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Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Synonym: MCAD Deficiency

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Summary

Clinical characteristics. Medium-chain acyl-coenzyme A dehydrogenase (MCAD) is one of the enzymes involved in mitochondrial fatty acid β-oxidation, which fuels hepatic ketogenesis, a major source of energy once hepatic glycogen stores become depleted during prolonged fasting and periods of higher energy demands. In a typical clinical scenario, a previously healthy child with MCAD deficiency presents with hypoketotic hypoglycemia, vomiting, and lethargy triggered by a common illness. Seizures may occur. Hepatomegaly and liver disease are often present during an acute episode, which can quickly progress to coma and death. Children are normal at birth and – if not identified through newborn screening – typically present between ages three and 24 months; 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.

Diagnosis/testing. Diagnosis of MCAD deficiency requires the integrated interpretation of multiple analyses, including consideration of the clinical status of the affected individual (i.e., acutely symptomatic vs asymptomatic) at the time of sample collection. Initial testing should include plasma acylcarnitine analysis, urine organic acid analysis, and urine acylglycine analysis and their proper interpretation. Further confirmatory testing can be by identification of biallelic pathogenic variants in *ACADM* or additional biochemical genetic testing (i.e., determination of fatty acid β-oxidation flux in fibroblasts or measurement of MCAD enzyme activity in leukocytes, fibroblasts or other tissues).

Management. *Treatment of manifestations:* Most important is giving simple carbohydrates by mouth (e.g., glucose tablets, or sweetened, non-diet beverages) or IV if needed to reverse catabolism and sustain anabolism.

Prevention of primary manifestations: The mainstay is avoidance of fasting: infants require frequent feedings; toddlers could be placed on a relatively low-fat diet (e.g., <30% of total energy from fat) and could receive 2 g/kg of uncooked cornstarch at bedtime to ensure sufficient glucose overnight.

Prevention of secondary complications: Weight control measures including proper nutrition and exercise.

Agents/circumstances to avoid: Hypoglycemia (e.g., from excessive fasting); infant formulas that contain medium-chain triglycerides as the primary source of fat.

Evaluation of relatives at risk: Evaluate plasma acylcarnitines and urine acylglycines in sibs and parents to permit early diagnosis and treatment of previously asymptomatic at-risk family members.

Genetic counseling. MCAD deficiency is inherited in an autosomal recessive manner. At conception, the sibs of an affected individual are at a 25% risk of being affected, a 50% risk of being asymptomatic carriers, and a 25% risk of

being unaffected and not carriers. The risk of being affected could be 50% if one of the parents is also affected. Because asymptomatic parents and sibs may have MCAD deficiency, biochemical evaluation and/or molecular genetic testing should be offered to both parents and all sibs. Because of the high carrier frequency for the *ACADM* p.Lys304Glu pathogenic variant in individuals of northern European origin, carrier testing should be offered to reproductive partners of individuals with MCAD deficiency. Prenatal testing for pregnancies at 25% or higher risk is possible by biochemical methods or, if both parental pathogenic allelic variants are known, by molecular genetic testing.

Diagnosis

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is a disorder of fatty acid β-oxidation. Fatty acid β-oxidation fuels hepatic ketogenesis, a major source of energy for peripheral tissues once glycogen stores become depleted during prolonged fasting and periods of higher energy demands (see Pathophysiology for more details.)

Suggestive Findings

MCAD deficiency may be suspected in the clinical scenarios of a **positive newborn screening**, **previously healthy individual who becomes symptomatic**, or **sudden and unexplained death**.

Positive newborn screening (NBS). Newborn screening utilizes a small amount of blood obtained by heel prick to quantitatively profile the acylcarnitines. In a population screening setting the specificity of tandem mass spectrometry (MS/MS) to identify MCAD deficiency appears to be 100%, with a few false negative results having been reported as a result of inappropriate cut-off selection [Maier et al 2009, McHugh et al 2011].

