Disease Name	**3-methylcrotonyl-CoA carboxylase deficiency**
Alternate name(s)	3-methylcrotonylglycinuria
Acronym	3-MCC
Disease Classification	Organic Acid Disorder
Variants	Late-onset form
Variant name	Late-onset 3-methylcrotonyl-CoA carboxylase deficiency
Symptom onset	Many individuals remain asymptomatic into adulthood. Others present in late infancy (generally after 3 months).
Symptoms	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.
Natural history without treatment	Primary manifestations appear to be muscular hypotonia and atrophy. Individuals with Reye-like illnesses may die or suffer neurologic insult during these episodes.
Natural history with treatment	Once over the initial crisis, most individuals have been intellectually normal. It is uncertain whether treatment modifies disease course.
Treatment	Protein restricted diet. Leucine-free medical foods. Possible carnitine supplementation. Giving treatment to asymptomatic individuals is of questionable value.
Other	Newborn screening has led to the diagnosis of asymptomatic women whose infants have transiently elevated isovalerylcarnitine.
Physical phenotype	None
Inheritance	Autosomal recessive
General population incidence	1:50,000
Ethnic differences	N/A
Missing Enzyme	3-methylcrotonyl-CoA carboxylase
MS/MS Profile	C5:1 (tigyl or 3-methylcrotonyl carnitine) elevated C5-OH (3-hydroxy-2-methylbutyryl carnitine) - elevated
OMIM Link	http://www.ncbi.nlm.nih.gov/omim/210200
Gene tests 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; **ß-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.

Diagnosis	Emergency Treatment Protocol	Gene Reviews	Genetics Home Reference
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-Methyglutaconic aciduria type I	-	-	-
Biotinidase deficiency	-	X	X