Kansas
Department of Health and Environment

HMG-CoA Lyase Deficiency
Information for Health Professionals

3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG-CoA lyase deficiency) is an organic acid disorder.

✓ Clinical Symptoms

Symptoms begin in about 1/3 of patients during the neonatal period and the rest develop symptoms between 3 and 11 months. HMG-CoA lyase deficiency causes periods of metabolic crisis, which are generally triggered by illness or infection, high protein intake, or fasting. Metabolic crises cause lethargy, behavioral changes, hypotonia, fever, nausea, vomiting, diarrhea, hypoketotic hypoglycemia, metabolic acidosis, hyperammonia, hepatomegaly, and if untreated can lead to breathing problems, seizures, coma, and death. In approximately 20% of untreated patients, the first metabolic crisis causes death. Repeated episodes of metabolic crisis can lead to white matter changes, intellectual disabilities, and epilepsy. Possible long-term effects include: cardiomyopathy with arrhythmia, pancreatitis, nonprogressive deafness, retinitis pigmentosa, learning disabilities or intellectual disabilities.

✓ Incidence

This condition occurs in less than 1 in 100,000 births.

✓ Genetics of HMG-CoA lyase deficiency

Mutations in the HMGCL gene cause HMG-CoA lyase deficiency. Mutations in this gene reduce or eliminate the activity of the enzyme HMG-CoA lyase. This enzyme is necessary for processing leucine, as well as for producing ketones from fats.

✓ How do people inherit HMG-CoA lyase deficiency?

HMG-CoA lyase 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 HMG-CoA lyase deficiency, 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 HMG-CoA lyase deficiency is critical to normal growth, development, and survival. Individuals should follow a low-leucine, high carbohydrate diet, which generally requires medical foods and formulas, and should avoid fasting. L-carnitine supplementation may be recommended. During periods of illness, children may need to be admitted for medical care to prevent a metabolic crisis.

✓ Screening Methodology

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

✓ What to do After Receiving Presumptive Positive HMG-CoA Lyase Deficiency 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 analysis or plasma acylcarnitine analysis on the baby.**
4) **Call KS Newborn Screening Program at 785-291-3363 with questions about the results.**
5) **Report clinical findings to the Newborn Screening Program at 785-291-3363.**
6) **Same birth siblings (twins, triplets) of infants diagnosed with HMG-CoA lyase deficiency should be re-screened; additional testing of these siblings also may be indicated.**
7) **Consider testing older siblings of an affected individual. Some people may have no symptoms and may go undiagnosed.**

✓ Confirmation of Diagnosis

The diagnosis of HMG-CoA lyase deficiency is confirmed through urine organic acid analysis and plasma acylcarnitine analysis.

✓ Communication of Results to Parents

If a baby has a presumptive positive HMG-CoA lyase 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 the baby is diagnosed with HMG-CoA lyase deficiency, the following points should be conveyed to parents:

- ***Parents should understand that treatment for HMG-CoA lyase deficiency will be lifelong.***
- ***Parent should understand that treatment is not curative and that all health problems and 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 pediatrics, dieticians, and a metabolic disease specialist.***
- ***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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