Published on *My46* (https://www.my46.org) 01/20/2022

My46 Trait Profile

3-methylcrotonyl-CoA carboxylase deficiency

Other Names: Biotin-resistant 3-methylcrotonyl Co-A carboxylase deficiency, 3-MCC, Methylcrotonylglycinuria

3-methylcrotonyl-CoA carboxylase deficiency is a rare genetic condition characterized by the body's inability to break down a certain amino acid called leucine. It is caused by mutations in either the MCCC1 or the MCCC2 gene that make parts of the enzyme called 3-methylcrotonyl-CoA carboxylase.

Characteristics of 3-methylcrotonyl-CoA carboxylase deficiency

3-methylcrotonyl-CoA carboxylase deficiency (3-MCC deficiency) is a rare inherited metabolic disorder in which the body is unable to metabolize (i.e., break down and use) certain proteins and fats properly. This is because it is not producing enough of an enzyme called 3-methylcrotonyl coenzyme A carboxylase which helps break down an amino acid called leucine. When leucine cannot be broken down, 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.

Signs and symptoms of 3-MCC deficiency usually appear in infancy or early childhood and can range from mild to life-threatening. However, some individuals may not have symptoms until adulthood or may never develop symptoms. 3-MCC deficiency causes episodes of what is called metabolic crises. These episodes may be triggered by an infection or a diet that's very high in protein. During an episode, individuals with 3-MCC deficiency may have vomiting, weak muscle tone (hypotonia), and excessive tiredness (lethargy). Seizures or coma may also occur. It is very important that individuals with 3-MCC deficiency 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 3-MCC deficiency have changes or mutations in the MCCC1 or MCCC2 genes. These genes make parts of the 3-methylcrotonyl-CoA carboxylase enzyme that is responsible for breaking down leucine. Mutations in these genes cause the enzyme to not be made or to not be made properly. This results in many of the health problems seen in individuals with 3-MCC deficiency.

Many babies with 3-MCC deficiency 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 3-methylcrotonyl-CoA carboxylase enzyme is working properly. NBS test results are confirmed with additional blood and urine chemical tests, and possibly genetic testing of the MCCC1 and MCCC2 genes.

Management/Surveillance

Individuals with 3-MCC deficiency 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 leucine 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 3-MCC deficiency to follow a customized low-protein diet. This diet usually includes a medical formula specially made to provide all amino acids except for leucine to ensure good nutrition. Specific medications and vitamin supplements (i.e. L-carnitine) are also often prescribed. In rare cases of 3-MCC deficiency, biotin supplements may be recommended. However, the vast majority of individuals with 3-MCC deficiency are not responsive to biotin.

It is recommended that an emergency treatment plan, often documented by an "Emergency Letter" is made to ensure that during times of illness or other metabolic stress, a child with 3-MCC deficiency 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 3-MCC deficiency adhere to their specific diet and treatment plans to avoid metabolic stress and/or crisis.

Mode of inheritance

3-MCC deficiency is inherited in an autosomal recessive pattern. This means that an individual has to inherit two gene mutations (i.e., one from each parent) to be affected with 3-MCC deficiency. If both parents are carriers of a mutation, they have a 1 in 4 (25%) chance with each pregnancy of having a child with 3-MCC deficiency. Babies born in the United States are screened for 3-MCC deficiency by newborn screening.

Risk to family members

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

Special considerations

None

Resources

Baby's First Test: 3-Methylcrotonyl-CoA carboxylase deficiency
http://www.babysfirsttest.org/newborn-screening/conditions/3-methylcrotonyl-coa-carboxylase-deficiency
Genetics Home Reference: 3-methylcrotonyl-CoA carboxylase deficiency
http://ghr.nlm.nih.gov/condition/3-methylcrotonyl-coa-carboxylase-deficiency
Medical Home Portal: 3MCC deficiency
http://www.medicalhomeportal.org/newborn/3mcc-deficiency
Organic Acidemia Association
http://www.oaanews.org
STAR-G Newborn Screening
http://www.newbornscreening.info/Parents/organicaciddisorders/3MCC.html

References

Baumgartner, MR. et al. (2001).The molecular basis of human 3-methylcrotonyl-CoA carboxylase deficiency." Journal of Clinical Investigation 107(4): 495-504.
Baumgartner, MR. et al. (2004).Isolated 3-methylcrotonyl-CoA carboxylase deficiency: evidence for an allele-specific dominant negative effect and responsiveness to biotin therapy." American Journal of Human Genetics 75(5): 790-800.
Nguyen, KV. et al. (2011).Novel mutations in the human MCCA and MCCB gene causing methylcrotonylglycinuria." Molecular Genetics and Metabolism 102(2): 218-21.
Seashore MR. (Updated 22 December 2009). The Organic Acidemias. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.ncbi.nlm.nih.gov/books/NBK1134/. Accessed [04/18/2014].

Created: 04/2014 **Created by:** Aditi Shankar, BA, Karin M. Dent, MS, LCGC
Updated: mm/yyyy **Edited by:** Seema Jamal, MSc, LCGC