EIMD

European registry and network for
Intoxication type Metabolic Diseases

For healthcare professionals

Methylmalonic Acidurias

www.e-imd.org

Methylmalonic acidurias (MMAurias) comprise a group of inborn errors of metabolism characterized by an isolated accumulation of methylmalonic acid (MMA) due to deficient activity of the enzyme methylmalonyl-CoA mutase.

Disease name + OMIM number + Synonyms

The following table lists the disease names of MMAurias, commonly used synonyms and the respective OMIM numbers.

Disease name	Synonyms	OMIM #
Methylmalonyl-CoA mutase deficiency	Mutase, mut or MCM deficiency	251000
Adenosylcobalamin synthesis defect, cblA	cblA deficiency	251100
Adenosylcobalamin synthesis defect, cblB	cblB or adenosyltransferase deficiency	251110
Adenosylcobalamin synthesis defect, cblD-var2	cblD-MMA, cblD-variant 2	277410

Epidemiology

Methylmalonic aciduria is a rare disorder and the true incidence in Europe is unknown. Estimates of incidence in Western populations range from 1:48,000 to 1:61,000 births, and overall incidence is believed to be ~ 1: 50,000.

Etiology

Methylmalonic aciduria is caused by the deficient activity of methylmalonyl-CoA mutase (MCM), a vitamin B_{12} dependent mitochondrial enzyme which is essential for the catabolism of the amino acids threonine, methionine, isoleucine, valine, as well as cholesterol and odd-chain fatty acids.

MCM catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA which can enter the tricarboxylic acid cycle. Deficient activity of MCM results either

from defects of the MCM apoenzyme (**mut**) or defects of intracellular synthesis of its cofactor, 5-deoxyadenosylcobalamin (AdoCbl), **cblA**, **cblB** and **cblD-variant 2**. The cblA, cblB and the variant 2 form of cblD (cblD-MMA) are distinct inborn errors linked to processes unique to AdoCbl synthesis.

Methylmalonyl-CoA mutase deficiency

- MCM contains an N-terminal mitochondrial leader sequence of 32 amino acids and the mature form is a dimer of identical subunits of 78.5 kD. Each subunit contains two main functional domains, an N-terminal domain with the substrate binding site and a C-terminal AdoCbl binding domain.
- The defects of MCM are inherited in an autosomal recessive manner and can be subdivided into two subgroups with virtually undetectable (mut^0) or low to moderate residual MCM activity (mut^-). To date up to 200 disease-causing mutations in the *MUT* gene (locus 6p21) have been reported, the majority being associated with the mut^0 phenotype. Most of the mutations are private and are scattered over the entire gene, with only a few occurring in several patients.

cblA deficiency

- The **cblA** protein contains an N-terminal mitochondrial leader sequence and cleavage site as well as Walker A and B ATP-binding motifs, a Mg(2+)-binding site and a GTP-binding site but its exact function is unclear. Recent evidence points to a role of the protein in the assembly and stabilisation of holo-MCM.
- The cblA defect is inherited in an autosomal recessive manner. Over 30 heterogeneous mutations have been identified in the *MMAA* gene (locus 4q31.1-q31.2) with one nonsense mutation found to be present in 43% of mutant alleles.

cblB deficiency

- The **cblB** enzyme is an adenosyltransferase containing a leader sequence and signal cleavage site consistent with localization to the mitochondrion.
- Adenosyltransferase deficiency is inherited in an autosomal recessive manner. The enzyme is encoded by the *MMAB* gene (locus 12q24) and various mutations have been described with one missense mutation accounting for 33% of mutant alleles patients who were of European origin and presented with a severe clinical phenotype.

cblD-variant 2 deficiency

- The cblD defect was first associated with combined MMAuria and homocystinuria but it is now known that two additional variant forms of this mutant class exist with either isolated homocystinuria (**cblD-variant 1**) or isolated MMAuria (cblD-variant 2).
- The cblD protein has sequence homology with a bacterial ATP-binding cassette transporter and contains a putative mitochondrial targeting sequence but its exact function is unknown. Recent evidence points to a role in channeling of cobalamin to cytosolic and mitochondrial targets.
- CblD deficiency is inherited as an autosomal recessive trait. The protein is encoded by the *MMADHC* gene (locus 2q23.2). Various mutations leading to a premature termination codon in the N-terminal part have been associated with isolated MMAuria.

