Lesson 257: PreAnesthetic Assessment of the Patient With Medium-Chain Acyl Coenzyme A Dehydrogenase Deficiency

The acyl coenzyme A (acyl-CoA) dehydrogenase deficiencies are a recently discovered group of inherited defects that impair the mitochondrial β-oxidation of fatty acids at different stages of the fatty acid chain—shortening process. The affected enzyme may be the very-long-chain acyl-CoA dehydrogenase (VLCAD), long-chain acyl-CoA dehydrogenase (LCAD), medium-chain acyl-CoA dehydrogenase (MCAD), or short-chain acyl-CoA dehydrogenase (SCAD). Table 1.

Pathogenesis

The β-oxidation pathway consists of 4 sequential reactions catalyzed first by a set of membrane-bound enzymes, then by action of acyl-CoA dehydrogenases, the first set of enzymes catalyzed first by a set of membrane-bound enzymes, then by action of acyl-CoA dehydrogenases, the first set of enzymes. At least 4 separate acyl-CoA dehydrogenases, the first set of enzymes known (the clinical phenotypes remain unclear); however, MCAD deficiency—although first recognized as recently as 1982—is now thought to be the most common inborn error of fatty acid metabolism.

PREANESTHETIC ASSESSMENT

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2) You must achieve a score of 80% or better to earn CME credit.
3) The estimated time to complete this activity is 2 hours.

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acids and dicarboxylic acids, such as octanoic acid. Previous studies demonstrated that experimentally induced octanoic acidemia damages neuronal mitochondria, and that octanoate reduces the oxidation of glucose by rat cerebral homogenates. Therefore, it is likely that both hypoglycemia and the toxic effects of medium-chain fatty acid–derived metabolic substances contribute to neurologic abnormalities in MCAD deficiency.

Secondary carnitine deficiency may be observed in patients with MCAD deficiency. Potentially toxic intermediates of the medium-chain fatty acids accumulate in the presence of inhibition of fatty acid β-oxidation. The mitochondrial translocation of these intermediates with carnitine leads to the formation of acylcarnitines and free CoA. These acylcarnitines readily cross cell membranes into the circulation and are excreted in the urine. While carnitine may play a role in eliminating the toxic metabolites of medium-chain fatty acids, the intracellular level of carnitine may be decreased secondary to the translocation process. In addition, the inhibition of carnitine reuptake in the renal tubules occurs secondary to elevations in the concentration of acylcarnitine in the urine. Thus, both a transposition of intracellular carnitine and a loss of carnitine from the urine may contribute to secondary carnitine deficiency observed in MCAD deficiency.

### Table 1. Acyl Coenzyme A Dehydrogenases

<table>
<thead>
<tr>
<th>Length of Fatty Acid</th>
<th>Enzyme</th>
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<tbody>
<tr>
<td>C16</td>
<td>Very-long-chain acyl-CoA dehydrogenase</td>
</tr>
<tr>
<td>C12-C16</td>
<td>Long-chain acyl-CoA dehydrogenase</td>
</tr>
<tr>
<td>C6-C12</td>
<td>Medium-chain acyl-CoA dehydrogenase</td>
</tr>
<tr>
<td>C6</td>
<td>Short-chain acyl-CoA dehydrogenase</td>
</tr>
</tbody>
</table>

Note: Affected enzymes are grouped according to the length of the carbon chain.

### Prevalence

MCAD deficiency is prevalent primarily among Caucasians, especially those of Northern European descent, although a few cases have been reported in Hispanic, African-American, Native American, and Asian populations. The overall frequency ranges from 1 in 4,900 to 1 in 18,000 live births, indicating that MCAD deficiency may be about twice as common as phenylketonuria. There are no national data available regarding the incidence of MCAD deficiency in the United States. A disease frequency of 1 in 8,500 has been reported through newborn screening programs in Pennsylvania, whereas a combined result in Pennsylvania and North Carolina has shown a frequency of 1 in 17,796. Variability of frequency may be related to the ethnic background of the population in different studies. Newborn screening for MCAD deficiency is an emerging concept, required at present in only 43 states and the District of Columbia (Table 2). In view of the potentially poor outcome and high incidence of MCAD deficiency, and the cost-effectiveness of screening, it is likely that more states will include MCAD deficiency in their newborn screening programs. This will help define the true incidence of MCAD deficiency in the United States.

