



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

MCAD Deficiency

Medium chain acyl-CoA dehydrogenase (MCAD) deficiency is one of a group of inherited disorders of fat metabolism that makes the body unable to generate sufficient 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 MCAD, an intermediate step in the breakdown of fats is missing or reduced. Today in the United States, the majority of MCAD patients are identified right after birth because of the expanded newborn screening program. For most infants in the United States, a blood spot for MCAD testing is obtained from the infant's heel before they go home from the birthing facility.

Signs and symptoms

Before newborn screening, medium chain acyl-CoA dehydrogenase (MCAD) deficiency, the most common of the fatty acid oxidation disorders, usually presented during the first 2 years of life with episodes of vomiting, enlarged liver (hepatomegaly), a special form of low blood sugar (hypoketotic hypoglycemia), and extreme tiredness (lethargy) progressing to coma and seizures after seemingly mild illnesses such as a viral illness or ear infection ([261](#)). During these acute episodes, ammonia, uric acid, liver transaminases, and creatine phosphokinase (CPK) were elevated in the blood, and their liver was often fatty ([262](#), [263](#)). This initial episode was fatal in about 25% of cases, some of which were grouped into Sudden Infant Death Syndrome. Today, most cases are diagnosed in the first three to four days of life through newborn screening of a blood spot rather than from clinical presentation. Usually, patients are well when identified, though at high risk for low blood sugar (hypoglycemia) with even simple illnesses, and deaths are rare ([243](#)). A few enzyme-deficient individuals born before newborn screening first still present with symptoms in adolescence or adult life and some have even never had an acute episode ([264](#), [265](#)).

The hypoketotic hypoglycemia found in MCAD is a special form of low blood sugar. When healthy people fast or use excessive calories in exercise, they start to 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 when glucose is limited ([216](#)). Since MCAD patients have a limited ability to break down any fats, they lack the basic ingredients to make these ketones (thus are hypoketotic). Unfortunately, this lack of ketones increases the risk for brain damage during hypoglycemic episodes.

Diagnosis

The majority of patients with MCAD defects are diagnosed through newborn screening of an infant's blood spot by tandem mass spectrometry and are not ill at diagnosis. As soon as the abnormal result is validated, infants are referred to a physician for immediate intervention.

Whether MCAD patients are sick or healthy, their blood nearly always has increased amounts of specific fats called acylcarnitines. MCAD patients uniquely accumulate fats of a medium carbon chain length, usually 8 or 10 carbons long (266). They occur in the blood in their carnitine form because they are transported there to help dispose of them. These are the same fats identified in newborn screening of MCAD patients. At the same time, free carnitine in blood is usually low. During episodes of acute illness, urine from MCAD patients also have high levels of several types of medium chain fat derivatives. If an ill child has not been screened for MCAD as a newborn, the presence of these medium chain species is suggestive that an MCAD workup is in order. Enzyme can be measured in fibroblasts or leukocytes, but molecular diagnosis is more readily available and often faster because of the presence of one very common mutation (see common mutation below under Genetics).

Because of the prevalence of the common mutation, prenatal diagnosis is usually done most rapidly by analysis for the common mutation from DNA obtained from the amniotic fluid or chorionic villus sampling (CVS). MCAD enzyme measurement can also be performed, but it takes a much longer to get results. In 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).

Genetics

[MCAD deficiency](#) occurs when an individual inherits one change (mutation) in the gene for MCAD (*ACADM*) from each parent (autosomal recessive). The vast majority of patients have a single common mutation (985A>G) that causes one change in the protein chain (270). In MCAD, 90% of the patients inherit this common mutation from at least one parent, while approximately 70% of patients inherit the same mutation from both parents. Thus, few MCAD patients do not have at least one 985A>G allele. The unusually high frequency of a single common mutation has made molecular diagnosis especially valuable in MCAD deficiency. Patients with the common mutation accumulate the highest levels of metabolites in the newborn period and are probably at risk for more severe disease than are many other mutations (271)

Treatment

Day-to-day management of MCAD consists of avoiding excessive fasting that can lead to coma. Overnight fasting in MCAD infants should be limited to no more than 8 hours. In children over 1 year of age, 12-18 hours without food is probably safe (268). Home blood glucose monitoring is not useful because symptomatic illness can begin before hypoglycemia has occurred. Although it is reasonable to modestly reduce dietary fat because this fuel cannot be used efficiently in MCAD deficiency, patients appear to tolerate normal diets. Formulas containing medium-chain triglyceride oil should be avoided. Although MCAD patients tend to have low blood levels of

carnitine, the use of carnitine supplementation is controversial (269). Some investigators suggest 50 to 100 mg/day of oral carnitine, but its usefulness is unproven.

Treatment of acute episodes in MCAD deficiency is primarily supportive and aimed at quickly stopping the body from depending on fat breakdown for energy (252). Low blood sugar (hypoglycemia) should be corrected with administration of intravenous dextrose (glucose) at a rate that maintains plasma glucose levels at, or slightly above, the normal range. Specific therapy for the mild hyperammonemia that may be present during acute illness is not usually required. Rarely, there is acute brain injury in the form of coma. The sensitivity of the brain in MCAD may not be entirely due to the hypoglycemia but it may also be affected by the fatty acid intermediates that accumulate (ref 4,7 chapter). Recovery is usually complete within 12 to 24 hours except where serious injury to the brain has occurred.

Investigational

The combination of chronic fasting avoidance and rapid glucose intervention in acute low blood sugar episodes usually allows MCAD children to thrive. As they age, children usually become less prone to these episodes.

Currently there are no active programs to develop additional specific interventions for MCAD. However, other potential interventions may appear as products that are effective on the entire class of fatty acid oxidation disorders are developed.

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

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