Disorders of Intracellular Cobalamin Metabolism

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Summary

Clinical characteristics. The clinical manifestations of disorders of intracellular cobalamin metabolism can be highly variable even within a single complementation group. The prototype and best understood is cblC; it is also the most common of these disorders. The age of initial presentation of cblC spans a wide range, including:

- Newborns, who can have intrauterine growth retardation (IUGR) and microcephaly;
- Infants, who can have poor feeding, failure to thrive, pallor, and neurologic signs, and occasionally hemolytic uremic syndrome (HUS) and/or seizures including infantile spasms;
- Toddlers, who can have failure to thrive, poor head growth, cytopenias (including megaloblastic anemia), global developmental delay, encephalopathy, and neurologic signs such as hypotonia and seizures; and
- Adolescents and adults, who can have neuropsychiatric symptoms, progressive cognitive decline, and/or subacute combined degeneration of the spinal cord.

Diagnosis/testing. The diagnosis of disorders of intracellular cobalamin metabolism relies on clinical, biochemical, complementation group, and molecular genetic data. Urine organic acid analysis and plasma amino acid analysis are the mainstays of biochemical testing. Diagnosis is confirmed by identification of biallelic pathogenic variants in one of the following genes (associated complementation groups indicated in parentheses): *MMACHC* (cblC), *MMADHC* (cblD and cblD variant 1), *MTRR* (cblE), *LMBRD1* (cblF), *MTR* (cblG), and *ABCD4* (cblJ).
Management. *Treatment of manifestations:* No therapy completely mitigates all disease manifestations. Critically ill individuals must be stabilized, preferably in consultation with a metabolic specialist, by treating acidosis and reversing catabolism. Treatment of thromboembolic complications (e.g., hemolytic uremic syndrome (HUS) and thrombotic microangiopathy) include initiation of hydroxocobalamin (OHCbl) and betaine or an increase in their doses. Long-term management focuses on improving the metabolic derangement by lowering plasma tHcy and MMA concentrations and maintaining plasma methionine concentrations within the normal range. Gastrostomy tube placement for feeding may be required; infantile spasms, seizures, congenital heart defects, and hydrocephalus are treated using standard protocols.

Prevention of primary manifestations: Early institution of therapy may reduce but not completely prevent primary manifestations. To prevent metabolic decompensations, patients are advised to avoid situations that result in catabolism, such as prolonged fasting and dehydration.

Surveillance: During the first year of life, infants may need to be evaluated once or twice a month by a metabolic specialist to assess growth, nutritional status, feeding ability, and developmental and neurocognitive progress. Other evaluations may include ophthalmologic examination for retinal and optic nerve changes in patients with cblC and cblG and if visual symptoms are present.

Agents/circumstances to avoid: Prolonged fasting (longer than overnight without dextrose-containing intravenous fluids); dietary protein intake below the recommended dietary allowance (RDA) for age or more than that prescribed by a metabolic specialist; methionine restriction; and the anesthetic nitrous oxide.

Evaluation of relatives at risk: If the pathogenic variants in the family are known, at-risk sibs may be tested prenatally to allow initiation of treatment as soon as possible after birth. If the newborn sib of an affected individual has not undergone prenatal testing, the infant can be tested in the first week of life by urine organic acids, plasma amino acids, measurement of total plasma homocysteine, and acylcarnitine profile analysis for the purpose of early diagnosis and treatment.

Genetic counseling. All disorders of intracellular cobalamin metabolism are inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants in a family are known. If molecular genetic testing is not possible, prenatal testing for pregnancies at 25% risk is possible by a combination of complementation analysis of cultured amniocytes and measurement of MMA and tHcy concentrations in amniotic fluid using mass spectrometric techniques.

GeneReview Scope

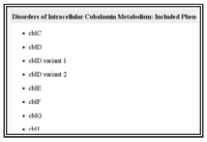

Table
cblC cblD

Diagnosis

Clinical Diagnosis

The disorders of intracellular cobalamin metabolism result from deficient synthesis of the coenzymes derived from vitamin B_{12}:

- Adenosylcobalamin (AdoCbl) - the coenzyme for methylmalonyl-CoA mutase enzyme
- Methylcobalamin (MeCbl) - the coenzyme for the enzyme methionine synthase (MTR) (Figure 1)

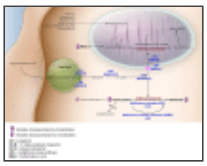

Figure 1.
Intracellular metabolism of cobalamin. The intracellular metabolism of cobalamin consists on the endocytosis of cobalamin bound to its blood-carrier transcobalamin. Inside the lysosome cobalamin is released from transcobalamin and then transported into (more...)

This *GeneReview* describes disorders with combined methylmalonic acidemia and homocystinuria caused by AdoCbl and MeCbl deficiency (Table 1 - B) and disorders associated with homocystinuria (MeCbl deficiency) (Table 1 - C). For disorders associated with isolated methylmalonic acidemia (AdoCbl deficiency) (Table 1 - A) see Methylmalonic Acidemia).

