METHYLMALONICACIDURIA, VITAMIN B12-RESPONSIVE, DUE TO DEFECT IN SYNTHESIS OF ADENOSYLCOBALAMIN, cblB COMPLEMENTATION TYPE)</i>	
<b>Classification:</b>	Organic aciduria
<b>Genetic Information</b>	
<b>Inheritance:</b>	Autosomal recessive.
<b>Population Incidence:</b>	Unknown.
<b>Ethnic Incidence:</b>	No known population at increased risk.
<b>Gene &amp; Location:</b>	Cobalamin A disease- MMAA gene - 4q31.1-q31.2 Cobalamin B disease- MMAB gene - 12q24
<b>Common Mutation:</b>	No known common mutations.
<b>OMIM #</b>	#251100; #251110
<b>Disease Information</b>	
<b>Symptom Onset:</b>	Ranges from presentation in the first week of life to asymptomatic.
<b>Symptoms:</b>	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.
<b>Physical Findings:</b>	No dysmorphisms.
<b>Treatment:</b>	<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>
<b>Natural History without treatment:</b>	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.
<b>Natural History with treatment:</b>	<p><i>cblA</i>- They have the best prognosis because the biochemical and clinical abnormalities reverse in about 90 percent 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</p>

	deceased. Age of onset of symptoms can help prognosticate, those with later onset tend to have a more benign course. About 40 percent of these patients will respond with a drop in MMA level when given pharmacological doses of OH-cbl injections.	
<b>Metabolic Information</b>		
<b>Missing Enzyme &amp; Location:</b>	Cobalamin A ( <i>cblA</i> ) deficiency: defect in the mitochondrial cobalamin reductase. These patients are unable to make adenosylcobalamin. Cobalamin B ( <i>cblB</i> ) deficiency: defect of mitochondrial cob(I)alamin adenosyltransferase and the patients are unable to make adenosylcobalamin.	
<b>MS/MS profile:</b>	C3 (propionyl carnitine)- elevated. C3/C2 ratio – elevated.	
<b>Prenatal testing:</b>	Possible via enzyme assay on amniocytes or CVS.	
<b>Miscellaneous Information:</b>		
<b>Credit:</b>	<i>Prepared by the North West Regional Newborn Screening Program Judith Tuerck, RN, MS, and Lorinda Paradise at Oregon Health Services University in Portland, Oregon and by Sara Copeland MD, Iowa Neonatal Metabolic Screening Program.</i>	
<b>Sites of Reference:</b>	<b>OMIM - Methylmalonic Aciduria</b> <a href="http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?251000">www.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?251000</a>  <b>National Library of Medicine Genetics Home Reference</b> <u>Methylmalonic acidemia</u> <a href="http://ghr.nlm.nih.gov/condition=methylmalonicacidemia%20and%20">http://ghr.nlm.nih.gov/condition=methylmalonicacidemia%20and%20</a>	
<b>Support Groups:</b>	<b>Organic Acidemia Association</b> www.oaanews.org/ 13210 35th Avenue Plymouth, MN 55441 Contact: Kathy Stagni (763) 559-1797 OAAnews@aol.com	<b>Save Babies Through Screening Foundation, Inc</b> 4 Manor View Circle Malvern, PA 19355-1622 888-454-3383 610-993-0545 email@savebabies.org <a href="http://www.savebabies.org/index.htm">www.savebabies.org/index.htm</a>

<b>Disease Name</b>	
<b>VITAMIN B12 METABOLIC DEFECT WITH METHYLMALONICACIDEMIA AND HOMOCYSTINURIA (MMA Cbl C)</b>	
(COMBINED DEFICIENCY OF METHYLMALONYL CoA MUTASE AND HOMOCYSTEINE: METHYLTETRAHYDROFOLATE METHYLTRANSFERASE; <i>cbIC</i> ; VITAMIN B12 METABOLIC DEFECT, TYPE 2; METHYLMALONICACIDEMIA AND HOMOCYSTINURIA; <i>cbID</i> ; VITAMIN B12 LYSOSOMAL RELEASE DEFECT; COBALAMIN, DEFECT IN LYSOSOMAL RELEASE OF VITAMIN B12 STORAGE DISEASE; COBALAMIN F DISEASE; <i>cbIF</i> ; METHYLMALONICACIDURIA DUE TO VITAMIN B12-RELEASE DEFECT)	
<b>Classification:</b>	Organic aciduria
<b>Genetic Information</b>	
<b>Inheritance:</b>	Autosomal recessive.
<b>Population Incidence:</b>	Unknown, cobalamin C deficiency is the most common and less than 100 patients have been identified.
<b>Ethnic Incidence:</b>	No known population at increased risk.
<b>Gene &amp; Location:</b>	Cobalamin C ( <i>cbIC</i> ), cobalamin D ( <i>cbID</i> ) and the gene in Cobalamin F ( <i>cbIF</i> ) are unknown.
<b>Common Mutation:</b>	No known common mutations.
<b>OMIM #</b>	<i>cbID</i> - #277410; <i>cbIC</i> - *277400; <i>cbIF</i> - #277380
<b>Disease Information</b>	
<b>Symptom Onset:</b>	In a study of 50 patients with <i>cbIC</i> disease, 44 had onset in the first year of life and six had onset after six years of age. The median age of onset was one month and ranged from birth to 14 years. Patients in the <i>cbID</i> group generally do not have clinical problems until later in life. In <i>cbIF</i> disease, the patient may have signs or symptoms of the disorder at birth or shortly afterwards.
<b>Symptoms:</b>	<p><i>CblC</i> disease: Early onset patients have feeding problems; hypotonia; failure to thrive; seizures; microcephaly; developmental delay; cortical atrophy; hydrocephalus; nystagmus; pigmentary retinopathy; decreased visual acuity; bone marrow dysfunction and some have presented with renal failure and hemolytic uremic syndrome.</p> <p>Late onset patients present in childhood or adolescence with acute neurological changes: decreased cognitive performance; confusion; dementia; delirium; myelopathy; and tremor. Only one late-onset patient had pigmentary retinopathy. The hematology abnormalities are seen in late-onset patients. They may have progressive neurological deficits in spite of appropriate treatment.</p> <p>In <i>cbID</i> disease in general there are no clinical problems until later in life. Often they present with behavior pathology; mental retardation and neuromuscular symptoms. They do not tend to have bone marrow dysfunction.</p> <p>The <i>cbIF</i> patients tend to be small for gestational age at birth and present with the metabolic ketoacidosis from methylmalonic acidemia. They have poor feeding, growth retardation, and persistent stomatitis or rashes. Some patients have been noted to have minor facial anomalies, dextrocardia and macrocytosis. It has been found to be a cause of sudden death. One patient, each with hypertrophic cardiomyopathy and glomerulosclerosis, have been noted in the literature.</p>
<b>Physical Findings:</b>	There are no particular dysmorphisms specific for any of the three types but dysmorphisms are found frequently, except the <i>cbIF</i> patients have more minor facial anomalies reported.