### Genetics

MCAD deficiency, present from conception, is inherited in an autosomal-recessive and non–sex-linked manner. The phenotype is usually observed in the homozygote, and the typical pedigree demonstrates affected male and female siblings with normal parents and offspring. If both parents are normal heterozygotes (carriers), the segregation frequency with each pregnancy is 25% homozygous normal, 50% heterozygotes, and 25% homozygous affected. Therefore, the risk for being homozygous and affected is 50% if one of the parents is affected.

The gene for MCAD is located on the short arm of chromosome 1 (1p31). The K304E mutation of an A-to-G substitution at the position of nucleotide 985 accounts for about 71% of the mutant alleles in patients with MCAD deficiency. Approximately 52% of patients are homozygous for the K304E mutation. Patients have been identified who are compound heterozygous for the common K304E mutation and 2 non–K304E mutations. Clinical Presentation

Individuals with MCAD deficiency appear to be entirely normal at birth. Symptoms often begin to appear between the second month and second year of life, although presentation in adulthood is also possible. Symptoms occur in response to the metabolic stress of prolonged fasting (eg, after nocturnal feedings have ceased) or infections (eg, the common cold, otitis media, acute upper respiratory infection, or immunization), when the demands on fatty acid oxidation are particularly high. Typical symptoms include lethargy, vomiting, hypoketotic hypoglycemia, seizures, coma, metabolic acidosis, cardiovascular arrest, and sudden unexplained death, so that the condition can resemble Reye’s syndrome or sudden infant death syndrome. In some patients, sudden and unexpected death is the first manifestation.

Hepatomegaly secondary to fatty infiltration of the liver is usually present. Abnormal laboratory findings include hypoglycemia, increased anion gap, elevated liver enzymes, hyperuricemia, and hyperammonemia. Rapid clinical deterioration that is disproportionate in the setting of a benign clinical situation should raise suspicion of MCAD deficiency. Without a prior diagnosis of the disease, or if treatment is not initiated immediately, at least 18% of patients may die during the first episode. Patients are usually asymptomatic between episodes. After several episodes of metabolic decompensation, survivors may have significant developmental disability, chronic muscle weakness, failure to thrive, cerebral palsy, or attention-deficit disorder. Although the presentation of MCAD deficiency is almost exclusively a “hepatic” type of presentation, an extrapleural defect in the enzymes may be present in cardiac and skeletal muscle.

**Figure.** β-Oxidation of fatty acids.

FAD, flavin adenine dinucleotide; FADH2, reduced form of flavin adenine dinucleotide; NAD, nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide.
Involvement of these organs is probably responsible for clinical deterioration and sudden death during an attack. Some patients remain asymptomatic for a long time, even into adulthood. Attacks become less frequent in adults, likely because fasting tolerance with increasing body mass. However, the penetrance of the genotypes and the genotypic–phenotypic relationship in MCAD deficiency are still unknown. It is uncertain which patients will manifest symptoms. Examples include a 14-year-old girl (in whom MCAD deficiency was ultimately diagnosed) who became comatose after enrolling in a weight loss program, and an asymptomatic 30-year-old man with MCAD deficiency who presented with acute encephalopathy after strenuous exposure to a cold environment without adequate food intake. The sudden, unexpected death of a 45-year-old woman (subsequently confirmed to have had MCAD deficiency) has also been reported.

Researchers have found that genetic defects in fetal fatty acid oxidation are associated with maternal complications. Maternal hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome and acute fetal liver are possible when a fetus has MCAD deficiency. Prenatal diagnosis with increased levels of free fatty acids caused by increased activity of the hormone-sensitive lipase in combination with gestational resistance to insulin; these provide a source of energy production for the parturient and the fetus. An accumulation of fetal metabolic intermediates of fatty acids resulting from defective β-oxidation in the fetoplacental unit may play a role in the etiology of maternal HELLP syndrome. Patients who are compound heterozygotes for an MCAD mutation may have inefficient enzyme activity for the metabolism of medium-chain fatty acids. These patients may be clinically asymptomatic because of the presence of an intermediate level of MCAD activity. In one case report, a parturient with compound heterozygous MCAD deficiency underwent an uneventful labor and delivery with spinal–epidural anesthesia. However, such individuals should still be considered at risk for clinical manifestations. Further evaluation that includes a fasting test conducted, controlled setting and with the establishment of intravenous (I.V.) access should be considered.