The positive predictive value (PPV) of acylcarnitine analysis to identify MCAD deficiency varies significantly (8%-78%) among screening laboratories [Lindner et al 2010]; nonetheless, it is generally much higher than the PPV for the disorders screened by the traditional, non-MS/MS methods (0.5%-6.0%) [Kwon & Farrel 2000]. Of note, it is also possible to encounter newborns with evidence of carnitine deficiency born to an affected but previously undiagnosed mother with MCAD deficiency [Leydiker et al 2011].

The false positive rate for MCAD deficiency most likely varies among screening programs because of differences in acylcarnitine analysis and profiling [Lindner et al 2010]. Programs that screen for MCAD deficiency but not other fatty acid β-oxidation disorders often limit their analysis to octanoylcarnitine, the predominant marker for MCAD deficiency. However, octanoylcarnitine is not specific for MCAD deficiency and is expected to be elevated in other disorders (i.e., glutaric acidemia type II, and possibly medium-chain 3-keto acyl-CoA thiolase deficiency) and in newborns treated with valproate or fed a diet rich in medium-chain triglycerides [Smith & Matern 2010]. Note: Integrated analysis, post-analytical interpretation and differential diagnosis of acylcarnitine results deemed to be abnormal could be aided by tools developed through the Region 4 Stork (R4S) project (www.clir-r4s.org) [McHugh et al 2011, Marquardt et al 2012, Hall et al 2014], currently supported by the Newborn Screening Translational Research Network (NBSTRN).

Note: (1) The diagnostic algorithm provided by the American College of Medical Genetics and Genomics for follow up of an abnormal newborn screening result suggestive of MCAD deficiency can also be applied to individuals who are clinically symptomatic. (2) A newborn whose blood sample has been submitted for newborn screening may become symptomatic before the screening results are available [Ensenauer et al 2005, Wilcken et al 2007, Lindner et al 2011, Andresen et al 2012, Lovera et al 2012, Tal et al 2015]; thus, clinical suspicion of critical conditions such as MCAD deficiency must remain high.

A previously healthy individual who becomes symptomatic with:

- Hypoketotic hypoglycemia, lethargy, seizures, and coma triggered by a common illness

- Hepatomegaly and acute liver disease (sometimes confused with a diagnosis of Reye syndrome, which is characterized by acute noninflammatory encephalopathy with hyperammonemia, liver dysfunction, and fatty infiltration of the liver)

The first acute episode usually occurs before age two years, but affected individuals may present at any age including adulthood [Raymond et al 1999, Schatz & Ensenauer 2010].

Rapid clinical deterioration that is disproportionate in the setting of a common and generally benign infection should raise the suspicion of MCAD deficiency or other fatty acid β-oxidation disorders and should prompt administration of intravenous glucose and the collection of urine and blood samples for metabolic testing.

Sudden and unexplained death. Most FAO disorders including MCAD deficiency frequently manifest with sudden and unexpected death [Rinaldo et al 2002]. The following information supports the possibility of MCAD deficiency:

- A family history of sudden death or Reye syndrome in sibs
- Evidence of lethargy, vomiting, and/or fasting in the 48 hours prior to death
- Frequently, diffuse fatty infiltration of the liver and potentially other organs on autopsy (if performed)

Establishing the Diagnosis

Establishing the diagnosis of MCAD deficiency in **a newborn with a positive NBS** and in **a previously healthy young child with acute liver dysfunction associated with impaired vigilance** requires the integrated interpretation of multiple analyses, including consideration of the clinical status of the affected individual (acutely symptomatic vs asymptomatic) at the time of sample collection.

Because most individuals with MCAD deficiency remain asymptomatic for long periods of time, some for their entire lives [Fromenty et al 1996], diagnostic methods for MCAD deficiency should be sensitive enough to identify asymptomatic affected individuals without provocative tests.

Initial Testing

Initial testing should include **plasma acylcarnitine analysis, urine organic acid analysis,** and **urine acylglycine analysis** and their proper interpretation.

