Disease Name — Beta-ketothiolase deficiency

Alternate name(s)	Alpha-methylacetoacetic aciduria, 2-methyl-3-hydroxybutyric academi, Mitochondrial acetoacetyl-CoA thiolase deficiency, MAT deficiency, T2 deficiency, 3-oxothiolase deficiency, 3-ketothiolase deficiency, 3-KTD deficiency
Acronym	BKT
Disease Classification	Organic Acid Disorder
Variants	No, but there is considerable clinical heterogeneity
Variant name	N/A
Symptom onset	Late infancy or childhood. Mean age at presentation is 15 months (range 3 days to 48 months). There are documented cases of asymptomatic patients with enzyme deficiency. Frequency of decompensation attacks falls with age and is uncommon after the age of 10.
Symptoms	Symptoms include intermittent episodes of severe metabolic acidosis and ketosis accompanied by vomiting (often hematemesis), diarrhea and coma that may progress to death. There is great clinical heterogeneity between patients. Infancy is the period of highest risk for decompensation. Death or neurologic complications can occur. Neurologic damage includes striatal necrosis of the basal ganglia, dystonia and/or mental delays. Other symptoms include cardiomyopathy, prolonged QT interval, neutropenia, thrombocytopenia, poor weight gain, renal failure and short stature. If neurologically intact, patients are normal between episodes.
Natural history without treatment	Clinical outcome varies widely with a few patients suffering severe psychomotor delays or death as a result of their initial attack and others with normal development and no episodes of acidosis.
Natural history with treatment	Despite severe recurrent attacks, appropriate supportive care can result in normal development.
Treatment	Avoidance of fasting. Bicarbonate therapy and intravenous glucose in acute crises. Possible protein restriction. Consider carnitine supplementation.
Physical phenotype	No dysmorphisms
Inheritance	Autosomal recessive
General population incidence	unknown
Ethnic differences	None known
Population	N/A
Ethnic incidence	N/A
Enzyme location	Converts 2-methylacetoacetyl-CoA to propionyl-CoA and acetyl-CoA.
Enzyme Function	Catalyzes the decarboxylation of oxoacids.
Missing Enzyme	Mitochondrial acetoacetyl-CoA thiolase enzyme
Metabolite changes	Increased urinary excretion of 2-methyl-3-hydroxybutyric acid, 2-methylacetoacetic acid, tiglylglycine, 2-butanone, and ketone bodies (acetoacetic acid, 3-hydroxybutyric acid).
Prenatal testing	Enzyme analysis in amniocytes or CVS tissue. If mutations have been identified, DNA testing is possible.
MS/MS Profile	C5:1 tiglycarnitine – elevated
OMIM Link	www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=203750
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

4-26-2010 Update

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

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