**Diagnosis**

Because of the nonspecific clinical presentation of MCAD deficiency, a correct diagnosis requires a consideration of the clinical manifestations and laboratory analyses. Biochemical analyses comprise only the initial testing and require appropriate interpretation. MCAD enzymatic activity and molecular genetic techniques aid in evaluating homozygotes and carrier status.

**Routine Blood and Urine Tests.** Initial laboratory examination of the blood may reveal hypoglycemia, mild metabolic acidosis, mild lactic acidosis, hyperammonemia, elevated blood urea nitrogen, elevated liver transaminases, and high uric acid levels. Urinalysis often reveals low or absent ketones.

**Biochemical Analyses.** Low levels of serum and urine carnitines are often found in untreated patients. Plasma profiles show elevated levels of medium-chain fatty acid-derived acylcarnitine compounds, especially octanoylcarnitine. Analysis of plasma free fatty acids reveals elevated concentrations of octanoylcarnitine, cis-4-decenoylcarnitine, and deacanoylcarnitine in both asymptomatic and symptomatic patients. A generalized dicarboxylic aciduria is present, characterized by elevated levels of medium-chain dicarboxylic acids such as suberoylglutamine.

**Measurements of MCAD Enzymatic Activity.** Confirmation of MCAD deficiency and carrier status can be achieved by measurement of MCAD activity in leukocytes, fibroblasts, the liver, the heart, or amniocytes. Homozygotes affected with MCAD deficiency show less than 10% of normal MCAD enzymatic activity, whereas heterozygous carriers are found to have intermediate levels of about 49%.

**Molecular Genetic Testing.** Molecular genetic analysis is becoming a recommended tool to confirm the status of patients initially identified by screening tests as affected (homozygotes), and to detect carriers. The MCAD mutation can be determined by the polymerase chain reaction method. Mutation analysis to detect the common K304E allele and sequence analysis to detect the non-K304E mutations are both widely available.

**Newborn Screening.** Tandem mass spectrometry, a relatively new test for the population-based screening of newborns for fatty acid oxidation disorders, has become an integral procedure in biochemical genetics and newborn screening laboratories. The technology detects medium-chain fatty acid–derived metabolites (10 carbons or acylcarnitines) by using blood spots. Such marker-based screening does not detect heterozygotes, who are readily identified by molecular methods. Newborn screening for MCAD deficiency is cost-effective because of the high incidence of the disease and because catastrophic episodes can be prevented through relatively simple dietary means if the disease is recognized before severe sequelae can develop.

**Prenatal Testing.** An increased risk for MCAD deficiency can be determined prenatally by DNA analysis, by assay of MCAD enzymatic activity, or by biochemical profiling. Amniocytes are obtained by amniocentesis (usually performed at 15-16 weeks of gestation), or chorionic villi are obtained by chorionic villus sampling (gastrosentesis). However, the risk for miscarriage associated with amniocentesis and chorionic villus sampling should be weighed against the benefits of prenatal testing for MCAD deficiency.

**Therapy**

The mainstay of treatment for MCAD deficiency is the avoidance of prolonged periods of starvation, particularly during intercurrent illnesses. Although some patients seem to tolerate fasting well in the absence of illness, they may become symptomatic during fasting associated with illness (eg, caused by a decreased appetite). The metabolic complications of MCAD deficiency are seen only when body tissues become primarily dependent on fatty acids as a source of energy. High levels of carbohydrate intake should be encouraged during illness. Hypoglycemia must be avoided by the I.V. administration of glucose (10%). A relatively low-fat diet that especially limits medium-chain fatty acids (eg, coconut oil and butter) may be beneficial. An acute attack must be treated immediately with an appropriate dose of I.V. glucose. This regimen must be followed throughout the lifetime of the affected individual.

For patients with MCAD deficiency who are acutely ill, carnitine supplementation is recommended, although its therapeutic role remains unestablished. I.V. infusion of carnitine may be considered if an exacerbation of neurologic symptoms occurs with the I.V. infusion of glucose. The therapeutic rationale includes the conjugation or excretion of potentially toxic intermediates of medium-chain fatty acid metabolism and the relief of secondary carnitine deficiency. However, long-term carnitine supplementation does not correct the underlying defect of MCAD deficiency and, therefore, may be unnecessary.

