



International Network for Fatty Acid Oxidation Research and Management

CPT1a deficiency

The breakdown of fats to provide energy occurs in segregated membrane-bound compartments of the cell known as mitochondria. Carnitine palmitoyltransferase Ia (CPT1a) is a protein that is the first in a three protein unit that transfers fats across the inside mitochondrial membrane. It functions as a sentry at the outside entrance to mitochondria in certain tissues, especially the liver, where it regulates the amount of fat can enter the mitochondria to produce needed energy. Inside the cell, when fats are transported, they are attached to a molecule called coenzyme A. Fats can only cross the inner mitochondrial membrane if that coenzyme A group on the fatty acid is exchanged for a carnitine. If CPT1a is lost or reduced or if it functions poorly, the fatty acid stays in its coenzyme A form and cannot be picked up by the associated transport protein to cross the inner mitochondrial membrane. Shorter chain fatty acids containing 10 or fewer carbons can enter mitochondria without interacting with CPT1a. Unfortunately, these fatty acids are rare and provide much less energy than a typical long chain fatty acid. Most cases of CPT1a deficiency in the United States are identified during newborn screening of bloodspots taken in the first couple of days of life.

Signs and symptoms

The severe forms of CPT1a deficiency usually show up early in infancy and are episodic, usually appearing when an infant is stressed by fasting or illness. The most common symptom is low blood sugar (hypoglycemia) with low levels of fat-based energy preservation products known as ketones (hypoketotic) and may progress to coma and seizures. The build-up of

unused fats in tissues can cause poor liver function and enlargement (hepatomegaly) and eventually failure of other organs. During acute episodes, infants may have high blood ammonia levels (hyperammonemia) and elevated creatine phosphokinase (CPK).

Many children with milder CPT1a defects have been identified by newborn screening as noted above. Some with mild defects may never become symptomatic. CPT1a deficiency differs in presentation from all other fat oxidation defects in that patients have no skeletal muscle involvement because a different protein performs this function in skeletal muscles.

Diagnosis

To make the clinical diagnosis, blood is analyzed by tandem mass spectrometry (acylcarnitine analysis) and urine by gas-chromatography mass spectrometry to differentiate CPT1a from other fatty acid defects with similar symptoms. Because these children cannot bind the fatty acid to carnitine, they will have normal to high levels of free carnitine with low levels of most fatty acid-carnitine complexes, when compared to normal children of the same age. Their urine organic acids will not show anything abnormal except for the absence of ketones. CPT1a defects are more difficult to diagnose by tandem mass spectrometry than some other fat oxidation disorders. For this reason, CPT1a activity assays in cells (fibroblasts, leukocytes from blood) or tissues are essential here. Some of those inheriting the milder variants may not express abnormal blood and urine profiles right after birth, but they will become abnormal when they are ill.

CPT1a is one of the fatty acid oxidation defects where the stress from carrying a CPT1a defective fetus in a mother with one mutation can cause her to have a life threatening syndrome called HELLP (red blood cell breakdown (hemolysis), elevated liver enzymes, and low numbers of blood coagulation cells (platelets)). Fortunately, diagnosis can be made during pregnancy by

CPT1a 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

CPT1a deficiency occurs when an individual inherits one change (mutation) in the gene for CPT1a from each parent (autosomal recessive). If parents have a child with CPT1a deficiency, in each succeeding pregnancy, they have a 25% or 1 in 4 chance of having another child with changes in both parental genes. The severe form of the CPT1a deficiency is very rare.

However, a mild CPT1a defect is found frequently in the Inupiaq and Yu'pik and the Inuit nations in Alaska and Canada, respectively, and in Hutterite populations. In both cases, the altered CPT1a protein activity is usually identified through newborn screening. In the Inupiaq and Yu'pik nation in Alaska, around 50% of the population has two copies of the CPT1A gene with the so called "arctic variant". Consequently, about 50% of the children born within this community will also have the arctic variant. Incidentally, this arctic variant would only be this abundant if it gives a survival advantage to the population in this extreme climate. For this reason, it is considered a variant rather than a defect. Even so, infants inheriting the variant can develop dangerously low blood sugar during illnesses as described above.

Treatment

As with most fatty acid oxidation defects, fasting should be avoided. As the child gets older, they will become more stable and can go longer between feedings, up to 6-8 hours from the initial 2-3 hours. Since prevention of fasting is the mainstay of therapy, in severe disease, continuous

feeding by a stomach tube may be necessary, especially at night. Medium chain tryglycerides (MCT oils), artificial fats, can also be fed as a supplement because they do not depend on CPT1a to enter the inner mitochondrial space.

Mildly ill children with low CPT1a should be given liquids that contain glucose or sugars frequently. Parents should call their health care provider immediately whenever these infants become excessively sleepy, are vomiting, have diarrhea, a fever, poor appetite, or an infection. These acute episodes of hypoketotic hypoglycemia can be rapidly reversed by giving intravenous glucose-containing fluids that provide at least 8-10 mg/kg/min of glucose along with normal body salts. The accompanying high blood ammonia (hyperammonemia) usually reverses with correction of the hypoglycemia. If it does not correct, dialysis may be required. These crises usually decrease in frequency with age and are rare after age 3 years.

Investigational

A Phase 3 clinical trial is currently being conducted on treatment of CPT1a 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.

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](#)

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