

Disease Name	Hydroxymethylglutaric aciduria (3-OH 3-CH3 glutaric aciduria)
Alternate name(s)	Methylglutaric aciduria (3-hydroxy-3-methylglutaryl-CoA lyase deficiency)
Acronym	HMG - CoA lyase deficiency
Disease Classification	Organic Acid Disorder
Variants	No
Variant name	N/A
Symptom onset	Infancy (6 months to 2 years)
Symptoms	Persistent vomiting, lethargy, hypotonia, coma, seizures, apnea, hepatomegaly.
Natural history without treatment	Recurrent episodes of acute illness usually in response to fasting or to viral infection. Any episode can lead to death or developmental delay if severe enough.
Natural history with treatment	Normal IQ and development are possible. Severe hypoglycemic episodes may result in seizures and mental delays.
Treatment	Avoidance of fasting. Low fat, protein and high carbohydrate diet. Cornstarch supplementation. Carnitine supplementation. Intravenous glucose to treat hypoglycemia during crisis episodes.
Other	Crises consist of severe acidosis and hypoglycemia treated with IV glucose and bicarbonate administration.
Physical phenotype	Possible microcephaly
Inheritance	Autosomal recessive
General population incidence	Rare
Ethnic differences	No
Population	N/A
Ethnic incidence	N/A
Enzyme location	Liver, fibroblasts and leukocytes
Enzyme Function	Catalyzes the final step of leucine degradation and plays a role in ketone formation.
Missing Enzyme	HMG CoA lyase
Metabolite changes	3-hydroxy-3-methylglutaric acid in urine, increased levels of glutaric and adipic acids may be elevated in urine during crisis, notable absence of ketosis.
Prenatal testing	Prenatal testing has been accomplished by analysis of metabolites in maternal urine at 23 weeks. Enzyme is active in amniocytes and prenatal testing should be possible using this method.
MS/MS Profile	N/A
OMIM Link	http://www.ncbi.nlm.nih.gov/omim/231670
Genetests Link	www.genetests.org
Support Group	Organic Acidemia Association www.oaanews.org Save Babies through Screening Foundation www.savebabies.org Genetic Alliance www.geneticalliance.org

Newborn Screening ACT Sheet [Elevated C5-OH Acylcarnitine] Organic Acidemias

Differential Diagnosis: Most likely 3-methylcrotonyl-CoA carboxylase (3MCC) deficiency (infant or mother) | may be 3-hydroxy-3-methylglutaryl (HMG)-CoA lyase deficiency; β -ketothiolase deficiency | multiple carboxylase deficiency (MCD) including biotinidase deficiency and holocarboxylase synthetase deficiency, 2-methyl-3-hydroxybutyric acidemia (2M3HBA), 3-methylglutaconic aciduria (3MGA).

Condition Description: Each of the disorders is caused by a deficiency of the relevant enzyme. In most of the disorders, the substrate, for which the enzyme is named, accumulates as do its potentially toxic metabolites.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy).
- Consult with pediatric metabolic specialist.
- Evaluate the newborn (hypoglycemia, ketonuria, metabolic acidosis). If any of these parameters are abnormal or the infant is ill, initiate emergency treatment as indicated by metabolic specialist and transport IMMEDIATELY to tertiary center with metabolic specialist.
- Initiate timely confirmatory/diagnostic testing as recommended by specialist.
- Educate family about signs, symptoms and need for urgent treatment of metabolic acidosis (poor feeding, vomiting, lethargy).
- Report findings to newborn screening program.

Diagnostic Evaluation: Confirmatory tests include urine organic acids on infant and mother, plasma acylcarnitine analysis, and serum biotinidase assay. The organic acids analysis on infant and mother should clarify the differential except for holocarboxylase synthetase deficiency and biotinidase deficiency (the latter clarified by biotinidase assay).

Clinical Considerations: The neonate is usually asymptomatic in 3MCC deficiency. However, episodic hypoglycemia, lethargy, hypotonia, and mild developmental delay can occur at any time from the neonatal period through childhood for any of these disorders. There is beneficial treatment that is specific to each condition.

<u>Diagnosis</u>	<u>Emergency Treatment Protocol</u>	<u>Gene Reviews</u>	<u>Genetics Home Reference</u>
3-Methylcrotonyl-CoA carboxylase deficiency	X	-	X
Holocarboxylase synthetase deficiency	-	-	X
HMG-CoA lyase deficiency	X	-	X
2-Methyl-3-hydroxybutyric acidemia	-	-	-
β -Ketothiolase deficiency	-	-	X
3-Methylglutaconic aciduria type I	-	-	-
Biotinidase deficiency	-	X	X

Disclaimer: This guideline is designed primarily as an educational resource for clinicians to help them provide quality medical care. It should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. Adherence to this guideline does not necessarily ensure a successful medical outcome. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this guideline. Clinicians also are advised to take notice of the date this guideline was adopted, and to consider other medical and scientific information that become available after that date.

© American College of Medical Genetics, 2010 (Funded in part through MCHB/HRSA/HHS grant #U22MC03957)

