



State of CT
Genetics Newborn Screening Program
Health Care Provider Fact Sheet

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency (HMG)

Introduction

This disorder not only is a defect in the catabolism of Leucine but also has an important role in ketone body metabolism. The possibility of 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency should be considered in neonates and infants presenting with symptoms resembling Reye syndrome, neurologic dysfunction (such as obtundation, combativeness, and/or posturing), tachypnea, vomiting, hypoglycemia, hyperammonemia, hepatomegaly, and elevated transaminases in blood but without ketosis. Nonketotic hypoglycemia, or hypoketotic hypoglycemia should be an immediate clinical indication to consider this disorder.

In the presence of catabolism or substantially reduced food intake (e.g. infection, severe exertion), the combination of an increased cellular requirement for energy and reduced glucose intake results in proteolysis with release of amino acids and fatty acids. Enhanced leucine and fatty acid degradation is an attempt by the body to produce the needed energy in the form of ketones. When 3-HMG-CoA lyase is deficient, the increased fluxes in both leucine degradation and fatty acid oxidation result in an accumulation of 3-hydroxymethylglutaryl-CoA. The accumulated substrate produces metabolic acidosis, inhibits gluconeogenesis resulting in hypoglycemia, and inhibits the urea cycle resulting in hyperammonemia.

About 1/3 present in neonatal period (2-5days) and about 2/3 present between 3 and 11 months. There are reports of asymptomatic individuals detected because of an affected sibling. Between episodes the children are typically normal on exam. Instances of dilated cardiomyopathy with arrhythmia, pancreatitis, nonprogressive deafness, and retinitis pigmentosa have been reported. These may be related to neurological damage from the hypoglycemia.

Diagnosis

Newborn screening—Tandem mass spectrometry: C5OH

Confirmation—a second sample may be requested or follow up testing will be done at the Metabolic Treatment Center at Yale or UCONN Genetics.

Situations that risk metabolic decompensation

Metabolic decompensation can be triggered by the catabolic processes that occur in the course of infections, after an immunization, increased physical activity, protein loading, or with a prolonged period of fasting.

Monitoring

Clinical observation is the most important tool for monitoring patients with HMG. They should be observed and assessed for neurological status, recurrent vomiting, refusal to eat, increased lethargy, apnea or seizures. In these situations, immediate evaluation in the emergency room is necessary. In situations of metabolic decompensation hypoglycemia can develop, but a normal blood glucose does not rule out metabolic instability and should never be a reason to delay therapy. It is

also important for the primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.

Treatment

- Leucine restriction combined with general protein restriction. Fat intake restriction and avoidance of fasting with a high carbohydrate diet. Carnitine supplementation has been used, but efficacy unknown.
- The Metabolic Treatment Center will set a patient's diet prescription that determines the optimum percentage of fat, carbohydrate, and protein.
- The parents should have an emergency protocol with them at all times. This protocol, provided by the Metabolic Treatment Center, contains basic information about the disorder, necessary diagnostic investigations and guidelines for treatment.
- Infants and children with HMG should have regularly scheduled visits at the Metabolic Treatment Center.

Illness

- Any illness can potentially lead to metabolic decompensation
- Prevention and/or early intervention is of particular importance
- Care should be coordinated by the Metabolic Treatment Center

Immunization

- Immunizations must be kept current.

Surgical/surgical procedures

- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- A surgical procedure constitutes a potentially catabolic situation and preoperative fasting should be avoided with 10% dextrose being started preoperatively and continuing postoperatively until the child is eating and drinking well. Any procedure requiring anesthesia should be done at a hospital with a metabolic service.

Growth and development

- It is crucial to closely monitor all growth parameters on a regular basis.
- In cases with neurological deficits, the child should be referred to an early intervention program and developmental progress closely monitored by both the metabolic team and the primary care provider.
- Intellectual prognosis depends on early diagnosis and treatment and, subsequently, on compliance with the dietary and supplement plan.



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