Clinical features

Depending on the age at presentation, patients with MMAuria may be classified into the early onset and late onset forms.

- Patients with **early-onset methylmalonic aciduria** (MMAuria) present in the first few weeks of life with acute decompensation. Classically, infants are well at birth and as feeds are introduced, they develop symptoms such as:
    - lethargy
    - poor feeding
    - tachypnea
    - vomiting
    - seizures
    - progress to coma, apnoea and death if untreated.

  The symptoms are indistinguishable for those of a sick neonate due to any cause. Investigations at presentation typically reveal metabolic acidosis with increased anion gap and hyperammonaemia; pancytopenia, hypoglycemia and hypocalcemia may also be found.

- **Late-onset** cases of MMAuria may present later in infancy, childhood or later with a more heterogeneous clinical picture including:Vomiting
    - feeding difficulties
    - failure to thrive
    - psychomotor retardation
    - late-onset acute metabolic decompensation with acidosis, encephalopathy and hyperammonaemia
    - movement disorders that may arise following decompensation or insidiously

Natural history and long-term complications

The natural history of MMA is not well characterized, although a number of complications and sequelae are well known; most of these are derived from anecdotal reports and retrospective case series and there are no prospective studies that have described the long-term course and outcome.

- Survival: the long-term outcome in MMAuria is influenced by the underlying defect. Overall, patients with mut^0 and cblB defects have an earlier onset of symptoms and a higher frequency of complications and deaths than patients with mut- or cblA defects. Recent studies indicate 20 year survival rates of ~50% in early onset MMAuria and >90% for late onset MMAuria, in particular in patients with the cblA defect. Most surviving individuals with early onset MMAuria have chronic renal failure, varying degrees of developmental disability and neurological or other complications.

- Chronic progressive renal impairment: chronic renal failure develops gradually and may occur as early as 2 years of age in mut^0 and cblB defects, eventually requiring haemodialysis or renal transplantation. Secondary complications such as anaemia, arterial hypertension and renal osteopathy further aggravate the disease course. In the late-onset forms (mut-, cblA) renal impairment usually doesn't manifest before the second decade of life.

- Neurological sequelae: A number of neurological complications have been described, with or without concomitant or preceding metabolic decompensation:
  - Acute onset neurological symptoms or "metabolic strokes"
  - Basal ganglia damage to the caudate, globus pallidum and putamen
  - Extrapyramidal symptoms such as dystonia, chorea and athetosis
  - Seizures of different types, including generalized tonic-clonic, focal, myoclonic and atonic
  - Optic atrophy
  - Cerebral atrophy

- Developmental outcome: A majority of long-term survivors with early onset MMAuria have gross motor, fine motor and cognitive impairment and

require individualized learning plans in school.

- Skeletal muscle: Metabolic myopathy which may develop progressively in older children and adolescents as the result of secondary chronic energy impairment

- Gastrointestinal complications
  - Pancreatitis that may be recurrent and occur independently or with acute metabolic decompensation
  - Recurrent vomiting

- Other known rare complications
  - Immune dysfunction, recurrent infections and pancytopenia (particularly during acute metabolic crises)
  - An exfoliative dermatitis-like skin rash (termed “acrodermatitis acidemica”), often associated with isoleucine deficiency as a result of inadequate supply with essential nutrients and/or micronutrients
  - Decreased bone mineral density
  - Hyperglycaemia and insulin resistance

Diagnosis

- Basic metabolic tests that may lead to suspicion of MMAuria include metabolic acidosis with increased anion gap, hyperammonaemia, lactic acidosis and hypoglycaemia.

- Specific diagnostic tests include urine and plasma MMA, urine organic acid analysis and plasma or blood spot acylcarnitine profiles. On urine organic acid analysis, characteristic elevations of MMA, methylcitrate, 3-OH-propionate and propionylglycine are seen; additionally, other organic acids including 3-hydroxyisovalerate and 3-hydroxy-2-methylbutyrate may also be variably detected. On plasma acylcarnitine analysis

elevated levels of propionylcarnitine (C3 carnitine) and methylmalonylcarnitine are found, along with low levels of free carnitine.

