TFP / LCHAD: Mitochondrial Trifunctional Protein Deficiency / Long-Chain 3-Hydroxyacyl-CoA dehydrogenase Deficiency

Mitochondrial trifunctional protein deficiency, also known as TFP deficiency, and long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, also known as LCHAD deficiency, are two related types of genetic conditions categorized as a fatty acid oxidation disorders (also known as a FAODs). The body usually gets its energy by breaking down, or burning, fats and sugars. People with FAODs cannot properly break down certain types of fats. For those with TFP and/or LCHAD deficiency the enzymes that are needed to break down long-chain fats are unable to function properly. This prevents the body from creating needed energy during times of stress, illness, fasting, and exercise, which can lead to medical symptoms.

TFP is a protein complex with three separate enzymes that work together to break down long-chain fats. The LCHAD enzyme is the second enzyme in the TFP protein complex and is altered in LCHAD deficiency. TFP typically creates a deficiency in all three enzymes. When someone has a deficiency in the TFP protein complex, very little energy is created from long-chain fats.

Alternative Names

- TFP
- TFP deficiency
- LCHAD Deficiency
- Long-Chain 3-hydroxyacyl-CoA Dehydrogenase Deficiency

Cause and Genetics

TFP/LCHAD deficiency is caused by genetic changes in one of two genes: HADHa or HADHb. These genes both provide instructions for the body to make TFP. Most genetic changes in the gene HADHa cause problems with LCHAD function. Changes in the gene HADHb usually affect all three enzymatic functions of the TFP.

People usually have two copies of both of these genes, one inherited from each parent. TFP deficiency occurs when there are changes in both copies of either HADHa or HADHb (autosomal recessive inheritance). Someone who has a change in only one copy of either of these genes is called a carrier, and they usually do not have any medical symptoms. If both parents are carriers, there is a 1 in 4 chance with each pregnancy that their child will have TFP/LCHAD deficiency. Both males and females can have TFP deficiency/LCHAD deficiency.

Frequency

TFP deficiency is considered a rare condition and the exact number of affected individuals is not known. The number of people affected with LCHAD deficiency is also unknown, but may be more common in people from Finland. Newborn screening has confirmed an estimated incidence of 1.2/100,000.[1]

[1] *(Rücklová, Kristina et al. "Impact of Newborn Screening and Early Dietary Management on Clinical Outcome of Patients with Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency and Medium Chain Acyl-CoA Dehydrogenase Deficiency-A Retrospective Nationwide Study." Nutrients vol. 13,9 2925. 24 Aug. 2021.)*

Signs and Symptoms

People with TFP/LCHAD deficiency can have a wide range of signs and symptoms. Whether your child was diagnosed via newborn screening may also affect when, if, and how these symptoms present. Always check with your doctor if your child is doing something out of "their" normal, as every child may present with symptoms a little differently. Signs and symptoms may include:

- Extreme tiredness (lethargy) or acting "sluggish"
- Irritability
- Poor feeding
- Enlarged, weakened heart (cardiomyopathy)
- Abnormal heart rhythm (arrhythmia)
- Liver malfunctions that can become life-threatening
- Specific type of vision loss (pigmentary retinopathy)
- Low blood sugar (hypoglycemia)
- Nerve damage in the legs and hands (peripheral neuropathy)
- Low muscle tone (hypotonia)
- Muscle weakness (myopathy)
- Muscle breakdown (rhabdomyolysis)
- Reddish-brown urine (myoglobinuria)

The potential for muscle breakdown (rhabdomyolysis), is increased by illness, stress, cold/heat and exercise, and should be treated promptly.

Medical treatment should be sought immediately if there is loss of consciousness or severe confusion (decompensation), as these are signs of dangerously low blood sugar.

These signs and symptoms may vary depending on age, treatment, and if in crisis. With proper treatment some of these symptoms may be attenuated/controlled in patients between episodes of crisis.

Diagnosis

Most cases of TFP/LCHAD deficiency are identified by routine newborn screening. If newborn screening is suggestive of TFP/LCHAD deficiency, additional tests may be performed including:

- Measuring biochemical markers in the blood or urine
- Measuring enzyme activity in skin cells or white blood cells
- Performing a genetic test to look for changes in genes that can cause FAODs

Some people with milder cases of TFP deficiency are not diagnosed until adolescence. These individuals often present with:

- Repeated episodes of severe muscle pain
- Muscle breakdown, especially after heavy exercise (rhabdomyolysis)
- Reddish-brown urine (myoglobinuria)

In some cases, a diagnosis of TFP/LCHAD deficiency can be made before birth. If there is a family history of TFP/LCHAD deficiency, or if parents are known carriers, prenatal testing can be performed on amniotic fluid (the fluid surrounding a baby) or chorionic villi (a specific part of the placenta).

Some pregnant mothers will experience a life threatening syndrome called HELLP syndrome during pregnancy. This may include high blood pressure, abnormal liver functions, and decreased blood clotting.

Treatment and Management

Before beginning any treatment or therapy, please consult with your physician.

Treatment and management of TFP/LCHAD deficiency may include:

- Specialized medical formulas
- Regular eating schedules to prevent low blood sugar (hypoglycemia)
- Continuous feeding directly into the stomach in severe cases, especially at night
- Low-fat, high-carbohydrate diet (some dieticians may also increase protein)
- Medicine called triheptanoin (Dojolvi)
- MCT supplementation
- Intravenous (IV) sugar-containing fluids called D10 during metabolic crisis
- Supplementation with docosahexaenoic acid (DHA) to help prevent vision damage to part of the eye called the retina (retinopathy)

Parents should call their health care provider immediately if babies show symptoms like excessive sleepiness, vomiting, diarrhea, a fever, poor appetite, or an infection. Medical treatment should be sought immediately if there is loss of consciousness or severe confusion (decompensation), as these are signs of dangerously low blood sugar.

Patients should discuss the appropriate preparation for anesthesia with their metabolic team.
All patients should have an emergency protocol letter, written and signed by their doctor, that details their prescribed treatment during crisis and in emergency room settings, to manage severe episodes.

Clinical Trials

For specific details on other clinical trials, visit the MitoAction Clinical Trials page or www.clinicaltrials.gov.

Resources

- The National Institutes of Health: Mitochondrial trifunctional protein deficiency - About the Disease
- The INFORM Network: MTP/LCHAD Deficiency | Fatty Acid Oxidation Disorders Diagnosis
- Baby's First Test: Newborn screening information for trifunctional protein deficiency | Baby's First Test

Connecting with others who are impacted by a rare disease allows for important information to be shared about day-to day life, prevents isolation, and gives hope. Please contact MitoAction for peer support opportunities at 888-MITO-411 or email mito411@mitoaction.org. Other resources we recommend are:

- New Patient Kit for FAODs
- Planning and Preparation
- Monthly Expert Series
- Energy in Action Podcast

MitoAction does not provide medical advice, diagnosis, treatment, or legal advice. It is essential that all those living with or caring for someone with a Mitochondrial or FAOD disease have an emergency protocol letter. These letters, which are written and signed by a doctor, share details about prescribed treatment during crises and in emergency room settings. Always check with your doctor if you or your child has concerns as everyone may present with symptoms differently. Before beginning any treatment or therapy, please consult with your physician.