Plasma acylcarnitine analysis. The acylcarnitine profile of individuals with MCAD deficiency is characterized by accumulation of C6 to C10 species, with prominent octanoylcarnitine [Millington et al 1990, Chace et al 1997, Smith et al 2010].

Note: (1) A potential pitfall of acylcarnitine analysis in the diagnosis of MCAD deficiency is the possibility that individuals with secondary carnitine deficiency may not show a significant elevation of C6-C10 acylcarnitines [Clayton et al 1998]. Although free carnitine and acetylcarnitine are abnormally low in the profile of such individuals, such findings are nonspecific but indicative of a possible underlying metabolic disorder. For this reason, reliance on plasma acylcarnitine analysis as the sole biochemical screen is not advisable, and either urine organic acids (in acute episodes) or acylglycines should be analyzed to reach a correct biochemical diagnosis. (2) Integrated analysis, post-analytic interpretation, and differential diagnosis of acylcarnitine results deemed to be abnormal could be aided by tools developed through the Collaborative Laboratory Integrated Reports (CLIR) project.

Urine organic acid analysis. In symptomatic individuals, medium-chain dicarboxylic acids are elevated with a characteristic pattern (C6>C8>C10), while ketones are inappropriately low. During acute episodes, 5-hydroxy hexanoic acid, hexanoylglycine, phenylpropionylglycine, and particularly suberylglycine represent additional biochemical markers of MCAD deficiency [Gregersen et al 1983].

Note: (1) Although hypoketotic dicarboxylic aciduria is a common finding, ketone body production could be normal at times of acute decompensation [Patel & Leonard 1995; personal observations]; therefore, the detection of ketonuria by routine urinalysis should not be taken as evidence against a possible diagnosis of MCAD deficiency. (2) Standard urine organic acid profiles are often uninformative in individuals with MCAD deficiency who are stable and are not fasting [Rinaldo et al 2001] because under these conditions the urinary excretion of the three acylglycines is often less than 10 mmol/mol creatinine – levels not readily detectable by routine organic acid analysis. (3) Care should be taken not to interpret as possible MCAD deficiency the elevated concentrations of octanoic acid and decanoic acid with normal *cis*-4 decenoic acid seen in individuals receiving MCT-oil supplements.

Urine acylglycine analysis is based on the quantitative determination by stable isotope dilution analysis of urinary n-hexanoylglycine, 3-phenylpropionylglycine, and suberylglycine [Rinaldo et al 1988]. The corresponding free acids are endogenous intermediates of fatty acid metabolism or, for phenylpropionic acid, an end product of the anaerobic metabolism of intestinal bacteria. During an acute episode, affected individuals excrete large amounts of hexanoylglycine and suberylglycine, which are readily detected by organic acid analysis. The test, requiring only a random urine sample from asymptomatic individuals and no provocative tests, is informative immediately after birth [Bennett et al 1991].

Urine acylglycine analysis is the preferred test in persons who are clinically asymptomatic.

Note: Integrated analysis, post-analytic interpretation, and differential diagnosis of acylglycine results deemed to be abnormal could be aided by tools developed through the Collaborative Laboratory Integrated Reports (CLIR) project.

Confirmatory Testing

Further confirmatory testing for MCAD deficiency can be by identification of biallelic pathogenic variants in *ACADM* on **molecular genetic testing** (Table 1) or additional **biochemical genetic testing** to determine fatty acid β-oxidation flux in fibroblasts or MCAD enzyme activity in leukocytes, fibroblasts, or other tissues).