- Plasma amino acid analysis may reveal hyperglycinaemia and hyperalaninaemia.
- The complexity of causes of inherited isolated MMAuria necessitates characterization of the underlying defect in cultured skin fibroblasts using several assays. As a first step the overall conversion of propionate to succinate is determined by the incorporation of label from [^{14}C]propionate into cell proteins. Specific activity of MCM can be measured using a radioactive substrate in the presence and absence of Ado-Cbl. Distinction of isolated MMAurias into mut^0 or mut- is based on the somewhat arbitrary biochemical assessment of in vitro response to hydroxycobalamin. Cobalamin adenosyltransferase is measured by monitoring the conversion of OH-[^{57}Co]cobalamin to Ado-Cbl. Finally, complementation analysis can be performed by measuring the incorporation of [^{14}C]propionate into protein in patient cells mixed with cells of known complementation groups for cblB and cblD.
- Mutation analysis is available for diagnostic confirmation and involves analysis of the *MUT, MMAA, MMAB* and *MMADHC* genes.
- Prenatal diagnosis can be undertaken in the first trimester by mutation analysis on chorionic villous samples (preferred method if the genotype is known), or in the second trimester by direct assay of amniotic fluid for abnormal metabolites by GCMS and/or tandem MS.

Differential diagnosis

- The presenting clinical features are similar to those arising from a number of other inherited and acquired disorders, such as infections, toxicity and other inherited metabolic disorders. In an acutely sick neonate, a

high index of suspicion for inherited metabolic disorders including the organic acidurias should be maintained until exclusion as the features are indistinguishable from sepsis.

- Organic acid and blood acylcarnitine profiles similar to MMAuria can be seen in other disorders such as propionic aciduria, multiple carboxylase deficiency, biotinidase deficiency and mitochondrial disorders. Usually, elevated MMA and other characteristic metabolites help to distinguish between these conditions, but specific diagnostic tests should be carried out if the diagnosis is unclear as the treatment and prognosis of these conditions is different to (from?) MMAuria.

Prognosis

The long-term prognosis for MMAurias has improved considerably in the last 3 decades, and 20 year survival rates of >60% for the severe forms (mut^0 and cblB) and >90% for the late-onset forms (mut-, cblA) can be expected. Normal growth can be achieved with adequate dietary management. However, morbidity remains high, with a majority of early-onset patients having chronic renal failure, cognitive impairment, physical disability and neurological sequelae such as chorea, athetosis, dystonia and seizures.

Treatment

The treatment of MMAuria is complex and requires regular monitoring and frequent therapeutic and dietary adjustments. It is recommended that the treatment and follow up of these patients be supervised by an experienced multidisciplinary team in a tertiary setting, although many aspects of care, including emergency management, can be delivered at the local or secondary level.

Patients usually require 3-monthly follow up in order to monitor their clinical condition, nutritional status and growth and to make any changes to treatment

as necessary. Long-term surveillance must include annual renal assessments to detect and manage renal impairment early and because of the potential for developing cardiac arrhythmias and cardiomyopathy in later life.

Acute management in the newborn period

- The basic principles of acute management of any neonate with a disorder of protein catabolism should be followed, including fluid and electrolyte resuscitation, correction of acid-base status, stoppage of exogenous protein, provision of sufficient calories and promotion of anabolism with insulin infusion.
- Metabolites of alternative propionate oxidation are inefficiently cleared via the kidneys and haemofiltration or haemodialysis may be necessary in order to achieve sufficient toxin removal. Peritoneal dialysis is relatively inefficient in this situation.
- Treatment of acute hyperammonaemia with carbamylglutamate (100mg/kg/day in 2-4 divided doses) may help reduce ammonia in MMAuria levels without renal replacement therapy, and this medication should be tried if hyperammonaemia is thought to be a significant factor in causing acute encephalopathy.
- L-carnitine in a dose of 100-200mg/kg/day helps correct any carnitine depletion and facilitates removal of toxic organic acids.
- Feeds or parenteral nutrition should be commenced as soon as metabolic stabilization is achieved in order to prevent essential amino acid deficiency.
- When the infant is fit for discharge after stabilization, it is essential to educate the parents and carers about the condition and its management, including the specialized diet, medications, tube feeding and emergency

management. The day-to-day management of MMAuria is very complex and community-based services must be engaged in order to enable various aspects of care to be delivered effectively at home.

