

<b>Disease Name</b>	<b>3-methylcrotonyl-CoA carboxylase deficiency</b>
<b>Alternate name(s)</b>	3-methylcrotonylglycinuria
<b>Acronym</b>	3-MCC
<b>Disease Classification</b>	Organic Acid Disorder
<b>Variants</b>	Late-onset form
<b>Variant name</b>	Late-onset 3-methylcrotonyl-CoA carboxylase deficiency
<b>Symptom onset</b>	Many individuals remain asymptomatic into adulthood. Others present in late infancy (generally after 3 months).
<b>Symptoms</b>	Infants can present with a Reye-like syndrome of ketoacidosis, hypoglycemia, hyperammonemia which can lead to seizures, coma and possibly death. Others present with failure to thrive, hypotonia or spasticity. Late-onset 3-MCC may present as developmental delay without Reye-like syndrome. Symptomatic adults often report general weakness and fatigue. Many individuals are asymptomatic.
<b>Natural history without treatment</b>	Primary manifestations appear to be muscular hypotonia and atrophy. Individuals with Reye-like illnesses may die or suffer neurologic insult during these episodes.
<b>Natural history with treatment</b>	Once over the initial crisis, most individuals have been intellectually normal. It is uncertain whether treatment modifies disease course.
<b>Treatment</b>	Protein restricted diet. Leucine-free medical foods. Possible carnitine supplementation. Giving treatment to asymptomatic individuals is of questionable value.
<b>Other</b>	Newborn screening has led to the diagnosis of asymptomatic women whose infants have transiently elevated isovaleryl carnitine.
<b>Physical phenotype</b>	None
<b>Inheritance</b>	Autosomal recessive
<b>General population incidence</b>	1:50,000
<b>Ethnic differences</b>	N/A
<b>Missing Enzyme</b>	3-methylcrotonyl-CoA carboxylase
<b>MS/MS Profile</b>	C5:1 (tigyl or 3-methylcrotonyl carnitine) elevated C5-OH (3-hydroxy-2-methylbutyryl carnitine) - elevated
<b>OMIM Link</b>	<a href="http://www.ncbi.nlm.nih.gov/omim/210200">http://www.ncbi.nlm.nih.gov/omim/210200</a>
<b>Gene tests Link</b>	<a href="http://www.genetests.org">www.genetests.org</a>
<b>Support Group</b>	Organic Acidemia Association <a href="http://www.oaanews.org">www.oaanews.org</a> Save Babies through Screening Foundation <a href="http://www.savebabies.org">www.savebabies.org</a> Genetic Alliance <a href="http://www.geneticalliance.org">www.geneticalliance.org</a>

## 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;  $\beta$ -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	-	-	-
$\beta$ -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.

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