Molecular genetic testing approaches can include **targeted analysis for pathogenic variants** and **single-gene testing.**

- **Targeted analysis for pathogenic variants.** For persons of northern European ancestry:
  - Targeted analysis for the two most common *ACADM* pathogenic variants – p.Lys304Glu (985A>G) and p.Tyr42His (199C>T) – may be considered if it is available and more cost effective than sequence analysis.
  - If both pathogenic variants are identified, the diagnosis is confirmed; if neither or only one pathogenic variant is identified, perform sequence analysis.
- **Single-gene testing**. Perform sequence analysis of *ACADM* first, followed by deletion/duplication analysis if only one or no pathogenic variant is found.

Table 1.

Summary of Molecular Genetic Testing Used in Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Gene [1]	Continent [2]	Variant Detection Frequency by Test Method and Continent	
		Targeted c.985A>G analysis	Sequence analysis [3] and deletion/duplication analysis [4]
ACADM	Asia	0%	100% [5]
	Australia	67%	97% [6, 7]

Europe	50%	100% [8]
N. America	68%	96% [7, 9]

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants detected in this gene.
2. No data available for Africa or South America
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
5. Purevsuren et al [2012], Chien et al [2013]
6. Waddell et al [2006]
7. Deletion/duplication analysis may not have been included.
8. Andresen et al [2012], Sturm et al [2012], Thodi et al [2012], Touw et al [2012], Catarzi et al [2013]
9. Hsu et al [2008], Nichols et al [2008], Prasad et al [2012]

Biochemical testing

- **Analysis of fatty acid β-oxidation** in cultured fibroblasts involves acylcarnitine analysis of culture medium or a mix of culture medium and disrupted cells following the incubation of fibroblast cultures with labeled or non-labeled palmitic acid and non-labeled L-carnitine [Schmidt-Sommerfeld et al 1998]. The accumulation of C6-C10 acylcarnitines as described above for plasma analysis confirms the diagnosis [Matern 2014]. Note: An alternative cell-based method determines the release of tritiated water in the medium of fibroblasts following incubation with labeled medium-chain fatty acids [Olpin et al 1999].
- **Measurement of MCAD enzyme activity** (currently not available in the US) in cultured fibroblasts or other tissues (leukocytes, liver, heart, skeletal muscle, or amniocytes) by the ETF reduction assay reveals that individuals with MCAD deficiency usually exhibit less than 10% of normal MCAD enzymatic activity [Hale et al 1990].

  Very similar results were obtained by a different assay that uses ferricenium hexafluorophosphate as electron acceptor and 3-phenylpropionyl-CoA as substrate followed by measurement of the product of the reaction catalyzed by MCAD using HPLC coupled to UV detection or MS/MS. This assay is currently available in Europe [Wanders et al 2010].

Confirmatory postmortem testing

- Collection of postmortem blood [Chace et al 2001] and bile [Rashed et al 1995] spots on filter paper cards of the type used for newborn screening for subsequent acylcarnitine analysis. Collection of both specimens provides a better chance of detecting affected individuals and independently confirming the diagnosis. Note: Integrated analysis, post-analytic interpretation, and differential diagnosis of post-mortem acylcarnitine results in blood and bile could be aided by tools developed through the Collaborative Laboratory Integrated Reports (CLIR) project.
- Molecular genetic testing of *ACADM* using the postmortem blood spot or newborn screening blood spot retrieved from the screening laboratory can help confirm the diagnosis (see Table 1). Note: States store leftover

dried blood spot samples for variable lengths of time following newborn screening testing. These samples may be retrievable with parent/patient consent for retrospective biochemical or molecular genetic testing. See genes-r-us.uthscsa.edu for state-by-state newborn screening laboratory contact information.

Note: Although biochemical and/or molecular genetic testing of tissues and cultured skin fibroblasts collected postmortem is also possible [Rinaldo et al 2002], it is logistically impractical and thus rarely done.

Clinical Characteristics

Clinical Description

Fatty acid β-oxidation fuels hepatic ketogenesis, a major source of energy for peripheral tissues once glycogen stores become depleted during prolonged fasting and/or periods of higher energy demands (see Pathophysiology).

