FACT SHEET
Healthcare Provider

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

Description:
This disorder not only is a defect in the catabolism of leucine but also has an important role in ketone body metabolism. About one-third of individuals with HMG present in the neonatal period (2-5 days), and about two-thirds of individuals with HMG present between 3 and 11 months of age. 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.

Incidence in General Population:
1:100,000 live births

Symptoms:
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 raise the possibility of 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 increases fluxes in both leucine degradation and fatty acid oxidation result in an accumulation of 3-hydroxymethlglutaryl-CoA. The accumulated substrate produces metabolic acidosis, inhibits gluconeogenesis resulting in hypoglycemia, and inhibits the urea cycle resulting in hyperammonemia.

Diagnosis:
Newborn screening abnormality—Tandem mass spectrometry: increased C5OH.
A second dried blood spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

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, dehydration, 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 normal blood glucose does not rule out metabolic instability and should not 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 its efficacy is unknown.
- The Metabolic Treatment Center will determine the patient's diet prescription that establishes the optimum percentage of fat, carbohydrate, and protein.
- The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and it should contain 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 are of particular importance.
- Care should be coordinated by the Metabolic Treatment Center.

Immunization:

- Immunizations must be kept current. Influenza vaccinations are also recommended.

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 should be 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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