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Combined methylmalonic acidemia and homocystinuria, cblC type. I. Clinical presentations, diagnosis and management

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Abstract

Combined methylmalonic acidemia and homocystinuria, cblC type, is an inborn error of intracellular cobalamin metabolism with a wide spectrum of clinical manifestations that is stated to be the most common inherited disorder of cobalamin metabolism. This metabolic disease is caused by mutations in the *MMACHC* gene and results in impaired intracellular synthesis of adenosylcobalamin and methylcobalamin, cofactors for the methylmalonyl-CoA mutase and methionine synthase enzymes. Elevated methylmalonic acid and homocysteine with decreased methionine production are the biochemical hallmarks of this disorder. Awareness of the diverse clinical presentations associated with cblC disease is necessary to provide a timely diagnosis, to guide management of affected individuals and to establish a framework for the future treatment of individuals detected through expanded newborn screening. This article reviews the biochemistry, clinical presentations, genotype-phenotype correlations, diagnosis and management of cblC disease.

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References to electronic databases: Methylmalonic aciduria and homocystinuria cblC type: OMIM #277400. *MMACHC* gene: OMIM *609831. Methionine synthase: EC 1.16.1.8. Methylmalonyl-CoA mutase: EC 5.4.99.2.

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Introduction

Combined methylmalonic acidemia and homocystinuria, cblC type (OMIM #277400) is an inborn error of intracellular cobalamin metabolism. The disease is caused by mutations in the *MMACHC* gene (OMIM *609831) located on chromosome 1p34.1 (Lerner-Ellis et al. 2006). The altered function of *MMACHC* results in decreased intracellular production of adenosylcobalamin and methylcobalamin (MeCbl), cofactors for the methylmalonyl-CoA mutase (EC 5.4.99.2) and methionine synthase (EC 1.16.1.8) enzymes. The deficient activity of these enzymes causes an elevation of methylmalonic acid (MMA) and homocysteine and a decreased production of methionine. The clinical classification of early-onset and late-onset cblC disease can correlate with the genotype of patients. The diagnosis of cblC disease can be challenging because the clinical manifestations and age of presentation are highly variable. The importance of the early diagnosis is highlighted by the relentless progression of this multi-systemic disease in the absence of appropriate treatment.

Biochemistry

In 1969, Drs. Mudd, Levy and Abeles described the first disorder involving altered vitamin metabolism, a previously unrecognized abnormality due to defective synthesis of the active coenzymes derived from vitamin B₁₂ (Mudd et al. 1969; Levy et al. 1970). The biochemical hallmarks of elevated plasma and urine homocysteine and cystathionine, hypomethioninemia and methylmalonic aciduria were seen in this severely affected infant that failed to respond to intramuscular (IM) cyanocobalamin (CNCbl). Postmortem studies on the infant revealed abnormally low levels of adenosylcobalamin (AdoCbl) in the liver and low enzymatic activity of methylmalonyl-CoA mutase (EC 5.4.99.2) and methionine synthase (EC 1.16.1.8) that was restored in the presence of hydroxocobalamin (OHCbl). The coenzymes for these enzymatic reactions, AdoCbl and methylcobalamin (MeCbl) respectively, are generated by a series of steps in the intracellular metabolism of cobalamin (Fig. 1).

The second step in this pathway involves the protein encoded by the *MMACHC* gene [(for Methylmalonic Aciduria type C and Homocystinuria) OMIM *609831], identified as the cause of cblC disease in 2006 (Lerner-Ellis et al. 2006). The *MMACHC* protein acts as a “trafficking chaperone” for cobalamins (Kim et al. 2008; Banerjee 2006). *MMACHC* may interact with the lysosomal efflux transporter of cobalamin, *LMBRD1*, to accept a variety of cobalamin derivatives for passage into the cytoplasm (Banerjee et al. 2009). Depending on the type of cobalamin derivative encountered, *MMACHC* catalyzes a series of versatile reactions to produce suitable intermediates for coenzyme synthesis (Banerjee 2006; Kim et al. 2008; Hannibal et al. 2009); it can catalyze a reductive decyanation reaction when encountering CNCbl to yield cob(II)alamin (Kim et al. 2008) and a dealkylation reaction when encountering AdoCbl or MeCbl using glutathione as an electron donor (Hannibal et al. 2009; Kim et al. 2009). *MMACHC* is proposed to interact with *MMADHC*, a protein that sorts the cobalamin intermediates to the cytosol or the mitochondria for production of AdoCbl and MeCbl (Plesa et al. 2011). Additional roles in cobalamin transport and metabolism are suggested by the recent demonstration that *MMACHC* can be found in the mitochondria (Pagliarini et al. 2008).