The diagnosis of a disorder of intracellular cobalamin metabolism in a symptomatic individual is based on clinical, biochemical, complementation group, and molecular genetic data.

Since newborn screening (NBS) potentially allows early detection of certain disorders of intracellular cobalamin metabolism (see Testing Strategy), some affected individuals may be diagnosed prior to the onset of symptoms.

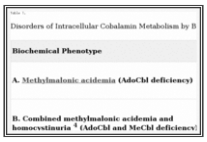

Table 1.
Disorders of Intracellular Cobalamin Metabolism by Biochemical Phenotype

Testing

Biochemical Testing

The identification of disorders of intracellular cobalamin metabolism relies first on establishing the biochemical phenotype (described in Table 1) using the following testing (Table 2):

- **Urine organic acid (UOA) analysis** to detect elevation of methylmalonic acid (MMA). Other secondary metabolites such as 3-hydroxypropionate, methylcitrate, and tiglylglycine may be seen transiently in affected individuals who are ill. Methylglutaconic aciduria can be seen on occasion [Adams et al 2006].

  Note: Quantitative serum MMA levels are more accurate than urine organic acid analysis for longitudinal monitoring.

- **Plasma amino acid (PAA) analysis.** Hypomethioninemia, seen in disorders with defective MeCbl synthesis, helps differentiate disorders of intracellular cobalamin metabolism from other causes of homocystinuria, such as cystathionine beta-synthase deficiency (see Differential Diagnosis, **Cystathionine beta synthase deficiency**).

  Other findings that can be seen on PAA analysis include:

  - Hyperhomocystinemia and mixed disulfides (which are also excreted in the urine);
  - Cystathionine (which is also excreted in the urine) in individuals with cblC.

- **Total plasma homocysteine (tHcy) analysis** is the preferred method of detecting and monitoring plasma homocysteine concentration in individuals with defective MeCbl synthesis.

  Note: Delays in separating serum from plasma after obtaining a blood sample can artificially increase total homocysteine by as much as 10% an hour [Ubbink 2000, Refsum et al 2004].

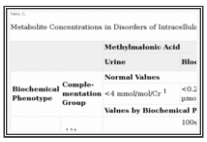

Table 2.
Metabolite Concentrations in Disorders of Intracellular Cobalamin Metabolism

Confirmatory Testing

Investigations on cultured fibroblasts obtained from a skin biopsy can help establish the diagnosis of specific disorders of intracellular cobalamin metabolism.

Complementation group analysis is a method used to identify the specific defect of intracellular cobalamin metabolism. The complementation groups currently known are cblA, cblB, cblC, cblD, cblE, cblF, cblG and cblJ.

Molecular genetic testing, when available, can be more convenient than complementation group analysis in confirming the diagnosis of a disorder of intracellular cobalamin metabolism.

- **Single gene testing**. One strategy is to perform sequence analysis of the genes according to which are most commonly mutated in the disorders (Table 3).

  Note: Sequencing of *MMACHC* is likely to be the most cost-effective method to arrive to a diagnosis in a patient in whom cblC is suspected based on clinical findings.

- **Multi-gene panel**. Another strategy is use of a multi-gene panel that includes the genes of interest. See Differential Diagnosis.

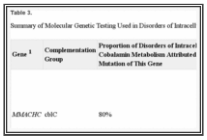

Table 3.
Summary of Molecular Genetic Testing Used in Disorders of Intracellular Cobalamin Metabolism

Testing Strategy

Confirmation of the diagnosis in a proband. The algorithm in Figure 2 may assist with the evaluation of a proband in the following clinical scenarios:

Figure 2.
Testing algorithm to confirm the diagnosis of a disorder of intracellular cobalamin metabolism in a proband Notes: 1. While diagnostic testing is being performed, contact metabolic team and initiate treatment immediately. 2. Normal values urine MMA: <4 (more...)

- Newborns from a family with a previously affected sib
- Symptomatic individuals, even if newborn screening was reported as normal [Chace et al 2001]
- Newborn with abnormal newborn screening based on elevated C3 propionylcarnitine or decreased methionine (see ACMG ACT Sheets C3 and Methionine)

Note: Detection by newborn screening depends on the C3 and C3/C2 ratio cut-off values used by reference laboratories and availability of detection of low methionine [Chace et al 2001, Weisfeld-Adams et al 2010].

Research molecular genetic testing. Because new technologies may facilitate gene identification in the near future, participation in research studies may be useful for individuals in whom a specific type of disorder of intracellular cobalamin metabolism cannot be established.

Clinical Characteristics

Clinical Description

Disorders of intracellular cobalamin metabolism have a variable phenotype (Table 4) and age of onset that is influenced by the severity and location in the pathway of the defect.

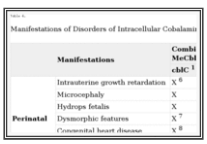

Table 4.
Manifestations of Disorders of Intracellular Cobalamin Metabolism

Combined Methylmalonic Acidemia and Homocystinuria (cblC, some variants of cblD, cblF, and cblJ)

cblC, likely the most common of the disorders of intracellular cobalamin metabolism, is the best understood clinically and is described here as a prototype for combined methylmalonic acidemia and homocystinuria. In cblC age of onset ranges from prenatal to adulthood. The infantile presentation is the most frequently recognized.

