

Trifunctional Protein And Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency

Mitochondrial trifunctional protein (MTP) deficiency and long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency are two related inherited disorders of fat metabolism. Their loss makes the body unable to generate enough energy during stress, illness and fasting. When the body has exhausted its stores of available sugars, it turns to fats to make energy. In each cell in the body, there are mitochondria, sac-like units that specialize in efficiently extracting energy from fats. MTP is a protein complex that is made up of two different types of protein. The assembled protein performs the last three enzymatic steps in mitochondrial β -oxidation of fats. The second of those three steps are the LCHAD activity and its loss is the most common of the MTP defects. LCHAD only acts on fatty acid intermediates called 3-hydroxyacyl-CoAs that are more than 8 carbons long ([240](#)). Without this activity, essentially no energy can be obtained from a fat molecule because MTP is required for the very first round of energy generation.

Signs and symptoms

Typically, infants with any form of MTP dysfunction will be sluggish (lethargic), feed poorly, be irritable and have poor muscle tone. Depending on which protein activities they have lost, patients with low MTP function can present with either of two patterns of systemic involvement. Those with loss of all three protein activities present primarily with symptoms of heart malfunction (cardiomyopathy), muscle breakdown (myopathy), and low blood sugar (hypoglycemia). Poor nerve function in the legs and hands (peripheral neuropathy) and reddish brown urine (myoglobinuria) can also occur ([284-288](#)). In contrast, the second more common group, deficient only in LCHAD activity, has liver malfunction (hepatocellular disease), low blood sugar (hypoglycemia) and a specific type of vision loss (pigmentary retinopathy) ([289](#), [290](#)). The liver dysfunction can become severe or life-threatening, causing blockage of bile outflow (cholestasis) and replacement of liver cells by scar tissue (fibrosis) ([291](#)). A few patients have symptoms that overlap between these two groups. LCHAD deficiency has also been found in patients originally believed to have recurrent Reye syndrome or in sudden infant death (SID) ([290](#)). Some milder cases of MTP deficiency do not appear until adolescence. Their main symptoms are repeated episodes of severe skeletal muscle pain from muscle breakdown (rhabdomyolysis), especially after vigorous exercise. The muscle loss is followed clinically as increased creatine kinase in the blood and a reddish brown breakdown product in the urine (myoglobinuria) ([284](#)).

The LCHAD defect in a fetus can also cause life threatening disease in its own mother. In this case, the stress from carrying a fetus that accumulates fats can cause the mother to have a

syndrome called HELLP (red blood cell breakdown (**hemolysis**), elevated liver enzymes, and low numbers of blood coagulation cells (**platelets**)) (292). HELLP syndrome is especially associated with the common LCHAD gene defect (see below).

Diagnosis

Today, MTP or LCHAD defects are usually identified by newborn screening of a blood spot taken before the infant leaves the birthing facility. The blood spots are promptly analyzed by tandem mass spectrometry for accumulation of specific fat products called acylcarnitines. Infants with LCHAD and MTP nearly always have increased amounts of all types of 16- and 18-carbon 3-hydroxyacylcarnitines in blood (266). The positive newborn test is then repeated to make certain it was correct, and the physician is notified to contact the parents as soon as possible. If urinary organic acids are analyzed, they often show increased 6- to 14-carbon 3-hydroxydicarboxylic acids. Unfortunately, because these same abnormalities have been reported in urine from patients with other defects, organic acid results from urine are not sufficient. For final diagnosis, usually cells, either skin cells (fibroblasts) or white blood cells from blood or, for prenatal diagnosis, amniocytes are tested for functional (enzyme) activity. Alternately, gene testing will also yield a final diagnosis and is especially useful where there is an identified mutation or, where symptoms point to LCHAD with its common defect (mutation).

For mothers potentially suffering from HELLP syndrome, LCHAD diagnosis of the fetus can be made during pregnancy by enzyme measurement of either cells obtained from the amniotic fluid or during chorionic villus sampling (CVS). With amniocentesis, a sample of fluid that surrounds the developing fetus is removed and analyzed, while CVS involves the removal of tissue samples from a portion of the placenta (the sack in the uterus that holds and feeds the fetus). If the mutations in a previously affected family member are known, direct mutation testing of prenatal samples is possible and more specific.

Genetics

[MTP deficiency](#) occurs when an individual inherits from each parent one change (mutation) in one of the two genes (HADHa or HADHb) whose products associate to make MTP (autosomal recessive). (256, 257). Multiple disease-causing mutations have been identified and most are located in HADHa (298, 299). Within the group of MTP patients, the majority with HADHa defects have a specific gene mutation called G1528C that interferes with only the second fat reduction step, named LCHAD. Among patients with isolated LCHAD deficiency, this mutation is inherited from both parents (homozygosity) in 65% and from one parent (heterozygosity) in the remaining 35% of those of European extraction (300). Defects in the b subunit (protein product of HADHb) usually interferes with the stability of the entire MTP protein, resulting in reduction of all three of the fat breakdown enzymatic steps (MTP deficiency) (286, 301, 302). Rarely, certain HADHa defects can also cause reduction in all three enzyme activities.

Parents of patients are carriers of the disease and have no symptoms. With each pregnancy, the parents have a 25% risk (1 in 4) chance to have another child with the same MTP or LCHAD deficiency. Genetic counseling will be of benefit for affected individuals, as well as their families. All siblings of the first identified patient should be tested for MTP or LCHAD defects,

in case a diagnosis was missed. In addition, the family should be asked whether any their children have had sudden infant death (SID), which can be caused by previously unrecognized MTP or LCHAD deficiency.

Standard therapies

The management and treatment of MTP and LCHAD deficiency are focused primarily on preventing and controlling acute episodes of low blood sugar (hypoglycemia). Preventive measures include avoiding fasting and using a very low-fat, high-carbohydrate diet, with frequent feeding (i.e. to keep periods of fasting to a minimum). Fasting in the first year of life can increase from 4 to 8 hours and should be limited to less than 10 hours after the age of 2 years. In some cases, continuous intragastric feeding with a tube may be necessary to avoid hypoglycemia, especially overnight. Additionally, your doctor may recommend special nutritional supplements such as medium-chain triglycerides (e.g., MCT oil). They may also advise carnitine (Carnitor) supplements. ([293-295](#)).

Medical treatment should be sought immediately if there is loss of consciousness or severe confusion (decompensation). If hospitalized for an acute episode, treatment requires the prompt administration of high volume intravenous glucose (10% dextrose) containing appropriate bodily salts and additional supportive measures as required. An emergency regimen should be available for each patient to use when they cannot tolerate their prescribed diet.

Other treatments that have been used include supplementation with docosahexaenoic acid, a polyunsaturated 22-carbon acid. It slows but does not stop or improve the retinopathy seen in LCHAD deficiency ([294](#)), but it does not alter the progression of neuropathy in complete TFP deficiency. A high protein diet and supplementation with MCT oil just prior to exercise may be beneficial ([296](#), [297](#)).

Investigational therapies

A clinical trial is currently being conducted on treatment of MTP and LCHAD with triheptanoin (UX007, Ultragenyx Pharmaceuticals), an artificial fat that is substituted for MCT oil in the diet. Published phase 2 studies indicate fewer episodes of low blood sugar and of muscle breakdown (rhabdomyolysis) and hospitalizations in patients treated with triheptanoin. Heart function may also be improved ([256](#), [257](#)).