Methylmalonic acidemia

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Barry Wolf MD PhD, editor. (Dr. Wolf of Lurie Children’s Hospital of Chicago has no relevant financial relationships to disclose.)

Originally released March 30, 1995; last updated January 29, 2017; expires January 29, 2020
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Introduction

This article includes discussion of methylmalonic acidemia, methylmalonic aciduria, L-methylmalonyl-CoA mutase deficiency, Mut methylmalonic acidemia, and D-methylmalonyl-CoA racemase deficiency. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

The authors provide an overview of the hereditary methylmalonic acidemias, a group of metabolic disorders with varied clinical presentations. This includes the most severe form of L-methylmalonyl-CoA mutase deficiency, termed mut(o) methylmalonic acidemia, which, together with the less severe deficiencies of L-methylmalonyl-CoA mutase, are the most common causes of methylmalonic acidemia. They review the natural history, clinical phenotypes, and available treatment modalities as well as the metabolic investigations required to establish the diagnosis. The newest advances in molecular genetics are updated.

Key points

- Acute metabolic decompensation in a patient with methylmalonic acidemia is a medical emergency.
- "Metabolic stroke" involving the basal ganglia is usually a life-changing event.
- Liver transplantation usually eliminates acute episodes of ketolactic acidosis but is not a cure as CSF levels of methylmalonic acid remain massively elevated.
- Patients with severe mut enzyme (L-methylmalonyl-CoA mutase) deficiency usually develop renal insufficiency/failure in the second-third decade of life.
- Both mut enzyme deficiency and defects in cobalamin (cbl) metabolism lead to methylmalonic acidemia, and some cobalamin defects may also be associated with homocystinuria.

Historical note and terminology

Methylmalonic acidemia and the disease associated with the more proximal defect in the same pathway, propionic acidemia, are the most common clinically significant genetic disorders of organic acid metabolism (Fenton and Rosenberg 1995). The key finding in methylmalonic acidemia is the accumulation of methylmalonic acid in body fluids and tissues. Association of methylmalonic acid with human disease was first made by Cox and White (Cox and White 1962) and Barness and colleagues (Barness et al 1963), who recognized that patients with vitamin B12 or cobalamin deficiency excrete increased quantities in urine. Aside from patients with pernicious anemia, infants of vegetarian mothers exclusively fed breast milk (Higginbottom et al 1978; Specker et al 1990; Kuhne et al 1991), patients with a history of gastric surgery, and the elderly (Pennypacker et al 1992) are at risk for cobalamin deficiency. The hereditary disease, methylmalonic acidemia, was first described by Oberholzer and colleagues (Oberholzer et al 1967) and Stokke and colleagues (Stokke et al 1967).

Methylmalonic acidemia may be due to several different enzyme defects, some of which primarily involve cobalamin metabolism (Fenton and Rosenberg 1995; Fowler 1998; Manoli et al 2016c). All are inherited as autosomal recessive traits. In these biochemical genetic disorders, as well as in simple nutritional cobalamin deficiency, the accumulation of methylmalonic acid is secondary to the buildup of mitochondrial methylmalonyl-CoA, an intermediate in the conversion of propionyl-CoA to succinyl-CoA. The synthesis of this coenzyme, in turn, depends on adequate delivery of vitamin B12 to tissues such as liver and brain; transport into cells through the phagolysosomal system; export and release of cob(III)alamin from lysosomes, cytosolic, and possibly mitochondrial reduction to cob(II)alamin; transport into the
mitochondrion; mitochondrial reduction to cob(I)alamin; and conversion to adenosylcobalamin. Methylmalonic acidemia may result from a defect in any of these steps. When it is secondary to an enzymatic block that is proximal in the pathways of cobalamin reduction or lysosomal efflux, it is also associated with homocystinuria because of impaired production of methylcobalamin, in the cytosol, cobalamin cofactor is required for the conversion of homocysteine to methionine (Fenton and Rosenberg 1995).

Most cases of methylmalonic acidemia are secondary to a complete or partial deficiency of L-methylmalonyl-CoA mutase, termed mut methylmalonic acidemia (Fenton and Rosenberg 1995). The deficiency of L-methylmalonyl-CoA mutase as a cause of methylmalonic acidemia was first reported by Morrow and Barness (Morrow and Barness 1969). The mut(o) and mut(-) designations refer to complete and partial deficiencies, respectively, determined by in vitro studies with cultured cells (Fenton and Rosenberg 1995). Some patients with primary defects in cobalamin metabolism such as impaired reduction of cobalamin (II) to cobalamin (I) or adenosylcobalamin synthase deficiency are responsive to cobalamin megatherapy (Rosenberg et al 1968a; Rosenberg et al 1968b; Lindblad et al 1969; Matsui et al 1983). Thus, methylmalonic acidemia in more than a third of patients is a vitamin-responsive inborn error of metabolism (Matsui et al 1983). Although the residual enzyme activity in the mut(-) state may be stimulated by high concentrations of hydroxycobalamin and adenosylcobalamin in vitro, most patients with L-methylmalonyl-CoA mutase deficiency do not respond to pharmacologic doses of cobalamin (Matsui et al 1983).