Prenatal manifestations. Intrauterine growth retardation (IUGR) has been seen in infants with cblC [Nogueira et al 2008, Frattini et al 2010] and cblF [Alfadhel et al 2011]. Other developmental manifestations can include microcephaly [Francis et al 2004, Smith et al 2006], congenital heart disease [Profitlich et al 2009], dilated cardiomyopathy, hydrocephalus, and mild dysmorphic features (long facies, flat philtrum and large low-set ears) [Cerone et al 2000].

Infantile presentation. This severe presentation is progressive and may be lethal unless treated. Infants may present with failure to thrive, poor feeding, and hypotonia in the first two weeks of life or with an acute metabolic derangement (high anion gap metabolic acidosis, ketonuria, and hyperammonemia). The absence of an acute metabolic presentation should not rule out the diagnosis of a disorder of intracellular cobalamin metabolism [Harding et al 2003]. Untreated infants may have multi-organ involvement, neurologic deterioration, seizures (i.e., infantile spasms), and encephalopathy.

Some infants present with hemolytic uremic syndrome (HUS) that may be fatal if treatment with daily hydroxocobalamin (OHCbl) is not initiated promptly [Kind et al 2002, Sharma et al 2007, Carrillo-Carrasco & Venditti 2012].

Progressive retinopathy typically develops in individuals with infantile cblC. The initial manifestations are “wandering eye movements,” ocular fixation difficulties, and nystagmus. Fundoscopic changes (which can be detected by careful examination as early as the first month of life) are characterized by abnormal macular pigmentation which evolves classically over the next few years into a "bull's-eye" macula and a pigmentary retinopathy and maculopathy.

Late-onset presentations of cblC and other inborn errors of cobalamin metabolism do not typically have ophthalmologic complications. Optic atrophy has been described in cblG [Poloschek et al 2005].

Early presentation (first years of life). Failure to thrive, poor head growth, cytopenias (including megaloblastic anemia), global developmental delay, encephalopathy, and neurologic signs such as hypotonia and seizures are typical.

Adolescent and adult presentation. Individuals with this presentation usually have predominant **neurologic and neuropsychiatric** manifestations including the following:

- Neuropsychiatric symptoms (behavioral and personality changes, social withdrawal, visual and auditory hallucinations, delirium, psychosis)
- Progressive cognitive decline (regression, deterioration in school or work performance, impaired dexterity and memory, speech difficulties, dementia, and lethargy) which is frequently described in the absence of other manifestations [Powers et al 2001, Boxer et al 2005, Ben-Omran et al 2007, Thauvin-Robinet et al 2008]
- Subacute combined degeneration of the spinal cord [Bodamer et al 2001, Ben-Omran et al 2007, Tsai et al 2007]. In some cases, improvement has been reported after initiation of treatment [Thauvin-Robinet et al 2008].

Brain MRI may reveal leukodystrophy ranging from isolated periventricular white matter hyperintensities to diffuse white matter loss [Rossi et al 2001, Longo et al 2005].

Isolated Homocystinuria (cblE, cblG, some variants of cblD)

Methylcobalamin deficiency secondary to methionine synthase reductase deficiency (cblE) is more common than methionine synthase deficiency (cblG) and cblD variant 1.

Most children with cblE present in the first two years of life with severe failure to thrive, megaloblastic anemia, and neurologic manifestations; isolated megaloblastic anemia may also be seen.

Individuals with cblG characteristically present in the first year of life with neurologic manifestations and megaloblastic anemia; however, phenotypic variability ranges from an infantile to an adult presentation. Neurologic manifestations may include weakness, hypotonia, seizures, mental status changes, and adult-onset leukoencephalopathy. Other unusual presentations of adult-onset cblG include megaloblastic anemia and progressive weakness (initially diagnosed as multiple sclerosis) [Carmel et al 1988] and neuropsychiatric illness [Hill et al 2004]. Optic nerve atrophy has been described in cblG [Poloschek et al 2005].

Individuals with cblD variant 1 leading to isolated methylcobalamin deficiency had cognitive impairment, neurologic signs, and megaloblastic anemia [Suormala et al 2004]. Thromboembolic complications, including clinically significant thrombophilia causing renal artery thrombosis [Watkins & Rosenblatt 1989], HUS, and pulmonary hypertension [Labrune et al 1999] have been described in patients with this biochemical phenotype.

