



Multiple Carboxylase Deficiency Information for Health Professionals

Multiple carboxylase deficiency, or holocarboxylase synthetase deficiency, is an organic acid disorder caused by a reduction or lack of the enzyme holocarboxylase synthetase activity.

✓ Clinical Symptoms

Many individuals present with symptoms within hours of birth, and most will have symptoms by two years of age. Multiple carboxylase deficiency can cause episodes of metabolic crisis. Symptoms of a crisis include feeding difficulty, lethargy, behavior changes, hypotonia, and severe eczema. Laboratory findings include hypoglycemia, low platelets, ketoacidosis, metabolic acidosis, and mild hyperammonemia. If untreated, a metabolic crisis may lead to tachypnea, seizures, brain swelling, coma, and possibly death.

Even without experiencing a metabolic crisis, untreated children can develop skin rashes, alopecia, vision/hearing loss, failure to thrive, developmental delays, spasticity, ataxia, and seizures. Death usually occurs if untreated.

✓ Incidence

Multiple carboxylase deficiency occurs in less than 1 in 100,000 births with no increased incidence based on sex or race.

✓ Genetics of multiple carboxylase deficiency

Mutations in the HLCS gene cause multiple carboxylase deficiency. Mutations prevent the production of or reduce the activity of the enzyme holocarboxylase synthetase (HCS). Normally, this enzyme activates multiple carboxylases by attaching the B vitamin, biotin, to the carboxylases. Deficiency of these carboxylases impairs fat, carbohydrate and protein metabolism.

✓ How do people inherit multiple carboxylase deficiency?

Multiple carboxylase deficiency 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 and symptoms of the condition. Each pregnancy between carrier parents has a 25% chance of producing a child affected with multiple carboxylase deficiency, 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

Immediate diagnosis and treatment of multiple carboxylase deficiency is critical to normal growth and development. Treatment is usually effective if started early. Recommended treatment is daily supplementation of biotin. Biotin can prevent symptoms and may reverse some health problems.

✓ **Screening Methodology**

Primary newborn screening for multiple carboxylase deficiency utilizes tandem mass spectrometry. Elevated C5-OH (3-hydroxyisovaleryl carnitine) indicates the possibility of multiple carboxylase deficiency. False positive and false negative results are possible with this screen.

✓ **What to do After Receiving Presumptive Positive MCD 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 for the baby.
- 4) Call KS Newborn Screening Program at 785-291-3363 with questions about results.
- 5) Report clinical findings to the Newborn Screening Program at 785-291-3363.
- 6) Same birth siblings (twins, triplets) of infants diagnosed with MCD should be re-screened; additional testing of these siblings also may be indicated.

✓ **Confirmation of Diagnosis**

The diagnosis of multiple carboxylase deficiency is confirmed through urine organic acid analysis, plasma acylcarnitine analysis, and serum biotinidase assay.

✓ **Communication of Results to Parents**

If a baby has a presumptive positive multiple carboxylase deficiency 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 MCD, the following points should be conveyed to parents:

- ***Parents should understand that treatment for multiple carboxylase deficiency will be life long.***
- ***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 includes pediatrics and a metabolic specialist.***
- ***Genetic counseling 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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