Molecular genetics

There are more than 50 known mutations identified in the *MMACHC* gene that cause cblC disease. The most frequent is c.271dupA (p.R91KfsX14), a frameshift mutation that accounts for at least 40% of disease-causing alleles (Morel et al. 2006). There are recognized phenotype-genotype correlations that may predict disease severity depending on mRNA stability and protein residual function. Many patients with early-onset, severe disease have the c.271dupA or the c.331 C>T (p.R111X) mutations in the homozygous or compound heterozygote state. Mutations usually associated with a late-onset presentation include c.394 C>T (p.R132X) and c.482 G>A (p.R161Q) (Morel et al. 2006; Wang et al. 2009; Nogueira et al. 2008; Lerner-Ellis et al. 2009). In a recent study, cell lines homozygous for the c.394 C>T (p.R132X) had significantly increased levels of *MMACHC* mRNA compared to early-onset mutations (Lerner-Ellis et al. 2009), suggesting that the transcript harboring this mutation may escape nonsense-mediated decay and have residual function. Patients that are compound heterozygotes for a missense allele (c.394 C>T, c.347 T>C, c.440 G>C, c.482 G>A) and c.271dupA appear to have a milder phenotype (Morel et al. 2006).

The wide clinical heterogeneity of cblC disease likely depends on the nature of the different *MMACHC* mutations. Other factors may include the environment, ethnicity, diet and individual background genetic variations. It is postulated that polymorphisms in other genes associated with cobalamin metabolism may modify the clinical presentation of cblC disease (Morel et al. 2006). The report of two sisters with cblC disease presenting with thrombotic microangiopathy, the younger of whom had more severe renal disease and was heterozygous for the 3254 T>C Factor H polymorphism (Guignon et al. 2005), supports this suggestion. In contrast, a recent study failed to identify the influence of common methylenetetrahydrofolate reductase (MTHFR) polymorphisms on the presentation or outcome of cblC disease (Nogueira et al. 2008). Genomic approaches may be required to examine modifier effects in a more global fashion.

Clinical presentation

The wide range of types and age of presentation (Table 1) (Mitchell et al. 1986; Rosenblatt et al. 1997; Shinnar and Singer 1984; Augoustides-Savvopoulou et al. 1999; Roze et al. 2003; Ben-Omran et al. 2007; Thauvin-Robinet et al. 2008), make the diagnosis of cblC disease a challenging one. The diagnosis can also be complicated by the history of normal newborn screening (Chace et al. 2001), and the absence of metabolic acidosis and other systemic disturbances that would prompt the consultation by a metabolic disease specialist (Harding et al. 2003). Metabolic acidosis and hyperammonemia have been reported but are unusual (Martinelli et al. 2010). The importance of the early diagnosis in cblC is highlighted by the relentless progression of the disease in the absence of appropriate treatment (Smith et al. 2006; Augoustides-Savvopoulou et al. 1999; Mudd et al. 1969; Brandstetter et al. 1990; Powers et al. 2001; Frattini et al. 2010).

Prenatal presentation

Manifestations of cblC disease can arise *in utero*. These developmental complications include intrauterine growth retardation (IUGR) (Fratini et al. 2010; Robb et al. 1984; Bartholomew et al. 1988; Smith and Bodamer 2002; Nogueira et al. 2008) mild dysmorphic features (long facies, flat philtrum and large low-set ears), (Cerone et al. 1999), microcephaly (Francis et al. 2004; Smith et al. 2006; Rosenblatt et al. 1997; Andersson et al. 1999), congenital heart disease (Profitlich et al. 2009b; Andersson et al. 1999) and fetal dilated cardiomyopathy De Bie et al. (2009).