Genotype-Phenotype Correlations

Genotype/phenotype correlations observed include the following:

cblC

- Early-onset, severe disease is associated with the *MMACHC* c.271dupA or the *MMACHC* c.331 C>T (p.Arg111Ter) pathogenic variants in the homozygous or compound heterozygote state.
- Late-onset disease is usually associated the *MMACHC* c.394C>T (p.Arg132Ter) and *MMACHC* c.482G>A (p.Arg161Gln) pathogenic variants [Morel et al 2006, Nogueira et al 2008, Lerner-Ellis et al 2009, Wang et al 2009]. It may also be associated with *MMACHC* c.271dupA if patients are compound heterozygotes for c.394C>T, c.347T>C, c.440 G>C, or c.482G>A [Morel et al 2006].

cblD. The location of pathogenic variants within *MMADHC* correlates with the type of enzyme deficiency:

- **AdoCbl deficiency.** Pathogenic variants are generally nonsense and frame-shifting variants in exons 3 and 4, encoding the region of the protein necessary for AdoCbl synthesis.
- **MeCbl deficiency.** Pathogenic variants are missense variants in exons 6 and 8, encoding the region of the protein necessary for MeCbl synthesis.
- **AdoCbl and MeCbl deficiency.** Pathogenic variants occur in the middle of the protein (exon 5, exon 8, and intron 7) [Stucki et al 2012].

cblE caused by the *MTRR* c.1361C>T (p.Ser545Leu) Iberian variant has a milder phenotype than other reported variants in *MTRR* and no evident neurologic involvement [Zavadakova et al 2002].

Clear genotype-phenotype correlations have not been described for cblF, cblG, or cblJ.

Prevalence

The true prevalence of the disorders of intracellular cobalamin metabolism is unknown.

The incidence of cblC has been estimated at 1:200,000 births. Recently, newborn screening suggested an incidence closer to 1:100,000 in New York State and of 1:60,000 in California, where an incidence of 1:37,000 was estimated in the Hispanic population [Cusmano-Ozog et al 2007, Weisfeld-Adams et al 2010].

Fewer than forty cases have been described for cblE and cblG, and fewer than 20 cases each for cblD and cblF.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *MMACHC, MMADHC, LMBRD1*, *MTR, MTRR*, or *ABCD4*.

Differential Diagnosis

The following disorders may cause clinical manifestations and laboratory abnormalities similar to those seen in disorders of intracellular cobalamin metabolism:

Disorders causing both methylmalonic acidemia and homocystinuria

- **Vitamin B_{12} deficiency.** Individuals with vitamin B_{12} deficiency can have methylmalonic acidemia and homocystinuria, as can the newborns of mothers who have vitamin B_{12} deficiency. To establish the diagnosis of vitamin B_{12} deficiency, it is necessary to measure serum vitamin B_{12} concentrations in both affected newborns and their mothers.

  B_{12} deficiency can occur in a breast-fed infant of a vegan mother and in an infant born to a mother with subclinical pernicious anemia. The mother may not necessarily have a very low serum concentration of vitamin B_{12}. Maternal vitamin B_{12} deficiency can result in elevated methylmalonic acid level in an infant with findings that range from severe encephalopathy [Higginbottom et al 1978] to elevated propionylcarnitine detected by newborn screening [Chace et al 2001].

  Intramuscular replacement therapy to normalize vitamin B_{12} serum concentration reverses the metabolic abnormality.

- **Imerslund Gräsbeck syndrome.** Features of this autosomal recessive disorder may include poor cobalamin absorption, abnormal renal tubular protein reabsorption, and urinary tract malformations. Biallelic pathogenic variants in one of two genes that encode intrinsic factor receptor components have been implicated: *CUBN* (encoding cubulin) and *AMN* (encoding amnionless) [Gräsbeck 2006].

- **Transcobalamin II deficiency.** Transcobalamin II (distinguished from transcobalamin I AKA haptocorrin) is required for the movement of cobalamin from intestinal enterocytes into cells throughout the body. Transcobalamin II deficiency, a rare condition, is characterized by the infantile onset of megaloblastic anemia, failure to thrive, neurologic disease, and immunologic disease. Serum

cobalamin concentrations are generally normal with a reduced (untreated) unsaturated B_{12} binding capacity (UBBS) and a reduced level of transcobalamin II (the latter detected by an immunoassay) [Kaikov et al 1991, Rosenblatt & Fenton 2001].

Disorders causing primarily isolated homocystinuria

- **Cystathionine beta synthase (CBS) deficiency** (classic homocystinuria) is a disorder of homocysteine catabolism with a Marfan syndrome-like phenotype, soft skin, lens dislocation, developmental delays/cognitive impairment, and thromboembolism. CBS deficiency is progressive with onset typically in childhood. Biochemically it is characterized by elevated serum concentration of methionine and decreased serum concentration of cysteine. Inheritance is autosomal recessive.
- **Methylenetetrahydrofolate reductase (MTHFR) deficiency** is a defect in folate-dependent methylation pathways that results in diminished conversion of homocysteine to methionine. The biochemical hallmark is moderate homocystinuria with low to normal plasma methionine levels. In contrast to methionine biosynthetic defects like cblE and cblG, megaloblastic anemia does not occur. The clinical course is characterized by varying severity, cognitive impairment, and white-matter disease [Fenton et al 2001]. Inheritance is autosomal recessive.
- **Mild homocystinuria** can result from folate deficiency, vitamin B_{12} deficiency, or mild pathogenic variants in enzymes in remethylation enzymes.

