Disease Name	**Multiple Carboxylase Deficiency**
Alternate name(s)	Holocarboxylase Synthetase Deficiency; Neonatal Form) Holocarboxylase Deficiency
Acronym	MCD
Disease Classification	Organic Acid Disorder
Variants	Neonatal Form
Variant name	Multiple Carboxylase Deficiency, Neonatal Form
Symptom onset	Anytime from birth to 15 months of age.
Symptoms	Infants generally present with food refusal, vomiting, breathing problems, hypotonia, seizures, and lethargy. Severe metabolic/lactic acidosis, organic aciduria, mild hyperammonemia and variable hypoglycemia can lead to coma and death if not treated. Survivors can have neurological damage. Patients may have skin rash and alopecia at later stages.
Natural history without treatment	Repeated bouts of acidosis, skin rashes, failure to thrive, coma, developmental delay and death.
Natural history with treatment	Children with holocarboxylase synthetase deficiency, treated with biotin have normal growth and development. However, some only partly respond to therapy and one has been reported to be unresponsive to biotin therapy.
Treatment	Majority of cases respond readily to biotin supplementation. Biotin increases the functional activation of the carboxylase enzymes.
Physical phenotype	None
Inheritance	Autosomal recessive
General population incidence	1:87,000
Ethnic differences	No known population at increased risk
Missing Enzyme	Holocarboxylase synthetase (HS) attaches biotin to the four carboxylase enzymes (pyruvate carboxylase; priopionyl CoA carboxylase; beta-methylcrotonyl CoA carboxylase; acetyl CoA carboxylase) in order to activate them. Deficiency of HS results in functional deficiencies of all the carboxylase enzymes.
MS/MS Profile	C3 (propionyl carnitine) – elevated C5-OH (3-hydroxyisovaleryl carnitine) - elevated
OMIM Link	http://www.ncbi.nlm.nih.gov/omim/210200
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; **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