**Clinical manifestations**

**Presentation and course**

The expression of disease in methylmalonic acidemia is varied (Kölker et al 2015a; Iker et al 2015b). Most dramatic is the phenotype with presentation in the first week of life, ie, the catastrophically ill newborn infant, moribund and requiring ventilatory assistance. These babies are full term, and although their condition mimics sepsis, they have an overwhelming ketolactic acidosis, frequently display hyperammonemia, and can die despite supportive therapy including dialysis.

The most common phenotype is presentation during infancy. The signs are variable, and their clinical recognition may be as early as the first few weeks of life or as late as the second year. Almost all of these infants will present with poor growth, feeding problems, developmental delay, and intermittent episodes of lethargy during which the clinical and laboratory findings are essentially those of metabolic acidosis except that the degree of obtundation may be out of proportion to the magnitude of acidemia. In some, intermittent emesis may be so pronounced as to suggest a primary gastrointestinal disorder. Seizures may occur but are more likely during episodes of metabolic decompensation with coma. Some infants never display clearly recognizable episodic illness but nevertheless have a mild chronic metabolic acidosis with ketosis. Hypoglycemia has been reported. Hepatomegaly due to fatty infiltration is not uncommon and correlates with metabolic control.

Less common is an intermittent phenotype. This form is also seen in other types of inborn errors of organic or fatty acid metabolism. Probably most of these patients come to clinical attention during early childhood. The hallmark of this form is that there was no evidence of clinical disease before the first episode of vomiting, dehydration, lethargy, or coma associated perhaps with respiratory distress, hepatomegaly, and seizures. As with the other phenotypes and other metabolic diseases, an intermittent episode may mimic sepsis or Reye syndrome. During one of these episodes of metabolic decompensation, the patient may die despite intensive intervention.

An adult or “benign” form of methylmalonic acidemia has also been reported (Giorgio et al 1976; Ledley et al 1984). It was reported that such a patient with increased, albeit mild, urinary excretion of methylmalonate secondary to mut(-) mutation may be prone to an acute episode of metabolic decompensation (Shapira et al 1991). Newborn screening in the province of Quebec identified a relatively large number of infants with mild to moderate urinary methylmalonic acid excretion. Follow-up revealed resolution in over 50% of patients, as well as an apparently benign persistent low-moderate hypermethylmalonic aciduria (Sniderman et al 1999). Additional patients with a relatively benign type of methylmalonic acidemia have been reported (Martens et al 2002; Shinka et al 2002). However, some of these patients may not have a defect in mut(-) activity or cobalamin metabolism but rather a deficiency in methylmalonic semialdehyde dehydrogenase activity that is not associated with secondary perturbations in propionyl-CoA disposal (Roe et al 1998).

Another disease that may present with increased concentrations of methylmalonate, as well as malonate, but without
the obligatory increases in 2-methylcitrate and propionylcarnitine, is CCMAMMA due to mutations in the ACSF3 gene (Alfares et al 2011; Sloan et al 2011).

In contrast to the ketoacidotic crisis presentation commonly seen in isolated methylmalonyl-CoA mutase deficiency, patients with primary defects in cobalamin metabolism resulting in methylmalonic academia and homocystinuria can have heterogeneous clinical phenotypes (Rosenblatt et al 1997), including a neonatal hemolytic-uremic syndrome (a severe neurologic presentation featuring developmental delay or regression), fever-induced encephalopathy (Grüner et al 2011), and seizures (Biancheri et al 2002). Severe neonatal hyperammonemia has been noted (Martinelli et al 2011). Rare patients may present as adolescents or adults (Gold et al 1996) with renal disease (Brunelli et al 2002; Van Hove et al 2002) or CNS disease (Boxer et al 2005). Cobalamin C deficiency can also present with psychiatric symptoms. Most individuals with cobalamin C disease present in the first year of life with macrocytic anemia (Rosenblatt et al 1997). The identification of the MMACHC gene, mutated in patients with cblC, has provided a number of fundamental insights into the disorder (Lerner-Ellis et al 2006a). An X-linked cobalamin disorder involving the transcriptional coregulator, HCFCI, has been described (Yu et al 2013).