Disorders causing primarily methylmalonic acidemia

- Disorders associated with isolated methylmalonic acidemia include methylmalonic acidemia caused by mutation of methylmalonyl-CoA mutase (*MUT*), cblA (*MMAA*), and cblB (*MMAB*); SUCLA2 deficiency [Carrozzo et al 2007, Ostergaard et al 2007]; "benign methylmalonic acidemia" [Sniderman et al 1999, Martens et al 2002]; Reye-like syndrome [Chang et al 2000]; and combined malonic and methylmalonic acidemia (CMAMMA) caused by mutation of *ACSF3* [Sloan et al 2011].
- For a more detailed description of other entities with isolated methylmalonic acidemia, see Methylmalonic Acidemia.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with a disorder of intracellular cobalamin metabolism, the following evaluations are recommended.

In an unstable patient:

- Serial metabolic evaluations of blood gases, electrolytes, glucose, ammonia, liver function, total and direct bilirubin, renal function, lactate dehydrogenase, plasma amino acids (methionine), plasma methylmalonic acid (MMA), and total plasma homocysteine (tHcy) to guide acute management until the patient stabilizes
- Complete blood count (CBC) with differential to evaluate for megaloblastic anemia, cytopenias
- Peripheral blood smear to evaluate for the presence of schistocytes, in the presence of other manifestations of hemolytic uremic syndrome (HUS)
- Molecular genetic testing to identify pathogenic variants, if not previously performed, to aid in genetic counseling and prediction of disease severity

Once the patient becomes stable:

- Clinical assessment of growth parameters, head circumference, ability to feed, developmental status, and neurologic status
- Laboratory assessment of nutritional status (electrolytes, albumin, prealbumin, plasma amino acids, vitamin levels [including thiamine and 25-hydroxyvitamin D], and trace minerals) and renal function; complete blood count to monitor for cytopenias
- Echocardiogram
- EEG and brain MRI in symptomatic individuals
- Ophthalmologic examination

Treatment of Manifestations

Prognosis is poor in patients with early-onset cblC who are undiagnosed and untreated [Rosenblatt et al 1997]. Institution of therapy during acute illness results in rapid improvement of clinical, biochemical, and hematologic manifestations in patients with early- and late-onset cblC [Bartholomew et al 1988, Rosenblatt et al 1997, Bodamer et al 2001, Tomaske et al 2001, Kind et al 2002, Van Hove et al 2002, Fowler et al 2008].

Parenteral hydroxocobalamin (OHCbl) is the mainstay of therapy and should be instituted as soon as a disorder of intracellular cobalamin metabolism is suspected. Infants are started with daily 1.0 mg intramuscular or subcutaneous injections. Patients with cblC are often highly responsive to this therapy.

Patients with elevated tHcy should also receive betaine (250 mg/kg/day) and folate or folinic acid.

Acute metabolic decompensation. Although less common in the disorders of intracellular cobalamin metabolism than in methylmalonic acidemia, severe acidotic/ketotic crises due to profound methylmalonic acidemia do occur. Such critically ill individuals should be managed in consultation with a metabolic specialist. MedicAlert® bracelets and emergency treatment protocols outlining fluid and electrolyte therapy should be available for all affected individuals.

Treatment includes volume replacement with isotonic solutions containing high (10%-12.5%) glucose to reverse catabolism, correction of metabolic acidosis with sodium bicarbonate, and prompt reintroduction of feedings — preferably enterally, but parenterally if enteral route cannot be established.

Thromboembolic complications a cause of mortality in cblC are likely associated with increasing plasma concentrations of tHcy [Carrillo-Carrasco & Venditti 2012]. The proper management of thromboembolic complications, such as hemolytic uremic syndrome (HUS) and thrombotic microangiopathy, should include initiation of OHCbl and betaine or an increase in their doses [Van Hove et al 2002, Sharma et al 2007].

Long-term management. The goals of long-term management include improving the metabolic derangement by lowering plasma tHcy and MMA concentrations and maintaining plasma methionine concentrations within the normal range. These are accomplished by:

- **Parenteral OHCbl.** The most experience derives from the treatment of patients with cblC. Infants are usually started at a daily dose of 1.0 mg (~0.3 mg/kg/d) of OHCbl given IM or SQ. Parenteral OHCbl (not the cyanocobalamin form or oral form) is the only effective preparation. Placement of a SQ catheter that minimizes cutaneous punctures [Freehauf et al 2011] and pre-filled injections may increase compliance.

  Weight-appropriate adjustment of the OHCbl dose is recommended and can be attained by the ability to concentrate OHCbl up to 30 mg/mL. Further titration of the dose may be empirically adjusted as needed for worsening clinical manifestations [Van Hove et al 2002] or for metabolic control of plasma tHcy, MMA, or methionine concentrations [Carrillo-Carrasco et al 2009].

