Mitochondrial Trifunctional Protein Deficiency

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Mitochondrial trifunctional protein deficiency is a rare condition that prevents the body from converting certain fats to energy, particularly during periods without food (fasting).

Keywords: genetic conditions

1. Introduction

Signs and symptoms of mitochondrial trifunctional protein deficiency may begin during infancy or later in life. Features that occur during infancy include feeding difficulties, lack of energy (lethargy), low blood sugar (hypoglycemia), weak muscle tone (hypotonia), and liver problems. Infants with this disorder are also at high risk for serious heart problems, breathing difficulties, coma, and sudden death. Signs and symptoms of mitochondrial trifunctional protein deficiency that may begin after infancy include hypotonia, muscle pain, a breakdown of muscle tissue, and a loss of sensation in the extremities (peripheral neuropathy).

Problems related to mitochondrial trifunctional protein deficiency can be triggered by periods of fasting or by illnesses such as viral infections. 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.

2. Frequency

Mitochondrial trifunctional protein deficiency is a rare disorder; its incidence is unknown.

3. Causes

Mutations in the *HADHA* and *HADHB* genes cause mitochondrial trifunctional protein deficiency. These genes each provide 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* or *HADHB* genes that cause mitochondrial trifunctional protein deficiency disrupt all three functions of this enzyme complex. Without enough of this enzyme complex, long-chain fatty acids from food and body fat cannot be metabolized and processed. 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, and muscles. This abnormal buildup causes the other signs and symptoms of mitochondrial trifunctional protein deficiency.

3.1. The Genes Associated with Mitochondrial Trifunctional Protein Deficiency

- HADHA
- HADHB

4. Inheritance

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.

5. Other Names for This Condition

- MTP deficiency
- TFP deficiency
- TPA deficiency
- trifunctional protein deficiency, type 2

References

1. Angdisen J, Moore VD, Cline JM, Payne RM, Ibdah JA. Mitochondrialtrifunctional protein defects: molecular basis and novel therapeutic approaches. Curr Drug Targets Immune Endocr Metabol Disord. 2005 Mar;5(1):27-40. Review.
2. Bo R, Yamada K, Kobayashi H, Jamiyan P, Hasegawa Y, Taketani T, Fukuda S, HataI, Niida Y, Shigematsu Y, Iijima K, Yamaguchi S. Clinical and molecularinvestigation of 14 Japanese patients with complete TFP deficiency: a comparison with Caucasian cases. J Hum Genet. 2017 Sep;62(9):809-814. doi:10.1038/jhg.2017.52.
3. Boutron A, Acquaviva C, Vianey-Saban C, de Lonlay P, de Baulny HO, Guffon N,Dobbelaere D, Feillet F, Labarthe F, Lamireau D, Cano A, de Villemeur TB, MunnichA, Saudubray JM, Rabier D, Rigal O, Brivet M. Comprehensive cDNA study andquantitative analysis of mutant HADHA and HADHB transcripts in a French cohort of52 patients with mitochondrial trifunctional protein deficiency. Mol Genet Metab.2011 Aug;103(4):341-8. doi: 10.1016/j.ymgme.2011.04.006.
4. Choi JH, Yoon HR, Kim GH, Park SJ, Shin YL, Yoo HW. Identification of novelmutations of the HADHA and HADHB genes in patients with mitochondrialtrifunctional protein deficiency. Int J Mol Med. 2007 Jan;19(1):81-7.
5. den Boer ME, Dionisi-Vici C, Chakrapani A, van Thuijl AO, Wanders RJ, Wijburg FA. Mitochondrial trifunctional protein deficiency: a severe fatty acid oxidationdisorder with cardiac and neurologic involvement. J Pediatr. 2003Jun;142(6):684-9.
6. Gillingham MB, Purnell JQ, Jordan J, Stadler D, Haqq AM, Harding CO. Effectsof higher dietary protein intake on energy balance and metabolic control inchildren with long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD) ortrifunctional protein (TFP) deficiency. Mol Genet Metab. 2007 Jan;90(1):64-9.
7. 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 duringearly human development. Pediatr Res. 2005 Jun;57(6):755-9.
8. Sperk A, Mueller M, Spiekerkoetter U. Outcome in six patients withmitochondrial trifunctional protein disorders identified by newborn screening.Mol Genet Metab. 2010 Oct-Nov;101(2-3):205-7. doi: 10.1016/j.ymgme.2010.07.003.
9. Spiekerkoetter U, Khuchua Z, Yue Z, Bennett MJ, Strauss AW. Generalmitochondrial trifunctional protein (TFP) deficiency as a result of either alpha-or beta-subunit mutations exhibits similar phenotypes because mutations in eithersubunit alter TFP complex expression and subunit turnover. Pediatr Res. 2004Feb;55(2):190-6.
10. 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.
11. Spiekerkoetter U, Mueller M, Cloppenburg E, Motz R, Mayatepek E, Bueltmann B, Korenke C. Intrauterine cardiomyopathy and cardiac mitochondrial proliferation inmitochondrial trifunctional protein (TFP) deficiency. Mol Genet Metab. 2008Aug;94(4):428-30. doi: 10.1016/j.ymgme.2008.04.002.
12. Spiekerkoetter U, Sun B, Khuchua Z, Bennett MJ, Strauss AW. Molecular andphenotypic heterogeneity in mitochondrial trifunctional protein deficiency due tobeta-subunit mutations. Hum Mutat. 2003 Jun;21(6):598-607.
13. Spierkerkoetter U, Khuchua Z, Yue Z, Strauss AW. The early-onset phenotype of mitochondrial trifunctional protein deficiency: a lethal disorder with multipletissue involvement. J Inherit Metab Dis. 2004;27(2):294-6.