**Prognosis and complications**

In general, the outcome in cobalamin-unresponsive methylmalonic academia is poor. Specifically the prognosis depends on the exact phenotype, time of initiation of adequate therapy, and complications (Rousson and Guibaud 1984). In the review of outcome by Matsui and colleagues, 60% of mut(o) patients had died, and the majority of survivors were growth retarded and had intellectual disabilities (Matsui et al 1983). In contrast, 69% of individuals with cobalamin A were alive and well, and 91% were cobalamin-responders. The prognosis is best for those who are detected early in life and treated appropriately, for those who have a partial enzyme deficiency, and especially for those who are cobalamin responsive. A retrospective, survey-based study (Baumgartner and Viardot 1995) indicated that outcomes for methylmalonic academia had improved since the study of Matsui and colleagues and highlighted the fact that renal disease is prevalent among affected patients and can occur even in patients with more mild enzymatic defects. There is precedent for high cognitive outcome in a mut(-) patient (Varvogli et al 2000). For the patients with cobalamin-unresponsive forms, there is currently no satisfactory therapy (Van der Meer et al 1994). For these patients, even on a strict low-protein diet, the concentrations of methylmalonic acid remain elevated in body fluids. Many patients so treated manifest poor appetite, intermittent emesis, gastroesophageal reflux, disease, poor growth, osteopenia, and signs of renal insufficiency even in the absence of intellectual disability, motor handicaps, overt acidosis, or episodes of severe decompensation. Various degrees of neurologic disease may be seen (Shevell et al 1993; O'Shea et al 2012; Nizon et al 2013). The etiology of these complications is unknown. Many investigators suspect that these are the manifestations of a chronic low-concentration methylmalonic acid toxicity, secondary evidence of oxidant stress and glutathione deficiency being markers of an underlying toxic state (Treacy et al 1993). The development of bilateral optic neuropathy as a chronic complication in patients with mut(o) disease (Williams et al 2009; Pinar-Sueiro et al 2010; Traber et al 2011; Martinez Alvarez et al 2016), megamitochondria in a patient with mut(o) disease (Zsengelligé et al 2014), and the demonstration of widespread mitochondrial morphological lesions in the kidney and liver of knockout mice with methylmalonic academia (Chandler et al 2009) lend credence to the hypothesis that the mechanism of disease in methylmalonic academia may be due to a secondary defect in mitochondrial oxidative phosphorylation (Brusque et al 2002; Ito et al 2004; Richard et al 2006; Hauser et al 2011; Melo et al 2011; Wajner and Goodman 2011). Studies have implicated 2-methylcitrate in the induction of mitochondrial dysfunction (Amaral et al 2016). The bilateral destruction of globus pallidus (Korf et al 1986; Heidenreich et al 1988; Takeuchi et al 2003; Michel et al 2004; Yesildag et al 2005; Lee et al 2008; Radmanesh et al 2008; Baker et al 2015), one of the vulnerable areas in brain, during an acute episode of metabolic decompensation may be due to underlying MMA-CoA- and/or MMA-induced perturbations in mitochondrial metabolism or respiratory chain function. Altered thiol status in patients with organic acidemias has been noted (Salmi et al 2012). This type of brain injury only involving other areas may even develop in patients after successful liver transplantation (Chakrapani et al 2002; Kayler et al 2002; Nyhan et al 2002; Kasahara et al 2006). This may be caused by continued elevated concentrations of MMA in the CNS. Cardiomyopathy is a “new” problem recognized in individuals with methylmalonic academia (Azar et al 2007; Prada et al 2011). Fetal dilated and noncompaction cardiomyopathy were reported with cobalamin C disease (De Bie et al 2009; Tanpaiboon et al 2013). Some patients with severe L-methylmalonyl-CoA mutase deficiency require daily alkali therapy to buffer the excess acid production. Renal disease is primarily of the tubulointerstitial variety (Broyer et al 1974; Walter et al 1989; Molteni et al 1991; Rutledge et al 1993). The majority of patients with mut(o) disease have severe renal insufficiency or failure by the second to third decade of life. The pathogenesis is unknown. There is suspicion that a component may involve congenital disease, perhaps renal hypoplasia or dysplasia (Oberholzer et al
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A full-term male infant was born after an uncomplicated pregnancy to nonconsanguineous parents. Birth parameters were proportionate and age appropriate. The infant became progressively obtunded during the first week of life, with decreased feeding, diminished arousability, and intermittent vomiting. He was brought to the local emergency room for evaluation. No odors were detected. Physical examination was remarkable for lethargy without focal signs. The fontanelle was flat. There were diminished movements of the extremities, and the infant could not be aroused. Laboratory values were significant for pancytopenia, severe metabolic acidosis (anion gap=25), and plasma

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ammonium concentration of 700 uM. The urine had a specific gravity of 1010 with 3+ ketones. An inborn error of metabolism was suspected, specifically an organic aciduria. A stat urine organic acid analysis using GC with MS confirmation revealed an enormous peak of MMA and large quantities of methylcitrate. Plasma amino acid analysis showed hyperglycinemia without elevated homocysteine. Free carnitine was diminished, and propionylcarnitine was elevated. Plasma vitamin B12 concentrations were normal.

The constellation of findings in this case suggested that the infant had a severe enzyme deficiency associated with an isolated methylmalonyl-CoA mutase deficiency, likely mut(o) MMA. Cobalamin B and cobalamin A deficiencies were also possibilities, but statistically, a mutase deficiency was more common.

