

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

### Background

3-Hydroxy-3-Methylglutaryl-CoA (HMG-CoA) Lyase has a dual function in the breakdown of Leucine and in regulating production of ketone bodies. It is located predominantly in mitochondria, but is also found in peroxisomes. In the last step in Leucine metabolism, it cleaves 3-hydroxy-3-methylglutaryl-CoA, producing acetyl-CoA and acetoacetate, one of the ketone bodies. HMG-CoA Lyase Deficiency was first described in 1971 and more than 60 patients have subsequently been diagnosed.

### Clinical

HMG-CoA Lyase Deficiency typically presents within the first week of life, though some patients have onset later in the first year. The onset of symptoms is initiated by fasting, infection, dietary protein load, or simply the stress of birth. Symptoms progress from vomiting, lethargy, trachypnea and dehydration to coma and possibly death. Hepatomegaly and neurologic abnormalities are seen on physical exam. Laboratory studies reveal non-ketotic hypoglycemia, metabolic acidosis, hyperammonemia and elevated liver transaminases. Abnormal urine organic acids are present as well as the distinctive elevated plasma acylcarnitine species.

### Testing

Newborns can be screened for HMG-CoA Lyase Deficiency using tandem mass spectrometry analysis of a dried blood spot. The finding of elevated six-carbon dicarboxylic acylcarnitine (C6-DC) and C5-hydroxy acylcarnitine (C5-OH), suggests the metabolic defect. To make a diagnosis, further testing is required. Urine organic acid analysis of a patient with HMG-CoA Lyase Deficiency will reveal elevation of 3-hydroxy-3-methylglutaric, 3-methylglutaconic and 3-hydroxyisovaleric acids. A diagnosis should be confirmed by measurement of HMG-CoA Lyase enzyme activity in fibroblasts or leukocytes. Prenatal diagnosis is possible by measuring 3-hydroxy-3-methylglutaric acid in amniotic fluid and by assaying HMG-CoA Lyase enzyme activity in cultured amniocytes and chorionic villi cells. Mutations in the HMG-CoA Lyase gene on chromosome 1 have been identified in a number of patients and prenatal diagnosis can be accomplished using DNA analysis.

### Treatment

Acute symptoms of HMG-CoA Lyase Deficiency should be treated with IV glucose, bicarbonate for the metabolic acidosis and restriction of protein (Leucine). During an acute episode, patients may require assisted ventilation. For the long-term treatment, affected patients should avoid fasting and restrict protein intake.

Because the diagnosis and therapy of HMG-CoA Lyase Deficiency is complex, the pediatrician is advised to manage the patient in close collaboration with a consulting pediatric metabolic disease specialist. It is recommended that parents travel with a letter of treatment guidelines from the patient's physician.

### Inheritance

This disorder most often follows an autosomal recessive inheritance pattern. With recessive disorders affected patients usually have two copies of a disease gene (or mutation) in order to show symptoms. People with only one copy of the disease gene (called carriers) generally do not show signs or symptoms of the condition but can pass the disease gene to their children. When both parents are carriers of the disease gene for a particular disorder, there is a 25% chance with each pregnancy that they will have a child affected with the disorder.

## References

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