

**Disease Name:**

**HMG-CoA LYASE DEFICIENCY**

(HYDROXYMETHYLGLUTARIC ACIDURIA; 3-HYDROXY-3-METHYLGLUTARYL-CoA LYASE DEFICIENCY; HL DEFICIENCY; HYDROXYMETHYLGLUTARIC ACIDURIA)

**Classification:**

Defect of ketone metabolism- Disorder of the last step in branched chain (leucine) amino acid metabolism and ketogenesis

**Genetic Information:**

**Inheritance:**

Autosomal recessive

**Population Incidence:**

Unknown, rare

**Ethnic Incidence:**

Increased in Saudi Arabia- 16% of all organic acidurias

**Gene & Location:**

3-hydroxy-3-methylglutaryl-Coenzyme A lyase - 1p36.1-p35

**Common Mutation:**

R41Q and F305fs(-2) in Saudi Arabia  
G109T- some Southern European and Mediterranean populations

**OMIM #**

\*246450

**Disease Information:**

**Symptom Onset:**

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.

**Symptoms:**

Presentation with severe hypoketotic hypoglycemia, metabolic acidosis, hyperammonemia, vomiting, hepatomegaly and hypotonia. Unless recognized this may progress to coma and death in 20% of patients. The symptoms resemble Reye syndrome. Illness or fasting can precipitate an acute metabolic decompensation as can protein loading, decreased caloric intake and increased glucose needs. White matter changes, MR and epilepsy may occur following hypoglycemic episodes. Macrocephaly has been seen in some patients with severe neurological complications. 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. On pathology fatty deposits are seen in liver and in the brain, gliosis, spongiosis and increased glycogen in astrocytes.

**Physical Findings:**

Macrocephaly has been noted, as has short stature. Otherwise no particular dysmorphisms.

**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.

**Natural History without treatment:** White matter changes, MR and epilepsy may occur following hypoglycemic episodes. 20% mortality in unrecognized patients.

**Natural History with treatment:** If diagnosed early, treated patients may have normal development.

**Metabolic Information:**

**Missing Enzyme & Location:** 3-hydroxy-3-methylglutaryl CoA lyase normally cleaves 3-hydroxy-3-methylglutaryl CoA to acetoacetic acid and acetyl-CoA. The enzyme is located in mitochondria and peroxisomes of all tissues.

**MS/MS profile:** C5-OH (3-hydroxyisovaleryl carnitine)- elevated  
C6-DC (methylglutaryl carnitine)- elevated

**Prenatal testing:** Possible with enzyme assay and/or molecular analysis

**Miscellaneous Information:**

Prepared for the NW Regional Newborn Screening Program by Sara Copeland MD, Judith Tuerck RN MS and Lorinda Paradise at OHSU in Portland, OR.

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