**Biological basis**

**Etiology and pathogenesis**

In this disease, the clinical and laboratory abnormalities are ultimately the consequence of the accumulation of L- or D-methylmalonyl-CoA within mitochondria that are hydrolyzed to methylmalonic acid. As a consequence, other metabolites, such as D-methylmalonyl-CoA, propionyl-CoA, and propionate build up within cells (Zwickler et al 2012). In both methylmalonic acidemia and propionic acidemia there is an accumulation of propionyl-CoA, propionate, and other minor metabolites of propionyl-CoA, such as methylcitrate and propionylglycine, some of which are the result of activity of seldom used alternate pathways. Secondary impairments in cellular metabolism in both diseases lead to increased concentrations of lactic acid and ketone bodies. It is important to remember that quantitatively lactate, 3-hydroxybutyrate, and acetoacetate are much more important contributors to the anion gap of the metabolic acidosis than methylmalonic acid or related metabolites. Clearly, many of the clinical signs and symptoms of acute, as well as even chronic, disease are related to acidemia per se. It is thought, however, that methylmalonic acid itself serves as a toxin in certain cells in target organs such as the brain and kidney. Even in the “well” state, resting energy expenditure may be decreased (Feillet et al 2000). Provision of optimal daily calories is not always straightforward (Hauser et al 2011). Additional secondary biochemical abnormalities include hyperammonemia, hyperglycinemia, and L-carnitine deficiency. Occasionally, the degree of elevation in plasma ammonia may be severe. Hyperglycinemia, secondary to an impairment in the function of the glycine cleavage enzyme complex, previously led to the use of the term "ketotic hyperglycinemia." Hypoglycemia is an uncommon finding. States of metabolic decompensation may also affect the hematopoietic and lymphoid systems. Patients may develop leukopenia, thrombocytopenia, and anemia, especially during or after a ketoacidotic crisis. This is related to impaired maturation of hematopoietic precursors in bone marrow (Inoue et al 1981; Corazza et al 1996). Patients may also have chronic mucocutaneous infections with *Candida albicans*. This may be related to T-cell dysfunction.

Mitochondrial matrix L-methylmalonyl-CoA mutase is a homodimer. Each 78.5-kd subunit is catalytically active, binds 1 molecule of adenosylcobalamin, and must be imported into the mitochondria for assembly. Many disease-producing mutations are found in the L-methylmalonyl-CoA mutase gene, which has been characterized and mapped to chromosome 6p12-21.1 (Nham et al 1990), have been identified (Ledley et al 1990b; Crane et al 1992; Janata et al 1997; Ledley and Rosenblatt 1997; Adjalla et al 1998a; Adjalla et al 1998b; Mikami et al 1999; Acquaviva et al 2001; Acquaviva et al 2005; Benoist et al 2001; Berger et al 2001; Peters et al 2002). In the mut(o) form, mutations in the amino-terminal or carboxy-terminal half of the protein eliminating enzyme activity, methylmalonyl-CoA, and adenosylcobalamin binding mutations associated with reduced concentrations of L-methylmalonyl-CoA mutase mRNA, including a splice site mutation, as well as a mutation in the mitochondrial leader sequence leading to defective mitochondrial importation of L-methylmalonyl-CoA mutase have been described (Ledley et al 1990a; Ogasawara et al 1994; Ledley and Rosenblatt 1997; Adjalla et al 1998b; Mikami et al 1999; Berger et al 2001). A deletion-insertion mutation was reported (Fuchshuber et al 2000). Although there is significant variation among mutations seen in patients, some pathogenic changes are seen in diverse populations, such as R369C (Jung et al 2005). Mutations involving the putative adenosylcobalamin binding domain in the carboxyl-terminal portion have been detected in the mut(o) and mut(-) forms (Crane and Ledley 1994; Adjalla et al 1998); some of the mut(-) cell lines used for mutation analysis also showed an increased Km for adenosylcobalamin. Interallelic complementation (Raff et al 1991) between mutant alleles can occur in mut MMA, which complicates genotype-phenotype predictions. A large collection of mut patient cell lines have been studied by molecular genetics and the spectrum of mutations identified (Worgan et al 2006). The mutations are spread throughout the gene, and although several mutations may be more common in selected ethnic groups, most are unique to a family. Abramowicz and colleagues reported an interesting case of a newborn infant with methylmalonic acidemia and agenesis of pancreatic beta-cells, causing diabetes mellitus.
associated with isodisomy of chromosome 6 (Abramowicz et al 1994); Corazza described an unusual cytopenia seen in 1 patient (Corazza et al 1996).

Three other genes, MMAA, MMAB, MCEE, cause methylmalonic aciduria when mutated. Using the same technique that was employed for the identification of the human methylmalonyl-CoA racemase gene (Bobik and Rasche, 2001), the genes responsible for cobalamin A or cblA (Dobson et al 2002a) and cobalamin B or cblB deficiencies (Dobson et al 2002b; Leal et al 2003) have been identified. The MMAA gene is mutated in some patients with cblA class MMA (Dobson et al 2002a; Lerner-Ellis et al 2004), but the function of the putative gene awaits definitive biochemical analysis. Although this gene was originally predicted to encode a mitochondrial B12 transporter (Dobson et al 2002a), it more likely is a protein that protects the methylmalonyl-CoA mutase enzyme from catalytic inactivation (Korotkova and Lidstrom 2004), probably through a chaperone-like function (Padovani and Banerjee 2006). The MMAA gene is mutated in cblB class MMA (Dobson et al 2002b; Leal et al 2003) and encodes an ATP: Cob(I)alamin adenosyltransferase (Leal et al 2003). Several mutations have been identified in each gene, including deletions, splice site mutations, and point mutations (Dobson et al 2002a; Dobson et al 2002b; Yang et al 2004; Martinez et al 2005; Lerner-Ellis et al 2006b). Three reports have implicated malfunction of the MCEE gene product as a putative cause of isolated methylmalonic acidemia. One report described a patient originally designated as cblA class but was shown by mutation analysis to have 2 early stop codons in the MCEE gene (Dobson et al 2006). Another patient had mild methylmalonic aciduria and a progressive neurologic syndrome due to sepiapterin reductase deficiency and also was found to harbor mutations in the MCEE gene. Finally, an assessment of cobalamin genes in the model organism C elegans defined a defect in propionate incorporation in a deletion mutant of the MCEE gene (Chandler et al 2006). More patient studies will be required to define the clinical and biochemical spectrum of MCEE deficiency, but at this point, it appears to be a rare cause of mild methylmalonic aciduria. The gene underlying cblC deficiency has been cloned (Lerner-Ellis 2006a) and appears to encode a protein of unidentified function. Two motifs were discernible on analysis: a potential B12 binding domain and a domain that might allow interactions with other proteins involved in intracellular cobalamin transport (Lerner-Ellis et al 2006a). A number of recurrent mutations have been identified (Lerner-Ellis et al 2006a), and 40% of patients studied harbored a copy of the c.271dupA mutation in the MMACHC gene. This change produces a frameshift and introduces a premature truncation into the mutated gene product. The full spectrum of genotype-phenotype and enzymatic correlations in this condition is not defined (Hannibal et al 2011).

