Methylmalonic Acidemia - Acute Illness Protocol

This acute illness protocol is a guideline for healthcare professionals treating the sick infant or child who is known to have methylmalonic acidemia. The protocol was developed at Boston Children's Hospital under the direction of Dr. Harvey Levy, Senior Physician in Medicine/Genetics and Dr. Jonathan Picker, Fragile X Program Director, and was updated by Dr. Patroula Smpokou, Clinical Genetics Fellow.

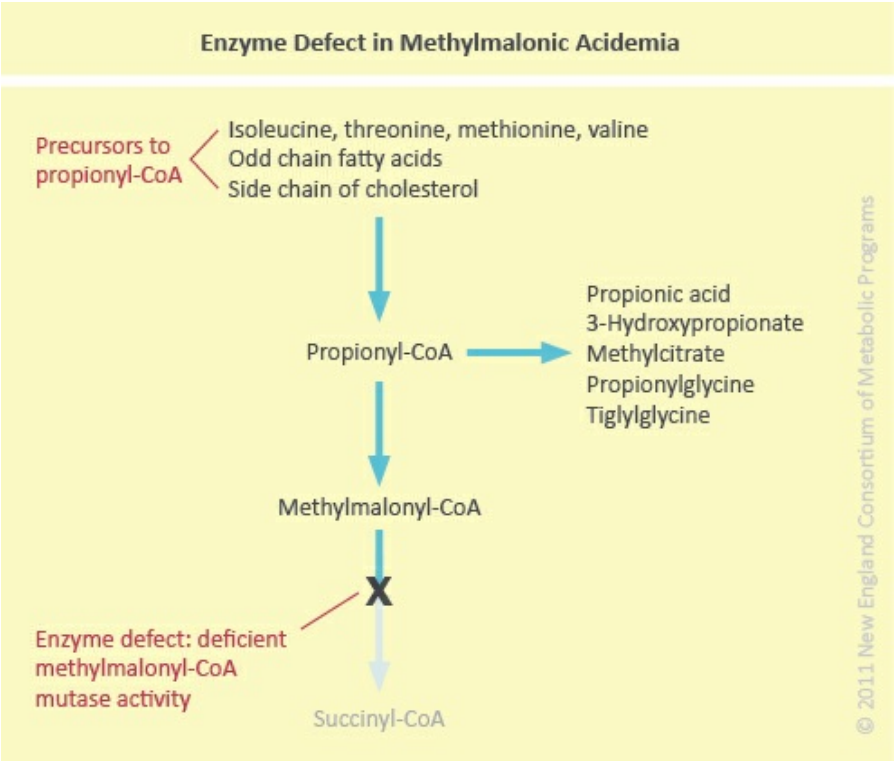
Disclaimer
Metabolic crises in infants and children with organic acid disorders are complex medical emergencies and must be treated as such to avoid death or serious brain injury. This protocol is only a guideline and should not be used for definitive treatment without metabolic consultation. It is essential to call or page the on-call genetics/metabolism fellow, or failing this, the on-call metabolic attending at your hospital or nearest pediatric tertiary care center, as rapidly as possible. Please read our Terms of Use.

Introduction

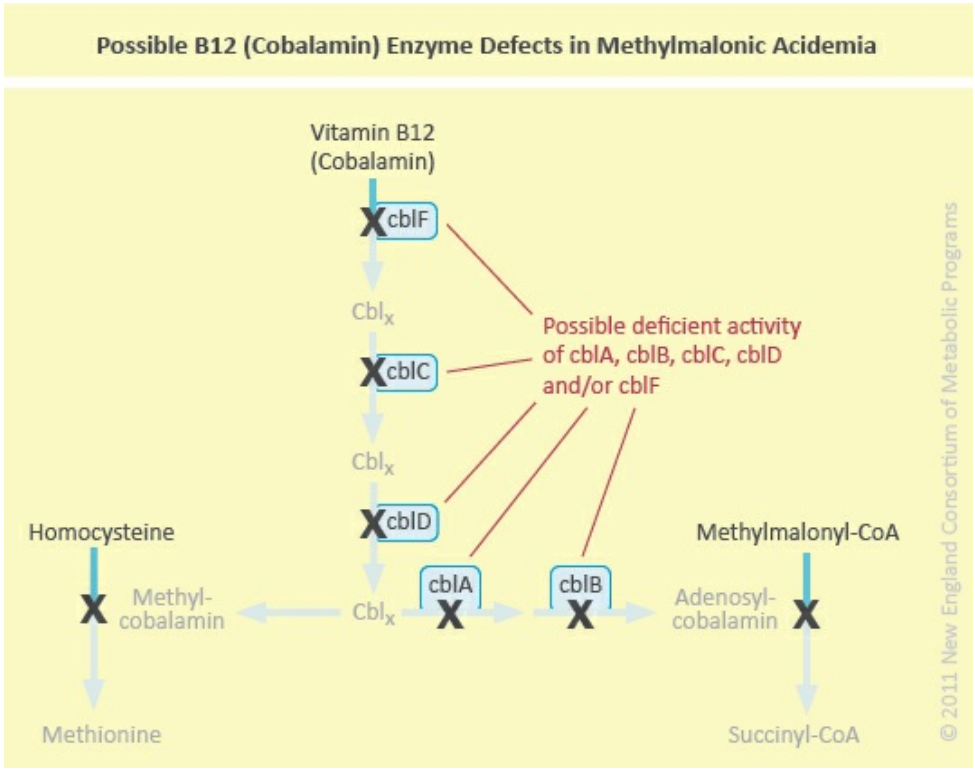
Methylmalonic Acidemia (MMA) is an autosomal recessively inherited organic acid disorder due to deficient activity of mitochondrial B12-dependent methylmalonyl-CoA mutase, an enzyme which limits the conversion of methylmalonyl-CoA to succinyl-CoA. Deficient activity may be due to a defect in the enzyme or reduced amount of B12 (cobalamin) cofactor.