Infantile presentation

The infantile presentation is the most frequently recognized form of cblC disease. It is severe, multi-systemic and progressive unless treatment is instituted. In the first weeks of life, the typical presentation may include IUGR, microcephaly, feeding difficulties, failure to thrive, hypotonia, hydrocephalus, neurological deterioration, hematological abnormalities, macular changes and the hemolytic uremic syndrome.

Non-infantile presentation

“Late-onset” cblC disease was recognized in the 1980s (Shinnar and Singer 1984) and the term has been historically applied for patients that have overt symptoms after 4 years of age. Patients can present in any decade of life with neurological regression, neuropsychiatric symptoms, progressive encephalopathy, subacute combined degeneration of the spinal cord, hematological manifestations and/or thromboembolic complications. They may have been previously asymptomatic or have a history of learning or emotional difficulties, hematuria, proteinuria, anemia or unexplained recurrent thrombosis (Bodamer et al. 2001; Guignonis et al. 2005; Thauvin-Robinet et al. 2008).

Diagnosis

Biochemical parameters

The clinical suspicion of cblC disease should lead to the immediate analysis of urine organic acids, serum MMA, tHcy, plasma amino acids and an acylcarnitine profile. Increased MMA, homocysteine and cystathionine and low methionine is the classical biochemical pattern of cblC and the other proximal defects of intracellular cobalamin metabolism (cblD and cblF). MMA, 2-methylcitrate and propionylcarnitine (C3) reflect AdoCbl production and methylmalonyl-CoA mutase activity while tHcy, plasma methionine and cystathionine are useful indicators of MeCbl production and methionine synthase function. Vitamin B₁₂ levels are normal and should always be measured initially to rule out nutritional deficiency, congenital disorders of the absorption of vitamin B₁₂ and cblF Laframboise et al. (1992).

Specialized biochemical testing as noted above provides means to monitor cblC disease. They should be monitored frequently during the acute phase of the disease, with every therapeutic intervention or clinical fluctuation and during episodes of rapid growth. Preferably, they should be monitored in a reproducible, standardized manner. This includes obtaining samples at the same time of the day and at OHCbl trough levels to yield comparable metabolic parameters across time (Carrillo-Carrasco et al. 2009; Bartholomew

et al. 1988). While there is no clear consensus for metabolite target levels or their clinical impact, the consequences of low methionine and elevated tHcy appear to be detrimental (Table 2).

Total plasma homocysteine (tHcy) is the preferred homocysteine parameter to monitor in patients with cblC disease. Other methods are not accurate because a modest elevation in homocysteine is confined to the protein-bound form and detectable only by tHcy, while considerable elevations saturate binding sites and rise the proportion of free homocysteine exponentially, from 2 to 5% when tHcy is <100 μ M and up to 10–25% when tHcy is 150–400 μ M (Mansoor et al. 1993; Wiley et al. 1988). Trough plasma B₁₂ and betaine levels can also be monitored to assess compliance, but elevated levels should not lead to a reduction of OHCbl dose; serial dilutions are needed to measure the target plasma B₁₂ levels of above 1,000,000 pg/ml (normal range: 170–800 pg/ml), a range where optimal biochemical response has been seen in several patients (Van Hove et al. 2002; Carrillo-Carrasco et al. 2009).

Molecular diagnosis

Sequencing of the *MMACHC* gene is clinically available and is more cost-effective and less time-consuming than complementation analysis for confirming the diagnosis of cblC disease. It has more than 95% chance of identifying causative mutations in affected individuals; in a recent study only six out of 109 individuals with cblC disease had one or no mutations identified through sequencing (Lerner-Ellis et al. 2009). A portion of these might include exonic deletions that can be detected by deletion/duplication analysis.