Classic MCAD deficiency. Individuals with MCAD deficiency appear normal at birth and usually present between ages three and 24 months, although presentation in adulthood is also possible [Duran et al 1986, Raymond et al 1999, Lang 2009]. Affected individuals tend to present in response to either prolonged fasting (e.g., weaning the infant from nighttime feedings) or intercurrent and common infections (e.g., viral gastrointestinal or upper respiratory tract infections), which typically cause loss of appetite and increased energy requirements when fever is present. 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.

Sudden and unexplained death is often the first manifestation of MCAD deficiency [Iafolla et al 1994, Rinaldo et al 1999, Chace et al 2001]. If the diagnosis of MCAD has not been previously established, at least 18% of affected individuals die during their first metabolic crisis [Iafolla et al 1994].

Hepatomegaly is usually present during acute decompensation, which is also characterized by hypoketotic (not necessarily nonketotic) hypoglycemia, increased anion gap, hyperuricemia, elevated liver transaminases, and mild hyperammonemia.

Individuals with classic MCAD deficiency 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 was observed in 18% of individuals who experienced several episodes of metabolic decompensation [Iafolla et al 1994]. In a long-term study of individuals with MCAD deficiency who were diagnosed prior to newborn screening, many tended to complain about fatigue, muscle pain, and reduced exercise tolerance; however, no physical correlate, in particular no cardiac involvement, was identified [Derks et al 2006].

Published reports on newborn screening outcomes document that individuals identified and treated presymtomatically can be saved from metabolic decompensations and relevant sequelae [Wilcken et al 2007, Lindner et al 2011, Catarzi et al 2013, Tal et al 2015]. However, these reports also show that some patients with MCAD deficiency present (sometimes fatally) in the first few days of life making it impossible to obtain screening results prior to their clinical manifestation. Although the prognosis is excellent once the diagnosis is established, unexpected death during the first metabolic decompensation is common [Iafolla et al 1994, Rinaldo et al 1999, Chace et al 2001] and may occur as late as adulthood (e.g., during metabolic stress precipitated by surgery) [Raymond et al 1999]. Findings at autopsy include cerebral edema and fatty infiltration of the liver, kidneys, and heart [Boles et al 1998].

In a woman with MCAD deficiency, pregnancy complications such as HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelets) and *a*cute *f*atty *l*iver of *p*regnancy (AFLP) may be more frequent (as for other fatty acid β-oxidation disorders) when the fetus also has MCAD deficiency [Nelson et al 2000, Rinaldo et al 2001, Yang & Ibdah 2002, Santos et al 2007].

"Mild" MCAD deficiency. The expansion of newborn screening programs using tandem mass spectrometry

(MS/MS) led to the identification of individuals with milder abnormalities in their acylcarnitine profiles (see Genotype-Phenotype Correlations).

Over a relatively short follow-up period, none of these individuals identified through newborn screening had metabolic crises while being treated. However, one person with a mild biochemical phenotype who was compound heterozygous for the common p.Lys304Glu pathogenic variant and a novel pathogenic variant (p.Gln24Glu) developed hypoglycemia and became comatose during a second metabolic decompensation [Dessein et al 2010]. Therefore, despite having higher residual MCAD enzymatic activity [Zschocke et al 2001], such individuals should be considered at risk of developing clinical manifestations and thus treatment should be initiated [Rinaldo et al 2002].

Pathophysiology

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is a disorder of mitochondrial fatty acid β-oxidation. Fatty acid β-oxidation fuels hepatic ketogenesis, a major source of energy for peripheral tissues once glycogen stores become depleted during prolonged fasting and periods of higher energy demands.

Fatty acid β-oxidation consists of four sequential reactions catalyzed by two sets of chain length-specific enzymes, producing at the end of each cycle a molecule of acetyl-CoA and a molecule of acyl-CoA with two fewer carbons. MCAD is responsible for the initial dehydrogenation of acyl-CoAs with a chain length between four and 12 carbon atoms. A defect of MCAD impairs energy supply to peripheral tissues through ketogenesis and increases glucose dependency and utilization. Metabolites detectable in body fluids (blood, urine, bile) include medium-chain fatty acids, corresponding fatty acyl glycine- and carnitine-esters, and dicarboxylic acids. Accumulation of these metabolites may cause oxidative damage [Derks et al 2014].

