



Methylmalonic Acidemia (MUT) Information for Health Professionals

Methylmalonic acidemia (MMA) is an organic acid disorder. MMA can generally be classified into two types; vitamin B12 non-responsive and vitamin B12 responsive. Two types of MMA that are non-responsive to vitamin B12 and caused by mutations in the MMA-CoA mutase (MUT) gene are referred to as mut⁰ and mut⁻.

✓ Clinical Symptoms

Most newborns do not have symptoms at birth, but will soon develop lethargy, vomiting, and dehydration. Other findings can include intellectual disabilities, movement disorders, metabolic stroke, failure to thrive, hepatomegaly, encephalopathy, and hyperammonemia.

✓ Incidence

MMA (MUT) occurs in greater than 1 in 75,000 births with no increased incidence based on sex or race.

✓ Genetics of methylmalonic acidemia

Approximately half of methylmalonic acidemia cases are caused by mutation the MUT gene. Many mutations in the MUT gene have been identified. Mutations prevent the production of or reduce the activity of methylmalonyl CoA mutase, resulting in impaired catabolism of fatty acids as well as some amino acids. This results in an accumulation of methylmalonyl CoA which causes the symptoms of methylmalonic acidemia.

Mutations that do not allow production of functional enzyme are designated mut⁰. Mutations that cause a change in the structure of the enzyme but allow it to remain partially functional are designated mut⁻, and this form is typically less severe and more clinically variable than the mut⁰ form. Both forms are referred to as “vitamin B12 non-responsive”.

✓ How do people inherit methylmalonic acidemia?

Methylmalonic acidemia is inherited in an autosomal recessive manner. Parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs or symptoms of the condition. Each pregnancy between carrier parents has a 25% chance of producing a child affected with MMA, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

✓ Treatment

Even with early diagnosis, mortality rates remain high. This is particularly true in vitamin B12 non-responsive methylmalonic acidemia. Affected individuals should follow a low-protein, high carbohydrate diet, which generally requires medical formulas and foods that restrict isoleucine, valine, threonine, and methionine. L-carnitine supplementation may be recommended. During periods of illness, children may need to be admitted for medical care to prevent a metabolic crisis. Combined liver and kidney transplantation may be curative in patients with MMA and renal insufficiency.

✓ Screening Methodology

Primary newborn screening for MMA utilizes tandem mass spectrometry to determine the propionylcarnitine (C3) level. Elevated propionylcarnitine, and occasionally methylmalonyl carnitine (C4DC), indicates the possibility of MMA. False positives and false negatives are possible with this screen.

✓ What to do After Receiving Presumptive Positive Methylmalonic Acidemia Screening Results

- 1) The clinician should immediately check on the clinical status of the baby.
- 2) Consultation with a metabolic specialist is essential.
- 3) The specialist may request urine organic acid analysis and other labs on baby.
- 4) Call KS Newborn Screening Program at 785-291-3363 with questions about results.
- 5) Report Clinical Findings to Newborn Screening Program at 785-291-3363.
- 6) Same birth siblings (twins, triplets) of infants diagnosed with MMA should be re-screened; additional testing of these siblings also may be indicated.

✓ Confirmation of Diagnosis

The diagnosis of methylmalonic acidemia is confirmed through organic acid analysis of urine or plasma revealing elevated methylmalonic acid. To establish the specific form of methylmalonic acidemia, additional studies must be done. These include vitamin B12 responsiveness, complementation analysis, C14 propionate tracer assay, and cobalamin distribution.

✓ Communication of Results to Parents

If a baby has a presumptive positive methylmalonic acidemia newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with MMA, the following points should be conveyed to parents:

- ***Parents should understand that treatment for methylmalonic acidemia will be lifelong.***
- ***Parents should understand that treatment is not curative and that all morbidity cannot necessarily be prevented. Long-term management, monitoring and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended and should include the following specialties: pediatrics, metabolic genetics and nutrition. Periodic blood and urine analysis is needed.***
- ***Genetic counseling services may be indicated. A list of counselors and geneticists, whose services are available in Kansas, should be given to the parents if they have not already seen a geneticist.***

For consultation, contact:

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