



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

Multiple Acyl-CoA Dehydrogenase Deficiency/Glutaric Acidemia Type II

Introduction

[Multiple Acyl-CoA Dehydrogenase Deficiency \(MADD\)](#) is an inherited disorder where the body has a reduced ability to obtain energy from most proteins and fats. It is also called glutaric acidemia Type II because these patients excrete glutaric acid in their urine. For routine body maintenance, the body uses carbohydrates and their sugar products, but this energy pool is limited. Whenever this pool of carbohydrates has been exhausted by either lack of food ingestion (fasting) or from increased demand from illness, trauma or exercise, the body turns to fatty acids and amino acids, both highly efficient energy sources. Amino acids come from and are the building blocks of proteins and fatty acids are the core component of fats. Most amino acids and all fatty acids are broken down into energy in subunits of every cell known as mitochondria. Patients with MADD cannot process the energy taken from fats and amino acids because either of two proteins, electron transfer flavaprotein (ETF) or electron transfer flavoprotein dehydrogenase (ETF_{DH}) is defective. Without these proteins, not only is there an inability to generate energy for the cell's work, but the unused fats and amino acids accumulate in quantities that are toxic. Riboflavin, also called Vitamin B₂, is an essential partner of both proteins that can malfunction in MADD.

Clinical

MADD can be a very severe or a mild defect. It varies from being apparent at birth and incompatible with life to only appearing as a mild disease in adolescence or young adulthood. Symptoms also vary by age of presentation. The most severely affected, who present as newborns, visually are very limp (hypotonic), have abnormal features of both face and body, may have a large liver, and may have a characteristic smell like sweaty feet. Upon closer observation, they may have brain abnormalities, weak and enlarged hearts (dilated cardiomyopathy), and kidneys with fluid filled sacs (cystic). Routine laboratory studies in blood show low sugar (hypoglycemia), lack of the fatty acid products known as ketones (hypoketotic), elevated blood ammonia (hyperammonemia), and lactic acid accumulation. Infants and children with milder forms of the disease are common and usually only present at their first episode of mild stress such as an ear infection or gastrointestinal distress. At that time, they can be difficult to awaken (lethargic), limp, irritable, or vomiting. Laboratory studies will show hypoketotic hypoglycemia, and/or intermittent lactic acidosis. (311,312). The mildest patients may only show muscle pain and weakness and may only present in adolescence or young adulthood.

Diagnosis

MADD blocks the mitochondrial breakdown of many different sources of energy and these many unused products form the basis of its diagnosis. The two major diagnostic tests are organic acid analysis in urine and tandem mass spectrometry analysis of blood. The organic acid analysis usually shows both increased amino acid products (ethylmalonic, glutaric, 2-hydroxyglutaric, and 3-hydroxyisovaleric acids and isovalerylglycine), together with increased fatty acid products (6-, 8-, and 10-carbon dicarboxylic acids). Tandem mass spectrometry in blood shows accumulation of both amino acid products (glutaryl-carnitine and isovaleryl-carnitine) and fatty acid products (4-, 8-, 10-, 10:1-, and 12-carbon acyl-carnitines) ([266](#), [319](#)). Blood carnitine is usually low. There is also increased serum sarcosine apparent even in patients with mild disease. Fortunately, today most MADD patients are identified in early infancy through expanded newborn screening with tandem mass spectrometry.

If necessary, further studies can determine whether the defect is in ETF or ETFDH. Both can be identified by analysis of either activity or its presence or absence in cells (immunoblot analyses). ETF is formed from two proteins that assemble together called ETFa and ETFb. Either component can be defective. ETFDH has only one component. Since a specific DNA sequence codes for each of the three proteins, molecular testing for their defect is another approach and is usually more available than protein diagnostics.

Severe forms of MADD can be diagnosed before birth by using organic acid analysis to identify increased glutaric acid in amniotic fluid. In addition, sometimes ultrasound examination of the fetus will show cysts in their kidneys ([320-322](#)).

Treatment

Patients with the most severe MADD defects often die during the first weeks of life, usually from heart associated problems. Many of those with less severe defects will be identified first by newborn screening. This early identification allows them early treatment so that most can survive well into adult life. The first rule of treatment is the avoidance of going without food (fasting). Feedings are closely spaced, every 2-3 hours, to start. In some cases, continuous feeding of carbohydrates through a stomach tube may be necessary to prevent low blood sugar, especially at night. A riboflavin (100-400 mg/kg/day) supplement is usually given and may help some patients by stabilizing the defective protein. Pharmacologic doses of carnitine (50-100 mg/kg/day) are given to help remove unused fats and amino acids.

Mildly ill children with MADD 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. In hospital, these children will be given sugar by vein to provide energy.

Genetics

MADD is a genetic disorder that can result from defects in any of three genes: ETFa, ETFb, and ETFDH. It occurs when a child inherits a mutation in the gene for one of the ETFs or ETFDH from each carrier parent. A couple in which both parents are carriers for MADD have a 25% chance with each pregnancy of having another child with this genetic disorder. One common a-

ETF gene mutation has been described ([266](#)). MADD is a rare disorder and its frequency is unknown.