



Methylmalonic Acidemia (Cbl A,B) 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. Vitamin B12 responsive forms include Cobalamin A (CblA) and Cobalamin B (CblB) deficiencies.

✓ **Clinical Symptoms**

Most newborns do not have symptoms at birth. Symptoms generally occur during the first few months or years of life. Individuals will develop feeding problems, failure to thrive, developmental delay, and hypotonia. Some individuals will have protein aversion and infants are at an increased risk for a metabolic crisis.

✓ **Incidence**

MMA (Cbl A,B) occurs in less than 1 in 100,000 births with no increased incidence based on sex or race. Vitamin B12 responsive forms account for approximately half of the cases of MMA.

✓ **Genetics of methylmalonic acidemia**

Mutations in the MMAA or MMAB genes can cause methylmalonic acidemia. These genes produce cobalamin reductase and cobalamin adenosyltransferase. The MMAA protein is necessary for transportation of Cbl for use in adenosylcobalamin synthesis and the MMAB protein is an adenosyltransferase.

✓ **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. The recurrence risk for carrier parents is 25% with each pregnancy.

✓ **Treatment**

Immediate diagnosis and treatment of methylmalonic acidemia is critical to normal growth and development. 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. Liver and kidney transplantations are not curative, but may be beneficial. During periods of illness, children may need to be admitted for medical care to prevent a metabolic crisis.

✓ **Screening Methodology**

Primary newborn screening for MMA utilizes tandem mass spectrometry to determine the C3 levels. Elevated C3 (propionylcarnitine) indicates the possibility of MMA or Propionic acidemia. Additional testing is needed to distinguish them. False positive 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) Confirmatory labs should be performed with direction from the metabolic specialist.
- 3) Call KS Newborn Screening Program at 785-291-3363 with questions about results.
- 4) Report Clinical Findings to Newborn Screening Program at 785-291-3363.
- 5) 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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