Pathophysiology

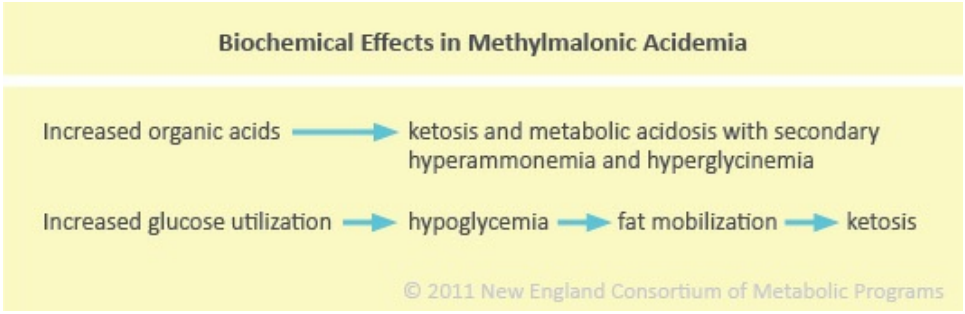
The metabolic precursor of methylmalonyl-CoA is propionyl-CoA, which is the product of the degradation of four essential amino acids, isoleucine, valine, methionine, and threonine as well as the degradation of odd-chain fatty acids and cholesterol. Catabolism of these precursors leads to the production of methylmalonyl-CoA by way of propionyl-CoA (see figure below).



Certain disorders of intracellular cobalamin (vitamin B12) metabolism (cblA, cblB, cblC, cblD, and cblF deficiency) give rise to MMA. These include cblA and cblB deficiency which produce MMA alone and can present acutely, and cblC, cblD, and cblF deficiencies which result in MMA and, in addition, in increased homocysteine and reduced methionine levels. These latter conditions rarely present acutely (see figure below).



In catabolic stress in MMA due to acute illness (e.g. perinatal stress, infection, injury, surgery with endogenous protein breakdown) or when excessive protein is ingested, there is an increase in the offending amino acids (isoleucine, valine, methionine and threonine) as well as in propionic acid, leading to an accumulation of methylmalonic acid with the central emergency biochemical features of profound metabolic acidosis (due to ketone body production and organic acid accumulation), hypoglycemia, and hyperammonemia (see figure below).



Hence, the constellation of laboratory findings in MMA is the following:

- Metabolic acidosis with anion gap
- Ketonuria
- Hypoglycemia
- Hyperammonemia
- Hyperglycinemia

The ketoacidosis, hyperammonemia and hypoglycemia can explain the lethargy and obtundation that are sometimes seen in MMA patients during an acute crisis. The ketoacidosis also produces vomiting. Mobilized free fatty acids from body fat enter the liver resulting in a fatty liver. Prolonged metabolic decompensation can lead to bone marrow suppression with resulting neutropenia.

Acute Presentation

- Lethargy, altered mental status
- Nausea, vomiting
- Hepatomegaly

Laboratory Findings

- Hypoglycemia
- Metabolic acidosis with anion gap
- Hyperammonemia

There are two types of presentation, depending on the severity of the metabolic defect. The neonatal form presents within the first days of life with a life-threatening picture of severe lethargy progressing to obtundation. This presentation can resemble overwhelming neonatal sepsis. The infantile or late-onset form has a more insidious presentation with failure to thrive, developmental delay, and perhaps other neurologic features such as seizures and spasticity. These children can decompensate acutely during catabolic stress, usually brought on by infection, and, thus, present as acute illness.