Of the other proteins involved in cobalamin handling, only the genes that encode transcobalamin I, transcobalamin II, intrinsic factor, intrinsic factor-cobalamin receptor, and the cobalamin-transcobalamin receptor have been identified (Aminoff et al 1999; Quadros et al 2010). The deficit in mitochondrial handling of methylmalonyl-CoA that is common to the mut, cblA, and cblB forms of methylmalonic acidemia can be demonstrated in vivo by administration of the precursor, [1-13C]propionate, with measurement of 13CO2 in expired air (Barshop et al 1991). All of these defects that result in methylmalonic acidemia are inherited in an autosomal recessive manner. Genetic complementation studies using biochemical analyses and cultured skin fibroblasts have allowed for the separation of the disorders of methylmalonic acidemia and cobalamin metabolism into distinct classes: (1) cobalamin A, discussed above; (2) cobalamin B, discussed above; (3) cobalamin C, discussed above; (4) cobalamin D, an unknown cobalamin defect leading to methylmalonic acidemia and homocystinuria; (5) cobalamin F, defective lysosomal metabolism of cobalamin; (6) cobalamin E and G, both with reduced synthesis of methyl-cobalamin leading to homocystinuria alone; and (7) cobalamin H (Watkins et al 2000), cobalamin D variant 2. The cobalamin D group is itself heterogeneous with the variant 2 subclass exhibiting isolated methylmalonic acidemia due to defective adenosylcobalamin synthesis and the variant 1 subclass exhibiting isolated homocysteinemia (Suormala et al 2004). Two pairs of siblings with an unusual syndrome of cobalamin-unresponsive hypermethylmalonic aciduria (200 to 300 µmoles methylmalonate per mmole creatinine), progressive neurodegenerative disease with microcephaly and cataracts, but with no evidence in vitro of L-methylmalonyl-CoA mutase deficiency, were reported (Stromme et al 1995; Mayatepek et al 1996). The etiology of this condition remains unknown.

Epidemiology"

The different forms of methylmalonic acidemia have been detected in different ethnic groups. It is thought that the frequency of methylmalonic acidemia is higher than 1 in 48,000 reported for Massachusetts newborn screening (Coulombe et al 1981) and 1 in 61,000 for Quebec (Lemieux et al 1988). Not unexpectedly, the frequency is greater in a population with a high rate of consanguinity (Ozand et al 1992).
Prevention

Prenatal diagnosis is available for most of the forms of methylmalonic acidemia (Morel et al 2005). Depending on the nature of the molecular defect and phenotype in a family, the following could be performed for ascertainment of the disease: methylmalonic acid or methylcitrate quantification in amniotic fluid (Morrow et al 1970; Gompertz et al 1974; Mahoney et al 1975; Naylor et al 1980; Fensom et al 1984; Coude et al 1990); acylcarnitine concentrations in amniotic fluid (Shigematsu et al 1996); enzyme analysis in a chorionic villus sample (Fowler et al 1988) or cultured amniocytes (Mahoney et al 1975); and DNA testing of a chorionic villus sample or amniocytes. In combined methylmalonic acidemia and homocystinuria, measurement of methylmalonic acid and total homocystine in amniotic fluid (Fowler and Jakobs 1998), and the incorporation rate of [14C]propionate into macromolecules plus production of cobalamin derivatives in cultured amniocytes may be reliable, but this does not seem to be the case, for the cobalamin-dependent [14C]methylene tetrahydrofolate incorporation into macromolecules in a chorionic villus sample (Merinero et al 1998). An alternative reliable assessment of the remethylation pathway in cultured amniocytes utilizes [14C]formate (Fowler and Jakobs 1998).