Complementation studies

Complementation analysis may have a role in the diagnosis of cblC in those patients not identified with molecular genetic analyses. Historically, the diagnosis of cblC relied upon complementation analysis, which consists of the fusion of a patient's cultured fibroblasts to fibroblast cell lines of a defined complementation group. Following fusion, an increase in the incorporation of [¹⁴C]-propionate into macromolecules indicates the cells belong to different complementation groups (Gravel et al. 1975; Byck and Rosenblatt 1991; Rosenblatt and Cooper 1987; Fowler and Jakobs 1998). Two cell lines belong to the same complementation group when there is a lack of incorporation following cell fusion. Cultured fibroblasts can also be used to evaluate the response to OHCbl (Van Hove et al. 2002; Willard et al. 1976).

Newborn screening

Elevations of C3 by expanded newborn screening can detect cblC disease depending on the C3 and C3/C2 ratio cut-off values used by the reference laboratory (Chace et al. 2001). Methionine, a metabolite also measured in expanded newborn screening for the detection of cystathionine beta synthase deficiency, may be low in patients with cblC disease (Weisfeld-Adams et al. 2010). Elevated tHcy is more reliable than methionine and is used in some laboratories as a first- or second-tier test to detect cblC disease (Tortorelli et al. 2010). Therefore, a normal newborn screening based solely upon C3 levels does not exclude the

presence of disorders of cobalamin metabolism and the diagnosis must still be considered in the face of typical manifestations (Chace et al. 2001).

Prenatal diagnosis

The early prenatal diagnosis of cblC disease is possible by molecular analysis of chorionic villus cells or cultured amniocytes (Morel et al. 2005). Metabolites can be measured and monitored in the amniotic fluid and in maternal urine (Huemer et al. 2005; Chadeaux-Vekemans et al. 1994).

Management

Acute management

The goals are to improve clinical manifestations, normalize serum methionine and lower both tHcy and MMA as soon as possible. An adequate caloric intake should be provided and fluid and base deficits need to be treated promptly if present. Treatment with OHCbl and betaine should be initiated as soon as there is a suspicion for cblC disease, without waiting for confirmatory testing and after determining baseline plasma metabolites and vitamin B₁₂ levels. A significant improvement in the clinical picture, growth and metabolic parameters is seen Fowler et al. (2008).

The recommended therapeutic interventions in cblC disease are summarized in Table 3.

The management of asymptomatic patients with cblC detected by newborn screening has not been studied. Patients with a genotype that has been associated with severe disease should be treated immediately. Long-term management of patients with a genotype predictive of late-onset disease has not been studied, but should probably include OHCbl supplementation and metabolic follow-up to monitor for disease manifestations.

OHCbl

Patients with cblC disease respond to parenteral OHCbl with a considerable improvement in biochemical parameters, resolution of hematological abnormalities (Mitchell et al. 1986; Mamlok et al. 1986; Bartholomew et al. 1988; Tomaske et al. 2001), a significant improvement in neurologic manifestations (Carmel et al. 1980; Shinnar and Singer 1984; Enns et al. 1999; Augoustides-Savvopoulou et al. 1999; Bodamer et al. 2001; Tomaske et al. 2001), growth parameters (Bartholomew et al. 1988; Kind et al. 2002), and amelioration of vascular complications (Van Hove et al. 2002). Normalization of visual evoked potentials and brain stem auditory potentials has also been reported (Mamlok et al. 1986).

The mechanism of response to OHCbl in patients with cblC is an active area of research. A recent study showed that mutant MMACHC proteins have increased binding affinity to OHCbl compared to a lack of affinity for CNCbl (Froese et al. 2009). Also, mutant MMACHC proteins are stabilized in the presence of high concentrations of intracellular cobalamin (Froese et al. 2010). In cell lines from cblC patients, OHCbl decreases the levels of intracellular reactive oxygen species (Richard et al. 2009).

Form and route of administration—Parenteral OHCbl (IV, SQ or IM) is the only form of cobalamin proven to be beneficial in patients with cblC disease. Daily SQ injections may be safer and better tolerated, while IM injections can give a greater volume of medication. Both routes of administration have been used successfully in cblC disease (Van Hove et al. 2002). The use of parenteral CNCbl (Andersson and Shapira 1998; Mellman et al. 1979; Mitchell et al. 1986; Brandstetter et al. 1990; Smith et al. 2006) and oral OHCbl alone (Bartholomew et al. 1988; Ribes et al. 1990; Brunelli et al. 2002; Boxer et al. 2005; Frattini et al. 2010) seems to be ineffective and should not substitute traditional therapy with OHCbl until further cobalamin responsiveness studies are performed. MeCbl seems to be less effective than OHCbl (Ribes et al. 1990; Linnell et al. 1983) and the effect of intranasal OHCbl in patients with cblC disease has not been studied.

