Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency

Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency is a rare condition that prevents the body from converting certain fats to energy, particularly during periods without food (fasting).

Signs and symptoms of LCHAD deficiency typically appear during infancy or early childhood and can include feeding difficulties, lack of energy (lethargy), low blood sugar (hypoglycemia), weak muscle tone (hypotonia), liver problems, and abnormalities in the light-sensitive tissue at the back of the eye (retina). Later in childhood, people with this condition may experience muscle pain, breakdown of muscle tissue, and a loss of sensation in their arms and legs (peripheral neuropathy). Individuals with LCHAD deficiency are also at risk for serious heart problems, breathing difficulties, coma, and sudden death.

Problems related to LCHAD deficiency can be triggered when the body is under stress, for example during periods of fasting, illnesses such as viral infections, or weather extremes. This disorder is sometimes mistaken for Reye syndrome, a severe disorder that may develop in children while they appear to be recovering from viral infections such as chicken pox or flu. Most cases of Reye syndrome are associated with the use of aspirin during these viral infections.

Frequency

The incidence of LCHAD deficiency is unknown. One estimate, based on a Finnish population, indicates that 1 in 62,000 pregnancies is affected by this disorder. In the United States, the incidence is probably much lower.

Genetic Changes

Mutations in the *HADHA* gene cause LCHAD deficiency. The *HADHA* gene provides instructions for making part of an enzyme complex called mitochondrial trifunctional protein. This enzyme complex functions in mitochondria, the energy-producing centers within cells. As the name suggests, mitochondrial trifunctional protein contains three enzymes that each perform a different function. This enzyme complex is required to break down (metabolize) a group of fats called long-chain fatty acids. Long-chain fatty acids are found in foods such as milk and certain oils. These fatty acids are stored in the body's fat tissues. Fatty acids are a major source of energy for the heart and muscles. During periods of fasting, fatty acids are also an important energy source for the liver and other tissues.

Mutations in the *HADHA* gene that cause LCHAD deficiency disrupt one of the functions of this enzyme complex. These mutations prevent the normal processing of long-chain fatty acids from food and body fat. As a result, these fatty acids are not

converted to energy, which can lead to some features of this disorder, such as lethargy and hypoglycemia. Long-chain fatty acids or partially metabolized fatty acids may also build up and damage the liver, heart, muscles, and retina. This abnormal buildup causes the other signs and symptoms of LCHAD deficiency.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- 3-hydroxyacyl-CoA dehydrogenase, long chain, deficiency
- LCHAD deficiency
- long-chain 3-hydroxy acyl CoA dehydrogenase deficiency
- long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency
- long-chain 3-OH acyl-CoA dehydrogenase deficiency
- trifunctional protein deficiency, type 1

Diagnosis & Management

Formal Diagnostic Criteria

- ACT Sheet: Elevated C16-OH +/- C18:1-OH and Other Long Chain Acylcarnitines https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/C16-OH.pdf

Formal Treatment/Management Guidelines

- New England Consortium of Metabolic Programs: Acute Illness Protocol http://newenglandconsortium.org/protocols/acute_illness/fatty-acid-oxidation-disorders/LCHADD.pdf

Genetic Testing

- Genetic Testing Registry: Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency https://www.ncbi.nlm.nih.gov/gtr/conditions/CN074230/

Other Diagnosis and Management Resources

- Baby's First Test
  http://www.babysfirsttest.org/newborn-screening/conditions/long-chain-l-3-hydroxyacyl-coa-dehydrogenase-deficiency
- MedlinePlus Encyclopedia: Hypoglycemia
  https://medlineplus.gov/ency/article/000386.htm
- MedlinePlus Encyclopedia: Peripheral Neuropathy
  https://medlineplus.gov/ency/article/000593.htm

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Hypoglycemia
  https://medlineplus.gov/ency/article/000386.htm
- Encyclopedia: Peripheral Neuropathy
  https://medlineplus.gov/ency/article/000593.htm
- Health Topic: Lipid Metabolism Disorders
  https://medlineplus.gov/lipidmetabolismdisorders.html
- Health Topic: Newborn Screening
  https://medlineplus.gov/newbornscreening.html

Genetic and Rare Diseases Information Center

- LCHAD deficiency
  https://rarediseases.info.nih.gov/diseases/6867/lchad-deficiency