Therapy with cobalamin has been initiated in utero (Ampola et al 1975; Evans et al 1997). Gene therapy remains an interesting possibility (Sawada and Ledley 1992; Wilkemeyer et al 1992). A human L-methylmalonyl-CoA mutase gene has been overexpressed in mice following in vivo gene transfer (Stankovics et al 1994). Adeno-viral as well as adeno-associated virus-mediated gene delivery rescues a neonatal lethal murine model of mut(o) methylmalonic aciduria (Chandler and Venditti 2008; Sénac et al 2012). Even partial correction of hepatic enzyme deficiency would dramatically alter the nature of the disease. It is unclear, however, whether some patients would be at risk for some manifestation of CNS disease, as methylmalonic acid is also generated de novo within certain brain cells. This may also apply to the kidney and its complications in methylmalonic acidemia. Orthotopic liver transplantation can be considered in some infants with the mut(o) phenotype (Kayler 2002; Hsui 2003; Kasahara 2006; Moriooka 2007; Chen et al 2010). This treatment can eliminate the occurrence of overt metabolic decompensation with metabolic acidosis and ketonuria and can also improve protein tolerance, but it does not correct the elevated concentrations of methylmalonic acid in cerebrospinal fluid or eliminate the elevation of methylmalonic acid in serum and urine (Kaplan et al 2006). Similar findings have been reported in an older patient following combined liver and kidney transplantation (van't Hoff et al 1998). Kidney transplantation alone for the treatment of methylmalonic acidemia deserves further study (Lubrano et al 2007; Clothier et al 2011). The effect of pregnancy in a patient with methylmalonic acidemia and kidney transplant was reported (Lubrano et al 2013).

Differential diagnosis

The differential diagnosis obviously is dependent on the phenotype in a particular patient. Not unexpectedly, the same genotype may give rise to different clinical syndromes depending primarily on environmental factors, ie, protein intake, the number or severity of episodes of fasting or infections, etc. The differential diagnosis may include:

(1) idiopathic developmental delay or mental retardation (cognitive impairment)
(2) cerebral palsy
(3) gastroesophageal reflux
(4) food allergy
(5) growth failure due to liver, renal, or endocrine disease
(6) Reye syndrome
(7) other defects in the metabolism of ammonia, amino acids, organic acids, and fatty acids

Diagnostic workup

The diagnosis of the specific type of methylmalonic acidemia requires the measurement of enzyme activity, usually via the indirect assessment of radio-labeled propionate incorporation into protein in cultured skin fibroblasts, or the identification of an abnormal disease-producing gene mutation. Guidelines have been published (Baumgartner et al 2014). Analysis of cultured cells will also permit assignment to a particular complementation group (mut(o), mut(-), cblA, cblB, cblC, cblD, and variants), which is especially important if the abnormality is not in the L-methylmalonyl-CoA mutase gene. Patients with cobalamin C and D abnormalities also have homocystinuria. Patients with cobalamin E and G abnormalities do not have methylmalonic acidemia but homocystinuria due to impaired methyl-cobalamin synthesis. The rare cobalamin F deficiency is due to impaired release of cobalamin from lysosomes, is similar in
gut bacteria may be useful in therapy (Snyderman et al. 1972; Bain et al. 1988; Koletzko et al. 1990). Using
important. Some patients require 1 to 3 mEq/kg per day to maintain acid-base balance. Antibiotics for sterilization of
growth hormone also improved growth and anabolism (Bain et al. 1995). Alkali therapy with bicarbonate or citrate is
protein to maintain adequate growth and positive nitrogen balance (Kelts et al. 1985). In one patient, therapy with
enhance the waste nitrogen burden and perhaps the propensity for further renal deterioration in certain susceptible
intake is controversial. Many investigators believe its utility in stimulating anabolism is limited, and its use may simply
supplemental amino acid mixtures that are free of isoleucine, valine, methionine, and threonine to enhance nitrogen
acidemia may be more accurately assessed by measuring serum methylmalonate concentrations. The use of
metabolite excretion, the poorly understood perturbations in renal creatinine handling, and, most importantly, renal
patients, particularly those who are not critically ill in the intensive care unit, the effect of hydration on urinary
management is the prime consideration in this section (Fraser and Venditti 2016). Less severely restricted diets and the
absence of acute crises now apply to some of the mut(-) patients and those in the other complementation groups
(Waggoner et al. 1998). Cobalamin responsiveness must first be determined using daily 1-mg intramuscular injections
of hydroxocobalamin. For chronic therapy, hydroxocobalamin may be given orally on a daily basis (Gordon and Carson
1976; Ninan et al. 1992). However, oral therapy with cyanocobalamin may not be best for all patients with different
forms of methylmalonic acidemia. Patients with cobalamin A disease may not respond to IM cyanocobalamin. In 2
patients with cobalamin C disease, hydroxycobalamin was more efficacious than cyanocobalamin (Andersson and
Shapira 1998). Betaine is also important for these patients (Urbon Artero et al. 2002). Adenosylcobalamin has also been
used to treat methylmalonic acidemia secondary to cob(II)alamin adenosyltransferase deficiency, but was ineffective
(Batshaw et al. 1984). For cobalamin nonresponders, treatment primarily consists of a low-protein diet. In general, the
goal is to provide enough protein of a high biological quality, such as egg protein, to allow for normal growth while
maintaining methylmalonic acid concentrations at a minimum (Kelts et al. 1985; Ney et al. 1985). For most patients, this
eliminates signs of severe disease. From a practical vantage point, this is often not possible, as some patients with
severe phenotypes will achieve methylmalonic acid concentrations that are associated with the absence of overt
disease only when protein restriction is so severe as to cause essential amino acid concentrations in plasma to drop
below the normal range, a condition obviously not compatible with normal growth. Accurate measurement of
methylmalonic acid in serum using an isotope dilution technique with gas-liquid chromatography-mass spectrometry is
useful in monitoring disease control (Caruso et al. 1993). Because a 24-hour urine collection is not feasible in most
patients, particularly those who are not critically ill in the intensive care unit, the effect of hydration on urinary
metabolite excretion, the poorly understood perturbations in renal creatinine handling, and, most importantly, renal
insufficiency in methylmalonic acidemia, the effect of dietary maneuvers or drug therapy in control of methylmalonic
acidemia may be more accurately assessed by measuring serum methylmalonate concentrations. The use of
supplemental amino acid mixtures that are free of isoleucine, valine, methionine, and threonine to enhance nitrogen
intake is controversial. Many investigators believe its utility in stimulating anabolism is limited, and its use may simply
enhance the waste nitrogen burden and perhaps the propensity for further renal deterioration in certain susceptible
patients (Levenson 2015; Manoli et al. 2016a; Manoli et al. 2016b). Alanine supplementation may reduce the need for
protein to maintain adequate growth and positive nitrogen balance (Kelts et al. 1985). In one patient, therapy with
growth hormone also improved growth and anabolism (Bain et al. 1995). Alkali therapy with bicarbonate or citrate is
important. Some patients require 1 to 3 mEq/kg per day to maintain acid-base balance. Antibiotics for sterilization of
gut bacteria may be useful in therapy (Snyderman et al. 1972; Bain et al. 1988; Koletzko et al. 1990). Using