Dose—Many centers manage infants by providing 1 mg of parenteral OHCbl daily; this roughly corresponds to a dose of 0.33 mg/kg/day assuming a body weight of 3 kg. As patients stabilize, the frequency of administration is sometimes decreased to minimize daily injections and the dose is frequently not increased to account for their weight gain. This practice is based on limited evidence (Bartholomew et al. 1988) and provides progressively lower cobalamin serum levels that may be sub-therapeutic (Carrillo-Carrasco et al. 2009). The provision of therapeutic doses can be achieved by the ability to concentrate OHCbl up to 30 mg/ml. It is possible that the progression of complications in patients with cblC disease arise in part because not enough OHCbl is given, as this is a critical component of the treatment regimen. Recent reports established that higher OHCbl doses helped in the resolution of thrombotic microangiopathy in patients with cblC disease (Van Hove et al. 2002) and provided better metabolic control (Carrillo-Carrasco et al. 2009). These studies also suggested that plasma B₁₂ levels near 1,000,000 pg/ml are required for an optimal metabolic response and highlighted the need for patients to be titrated individually.

Frequency—The need for daily doses of OHCbl is supported by clinical and pharmacokinetic data. The mean half-life of free and total cob(III)alamins is approximately 26–30 hours after parenteral administration (Houeto et al. 1996). A kinetic study in cblC disease patients showed that plasma B₁₂ levels peaked between 0.5 and 2 hours after administration and fell at a rate of approximately 12 mg/l/hr; the decrease in B₁₂ levels corresponded with an increase in metabolite levels (Van Hove et al. 2002). Marked clinical and neurological deterioration has been described in patients weaned from daily to less frequent dosing (Carmel et al. 1980; Augoustides-Savvopoulou et al. 1999; Roze et al. 2003). A girl who had a rapid clinical and neurological improvement with daily OHCbl injections worsened after the frequency of OHCbl injections was decreased; she had a marked improvement with the reintroduction of daily injections and achieved her prior academic level in school (Augoustides-Savvopoulou et al. 1999).

The main issues discouraging physicians and families to use daily OHCbl injections may include difficulties in providing daily injections, hypersensitivity reactions and the contraindication of IM injections in patients receiving coumadin therapy. Teaching patients with decreased visual acuity to administer pre-filled SQ or IM injections may help increase adherence to treatment in adolescent patients. Interventions such as SQ catheter placement

allow daily administration of OHCbl with a single needle exchange per week (Freehauf et al. 2011). Allergic reactions have been managed with diphenhydramine (Augoustides-Savvopoulou et al. 1999) and have disappeared when benzylalcohol is not used as a preservative in the formulation (Van Hove et al. 2002). The use of low-molecular weight heparin has been used successfully and safely in the treatment of thrombosis in a patient with cblC disease receiving IM OHCbl injections (Profitlich et al. 2009a).

Side effects—OHCbl has very few reported side effects at high doses. Red discoloration of the urine and skin are expected. Hypersensitivity and photosensitivity reactions, nausea, infusion site reactions and headache are less common. Up to 15,000 mg of parenteral OHCbl have been given acutely with no adverse effects reported. High blood pressure has been seen in a dose-dependent manner during the intravenous infusion of 5000 mg for the treatment of acute cyanide poisoning. For that indication, pediatric doses of 70mg/kg are recommended. It seems unlikely that chronic doses of 0.33 mg/kg, more than 100-fold lower than those used for other medical indications, would cause adverse effects in cblC patients. The use of OHCbl during pregnancy has not been associated with any fetal or neonatal adverse effects (Boneh et al. 2002; Deodato et al. 2002; Diss et al. 1995; Pierre et al. 2006).