Genotype-Phenotype Correlations

Inclusion of MCAD deficiency in newborn screening programs has led to the identification of individuals with less pronounced abnormalities in their acylcarnitine profiles who are compound heterozygotes either for the common *ACADM* pathogenic variant (p.Lys304Gly) and another pathogenic variant or for two non-p.Lys304Glu pathogenic variants [Albers et al 2001, Andresen et al 2001, Zschocke et al 2001, Maier et al 2005, Smith et al 2010]. One of these other pathogenic variants, p.Tyr42His, has an allele frequency of approximately 6% in MCAD-deficient newborns [Andresen et al 2001, Maier et al 2005, Waddell et al 2006, Nichols et al 2008] and is associated with some residual MCAD enzymatic activity [Andresen et al 2001].

Because individuals with a "milder" biochemical phenotype can still develop life-threatening symptoms [Dessein et al 2010] and because intrafamilial differences in the phenotypic expression of MCAD deficiency are common, a consistent genotype-phenotype correlation does not exist [Andresen et al 1997]. While it appears that residual enzyme activity levels better correlate with phenotype [Touw et al 2013], it is reasonable to assume that environmental factors (e.g., diet, stress, intercurrent illnesses) are critical in determining the natural history of this disorder.

Nomenclature

MCAD deficiency was first described in individuals presenting with a Reye-like syndrome and urine organic acid analysis that revealed overexcretion of medium-chain dicarboxylic acids and hexanoylglycine in the absence of significant ketosis [Kølvraa et al 1982]. Accordingly, it is likely that prior to MCAD deficiency having been better delineated, affected individuals were misdiagnosed as having Reye syndrome.

Prevalence

MCAD deficiency is prevalent in individuals of (especially northern) European descent (see below). A similar prevalence has been observed among the gypsies of Portugal [Rocha et al 2014] and Native Americans of California [Feuchtbaum et al 2012]. In the northern European and gypsy populations, the most frequent pathogenic variant is

985A>G (p.Lys304Glu) which has not been detected in affected individuals of Asian descent.

The number of newborns detected with MCAD deficiency through newborn screening programs exceeds that expected based on the population frequency of the common 985A>G pathogenic variant [Andresen et al 2001, Maier et al 2005, Wilcken et al 2009, Vilarinho et al 2010, Andresen et al 2012, Touw et al 2012].

Based on newborn screening programs or pilot studies worldwide, the incidence of MCAD deficiency has been determined in:

- Asia:
  - Japan: 1:51,000 live births* [Shigematsu et al 2002]
  - Saudi Arabia: 1:18,000 live births* [Al-Hassnan et al 2010]
  - Taiwan: 1:263,500 live births* [Chien et al 2013]
- Australia:
  - New South Wales: 1:19,000 live births [Wilcken et al 2009]
- Europe:
  - Austria: 1:24,900 live births [Kasper et al 2010]
  - Denmark: 1:9,000 live births [Andresen et al 2012]
  - England: 1:10,700 live birthds [Oerton et al 2011]
  - Northern Germany: 1:4,900 live births [Sander et al 2001]
  - Southern Germany: 1:8,500 live births [Maier et al 2005]
  - Southwest Germany: 1:13,400 live births [Lindner et al 2011]
  - Greece: 1:16,000 live births [Thodi et al 2012]
  - Central Italy: 1:23,000 live births [Catarzi et al 2013]
  - Portugal/Spain: 1:12,000 live births [Rocha et al 2014]
  - The Netherlands: 1:8,700 live births [Touw et al 2012]
- North America:
  - Canada: 1:23,400 live births [Prasad et al 2012]
  - California (USA): 1:19,000 live births [Feuchtbaum et al 2012]
  - New England (USA): 1:15,000 live births [Hsu et al 2008]
  - New Jersey (USA): 1:14,000 live births [Anderson et al 2012]
  - New York (USA): 1:19,000 live births [Nichols et al 2008]
  - North Carolina (USA): 1:13,000 [Frazier et al 2006]
  - Pennsylvania/North Carolina (USA): 1:15,700 live births [Chace et al 2002]

