Beta ketothiolase deficiency

Other Names: Mitochondrial acetoacetyl-CoA thiolase deficiency, 3-ketothiolase deficiency, 3-oxothiolase deficiency

Beta ketothiolase deficiency is a rare genetic condition characterized by the body’s inability to break down a certain amino acid called isoleucine. It is caused by mutations in the ACAT1 gene that makes an enzyme called mitochondrial acetyl-CoA acetyltransferase.

Characteristics of Beta ketothiolase deficiency

Beta ketothiolase deficiency (BKD) is an inherited metabolic disorder in which the body is unable to metabolize (i.e., break down and use) certain proteins and fats properly. As a result, other compounds can build up in blood, urine, and tissues. Too much of these compounds can be harmful to the body and cause health problems. People with BKD have difficulty breaking down an amino acid called isoleucine.

Signs and symptoms of BKD usually appear between the ages of 6 months and 2 years, and they can range from mild to life-threatening. Metabolic acidosis (too much acid in body fluids) is common because the body produces too much or cannot get rid of acid. Recurrent episodes of ketosis (i.e., too many ketones, or byproducts from the breakdown of fats, in the body) is also commonly seen. Finding ketones in the blood or urine is a sign that the body is using fat for energy because the blood glucose level is low. During these episodes of metabolic acidosis and ketosis, individuals with BKD may have vomiting, weak muscle tone (hypotonia), excessive tiredness (lethargy), and dehydration. Seizures or coma may also occur. It is very important that individuals with BKD get access to treatment. Failure to do so can lead to coma and sometimes, death. In general, the earlier the individual is diagnosed and treated, the better the outcomes.

Diagnosis/Testing

Most individuals with BKD have changes or mutations in the ACAT1 gene. This gene makes the mitochondrial acetyl-CoA acetyltransferase enzyme that is responsible for breaking down the amino acid called isoleucine. Mutations in the ACAT1 gene cause this enzyme to not be made or to not be made properly. This results in many of the health problems seen in individuals with BKD.

Many babies with BKD are diagnosed early in life through newborn screening (NBS). NBS tests a spot of blood from the baby’s heel, and looks to see if the mitochondrial acetyl-CoA acetyltransferase enzyme is working properly. NBS test results are confirmed with additional blood and urine chemical tests, and possibly genetic testing of the BKD gene.

Management/Surveillance

Individuals with BKD are typically managed by a team of specialty providers that can include: geneticists, genetic counselors, primary care doctors, nutritionists, and social workers. The amino acid isoleucine is found in many of the foods we eat, usually in what we would call “protein-rich foods.” This also includes breast milk and infant formulas. This means it is very important for individuals with BKD to follow a customized low-protein diet. This diet usually includes a medical formula specially made to provide all amino acids except for isoleucine to ensure good nutrition. Specific medications and vitamin supplements (i.e. L-carnitine) are also often prescribed.

It is recommended that an emergency treatment plan, often documented by an “Emergency Letter” is created to ensure
that during times of illness or other metabolic stress, a child with BKD will be assessed for signs and symptoms of a metabolic crisis (e.g., poor feeding, vomiting, lethargy, excessive sleepiness, irritability) and given appropriate medical attention. It is of upmost importance that individuals with BKD adhere to their specific diet and treatment plans to avoid metabolic stress and/or crisis.

**Mode of inheritance**

BKD is inherited in an autosomal recessive pattern. This means that an individual has to inherit two ACTA1 mutations (i.e., one from each parent) to be affected with BKD. If both parents are carriers of an ACAT1 mutation, they have a 1 in 4 (25%) chance with each pregnancy of having a child with BKD. Babies born in the United States are screened for BKD by newborn screening.

**Risk to family members**

Parents of a child with BKD are carriers of BKD. If a sibling of a child with BKD is unaffected, he/she has a 2 in 3 (66%) chance of being a carrier of BKD.

**Special considerations**

None

**Resources**

Baby’s First Test
http://www.babysfirsttest.org/newborn-screening/conditions/beta-ketothiolase-deficiency

Genetics Home Reference: Beta-ketothiolase deficiency

Ketone Utilization Disorder: A Guide for Parents (PacNoRGG publication)
http://www.westernstatesgenetics.org/pacnorgg/PDFs_all-081409/ketone_util_eng.pdf

Organic Acidemia Association
http://www.oaanews.org

STAR-G Newborn Screening
http://www.newbornscreening.info/Parents/organicaciddisorders/BKD.html#1

**References**

Fukao, T. et al. (2001). The Clinical Phenotype and Outcome of Mitochondrial Acetoacetyl-CoA Thiolase Deficiency (B-Ketothiolase or T2 Deficiency) in 26 Enzymatically Proved and Mutation Defined Patients.” Molecular Genetics and Metabolism 72(2): 109-114.


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Created by: Aditi Shankar, BA, Seema Jamal, MSc, LCGC
Edited by: Karin M. Dent, MS, LCGC