Management

The therapeutic approach to the patient with mut(o) disease who requires strict control and a meticulous attention to
detail is the prime consideration in this section (Fraser and Venditti 2016). Less severely restricted diets and the
absence of acute crises now apply to some of the mut(-) patients and those in the other complementation groups
(Waggoner et al. 1998). Cobalamin responsiveness must first be determined using daily 1-mg intramuscular injections
of hydroxocobalamin. For chronic therapy, hydroxocobalamin may be given orally on a daily basis (Gordon and Carson
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growth hormone also improved growth and anabolism (Bain et al. 1995). Alkali therapy with bicarbonate or citrate is
important. Some patients require 1 to 3 mEq/kg per day to maintain acid-base balance. Antibiotics for sterilization of
gut bacteria may be useful in therapy (Snyderman et al. 1972; Bain et al. 1988; Koletzko et al. 1990). Using
metronidazole, it was estimated that approximately one quarter of daily methylmalonic acid production is derived from propionate synthesized in the large colon by anaerobic bacteria (Thompson et al 1990). This or related agents may be particularly helpful during metabolic decompensation. Chronic administration, however, may not be warranted because of the problem of drug resistance. Propionate derived from odd-chain fatty acids during fasting is also important and may account for an additional 30% to 35% of the daily synthesis of methylmalonic acidemia (Thompson and Chalmers 1990; Thompson et al 1990; Wendel et al 1993; Sbai et al 1994). Of interest, the urinary excretion of propionylcarnitine may not be affected by metronidazole therapy in methylmalonic acidemia and propionic acidemia (Burns et al 1996).

The experience of many centers is that the majority of patients with neonatal-onset methylmalonic acidemia or a severe phenotype have serious problems with poor feeding and vomiting that they cannot maintain adequate nutritional intake without the use of gastrostomy tube feedings. A nasogastric tube is a useful temporary measure. A gastrostomy tube placed prophylactically in early infancy may represent the safest mode of therapy for those babies, the majority of whom have cobalamin-unresponsive disease. In some instances, total parenteral nutrition may be necessary to reestablish metabolic balance (Kahler et al 1989), particularly in those with nutritional deficiencies in whom chronic anorexia, vomiting, upper gastrointestinal bleeding, pancreatitis, dermatitis, and anorexia are coexistent (Marquard et al 2011).

Patients usually develop a secondary deficiency of free L-carnitine (Chalmers et al 1984a; Di Donato et al 1984). This is associated with increased concentrations of propionylcarnitine as the esterified form of L-carnitine (Minkler and Hoppel 1993). Several investigators have administered oral L-carnitine (50 to 200 mg/kg per day) to reduce toxicity of methylmalonic acid in either the acute or chronic state (Roe et al 1983; Chalmers et al 1984b; Penn et al 1986). Biochemical studies support the concept that patients with methylmalonic acidemia have a deficiency of mitochondrial L-carnitine. At the present, the use of L-carnitine as a treatment modality is controversial, specifically because there are no studies that demonstrate that a deficiency of free L-carnitine as seen in methylmalonic acidemia is of any physiological or clinical significance. Treacy and colleagues reported that a patient with a mild phenotype of methylmalonic acidemia developed secondary glutathione deficiency following acute illness that, along with a secondary lactic acidosis, was responsive to ascorbate megatherapy (Treacy et al 1993; Treacy et al 1996).

