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

CACT Deficiency

Carnitine acylcarnitine translocase deficiency (CACT) is a rare inherited disorder that occurs when the protein that transfers fats into sac-like bodies called mitochondria is defective. Mitochondria are the site within cells where energy from fat is generated very efficiently. When the body has exhausted its stores of available sugars, it must turn to fats to produce energy. This change in energy source is particularly important during stress, illness and fasting and intense exercise. The entry of fats into mitochondria is highly regulated at the point where they cross the inner membrane of the mitochondria. In order to cross, free fats, known as fatty acids, are first linked to a molecule called carnitine. This fatty acylcarnitine next crosses the inner mitochondrial membrane to the inside of the mitochondria via a carnitine translocase protein (CACT). In the third step, using a protein called carnitine palmitoyltransferase 2 (CPT2), the carnitine molecule is detached and a replaced with coenzyme A. Then, the fatty acid can be broken down to generate energy.

Although few cases of CACT deficiency have been identified, at this point its presentation and diagnosis have paralleled that of the more abundant CPT2 defect. Similarly, its management parallels that of CPT2.

Signs and symptoms

CACT is a very rare disorder and the majority of those diagnosed have had the severe presentation with little or no active protein. It is possible that milder forms of the disease will be identified in the future. When stressed, infants with limited CACT may look listless (lethargy) and be irritable and be difficult to wake. They may have episodes of life threatening low blood sugar (hypoglycemia) which may lead to a coma or seizures within days or weeks after birth. Blood ammonia may also be high, and the liver may be noticeably enlarged (hepatomegaly), especially when they are sick. 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.,

Patients with severe CACT and similar diseases that interfere with the breakdown of fats have repeated episodes where they have a distinct form of low blood sugar called hypoketotic hypoglycemia. When healthy people fast or burn excessive calories in exercise, they burn fat to

maximize calorie efficiency and to save glucose. At the end of this fat oxidation, some of its products are turned into protective molecules called ketones that provide energy for the brain. Since CACT patients have a limited ability to break down any fats, they lack the basic ingredients to make these ketones (thus are hypoketotic). This lack of ketones adds to the risk of damage to their brains from hypoglycemia.

Diagnosis

Next, clinical studies of blood and urine by tandem mass spectrometry (acylcarnitine analysis) and GC-mass spectrometry (organic acid analysis), respectively, will differentiate the patients with defective CACT or CPT2 from other fatty acid defects with similar signs and symptoms. Specifically, CACT and CPT2 deficiency have a characteristic blood pattern that includes increases in long chain fatty acids (16-18-carbon) that are complexed to carnitine (acylcarnitines) and low free carnitine levels. Organic acids are usually normal. Because both CACT and CPT2 have the same laboratory and symptom profile, the CACT defects can only be validated by showing reduced CACT activity in blood or skin cells or by positive genetic testing for CACT mutations. Fortunately, the treatments for CACT and CPT2 defects are identical, so that as soon as the newborn screening results are verified, treatment can begin, hopefully minimizing damage from the defect.

Genetics

CACT deficiency occurs when an individual inherits one change (mutation) in the gene for CACT (SLC25A20) from each parent (autosomal recessive). Although CACT deficiency is very rare, there is a specific mutation in Asian populations (). 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 CACT deficiency. Genetic counseling will also be of benefit for affected individuals, as well as their families. Subsequent siblings of the index case should be tested for CACT defects, in addition, the family should be asked whether there have been episodes of sudden infant death (SID), which can be caused by previously unrecognized CACT.

Treatments

Because the treatment for both CACT and CPT2 is the same, treatment can begin as soon as the characteristic abnormality in acylcarnitines and carnitine are identified. Prevention of fasting is the mainstay of chronic therapy in CACT deficiency. 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 the severe form, continuous feeding of carbohydrates directly into the stomach (intragastric) may be required to prevent low blood sugar. For most patients, time between feedings can increase as the child grows older. Additionally, your doctor may recommend special nutritional supplements such as medium-chain triglycerides (e.g., MCT oil). Carnitine (Carnitor) supplementation does not usually improve severe disease but will be considered when free carnitine is extremely low, and the patient has some CACT protein activity.

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. Home blood glucose monitoring is not useful because symptomatic illness can begin before hypoglycemia has occurred. At the medical facility, the hypoketotic hypoglycemia of CACT will be treated with intravenous glucose-containing fluids, usually at a rate of at least 8-10 mg/kg/min of glucose. The elevated blood ammonia usually reverses with correction of the low blood sugar. If it is not corrected, dialysis can be added to reduce the ammonia level.

Investigational Therapies

A Phase 3 clinical trial is currently being conducted on treatment of CACT 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 CACT protein in cells (Van.. Brain Dev 2014). However, Reneo Pharmaceuticals has developed a similar but more powerful potential drug that will soon be evaluated in clinical trials for CACT 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 your questions about CACT. Please note that specific questions about your individual child's medical problems cannot be answered.