Overall, the evidence suggests that daily administration of weight-adjusted doses of parenteral OHCbl, concentrated as needed, is safe and improves metabolic control in patients with cblC disease (Van Hove et al. 2002; Carrillo-Carrasco et al. 2009). The use of cultured fibroblasts may help evaluate the response of certain patients to OHCbl and guide treatment, if necessary (Gold et al. 1996). More studies are needed to investigate the optimal dose and the long-term beneficial effects of parenteral OHCbl.

Betaine

Betaine or *N,N,N*-trimethylglycine, is a potent methyl group donor that remethylates homocysteine to methionine via betaine-homocysteine methyltransferase, bypassing the MeCbl-dependent methionine synthase pathway (Fig. 1). The synergistic effect of OHCbl and betaine is needed to improve plasma tHcy levels and normalize methionine in patients with cblC disease (Ribes et al. 1990; Rosenblatt et al. 1997; Bartholomew et al. 1988; Urbon Artero et al. 2002). Betaine or OHCbl alone are not able to maintain appropriate levels of tHcy or methionine (Bartholomew et al. 1988). Anhydrous betaine powder is given diluted in liquid twice daily at a dose of 250 mg/kg/day. Although it is well tolerated with few side effects, the smell is unpleasant to some patients. Higher betaine doses (~500 mg/kg/day) have been reported to decrease tHcy, increase plasma methionine levels and improve the calculated brain uptake of methionine in MTHFR patients (Strauss et al. 2007), and could have the same effects in patients with cblC disease.

Adverse effects of betaine have been reported in conditions leading to hypermethioninemia (Lawson-Yuen and Levy 2006), but not in patients with cblC disease. Betaine has been used during pregnancy with no neonatal adverse effects (Pierre et al. 2006; Yap et al. 2001). The main limitations for the use of betaine at recommended doses are the elevated cost, compliance when the amounts become difficult to tolerate by the oral route, and, at times, limited availability.

Levocarnitine

Levocarnitine can be given at a dose of 50–200 mg/kg/day. It facilitates the excretion of propionyl groups and prevents carnitine deficiency (Bartholomew et al. 1988). The de novo synthesis of carnitine depends on methionine and may be decreased in patients with cblC. However, the beneficial effects of carnitine supplementation in patients with cblC disease has not been proven (Ogier de Baulny et al. 1998).

Folinic acid

Folic acid supplementation is used as an adjunctive therapy in patients with cblC disease. Folinic acid is frequently used because it crosses the blood brain barrier more efficiently than folic acid (Spector 1979). Theoretically, it provides a bypass for the 5-methyltetrahydrofolate trap that results from decreased methionine synthase activity (Smulders et al. 2006). This could be especially relevant in patients receiving long-term betaine therapy, as 5,10 methylene-tetrahydrofolate is required by the betaine-homocysteine methyltransferase reaction (Ogier de Baulny et al. 1998). The effect of folate supplementation in a short-term study of three children with cblC disease showed no major differences (Bartholomew et al. 1988) but no long-term studies have been performed.

Diet

The use of a low-protein diet in patients with cblC is controversial. Dietary protein has a very low homocysteine content (less than 1 mg/kg) and its restriction is likely to have minimal effect on tHcy levels (Pexa et al. 2008). Further clinical studies are needed to clarify this dietary approach in the management of patients with cblC. Protein restriction should not be necessary to reduce methylmalonic acid levels in patients receiving appropriate OHCbl doses. Furthermore, protein restriction poses the risk of limiting the daily intake of methionine and may accentuate hypomethioninemia in patients with cblC.

Methionine is an essential amino acid in patients with cblC and it is critical to assure appropriate intake to maintain normal plasma levels. Methionine-free formulas given to infants with methylmalonic acidemia should be avoided as they pose the risk of causing severe iatrogenic hypomethioninemia. In cblC, low methionine can have detrimental effects (Ogier de Baulny et al. 1998) including failure to thrive (De Bie et al. 2009; Ribes et al. 1990) and may contribute to a poor neurological (Rossi et al. 2001; Surtees 1998) and ophthalmological outcome (Gerth et al. 2008).

Methionine supplements are usually not required to maintain normal plasma methionine levels in patients with an adequate intake and receiving appropriate treatment with OHCbl and betaine (Chenel et al. 1993).