- **Betaine.** Oral betaine (starting at ~250 mg/kg/day) is recommended in patients with defective MeCbl production (cblC, cblD, cblE, cblF, cblG, and cblJ). Betaine augments the non-methionine synthase-dependent conversion of homocysteine to methionine (however, this is not uniformly accepted). Optimal dosing and monitoring have not been adequately established.

- **Folate and folinic acid.** Folic acid and folinic acid can potentially augment remethylation and may help improve plasma tHcy and methionine concentrations. Folinic acid may be preferred as it crosses the blood brain barrier more efficiently than folic acid. The adult dose of folate is 1.0 mg by mouth per day, titratable down to 0.5 mg for maintenance. Doses for children and infants are available in the Harriet Lane Handbook [Tschudy & Arcara 2012] and other common reference texts.

- **Dietary management.** Patients may be able to tolerate a normal diet: the use of a low-protein diet is under debate and needs further clinical studies to clarify the benefits of its use.

  Most importantly, methionine restriction should be avoided, as hypomethioninemia can be detrimental [Ribes et al 1990, Rossi et al 2001, De Bie et al 2009].

  Gastrostomy tube placement may be required in the present of feeding difficulties and failure to thrive.

Other therapeutic considerations that have not been fully validated:

- **Methionine supplementation.** Hypomethioninemia is usually responsive to appropriate treatment with OHCbl and betaine. The need for exogenous methionine supplementation may be minimized by these strategies, as the efficacy of this therapy is uncertain [Smith et al 2006].
- **Pyridoxine.** Vitamin B_6 is a cofactor for cystathionine beta synthase and, therefore has been proposed as a means of maximizing the removal of homocysteine. Persons with disorders of intracellular cobalamin metabolism generally do not respond to pyridoxine unless they have a dietary deficiency.
- **Levocarnitine.** Indicated for low plasma carnitine levels

Treatment of infantile spasms, seizures, congenital heart defects, and hydrocephalus is done in a routine manner.

Prevention of Primary Manifestations

Early institution of therapy may reduce but not completely prevent primary manifestations.

To prevent metabolic decompensations, patients should be advised to avoid situations that result in catabolism, such as prolonged fasting and dehydration. Of note, during an intercurrent illness patients may be treated with glucose-containing IV fluid.

Flu prevention (i.e., immunization) should be a routine part of health maintenance.

Prevention of Secondary Complications

Antiplatelet doses of aspirin may be given to patients with isolated homocystinuria to decrease the risk for thrombosis [Brunel-Guitton et al 2010].

Surveillance

The following evaluations are performed at different intervals depending on age and disease severity.

During the first year of life, infants may need to be evaluated once or twice a month by a metabolic specialist.

Clinical evaluation should include assessment of:

- Growth including weight, linear growth, and head circumference;
- Nutritional status;
- Feeding ability;
- Developmental and neurocognitive progress, as age-appropriate.

Laboratory evaluation should include:

- Metabolic studies: urine organic acids, plasma MMA concentration, plasma amino acids (methionine), plasma tHcy concentration;
- Complete blood count (CBC) to monitor for cytopenias;
- Nutritional studies, if indicated: electrolytes, albumin, prealbumin, plasma amino acids, vitamin levels (including thiamine and 25-hydroxyvitamin D), and trace minerals.

Routine evaluations should include:

- Ophthalmologic evaluation for retinal and optic nerve changes in patients with cblC and cblG and if visual symptoms are present;
- Neurologic evaluations for early signs of psychomotor retardation, behavioral disturbances, seizures, and myelopathy;
- Brain MRI and/or EEG as clinically indicated.

Agents/Circumstances to Avoid

Potentially exacerbating circumstances:

- Prolonged fasting (longer than overnight without dextrose-containing intravenous fluids)
- Dietary protein intake below the recommended dietary allowance (RDA) for age or more than that prescribed by a metabolic specialist
- Methionine restriction. Methionine-free formulas given to infants with methylmalonic acidemia should be avoided as the decreased methionine intake may worsen hypomethioninemia in patients with decreased methionine production.
- Nitrous oxide, an anesthetic that is potentially toxic as it depletes the body stores of vitamin B_{12} and inhibits methionine synthase activity [Abels et al 1990, Drummond & Matthews 1994]

Evaluation of Relatives at Risk

If the pathogenic variants in the family are known, at-risk sibs may be tested prenatally to allow initiation of treatment as soon as possible after birth.

If the newborn sibling of an affected individual has not undergone prenatal testing, the infant can be tested in the first week of life by urine organic acids, plasma amino acids, measurement of total plasma homocysteine, and acylcarnitine profile analysis for the purpose of early diagnosis and treatment. If the pathogenic variants in the family are known, molecular genetic testing can be used to confirm the diagnosis.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

A good pregnancy outcome was reported in a woman with cblC treated with OHCbl 1.0 mg IM, folic acid 5.0 mg per day, aspirin 80 mg per day, levocarnitine, and low-protein diet [Brunel-Guitton et al 2010].