Educational Resources

- Disease InfoSearch: LCHAD deficiency
  http://www.diseaseinfosearch.org/LCHAD+deficiency/4126
- Illinois Department of Public Health
  http://www.idph.state.il.us/HealthWellness/fs/mcad.htm
- MalaCards: long-chain 3-hydroxyacyl-coa dehydrogenase deficiency
  http://www.malacards.org/card/long_chain
  _3_hydroxyacyl_coa_dehydrogenase_deficiency
- Merck Manual Professional Version
  https://www.merckmanuals.com/professional/pediatrics/inherited-disorders-of-metabolism/beta-oxidation-cycle-disorders#v25254053
- New England Consortium of Metabolic Programs
  http://newenglandconsortium.org/for-families/other-metabolic-disorders/fatty-acid-oxidation-disorders/lchadd/
- Orphanet: Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=5
- Screening, Technology, and Research in Genetics
  http://www.newbornscreening.info/Parents/fattyaciddisorders/LCHADD.html
- Virginia Department of Health
  http://www.vdh.virginia.gov/content/uploads/sites/33/2016/11/Parent-Fact-Sheet_LCHAD_English.pdf

Patient Support and Advocacy Resources

- Children Living with Inherited Metabolic Diseases (CLIMB)
  http://www.climb.org.uk
- Children's Mitochondrial Disease Network (UK)
  http://www.cmdn.org.uk/
- FOD (Fatty Oxidation Disorders) Family Support Group
  http://www.fodsupport.org/lchad.htm
- United Mitochondrial Disease Foundation
  http://www.umdf.org/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28long-chain+3-hydroxyacyl-CoA+dehydrogenase+deficiency%5BTIAB%5D%29+OR+%28LCHAD%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

OMIM

- LONG-CHAIN 3-HYDROXYACYL-CoA DEHYDROGENASE DEFICIENCY
  http://omim.org/entry/609016

Sources for This Summary

- Angdisen J, Moore VD, Cline JM, Payne RM, Ibdah JA. Mitochondrial trifunctional protein defects: molecular basis and novel therapeutic approaches. Curr Drug Targets Immune Endocr Metabol Disord. 2005 Mar;5(1):27-40. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15777202
- Fahnehjelm KT, Holmström G, Ying L, Haglind CB, Nordenström A, Halldin M, Alm J, Nemeth A, von Döbeln U. Ocular characteristics in 10 children with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency: a cross-sectional study with long-term follow-up. Acta Ophthalmol. 2008 May;86(3):329-37. Epub 2007 Dec 19. Erratum in: Acta Ophthalmol. 2008 Jun;86(4):466.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18162058
- Gillingham MB, Purnell JQ, Jordan J, Stadler D, Haqq AM, Harding CO. Effects of higher dietary protein intake on energy balance and metabolic control in children with long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD) or trifunctional protein (TFP) deficiency. Mol Genet Metab. 2007 Jan; 90(1):64-9. Epub 2006 Sep 22.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16996288
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2813195/
- Oey NA, den Boer ME, Wijburg FA, Vekemans M, Augé J, Steiner C, Wanders RJ, Waterham HR, Ruiter JP, Attié-Bitach T. Long-chain fatty acid oxidation during early human development. Pediatr Res. 2005 Jun;57(6):755-9. Epub 2005 Apr 21.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15845636
- Rinaldo P, Matern D, Bennett MJ. Fatty acid oxidation disorders. Annu Rev Physiol. 2002;64: 477-502. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11826276
- Sims HF, Brackett JC, Powell CK, Treem WR, Hale DE, Bennett MJ, Gibson B, Shapiro S, Strauss AW. The molecular basis of pediatric long chain 3-hydroxyacyl-CoA dehydrogenase deficiency associated with maternal acute fatty liver of pregnancy. Proc Natl Acad Sci U S A. 1995 Jan 31; 92(3):841-5.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/7846063
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC42716/
- Spiekerkoetter U, Lindner M, Santer R, Grotzke M, Baumgartner MR, Boehles H, Das A, Haase C, Hennermann JB, Karall D, de Klerk H, Knerr I, Koch HG, Plecko B, Röschinger W, Schwab KO, Scheible D, Wijburg FA, Zschocke J, Mayatepek E, Wendel U. Management and outcome in 75 individuals with long-chain fatty acid oxidation defects: results from a workshop. J Inherit Metab Dis. 2009 Aug;32(4):488-97. doi: 10.1007/s10545-009-1125-9. Epub 2009 Apr 29.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19399638
- Tyni T, Paetau A, Strauss AW, Middleton B, Kivelä T. Mitochondrial fatty acid beta-oxidation in the human eye and brain: implications for the retinopathy of long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. Pediatr Res. 2004 Nov;56(5):744-50. Epub 2004 Sep 3.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15347768

- Tyni T, Pihko H. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. Acta Paediatr. 1999 Mar;88(3):237-45. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/10229030
- den Boer ME, Wanders RJ, Morris AA, IJlst L, Heymans HS, Wijburg FA. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency: clinical presentation and follow-up of 50 patients. Pediatrics. 2002 Jan;109(1):99-104.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11773547

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/long-chain-3-hydroxyacyl-coa-dehydrogenase-deficiency

Reviewed: May 2017
Published: July 17, 2018

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services