International Network for Fatty Acid Oxidation Research and Management

CPT2 Deficiency

Carnitine palmitoyl transferase 2 deficiency (CPT2) is a rare inherited disorder that occurs when the last step in the entry of fats into sac-like bodies called mitochondria is blocked. 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, must be linked to a molecule called carnitine. This fatty acylcarnitine next crosses the inner mitochondrial membrane via a carnitine translocase protein. In the last step of this transit, CPT2 returns this fatty acylcarnitine to its original fatty acyl-coenzyme A form that can enter the pathways to generate energy (fatty acid oxidation).

Signs and symptoms

Mild CPT2 deficiency is the most common fatty acid oxidation defect. Patients usually present in adolescence or early adulthood with brownish red urine (myoglobinuria) and muscle weakness or pain after prolonged exercise or other physical stress. During acute episodes, they will have elevated blood levels of creatine kinase (CPK), a marker for muscle injury (rhabdomyolysis) but they rarely will have low blood sugar (hypoglycemia).

More rarely, CPT2 defects occur in a severe newborn form. Overall, infants may look tired and listless (lethargy), be irritable, and not eat well. Affected children have life threatening low blood

sugar (hypoglycemia) which may result in a coma or seizures within days or weeks after birth. Blood ammonia may also be high and their 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 problems including a weakened heart muscle (cardiomyopathy), abnormal heart rhythms, and even total failure of the combined lung and heart function.

Patients with severe CPT2 and similar diseases that interfere with the breakdown of fats have 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 CPT2 patients have a limited ability to break down any fats, they lack the basic ingredients to make these ketones (thus are hypoketotic). Consequently, they are at a greater risk for brain damage when they are hypoglycemic.

Diagnosis

CPT2 may be suspected when after a thorough clinical evaluation, the sick child has characteristic findings (e.g., hypoketotic hypoglycemia, severe skeletal muscle weakness, heart enlargement). If the suspected patient is an older child or young adult, findings characteristic of muscle breakdown such as myoglobinuria, elevated CPK, and severe skeletal muscle pain will be validated. Next, clinical studies of blood and urine by tandem mass spectrometry (acylcarnitine analysis) and GC-mass spectrometry (organic acid analysis), respectively, differentiate CPT2 and its associated translocase defect from other fatty acid defects with similar characteristics. Specifically, CPT2 deficiency has a characteristic blood pattern that

includes increases in long chain fatty acids (16-18-carbon), as well as their long chain dicarboxylic acids, all complexed to carnitine (acylcarnitines) and free carnitine levels are low. Organic acids are usually normal. Unfortunately, this laboratory profile is identical to that of the carnitine translocase (CACT) deficiency. To differentiate the two, the specific diagnosis must be confirmed by genetic testing for CPT2 mutations or by measurement of CPT2 activity in blood or skin cells. For mild CPT2 deficiency, there is a common CPT2 mutation that can be used as a mutation analysis starting point. Patients with the common mild CPT2 deficiency can have a normal fatty acid carnitine pattern on newborn screening (222) if they are not stressed. Fortunately, the medical treatments of CACT and CPT2 defects are identical. Consequently, as soon as the newborn screening results are verified, treatment can begin, minimizing damage from the defect.

Prenatal diagnosis is available by CPT2 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

CPT2 deficiency occurs when an individual inherits one change (mutation) in the gene for CPT2 from each parent (autosomal recessive). Parents of patients are carriers of the disease, but have no symptoms. With each pregnancy, the parents have a 25% risk (1 in 4) chance to have another child with CPT2 deficiency. Genetic counseling will benefit affected individuals, as well as their families. Existing and subsequent siblings of the index case should be tested for CPT2 defects. For example, with the mild form of the disease, the children may not have been

symptomatic during newborn screening or older children may not have been screened. With the severe form in particular, the family should be asked whether there have been episodes of sudden infant death (SID) or unexplained infant deaths, which may have been caused by previously unrecognized CPT2.

Treatments

Prevention of fasting is the mainstay of chronic therapy in CPT2 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 CPT2 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 CPT2 will be treated with high dose 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 clinical trial is currently being conducted on treatment of CPT2 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 CPT2 protein in cells from mildly affected patients (Yao, 2011). Limited clinical studies using benzafibrate to treat CPT2 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 CPT2 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.

.