



UPMC/CHILDREN'S HOSPITAL OF PITTSBURGH
INFORM / DEPARTMENT OF GENETICS
4401 PENN AVE, PITTSBURGH PA 15224

International Network for Fatty Acid Oxidation Research and Management

Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD)

A rare inherited disorder of fat metabolism that makes the body unable to generate energy during stress, illness and fasting. When the body has exhausted its stores of available sugars, it must turn to fats to make energy. In each cell in the body, this breakdown of fats takes place in a special sac-like bodies called mitochondria. Inside mitochondria energy is generated efficiently from the breakdown of fats, as well as from some protein components (in a process known overall as mitochondrial β -oxidation). In VLCADD, the first committed step in the breakdown of fats is missing or reduced. Today in the United States, the majority of VLCADD patients are identified right after birth because of the expanded newborn screening program. For most infants in the United States, a blood spot for VLCADD testing is obtained from the infant's heel before they go home from the birthing facility. VLCADD affected individuals may also be identified later in life, either because they were either not screened or not screened properly at birth or because they have a milder form of the deficiency that did not show up until later.

Signs & Symptoms

VLCADD can present at any age from birth to adolescence and occasionally presents in early adulthood. The disorder varies from mild to life threatening and is associated with different symptoms in the same patient as they age. In the severe infantile presentation, children have life threatening low blood sugar (hypoglycemia) which may result in a coma within days or weeks after birth. Blood ammonia may also be high. From ages two or three months to about two years, affected infants are at risk for many serious heart associated problems including a weakened heart muscle (cardiomyopathy), abnormal heart rhythms, and even total failure of the combined lung and heart function. Overall infants may look tired and listless (lethargy), be irritable, and the liver may be noticeably enlarged (hepatomegaly) when they are sick. During later childhood and early adulthood, low blood sugar episodes associated with life threatening comas and cardiac episodes become less common. Instead patients start to have periodic attacks of severe muscle pain caused by skeletal muscle breakdown (rhabdomyolysis) with their urine showing a brownish red color (myoglobinuria). This muscle loss may occur chronically at low levels but is increased by illness, stress, cold/heat or exercise. Unchecked severe rhabdomyolysis is serious and must be treated promptly. The mildest patients typically only show symptoms for the first time as severe muscle pain (rhabdomyolysis) after a severe illness or intense exercise using during adolescence or young adulthood.

Patients with VLCADD and similar diseases that interfere with the breakdown of fats all have a distinct form of low blood sugar called hypoketotic hypoglycemia. When healthy people fast or expend excessive calories in exercise, they burn fat to maximize calorie efficiency. At the end of

the β -oxidation of fat, some of its products are turned into protective molecules called ketones that provide energy for the brain. In disorders like VLCADD, few ketones are found in the blood or urine after stress because formation of ketones requires a component that comes from the β -oxidation of fats. Since VLCADD patients cannot even begin to oxidize fat, their hypoglycemia comes without ketones (hypoketotic hypoglycemia), a paired finding that is unique to fatty acid β -oxidation disorders.

In between acute episodes, some individuals with VLCADD deficiency may be well, but others may have poor muscle tone (hypotonia) and/or chronic cardiomyopathy. Cardiomyopathy leads to weakening in the force of heart contractions, decreased efficiency in the circulation of blood through the lungs and to the rest of the body (heart failure), and various associated symptoms that may depend upon the nature and severity of the condition, patient age, and other factors. Abnormalities of heart rhythm can occur at any age and may be life threatening.

Diagnosis

VLCADD may be suspected when after a thorough clinical evaluation, the sick child or adult has characteristic findings (e.g., hypoketotic hypoglycemia, severe skeletal muscle weakness, heart enlargement). Next, clinical studies of blood and urine by tandem mass spectrometry (acylcarnitine analysis) and GC-mass spectrometry (organic acid analysis), respectively, are done to differentiate VLCADD from other fatty acid defects with similar presentations. Specifically, VLCADD has a characteristic pattern that includes increases in several fatty acid species called acylcarnitines in the blood and several organic acid species in the urine. The specific diagnosis will be confirmed by genetic testing for mutations or by measurement of VLCAD activity in blood or skin cells.

Prenatal diagnosis is available by VLCAD 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

Genetics

[VLCAD deficiency](#) occurs when an individual inherits one change (mutation) in the gene for VLCAD (*ACADVL*) from each parent (autosomal recessive). The incidence of VLCADD in the general population is ~1:40,000 births and it can usually be identified by newborn screening in babies before they get sick. 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 VLCAD deficiency. In addition, pregnant women have an increased risk for pregnancy complications if they are carrying an affected baby (HELLP syndrome). Genetic counseling will also be of benefit for affected individuals, as well as their families. Existing and subsequent siblings of the index case should be tested for VLCAD, in case a diagnosis was missed. In addition, the family should be asked whether there have been episodes of sudden infant death (SID), which can be caused by previously unrecognized VLCADD. Initially, VLCAD deficiency

was mistakenly called LCAD deficiency, but all previously published cases of LCAD deficiency were, in fact, VLCAD deficiency.

Treatment

The management and treatment of VLCADD 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) and/or riboflavin (Vitamin B2) supplements. Those with the milder disease forms may find that limiting exercise and cold/heat exposure and avoiding fasting will be sufficient to control the symptoms.

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 needed. An emergency regimen should be available or each patient to use when they cannot tolerate their prescribed diet.

Investigational Therapies

A clinical trial is currently being conducted on treatment of VLCADD 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.

Bezafibrate is an experimental medication originally developed to lower blood cholesterol. It has coincidentally been shown to increase the amount of VLCAD protein in cells. Limited clinical studies using bezafibrate to treat VLCAD deficiency have been published, but no active clinical trials are in progress. However, Reneo Pharmaceuticals has developed a similar but more powerful potential drug that will soon be evaluated in clinical trials for VLCADD in the US.

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

References

[Click here](#) for a list of references in the scientific literature

[Ask an FAOD expert a question](#) about VLCADD. Please note that specific questions about your individual child's medical problems cannot be answered.