Prenatal therapy of an affected fetus by administration of intramuscular OHCbl to the mother may decrease developmental abnormalities and improve neurocognitive outcome [Huemer et al 2005, Trefz et al 2012] but does not appear to affect the ophthalmologic outcome [Patton et al 2000]. The dose and frequency of administration of IM OHCbl has not been established. Favorable outcomes of prenatal treatment have been reported by using dosages between 1 to 10 mg per day, 2-3 times a week, starting as early as 15 weeks' gestational age [Huemer et al 2005, Trefz et al 2012].

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

All of the disorders of intracellular cobalamin metabolism are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one mutated allele).
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with a disorder of intracellular cobalamin metabolism are obligate heterozygotes (carriers) for a pathogenic variant.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Molecular genetic testing. If the pathogenic variants in an affected family member are known, carrier testing using molecular genetic techniques is possible.

Biochemical genetic testing is not reliable for carrier testing.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk for a disorder of intracellular cobalamin metabolism and preimplantation genetic diagnosis are possible options.

See Pregnancy Management for information on prenatal therapy.

Biochemical testing. If molecular genetic testing is not possible, prenatal testing for pregnancies at 25% risk for a disorder of intracellular cobalamin metabolism is possible by a combination of:

- Complementation analysis of cultured amniocytes [Morel et al 2005, Watkins & Rosenblatt 2014]
- Measurement of MMA and tHcy concentrations in amniotic fluid using mass spectrometric techniques [Morel et al 2005, Watkins & Rosenblatt 2014].

Note: The most prudent recommendation is to perform both metabolite analysis AND complementation assays of cultured CVS or amniocytes.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Methylmalonic acidemia
- **Organic Acidemia Association**
  Phone: 763-559-1797
  Fax: 866-539-4060 (toll-free)
  Email: kstagni@oaanews.org; menta@oaanews.org
  www.oaanews.org
- **European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)**
  www.e-imd.org/en/index.phtml

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.
Disorders of Intracellular Cobalamin Metabolism: Genes and Databases

Table B.
OMIM Entries for Disorders of Intracellular Cobalamin Metabolism (View All in OMIM)

Molecular Genetic Pathogenesis

See Figure1.

MMACHC

Gene structure. *MMACHC* is 11 kb and comprises five exons [Lerner-Ellis et al 2006]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. More than 50 pathogenic variants have been identified in persons with cblC.

- In individuals of European ancestry, the c.271dupA frameshift variant (reference sequence NM_015506.2) accounts for approximately 40% of disease alleles [Lerner-Ellis et al 2009]. This variant results in a change of amino acid 91 from arginine to lysine followed by a frameshift causing a premature stop codon (pathogenic variant NP_056321.2:p.Arg91LysfsTer140) [Lerner-Ellis et al 2006].
- The c.609G>A (p.Trp203Ter) nonsense variant is common in Chinese [Liu et al 2010]; the c.331C>T (p.Arg111Ter) in Cajuns and French Canadians [Lerner-Ellis et al 2009]; and the c.394C>T (p.Arg132Ter) variant in people of Indian and Middle Eastern ancestry [Lerner-Ellis et al 2009].

Normal gene product. The methylmalonic aciduria and homocystinuria type C protein is 282 amino acids and has a predicted molecular weight of 37.1 kd. The C-terminal region may fold similarly to TonB, a bacterial protein involved in energy transduction for cobalamin uptake. A putative vitamin B_{12}-binding pocket may also be present.

Abnormal gene product. Defects in MMACHC disrupt its ability to process newly internalized cobalamins in the cytosol [Hannibal et al 2009].

MMADHC

Gene structure. *MMADHC*, previously known as *C2orf25*, is 18 kb and comprises eight exons [Coelho et al 2008]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. There are no clearly identified common disease-causing variants. The pathogenic variants described to date are either missense or truncating (nonsense or frameshift) variants.

- Studies of individuals with cblD suggest that variants in exons 3 and 4 (c.57_64delCTCTTTAG, c.60insAT, c.133dupG, c.160C>T, and c.228dupG) encoding for the N-terminus of the protein cause AdoCbl deficiency (variant 2 cblD) [Coelho et al 2008, Plesa et al 2011, Stucki et al 2012].
- Missense variants in exons 6 and 8 (c.545C>A, c.737A>G, c.746A>G, c.776T>C) encoding the C-terminus cause MeCbl deficiency (variant 1).
- Truncating variants in exons 5 and 8 and intron 7 (c.419dupA, c.683>G, c.696+1_4delGTGA, c.748C>T) caused combined AdoCbl and MeCbl deficiency.

Normal gene product. The *MMADHC* product is predicted to have 296 amino acids with a calculated molecular mass of 32.8 kd and has domains responsible for mitochondrial targeting, AdoCbl synthesis, and MeCbl synthesis [Stucki et al 2012]. There is an N-terminal mitochondrial leader sequence and a predicted B_{12} binding sequence [Coelho et al 2008]. The C-terminus is thought to guide vitamin B_{12} to methionine synthase [Plesa et al 2011].