Basic (well-day) treatment

This comprises dietary treatment and pharmacotherapy.

- Dietary treatment:

The basic principles of dietary treatment include:

- dietary natural protein restriction to reduce the load of precursor amino acids (i.e., isoleucine, methionine, threonin, valine)
- prevention of a catabolic state
- provision of sufficient protein and energy to allow normal growth
- provision of vitamin and mineral supplements to prevent deficiency states

Individual protein tolerance varies and in some cases, especially in early-onset patients, precursor-free amino acid mixtures may be helpful in achieving adequate protein intake. Most children with early-onset MMAuria have a very poor appetite and nasogastric or gastrostomy tube feeding is almost always required in order to maintain adequate nutritional intake. The dietary management must be supervised by a metabolic specialist dietetic team.

- Pharmacotherapy
  - L-carnitine: long-term oral/enteral carnitine in a dose of 100mg/kg/day is helpful in preventing carnitine depletion and in helping conjugate and excrete methylmalonic and propionic acid and related toxic metabolites.
  - Metronidazole: Studies have shown that 20-30% of the body's propionic acid load is derived from microbial bacteria

and suppression of gut flora has been shown to reduce urinary excretion of propionate metabolites. Metronidazole in a dose of 10-20mg/kg/day for 7-10 days every 1-3 months or alternatively given continuously in a low dose (5-7mg/kg/day) may be of significant benefit.

- Additional medications may be required to treat specific complications, e.g. chronic renal failure and its complications, dystonia, seizures and recurrent pancreatitis.

Emergency management during acute illnesses

Any catabolic state, such as intercurrent infections, anaesthesia, surgery, immunization or prolonged starvation can potentially result in acute metabolic decompensation that may be life-threatening. The aim of emergency management is to prevent metabolic decompensation from occurring during these potentially catabolic situations.

The general principles of emergency management include:

- Reducing or stopping protein intake temporarily.
- Regular enteral administration of a high energy (carbohydrate or carbohydrate and lipid-based) feeds
- Normal feeds must be reintroduced within 24-48 hours
- If the emergency diet is not tolerated or there is clinical deterioration, the child must be admitted to hospital for urgent clinical and biochemical evaluation.
- In this situation, rehydration using intravenous 10% dextrose-based solutions (adapted to the age-dependant demand) usually result in clinical improvement within 24-48 hours, when regular feeds can be reintrodu-

ced. If feeds cannot be introduced in this time because of the clinical condition, a short period of parenteral nutrition may be necessary.

- Intravenous carnitine should be given in a dose of 200mg/kg/24 hours in 3 or 4 divided doses.
- Any specific biochemical disturbances (e.g. severe acidosis, hyperammonaemia, electrolyte disturbances) may require specific correction on advice from a tertiary metabolic unit. An insulin infusion with high-concentration dextrose may help promote anabolism.
- In cases of severe decompensation and worsening clinical and/or biochemical status despite the above measures, haemodialysis or haemofiltration may be necessary to enable toxin removal.

Emergency management guidelines are available via the website of the British Inherited Metabolic Disease Group website www.bimdg.org.uk

Liver/kidney transplantation

As a large part of methylmalonyl-CoA mutase activity resides in the liver and to a lesser extent in the kidneys, liver and/or kidney transplantation (depending on the underlying defect) can be expected to significantly improve the biochemical abnormalities. The few reported cases of combined liver/kidney and isolated liver or kidney transplantation in MMAuria suggest improved metabolic stability; dietary relaxation may also be achieved. The experience with organ transplantation in MMAuria, however, is limited and carries its own risks, such as increased perioperative mortality. Furthermore, as the enzyme is ubiquitously expressed, tissue-specific biochemical abnormalities persist and neurological deterioration may occur even after transplantation.

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For more information: http://ec.europa.eu/health/programme/policy/index_en.htm

For more information about e-imd: www.e-imd.org