Other therapies

Dyslipidemias and other risk factors predisposing to thrombosis should be monitored and treated promptly. With the aim of decreasing the risk of thrombosis, antiplatelet doses of aspirin have been given to some patients with cblC disease without complications (Brunel-Guitton et al. 2010). The potential benefits of giving antioxidants, choline, creatine and

combined formulations of methylfolate, pyridoxal 5'-phosphate and MeCbl have not been studied.

Prenatal therapy

Early prenatal treatment may also have an impact on the long-term complications associated with cblC disease. Prior studies have evaluated the effects of prenatal OHCbl administration and showed a decrease in maternal metabolites (Huemer et al. 2005) and in one case, no evidence of systemic disorders or developmental delay by 9 months of age (Spada et al. 1999). However, disease-related complications including retinopathy (Huemer et al. 2005; Patton et al. 2000) have been documented in patients receiving prenatal therapy. Future studies with the aim of determining the long-term benefits of daily parenteral OHCbl started soon after conception in mothers at risk should be considered. In a strategy resembling the one used in congenital adrenal hyperplasia, early prenatal diagnosis can determine whether therapy needs to be continued (Merke and Bornstein 2005).

Anesthesia and other surgical considerations

Nitrous oxide is potentially toxic to patients with cblC disease because it depletes the body stores of B₁₂ and inhibits methionine synthase activity (Drummond and Matthews 1994; Abels et al. 1990). The death of a child with MTHFR deficiency (Selzer et al. 2003) and several cases of acute neurologic deterioration in children with B₁₂ deficiency (Felmet et al. 2000; McNeely et al. 2000; Wacławik et al. 2003; Schilling 1986; Kinsella and Green 1995) have been reported in association with nitrous oxide. Patients with cblC have undergone successful cardiac surgery by providing sufficient metabolic substrates during surgery and priming the bypass system with OHCbl (Tomaske et al. 2001).

Future therapies

The study of new therapies is currently limited by a lack of an animal model of cblC disease. Whether gene or cell-based therapies will be efficacious in the treatment of cblC disease remains to be tested.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AdoCbl	5'-deoxyadenosylcobalamin
C3	Propionylcarnitine
cblC	Cobalamin C disease

CNCbl	Cyanocobalamin
IM	Intramuscular
IUGR	Intrauterine growth retardation
MeCbl	Methylcobalamin
MMA	Methylmalonic acid
MTHFR	Methylenetetrahydrofolate reductase
OHCbl	Hydroxocobalamin
SQ	Subcutaneous
tHcy	Total plasma homocysteine

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Fig. 1.

Intracellular metabolism of cobalamin and intersecting pathways. The steps of the intracellular cobalamin metabolism, their complementation groups and corresponding genes are shown. The folate cycle, 1-carbon metabolism and the betaine-homocysteine methyltransferase reaction are shown for their importance in the pathophysiology and treatment of cblC disease. **Abbreviations.** **AdoCbl:** 5'-deoxyadenosylcobalamin; **Cbl:** Cobalamin; **Cbl III:** Dietary cobalamin contains a cobalt in the 3+ state (oxidized) and it is reduced to **Cbl II** and **Cbl I**, for its use in coenzyme synthesis. **CBS:** Cystathionine beta synthase; **Gly:** Glycine; **LMBRD1:** Lysosomal cobalamin exporter, defective in methylmalonic acidemia and homocystinuria, cblF type; **MeCbl:** Methylcobalamin; **MMAA:** Gene responsible for methylmalonic acidemia, cblA type; **MMAB:** Gene responsible for methylmalonic acidemia, cblB type; **MMACHC:** Gene responsible for methylmalonic acidemia and homocystinuria, cblC type; **MMADHC:** Gene responsible for methylmalonic acidemia and/or homocystinuria, cblD type; **MUT:** methylmalonyl-CoA mutase; **MTR:** 5-methyltetrahydrofolate-homocysteine S-methyltransferase also known as methionine synthase; **MTRR:** Methionine synthase reductase; **SAM:** S-adenosylmethionine; **Ser:** Serine; **THF:** Tetrahydrofolate