Gene therapy is an attractive option for patients with MCAD deficiency. In theory, genetic supplementation could lead to long-lasting correction of the diacetyl phosphate. An improvement in abnormal acylcarnitine profiles in MCAD-deficient human fibroblasts was demonstrated after a fibroblast had been infected with an adenovirus vector expressing human MCAD. However, to date, gene therapy has not been attempted in humans with MCAD deficiency.

**Anesthetic Considerations**

Limited information is available regarding the anesthetic management of patients with MCAD deficiency. Reports of 3 patients between 3 and 8 years of age who underwent undiagnosed surgery have been published. In other patients with identified MCAD deficiency as neonatal screenings in susceptible families become widespread. In addition, enhanced recognition of complex heterozygosity and more effective treatment of homozygotes in childhood are likely to result in an increased prevalence of MCAD deficiency in adults. The preoperative assessment should include an evaluation of the medical history, neurologic status, results of liver function tests, and blood glucose levels. Because of variations in age at initial presentation and the high risk for sudden death in patients with undiagnosed disease, a determination of the genotype or biochemical profiling should be considered if a history of MCAD deficiency is found in the patient’s family. Preoperative electrocardiography is recommended because the MCAD enzymatic defect may be present in cardiac myocardium. The coagulation profile should be examined, especially when regional anesthesia is chosen, because a marked accumulation of fat in the liver may develop during recurrent episodes. The potential development of HELLP syndrome in the parturient who carries an affected fetus needs to be considered.

Patients should be scheduled for surgery early in the day if possible. Preoperative fasting should last less than 4 hours in infants, and 12 hours in older patients. Clear liquids that contain a high amount of carbohydrate (eg, oral glucose solution) may be provided until 2 to 3 hours before surgery. In homozygotes or symptomatic heterozygous patients with MCAD deficiency, an I.V. infusion of 10% glucose should be started preoperatively and continued intraoperatively. Frequent measurements of the glucose level to avoid hypoglycemic episodes are required for all patients. The I.V. administration of carnitine should be considered if neurologic symptoms occur in the presence of normoglycemia. The effect of muscle relaxants dependent on hepatic clearance mechanisms may be prolonged in the presence of liver dysfunction. There is a potential for altered responses to succinylcholine and nondepolarizing muscle relaxants in patients with skeletal muscle weakness is prominent.

Carinilene deficiency may sensitize patients to challenges that either overwhelm (infusion of fat emulsion) or inhibit (propofol) β-oxidation or mitochondrial function. Propofol– in even in small doses—may cause bradycardia and hypotension. Severe dysrhythmia was recently reported following a small subcutaneous dose of bupivacaine in a patient with systemic carnitine deficiency. The authors concluded that patients with known mitochondrial disease should not receive propofol, and a patient presenting with unexplained acidosis or cardiac dysfunction after a usual dose of propofol should be screened for metabolic deficiencies.

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**Table 2. Current Status of Newborn Screening Programs for MCAD Deficiency In the United States (September 2006)**

<table>
<thead>
<tr>
<th>State</th>
<th>Screening offered to selected populations or by request</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Mexico</td>
<td>Montana, Pennsylvania</td>
</tr>
</tbody>
</table>

**Screening not offered:**

- Arkansas, Kansas, West Virginia
Inability to use fat as fuel. Symptoms include vomiting, bodies cannot be produced in quantities sufficient to meet between the second month and the second year of life, d. All of the above are true.

4. Which of the following describes the inheritance 

c. hypoglycemia

d. phenylketonuria

3. Signs and symptoms of MCAD deficiency include: 
a. seizures 
b. encephalopathy 
c. hypoglycemia 
d. all of the above

2. Which of the following is a true statement about 
a. African-Americans 
b. Asians 
c. Caucasians 
d. Hispanics

7. The precipitating factor for an episodic attack of 
a. An I.V. glucose infusion should be started preoperatively 
b. Hyperthyroidism 
c. During periods of metabolic stress 
d. Coagulation profiles should be examined, especially in the 

5. Symptoms of MCAD deficiency usually appear and are 
a. at birth 
b. in late adulthood 
c. during periods of metabolic stress 
d. in early adulthood