Abnormal gene product. The type and localizations of pathogenic variants within the protein is thought to determine whether the synthesis of AdoCbl, MeCbl, or both is affected. Studies have indicated a protein truncation. Pathogenic variants in the mitochondrial targeting sequencing (position 1-61) affect AdoCbl synthesis.

LMBRD1

Gene structure. *LMBRD1* is 121 kb and comprises 16 exons [Rutsch et al 2009]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. Rutsch et al [2009] studied 12 unrelated individuals with cblF confirmed by complementation analysis. A 1-bp deletion, c.1056delG, was seen on 18 independent alleles, suggesting a founder effect; this variant causes a frameshift yielding a premature stop codon in exon 11 [Rutsch et al 2009].

Altogether five different DNA variants accounted for 22 of 24 observed pathogenic variants.

A 6785-bp deletion spanning exon 2 has been reported [Miousse et al 2011].

Normal gene product. The probable lysosomal cobalamin transporter LMBR1 domain-containing protein 1 is 540 amino acids and has a predicted molecular weight of 61.3 kd (the longest isoform). The predicted protein structure includes nine transmembrane regions and multiple potential glycosylation sites. The protein has been shown by immunocytofluorescene to colocalize with the lysosomal marker LAMP1. The protein is predicted to be a lysosomal membrane transporter; however, the exact ligand remains to be identified [Rutsch et al 2009].

Abnormal gene product. Pathogenic variants affect the defective release of cobalamin from lysosomes.

MTR

Gene structure. *MTR* is 105.24 kb and comprises 33 exons [Brody et al 1999]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. More than 20 pathogenic variants have been identified.

- The most common disease-causing allele in persons with cblG is a missense variant c.3518C>T (p.Pro1173Leu), accounting for 40% of alleles [Watkins et al 2002].
- A subset of severe pathogenic variants including deletions (c.12-13delGC, c.381delA, c.2101delT, c.2112-2113delTC, c.2669-2670delTG, c.2796-2800delAAGTC), nonsense variants (p.Arg585Ter, p.Glu1204Ter) [Watkins et al 2002], and IVS3-166A>G are thought to result in premature translation termination and mRNA instability [Wilson et al 1998, Watkins et al 2002].
- Leclerc et al [1996] identified two pathogenic variants specifically near the cobalamin binding domain.

Normal gene product. The MTR enzyme has 1265 amino acids and weighs 140.5 kd. There are at least three functional domains:

- The 38-kd C-terminal domain binds AdoMet.
- A domain comprising amino acids 650 to 896 includes the binding domain for the required cofactor methylcobalamin.
- The 70-kd N-terminal domain binds homocysteine and methyltetrahydrofolate.

The latter two activities may be on separate domains within this region [Goulding et al 1997].

Abnormal gene product. Pathogenic variants are expected to decrease enzymatic activity.

MTRR

Gene structure. *MTRR* is 31.95 kb and comprises 15 exons [Leclerc et al 1998]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants

- The most common disease-causing allele, accounting for 25% of alleles, is a deep intronic variant (c.903+469T>C) [Homolova et al 2010].
- The c.1361C>T (p.Ser545Leu) variant is common in persons of Iberian ancestry. Reports suggest a milder phenotype with no neurologic involvement [Zavadakova et al 2002].
- Other pathogenic variants have been described [Leclerc et al 1998, Zavadakova et al 2002]. Most reported pathogenic variants have been non-conservative missense variants. 903>904ins140 is likely to be a splice-affecting variant in intron 6 of MTRR [Zavadakova et al 2002].

Normal gene product. The MTRR protein contains 725 amino acids and has a mass of 80.4 kd. It shares 38% sequence identity with human cytochrome P450 reductase [Leclerc et al 1998]. MTRR has some chaperone-like activity with regard to MTR [Yamada et al 2006]. A mitochondrial isoform of MTRR has been predicted [Leclerc et al 1999].

Abnormal gene product. Pathogenic variants are expected to decrease enzymatic activity

ABCD4

Gene structure. *ABCD4* is 16 kb and comprises 19 exons [Holzinger et al 1998]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. Missense (c.423C>G [p.Asn141Lys], c.956A>G [p.Tyr319Cys]), frameshift (c.1746_1747insCT [p.Glu583LeufsTer9]), and exon-skipping variants (c.542+1G>T [exon 5 skipping], c.1456G>T [exon 13, 14 skipping]) have been identified [Coelho et al 2012, Kim et al 2012].

c.542+1G>T results in the skipping of exon 5 which encodes a transmembrane domain, and c.1456G>T results in skipping of exons 13 and 14 in the cytosolic nucleotide binding domain [Kim et al 2012].

Normal gene product. The ABCD4 protein contains 606 amino acids and has a mass of 73 kd [Shani et al 1997]. It is an ATP-binding cassette (ABC) transporter that colocalizes with lysosomal proteins LAMP1 and LMBRD1 (cblF). It is thought that its ATPase activity may be involved in the intracellular processing of cobalamin [Coelho et al 2012].

Abnormal gene product. Pathogenic variants are expected to affect the lysosomal transport of cobalamin into the cytoplasm [Coelho et al 2012].

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