What is MCAD deficiency?

MCAD is one of the enzymes involved in the conversion of fats to provide the body with energy. Normally, the major source of energy for our cells is glucose, but this can become depleted during prolonged fasting and periods of higher energy demands. In a typical clinical scenario, a previously healthy child presents with hypoketotic hypoglycemia, vomiting, and lethargy triggered by a common illness. Seizures may occur. Such an episode may quickly progress to coma and death. Hepatomegaly and acute liver disease are often present. Patients are normal at birth and typically present between three and 24 months of age; later presentation, even into adulthood, is possible. The prognosis is excellent once the diagnosis is established and frequent feedings are instituted to avoid any prolonged period of fasting.

What effects does MCAD have?

Patients with MCAD deficiency appear normal at birth and usually show signs of having the condition between 3 and 24 months of age after either prolonged fasting (e.g., weaning the infant from night time feedings) or mild illnesses and infections (e.g., viral gastrointestinal or upper respiratory tract infections), which typically cause loss of appetite and increased energy requirements when fever is present. Later presentation in adulthood is also possible. Such instances of metabolic stress lead to vomiting and lethargy, which may quickly progress to coma and death. The episodes may also begin with or be accompanied by seizures. Hepatomegaly is usually present during acute decompensation, which is also characterized by hypoketotic (not necessarily non-ketotic) hypoglycemia, increased anion gap, hyperuricemia, elevated liver transaminases, and mild hyperammonemia. Patients are at risk of losing developmental milestones and acquiring aphasia and attention deficit disorder, which are thought to be secondary to brain injury occurring during the acute metabolic event. Chronic muscle weakness is observed in 18% of patients who experience several episodes of metabolic decompensation (Lafolla et al 1994). McCandless and colleagues (2002) recently reported that of 41 newborns with MCAD deficiency identified by newborn screening in North Carolina since 1997, all are developing normally. None experienced hypoglycemia episodes, but some required precautionary hospitalization during episodes of intercurrent illness. Although the prognosis is excellent once the diagnosis is established, unexpected death during the first metabolic decompensation is common and may occur as late as adulthood (e.g., during surgery causing metabolic stress Raymond et al 1999).
How is MCAD treated?
Treatment for MCAD deficiency is simple and allows for a good prognosis, especially when started prior to the development of a metabolic crisis. However, if the diagnosis is not known, at least 18% of the patients die during their first metabolic crisis. Although a relatively low-fat diet (e.g., <30% of total energy from fat) could be beneficial, the mainstay in the treatment of MCAD deficiency is avoidance of fasting for more than 12 hours. Infants require frequent feedings. It is recommended that toddlers receive 2 g/kg of uncooked cornstarch as a source of complex carbohydrates at bedtime to ensure sufficient glucose supply overnight. All patients should be provided with a frequently updated "emergency" letter to be given, if needed, to health care providers who may not be familiar with MCAD deficiency. This letter should include a detailed explanation of the management of acute metabolic decompensation, emphasizing the importance of preventive measures (e.g., intravenous glucose regardless of "normal" laboratory results, overnight in-hospital observation), and the telephone numbers of the patient's metabolic specialist. 

Although a tangible clinical benefit of carnitine supplementation in patients with MCAD deficiency has not been proven, several authors recommend oral supplementation with carnitine to correct the frequently observed secondary carnitine deficiency and to enhance the elimination of toxic metabolites [Roe & Ding 2001]. This approach is popular despite the fact that carnitine-mediated detoxification of medium-chain fatty acids, assessed by urinary excretion of medium-chain acylcarnitines, is quantitatively negligible (Rinaldo et al 1993 and carnitine supplementation does not, under controlled circumstances, improve the response to a fasting challenge (Treem et al 1989). The cost of long-term supplementation with carnitine could be significant. On the other hand, no untoward effects of L-carnitine have been reported in patients with MCAD deficiency, in contrast to LCHAD deficiency, in which the formation of long-chain 3-hydroxy acylcarnitine species is believed by some authors to be detrimental (Ribes et al 1992, Rocchiccioli et al 1990).

How is MCAD diagnosed?
In South Australia, MCAD is usually diagnosed by the tandem mass spectrometry newborn screening programme. All babies have 3 spots of blood collected a few days after they are born. This blood is tested for signs of several different diseases, including MCAD. Initial testing includes analysis of blood and urine, including: plasma acylcarnitines, plasma fatty acid (free or total) profile, urine organic acids, and urine acylglycines. If these levels are found to be irregular, then a small fibroblast (tissue) sample will be taken to measure the activity of the MCAD enzyme. If there is little or no MCAD enzyme present, then the baby will be diagnosed with MCAD deficiency.

How is MCAD inherited?
All the cells in a person's body contain many, many sets of instructions on how to make the chemicals which make up our bodies. These instructions are called genes and are made of DNA. It is estimated that we all have between 50,000 and 100,000 different genes. We each carry two copies of all our genes; one copy of each gene is inherited from our father, and one from our mother. Mistakes can happen in the gene for the enzyme which is missing in MCAD. A child with mistakes in both copies of the gene will have MCAD. If a person has a mistake (also known as a mutation) in one copy of the gene, but the other copy of the gene is normal, that person is a ‘carrier’ of MCAD. Being a carrier has no effect on a person's health. In order for a person to have MCAD, both of their parents must be carriers.

What will happen to future children?
If a couple, both of whom are carriers of mistakes in the MCAD gene, have a child, there are three things that can happen. There is a one in four chance, every time that they have a child, that the child will have MCAD. There is a one in two chance that the child will be a healthy carrier, like its parents. Lastly, there is a one in four chance that the child will not even be a carrier. These chances apply for each pregnancy, regardless of what has happened before. While it is impossible to say in advance what will happen each time, it is usually possible to do a test early in pregnancy which will show whether or not the baby is affected by MCAD.

How do I know if I am a carrier of MCAD?
However, if someone in your family has MCAD, your chance of being a carrier may be much higher. In South Australia, about one person in 100 is a carrier of a mistake in the MCAD gene. A parent who is a carrier must have inherited the MCAD gene with the mistake in it from one of his or her parents. Therefore one of each set of grandparents of a person with MCAD deficiency is a carrier. There is one common MCAD gene in the Caucasian population, responsible for about 80% of mutations.

Not all people want or need to know whether or not they are carriers of MCAD. It is usually helpful to discuss the issues of testing with a geneticist or genetic counsellor, before the test is done.

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