Parents of children with diagnosed metabolic disorders know the signs of decompensation in THEIR children. It is important to listen to the parents' insight into their child's illness.

Immediate Assessment

- dextrose stick for blood glucose
- vital signs, cardiovascular stability
- hydration status
- presence of fever; signs of infection
- hepatomegaly
- neurologic status; evidence of increased intracranial pressure

Labs

Blood

- venous blood gas for blood pH
– electrolytes, measured CO2, glucose
– blood ammonia (NOTE: draw WITHOUT tourniquet, from free-flowing blood, place on ice and transport STAT to lab to be run immediately)
– AST, ALT, AlkPO4, PT, PTT, INR
– amylase, lipase (pancreatitis can accompany an acute illness)
– renal function (BUN, creatinine)
– plasma amino acids
– plasma total and free carnitine
– CBC, differential WBC count, platelet count
– blood culture (if indicated)

Urine

- urinalysis for specific gravity and ketones
– urine for organic acids
– urine culture (if indicated)

NOTE: organic acids and ammonia are toxic to the brain and accumulations of these may result in cerebral edema. Caution should be exercised when considering the need for a lumbar puncture.

Management

Specific management guidelines are listed here, with details below:

1. Stop all protein intake

2. Provide hydration with high caloric supplementation
3. Correct biochemical abnormalities
4. Eliminate toxic metabolites
5. Treat precipitating factor(s)
6. Provide cofactor supplementation
7. Prevent associated sequelae

1. Protein intake

All protein intake should be halted for 48-72 hours in the setting of a metabolic crisis. Subsequent to that and when the patient is recovering, protein should be introduced slowly in the forms of parenteral nutrition and/or a specialized formula mixture that contains only “non-offending” amino acids (see “hydration/caloric supplementation” category below).

2. Hydration/caloric supplementation

In a metabolic crisis, a patient with MMA should receive high rate intravenous fluids (either via a peripheral venous catheter or a central venous catheter) for rehydration purposes and also for provision of calories. High dextrose-containing fluids (10% dextrose) should be administered with the addition of electrolytes (sodium as half- or full-normal saline solution, and also potassium if urine output is adequate and renal function is sufficient) at a high rate of 1.5 times the maintenance rate for the particular patient. Intravenous fluids should ideally be maintained until the patient is able to tolerate oral fluids or nutrition or until rehydration goals are reached.

Any patient with MMA in metabolic crisis should receive high caloric supplementation to achieve an anabolic state. A state of catabolism precipitated by any stressor can contribute to exacerbation of the underlying metabolic decompensation and promote worsening metabolic acidosis, ketosis, and also possibly hyperammonemia. An intravenous lipid infusion consisting of even-chain fatty acids (e.g. intralipid) should be considered to provide increased calories. Protein can be added to the nutritional regimen at a slow rate once the patient is able to tolerate protein depending on a combination of different factors, including clinical status, mental status, laboratory derangements and improvement of those.

Amino acid therapy may be very beneficial in facilitating clinical improvement but should be implemented only under the supervision of a physician/nutritionist with expertise in metabolic management. Providing an amino acid preparation which includes only “nonoffending” amino acids (i.e., avoiding isoleucine, valine, threonine, and methionine) during the initial crisis period may not only stimulate anabolism but help prevent significant weight loss. If the patient is not significantly neurologically compromised, these preparations can be provided enterally. Specialized formula preparations for MMA provide the appropriate mix of amino acids. Where there exists a high risk for aspiration or a contraindication to enteral feeding, consideration should be given to providing a specialized parenteral amino acid solution available through specific TPN pharmacies.

3. Correct biochemical abnormalities

a. Metabolic acidosis: this should slowly correct with rehydration and high caloric intake; if bicarbonate level is less than 15, or depending on clinical status, one should consider the administration of intravenous or oral bicarbonate in the form of sodium bicarbonate or sodium acetate.

b. Hypoglycemia: if blood glucose is below 50, then give 5-10 mL/kg bolus of D10 intravenously (alternatively may give: 1-2 mL/kg of D50 or 2-4 mL/kg of D25). This should be followed by a continuous infusion of D10 with electrolytes (potassium should be added after patient is able to void and has not hyperkalemia) at a rate of 1.5 times the maintenance rate for the particular patient (based on current weight).

c. Hyperammonemia: if ammonia levels are extremely elevated, there are two modes of treatment: medical treatment (ammonul infusion which provides “scavenger” medications to reduce ammonia level) and hemodialysis (see acute illness protocols for urea cycle disorders).

