

Disease Name:

VITAMIN B12 METABOLIC DEFECT WITH METHYLMALONICACIDEMIA AND HOMOCYSTINURIA

(COMBINED DEFICIENCY OF METHYLMALONYL CoA MUTASE AND HOMOCYSTEINE: METHYLTETRAHYDROFOLATE METHYLTRANSFERASE; *cb1C*; VITAMIN B12 METABOLIC DEFECT, TYPE 2; METHYLMALONICACIDEMIA AND HOMOCYSTINURIA; *cb1D*; VITAMIN B12 LYSOSOMAL RELEASE DEFECT; COBALAMIN, DEFECT IN LYSOSOMAL RELEASE OF VITAMIN B12 STORAGE DISEASE; COBALAMIN F DISEASE; *cb1F*; METHYLMALONICACIDURIA DUE TO VITAMIN B12-RELEASE DEFECT)

Classification:

Organic aciduria

Genetic Information:

Inheritance:

Autosomal recessive

Population Incidence:

Unknown, cobalamin C deficiency is the most common and less than 100 patients have been identified

Ethnic Incidence:

No known population at increased risk

Gene & Location:

Cobalamin C (*cb1C*), cobalamin D (*cb1D*) and the gene in Cobalamin F (*cb1F*) are unknown

Common Mutation:

No known common mutations

OMIM #

cb1D- #277410; *cb1C*- *277400; *cb1F*- #277380

Disease Information:

Symptom Onset:

In a study of 50 patients with *cb1C* disease, 44 had onset in the first year of life and 6 had onset after 6 years of age. The median age of onset was 1 month and ranged from birth to 14 years. Patients in the *cb1D* group generally do not have clinical problems until later in life. In *cb1F* disease, the patient may have signs or symptoms of the disorder at birth or shortly afterwards.

Symptoms: *CblC* 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.

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.

In *cblD* 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.

The *cblF* 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.

Physical Findings: There are no particular dysmorphisms specific for any of the three types but dysmorphisms are found frequently, except the *cblF* patients have more minor facial anomalies reported.

Treatment: Treatment includes a protein-restricted diet, supplement with OH-Cbl and betaine in order to bypass the defect in the cobalamin synthesis.

Natural History without treatment: Clinical course ranges from sudden death to severe psychosis and developmental delay. Varies among family members.

Natural History with treatment: 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.

Metabolic Information:

Missing Enzyme & Location:

Precise defect in *cblC* and *cblD* is not known, but is thought to involve an early step in intracellular metabolism of cobalamin.

In *cblF* disease there is impaired efflux of free cobalamin from lysosomes.

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

Prenatal testing: Enzyme assay is available on chorionic villi or amniocytes in known families at risk.

**Miscellaneous
Information:**

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