Acute severe metabolic decompensation in a patient with methylmalonic acidemia constitutes a medical emergency. These patients are at risk for the development of necrosis of the basal ganglia, pancreatitis, a bleeding diathesis, irreversible shock, and death. Necessary diagnostic clinical or laboratory findings include anorexia, vomiting, dehydration, moderate to severe ketosis, acidosis, and hyperammonemia. Patients are usually lethargic but do not need to be stuporous or in a coma. Emergency therapy consists of fluids at 1 to 3 times the maintenance rate, alkali to correct the acidosis, and glucose to retard the catabolic surge. Protein intake is eliminated. Restoration of circulatory volume may also require intravenous boluses of saline or albumin. Aside from dialysis, which may be necessary in some instances, the best way to rid the body of methylmalonic acid is to enhance renal excretion. Sometimes this requires large volumes of fluid because of preexisting renal disease associated with impaired free water handling or because of excessive urinary solute wastage. Maximal excretion of methylmalonate can only be realized when the pH of renal filtrate is not low. Transfusions may be necessary to prevent complications from thrombocytopenia or severe anemia. Cobalamin megatherapy should always be utilized in the sick patient unless its ineffectiveness has been documented. Carglumic acid has been found to be beneficial in reducing plasma ammonia concentrations and is the subject of a clinical trial in the U.S. (Valayannopoulos et al 2016).

Outcomes

Chronic therapy of the patient with mut disease via a low-protein diet with an adequate amount of calories and nitrogen and/or alkali, L-carnitine, and intermittent metronidazole may allow for normal growth and development, prevent severe progressive brain damage, and decrease the frequency and/or severity of acute episodes of metabolic decompensation with ketolactic acidosis (Haarmann et al 2013; Baumgartner et al 2014). However, it cannot prevent cognitive impairment, language delay, speech defects, and brain atrophy in certain patients, nor can it prevent the development of renal insufficiency, especially in patients with mut(o) disease (Ktena et al 2015a; Sloan et al 2015). Timely and aggressive therapy of acute metabolic decompensation may prevent “metabolic strokes” and other complications outlined in the preceding sections in certain patients (Zwickler et al 2012). A liver and/or kidney transplantation may be appropriate for certain patients depending on the severity of the enzyme deficiency or gene defect and organ failure (Brassier et al 2013; Baumgartner et al 2014; Niemi et al 2015; Sloan et al 2015). However,
depending on the timing of this procedure and the severity of organ dysfunction, there may be postoperative complications and even death (Vernon et al 2014). In addition, the details of pre-operative preparation to avoid acute metabolic complications still need to be established (Kamei et al 2011; Vernon et al 2014).

Special considerations

Pregnancy

Diss and colleagues reported the first case of a 23-year-old woman with methylmalonic acidemia who became pregnant, withstood the rigors of labor, and delivered an apparently healthy newborn infant (Diss et al 1995).

Other reports also support that mothers with methylmalonic acidemia can deliver successfully (Wasserstein et al 1999; Langendonk et al 2012; Raval et al 2015).

Prenatal diagnostic testing is available for several of the subtypes of methylmalonic acidemia (Morel et al 2005).

Treatment of a patient with cobalamin C disease during pregnancy has been reported (Brunel-Guitton et al 2010).

Anesthesia

Patients with methylmalonic acidemia are at risk for intraoperative and postoperative metabolic decompensation with ketoacidosis because of the effect of stress, etc., on muscle protein catabolism. Fasting should be avoided, and the patients should receive intravenous fluids consisting of 10% glucose and appropriate electrolytes at all times if enteral feeds are not tolerated. For patients with severe enzyme defects, preadmission for hydration and glucose should be considered. Propofol administration to patients with methylmalonic acidemia may impose a risk (Ktena et al 2015b).

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**References especially recommended by the author or editor for general reading.

ICD and OMIM codes

ICD codes

ICD-9:
Methylmalonic acidemia: 270.3

ICD-10:
Methylmalonic acidemia: E71.1

OMIM numbers
Mut methylmalonic acidemia: #251000
Methylmalonic acidemia and homocystinuria: #277410

Profile

Age range of presentation
0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

Sex preponderance
male=female

Family history
family history may be obtained

Heredity
autosomal recessive

Population groups selectively affected
none selectively affected

Occupation groups selectively affected
none selectively affected

Differential diagnosis list
idiopathic developmental delay
idiopathic mental disability
cerebral palsy
gastroesophageal reflux
food allergy
growth failure due to liver, renal, or endocrine disease
Reye syndrome
defects in metabolism of ammonia
defects in metabolism of amino acids
defects in metabolism of organic acids
defects in metabolism of fatty acids
sepsis

Associated disorders
Anorexia
Cerebral palsy
Chronic mucocutaneous candidiasis
Extrapyramidal movement disorder
Gastroesophageal reflux
Growth failure
Homocystinuria
Intellectual disabilities
Osteopenia
Pancreatitis
Renal insufficiency
Renal tubular acidosis
Reye syndrome

**Other topics to consider**

Carbamyl phosphate synthetase I deficiency
Glutaric aciduria
Isovaleric acidemia
Propionyl-CoA carboxylase deficiency