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My46 Trait Profile

Trifunctional protein deficiency

Other Names: mitochondrial trifunctional protein deficiency

Trifunctional protein deficiency is a genetic condition in which the body cannot break down long chain fats for energy. It is caused by mutations in the HADHA and HADHB genes that make three enzymes in the trifunctional protein complex.

Characteristics of Trifunctional protein deficiency

Trifunctional protein (TFP) deficiency is a genetic condition in which the body cannot break down long chain fatty acids for energy. As a result, these long-chain fatty acids build up in the body. The accumulation of long-chain fatty acids can be harmful to the body and cause health problems. Importantly, an individual with TFP deficiency is also lacking an important energy source, as fatty acids are usually broken down to produce energy for the body.

There are many enzymes responsible for breaking down fatty acids in the body. The trifunctional protein enzyme complex contains three separate enzymes, including 2,3 long chain enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and 3-ketoacyl-CoA thiolase (LKAT). People can have changes in the gene that causes only the LCHAD enzyme to not work properly (LCHAD deficiency) or they can have changes in the gene that makes the entire TFP complex not work properly (TFP deficiency).

The most common presentation of TFP deficiency includes the onset of skeletal myopathy (muscle pain and weakness) and peripheral neuropathy (damage to the nerves carrying information back and forth to the brain) with no hypoglycemia (low blood sugar) or cardiomyopathy (heart dysfunction). The skeletal myopathy is often episodic, meaning it comes and goes and may be induced with exercise or exposure to cold temperatures. These symptoms may begin within the first 5 years of life, but most commonly appear in the second decade of life. TFP deficiency may also present in the newborn period with heart problems. Infants may have heart failure, sudden death from heart arrhythmias, or difficulty breathing. They may also have hypoglycemia without production of ketones (byproducts from the breakdown of fats).

Pregnant women carrying a baby affected with TFP deficiency may also have symptoms of the condition, though it does not always occur. The symptoms include maternal liver disease during the third trimester of pregnancy. These conditions are dangerous for the mother and baby and, in some cases, may lead to maternal death and/or premature delivery of the baby.

Diagnosis/Testing

Most individuals with TFP deficiency have changes or mutations in the HADHA or HADHB gene. These genes make the enzymes in the TFP enzyme complex that are responsible for breaking down long chain fatty acids. Mutations in this gene causing all three enzymes to not be made, or not be made properly, result in many of the health problems seen in individuals with TFP deficiency.

Many babies with TFP 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 there is a buildup of long chain fatty acids in the body, which suggests the enzymes in the TFP complex are not working properly. NBS test results are confirmed with additional blood or urine chemical tests. Testing of the HADHA and HADHB genes is required to distinguish TFP deficiency from isolated LCHAD deficiency.

Management/Surveillance

Individuals with TFP deficiency are usually followed by a doctor and dietitian specializing in metabolic diseases. Management of TFP deficiency focuses on decreasing the buildup of long-chain fatty acids and providing another source of energy for the body, especially during exercise and illness. Long-chain fatty acids come from food, standard infant formula, and breast milk. Individuals with TFP deficiency are placed on strict low fat diets, as they cannot break down the fats from regular foods. Some long chain fats are essential, meaning that our bodies need them to function properly. Oftentimes, individuals with TFP deficiency have to take essential fatty acid supplements. Blood tests are done regularly to test the amount of long chain fatty acids and essential fatty acids in the body. Individuals with TFP deficiency also often require supplementation with medium chain triglycerides (MCT). MCTs bypass the missing or dysfunctional enzymes and can be broken down for energy. MCTs are found in special infant formulas, supplemental oil, emulsion, and/or powder.

It is important for individuals with TFP deficiency to not go too long without eating (fasting). The body likes to use fatty acids, which are stored in the body, as a source of energy during fasting. This is especially true during illness. Illness increases the body's energy demands and often decreases our appetite. Individuals with TFP deficiency cannot use the fatty acids stored in the body for energy. Therefore, without a source of energy from food, they are at risk of low blood sugar and even coma or death. These individuals, especially children, often have to go to the emergency room to receive intravenous (IV) dextrose (sugar) during illness. Individuals should be given an emergency protocol letter that details the treatment that should be started.

Mode of inheritance

TFP deficiency is inherited in an autosomal recessive pattern. This means that an individual has to inherit two mutations (i.e. one from each parent) to be affected with TFP deficiency. If both parents are carriers of TFP deficiency, they have a 1 in 4 (25%) chance with each pregnancy of having a child with TFP deficiency.

Risk to family members

Parents of a child with TFP deficiency are carriers of TFP deficiency. Carriers of TFP deficiency do not show any signs of the condition. If a sibling of a child with TFP deficiency is unaffected, he/she has a 2 in 3 (66%) chance of being a carrier of TFP deficiency.

Special considerations

None

Resources

Medical Home Portal: LCHADD/TFP Deficiency
http://www.medicalhomeportal.org/diagnoses-and-conditions/lchadd-tfp-deficiency/description
Fatty Oxidation Disorders Family Support Group
http://www.fodsupport.org/lchad.htm
Genetics Home Reference: Mitochondrial trifunctional protein deficiency
http://ghr.nlm.nih.gov/condition/mitochondrial-trifunctional-protein-deficiency

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LCGC

Edited by: Seema Jamal, MSc, LCGC