Table 1

Recognized clinical presentations of cbIC disease

Onset	Main feature	Associated findings
Prenatal	Growth retardation and microcephaly	
	Fetal dilated cardiomyopathy ^{a,e}	
Infantile	Newborn screening	Elevated C3; increased tHcy
	Poor feeding, dehydration and lethargy (acute)	Recurrent vomiting
		Hypotonia
		Developmental delay
	Failure to thrive (chronic)	Microcephaly
		Encephalopathy
		Anemia, thrombocytopenia and/or neutropenia, megaloblastosis
	Hypotonia	
	Seizures	
	Visual inattention or nystagmus	Maculopathy, pigmentary retinopathy, optic atrophy
Childhood ^f	Hemolytic uremic syndrome	
	Hydrocephalus	
	Cor pulmonale ^b	
	Developmental delay and/or regression	Microcephaly
		Bouts of lethargy
		Progressive encephalopathy
	Chronic thrombotic microangiopathy	Microscopic hematuria and/or proteinuria
		Intermittent decrease in creatinine clearance
		Hypertensive encephalopathy
		Hematological signs may be present
Adolescence and adulthood	Progressive encephalopathy	Executive dysfunction
	Leukoencephalopathy	Decline on school or work performance
		Social withdrawal, personality changes
		Neuropsychiatric disturbances
		Dementia
		Progressive encephalopathy
		Acute mental confusion
	Subacute combined degeneration of the spinal cord	Numbness of extremities
		Incontinence
		Progressive gait disorder
		Progressive lower extremity weakness
		May progress to upper extremities and respiratory muscles ^c
	Thromboembolic events	Recurrent venous thrombosis
		Pulmonary thromboembolism
		Cerebrovascular complications ^d

References:

^aDe Bie et al. 2009.

^bBrandstetter et al. 1990; Profitlich et al. 2009a.

^cRoze et al. 2003.

^dBrunelli et al. 2002, Geraghty et al. 1992

^eSingle case report

^fIn addition to infantile presentations

Table 2

Laboratory parameters in cblC disease

Test	Presentation	Normal range ^a
Plasma tHcy	> 100 µM	5–15 µM
Plasma MMA	~ 100 µM	<0.27 µM
MMA (Urine organic acids)	~500 to 10,000 mg/gCr	<3 mg/gCr
Methionine (Plasma amino acids)	Low	13–42 µM
C3 (Acylcarnitine profile)	~ 5–10 µM	<0.88 µM
Plasma B ₁₂ levels	Normal	170–800 pg/ml
MCV	Normal/elevated	Varies with age
Hypersegmented neutrophils	Present	Absent

Degrees of hyperhomocysteinemia: Mild 16–25 µM; Moderate 26–50 µM and severe >50 µM Conversions: tHcy mg/LX 7.397 =µM; Plasma methionine mg/dl X 67.02=µM; Urine MMA= mmol/molCr X 118/113=mg/gCr

^aVaries by laboratory

Table 3

Suggested therapeutic interventions in cblC disease are provided to guide clinical decision-making. The response to therapeutic interventions may vary among patients

Medication	Recommended dose	Frequency	Target blood levels	Efficacy	Target biochemical parameter
OHCbl IM, SQ or IV	0.3 mg/kg/ day ^a	Once daily	Plasma B ₁₂ levels 1,000,000 pg/ml	Established	<ul style="list-style-type: none"> • Reduce serum MMA and tHcy levels • Normalize plasma methionine and hematological parameters
Betaine oral	250 mg/kg/ day ^b	Divided in 3 doses	Plasma betaine levels of 1mM	Established	
Folinic acid oral	5–15 mg/day	Divided in 2 or 3 doses	N/A	Theoretical	
Levocarnitine oral	50–100 mg/ kg/day	Divided in 3 doses	N/A	Theoretical	

The use of a low-protein diet is controversial and the use of methionine-free formulas may be detrimental

^aConsider starting early-onset patients at these doses and titrate as required to control biochemical parameters

^bDosing of betaine and its saturating effects at different ages needs to be delineated. Higher doses may be needed in patients with cblC