<b>Treatment:</b>	Treatment includes a protein-restricted diet, supplement with OH-Cbl and betaine in order to bypass the defect in the cobalamin synthesis.	
<b>Natural History without treatment:</b>	Clinical course ranges from sudden death to severe psychosis and developmental delay. Varies among family members.	
<b>Natural History with treatment:</b>	Early diagnosis and prompt institution of therapy may be the only way to change the outcome of these patients, which has been dismal thus far. It is not clear that treatment changes the natural history but may help to decrease some of the psychiatric complications, and hopefully, avoid some of the skin rashes and other secondary complications, like the pigmentary retinopathy and renal involvement.	
<b>Metabolic Information</b>		
<b>Missing Enzyme &amp; Location:</b>	Precise defect in <i>cblC</i> and <i>cblD</i> is not known, but is thought to involve an early step in intracellular metabolism of cobalamin. In <i>cblF</i> disease there is impaired efflux of free cobalamin from lysosomes.	
<b>MS/MS profile:</b>	C3 (propionyl carnitine)- elevated. C3/C2 ratio – elevated.	
<b>Prenatal testing:</b>	Enzyme assay is available on chorionic villi or amniocytes in known families at risk.	
<b>Miscellaneous Information:</b>	Differentiation between types is based on complementation studies of skin.	
<b>Credit:</b>	<i>Prepared by the North West Regional Newborn Screening Program Judith Tuerck, RN, MS, and Lorinda Paradise at Oregon Health Services University in Portland, Oregon and by Sara Copeland MD, Iowa Neonatal Metabolic Screening Program.</i>	
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<b>Disease Name</b>	
<b>METHYLMALONIC ACIDURIA, VITAMIN B-12 NONRESPONSIVE (Mutase)</b>	
<i>(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)</i>	
<b>Classification:</b>	Organic aciduria
<b>Genetic Information</b>	
<b>Inheritance:</b>	Autosomal recessive.
<b>Population Incidence:</b>	1:48,000 live births.
<b>Ethnic Incidence:</b>	No known population at increased risk.
<b>Gene &amp; Location:</b>	MUT, MCM genes- 6p12-q21.2
<b>Common Mutation:</b>	No known common mutations.
<b>OMIM #</b>	*251000
<b>Disease Information</b>	
<b>Symptom Onset:</b>	Severe <i>mut0</i> deficiency accounts for two-thirds of the mutase patients. Eighty percent become ill during the first week of life, 90 percent present by end of first month. Infants with the less severe <i>mut-</i> 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.
<b>Symptoms:</b>	Most common signs and symptoms are lethargy, failure to thrive, recurrent vomiting, and 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, and bilateral lucencies of globus pallidus on MRI. 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.
<b>Physical Findings:</b>	Some patients, in whom there was known consanguinity, have had associated birth defects, congenital heart defects, hydronephrosis and facial dysmorphisms.
<b>Treatment:</b>	<p>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.</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</p>

	made in the cerebral spinal fluid and brain.		
<b>Natural History without treatment:</b>	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.		
<b>Natural History with treatment:</b>	About 60 percent of patients die within the first year of life, and of those that survive, 40 percent 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.		
<b>Metabolic Information</b>			
<b>Missing Enzyme &amp; Location:</b>	Methylmalonyl CoA mutase catalyses methylmalonyl CoA to succinyl CoA. The designation, <i>mut0</i> , has little or no mutase activity while <i>mut</i> -has a structurally abnormal enzyme.		
<b>MS/MS profile:</b>	C3 (propionyl carnitine)- elevated. C3/C2 ratio – elevated.		
<b>Prenatal testing:</b>	Possible via enzyme assay on amniocytes or CVS.		
<b>Miscellaneous Information:</b>			
<b>Credit:</b>	<i>Prepared by the North West Regional Newborn Screening Program Judith Tuerck, RN, MS, and Lorinda Paradise at Oregon Health Services University in Portland, Oregon and by Sara Copeland MD, Iowa Neonatal Metabolic Screening Program.</i>		
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