4. Eliminate toxic metabolites

a. Hemodialysis: this is indicated in cases of intractable metabolic acidosis, severe hyperammonemia, unresponsive to treatment (blood ammonia level > 600 umol/L), coma, and severe electrolyte disturbances. This mode of intervention should be instituted in consultation with a pediatric nephrology service.

b. L-carnitine (oral or intravenous) to conjugate and detoxify propionyl-CoA and methylmalonyl-CoA, thus forming

propionylcarnitine and methylmalonylcarnitine and reducing propionic acid and methylmalonic acid. In addition, free carnitine levels are generally low in MMA due to increased esterification of organic acid metabolites, requiring carnitine supplementation for repletion. While carnitine supplementation is controversial, case reports have shown that it is helpful during acute metabolic decompensation. Carnitine should be mixed in 10% glucose solution and run as an infusion to provide 100 mg/kg/day divided every 8 to 12 hours (maximum dose 5 grams/day). When patient is able to tolerate oral intake, the carnitine can be given orally a a dose of 100mg/kg/day divided every 8 or 12 hours.

c. Antibiotics: Gut bacteria are a significant source of propionic acid and, thus, eradicating this source of organic acid production with short, intermittent courses of antibiotics, may help to decrease the propionic acid and, in turn, the methylmalonic acid load and help in an acute crisis.

5. Precipitating factors

An acute metabolic decompensation in a patient with MMA is almost always precipitated by a stressor, such as infection, injury, surgery, hormonal changes, or significant dietary changes (involving increased protein intake). It is of utmost importance to identify and address the precipitating factor for the patient's metabolic decompensation as treatment of the stressor will facilitate treatment of the metabolic derangements.

In the case of infection, antibiotics should be provided to treat the particular infection. For any type of surgery, prevention of a metabolic decompensation as a result of the stress of surgery should be undertaken prior to surgery by providing adequate hydration prior to and after surgery, avoiding prolonged fasting to the extent possible, addressing pain issues, and providing adequate calories to promote fast healing.

In the case of hormonal changes, the particular patient situation needs to be assessed and possible dietary changes should be made in accordance with the patient's hormonal status (e.g. puberty, growth spurt, menarche, thyroid disorder).

A change in the patient's diet, with excessive protein intake, should be assessed as this would be an easy situation to address by adjusting the protein intake.

6. Cofactor supplementation

Hydroxycobalamin (vitamin B12) 1mg intramuscularly (IM) might be useful in cases of vitamin-responsive enzyme deficiencies (found in about half of patients with MMA). In children with an established diagnosis of MMA, parents will often know whether or not their child is a responder.

Clinical sequelae associated with an acute crisis

- Acute pancreatitis: one should be aware of this sequela and check serum amylase and lipase levels if there are any signs that indicate the possibility of acute pancreatitis. These include vomiting, abdominal pain, and feeding intolerance.
- Stroke (particularly involving the basal ganglia): any neurologic deterioration in a patient with MMA in metabolic crisis should be addressed emergently as the risk of neurologic stroke is higher in this patient population. A brain CT or MRI should be performed in the presence of any neurologic signs that suggest the possibility of a stroke. Changes in the basal ganglia, particularly the globus pallidus, characterize the "metabolic stroke" of MMA. Management of increased intracranial pressure is similar to that for any other neurologic disorder causing increased intracranial pressure, including elevation of the head of the bed, hyperventilation (if patient is mechanically ventilated), mannitol, and other diuretics.
- Renal failure: patients with MMA are particularly susceptible to progressive renal failure from tubulointerstitial nephropathy and, thus, renal function should be monitored in any patient with MMA in acute crisis.

Monitoring the Patient

Clinical parameters

- Mental status
- Hydration status/fluid balance/oral intake
- Evidence of bleeding (if thrombocytopenic)
- Symptoms of infection (if neutropenic)
- Monitor for signs/symptoms of renal failure
- Monitor for signs/symptoms of cardiomyopathy (e.g. in cblC deficiency)

Biochemical parameters

- Electrolytes, measured CO2, glucose, ammonia, blood gases (q 4-6 hours or as indicated)
- CBC with differential, platelets (if needed)
- Renal function (if needed)
- Amylase, lipase (if needed)
- Urine for ketones and specific gravity with every void

Recovery

The patient should be kept NPO until his/her mental status is improved. Anorexia and nausea/vomiting during the acute crisis period makes a significant oral intake unlikely. If the patient is not significantly neurologically compromised, consideration should be given to providing the patient (PO or by NG tube) with a modified formula preparation containing all but the offending amino acids.

When the infant/child is able to take fluids orally/per NG/gastrostostomy tube, please contact the Metabolism fellow/staff or the Metabolism nutritionists since each patient has a unique, modified diet. Each day, the nurses caring for the patient should review the menu with the parents or the nutritionists to avoid potential dietary mistakes; these do happen and can be disastrous in the peri-crisis period.

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