*The common p.Lys304Glu pathogenic variant has not been observed among Asian populations.

Maier et al [2005] found the disorder to be equally common among Germans and Turks.

MCAD deficiency was considered less common in the Hispanic, African American, and Native American populations in the US. However, this view was corrected by implementation of newborn screening for MCAD deficiency. Available data from California now demonstrate that MCAD deficiency may be as prevalent in Native Americans (1:7,500 live births) as it is among "Native" northern Europeans, and prevalences are similar among newborns of Hispanic, black, and Middle Eastern origin (1:23,000 live births) [Feuchtbaum et al 2012].

The carrier frequency for the *ACADM* p.Lys304Glu pathogenic variant is between 1:40 and 1:100 in northern Europeans, suggestive of a founder effect [Gregersen et al 1993, Tanaka et al 1997].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be caused by mutation of *ACADM*.

Differential Diagnosis

Because of the nonspecific clinical presentation of MCAD deficiency, distinguishing it from other mitochondrial fatty acid β-oxidation disorders is an increasingly complex process that can hardly be achieved by a single test.

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency belongs to the acyl-CoA dehydrogenase (ACAD) gene family, which also includes three other dehydrogenases involved in the fatty acid β-oxidation pathway [Swigonová et al 2009]: short-chain acyl-CoA dehydrogenase (SCAD) encoded by *ACADS*, long-chain acyl-CoA dehydrogenase (LCAD) encoded by *ACADL*, and very long-chain acyl-CoA dehydrogenase (VLCAD) encoded by *ACADVL* [Ikeda et al 1985, Izai et al 1992]. Another gene, *ACAD9,* encodes a protein that has been reported to possibly play a role in fatty acid β-oxidation and in stabilization of complex I of the respiratory chain [Haack et al 2010]. Additional dehydrogenases with homology to MCAD are isovaleryl-CoA dehydrogenase (encoded by *IVD*), 2-methyl branched-chain acyl-CoA dehydrogenase (encoded by *ACADSB*) [Alfardan et al 2010], and isobutyryl-CoA dehydrogenase (encoded by *ACAD8*) [Pedersen et al 2006].

- SCAD deficiency is a highly heterogeneous disorder [Pedersen et al 2008] with phenotypic manifestations possibly modulated by two benign allelic variants that are found in 7% to 14% of the general population [Corydon et al 1998, Corydon et al 2001, Nagan et al 2003].
- Although the presentation of VLCAD deficiency is in some cases similar to that of MCAD deficiency, the majority of individuals with clinically diagnosed VLCAD present with cardiomyopathy [Mathur et al 1999].
- The first individuals detected with LCAD deficiency were two infants whose lung tissues were analyzed following their sudden and unexpected deaths. It was postulated that LCAD deficiency, contrary to manifestations in other ACAD deficiencies and expectations based on LCAD-deficient mice [Kurtz et al 1998], may cause pulmonary disease via disruption of normal surfactant function. However, the molecular basis of these speculations remains to be fully elucidated [Goetzman et al 2014].
- The phenotype of ACAD9 deficiency has not been fully delineated; however, recent reports suggest involvement in the stabilization of the respiratory chain complex I in persons with cardiomyopathy, encephalopathy, and lactic acidosis who have mutation of *ACAD9* [Haack et al 2010, Nouws et al 2014].

For further discussion of differential diagnosis in the newborn screening setting, see Suggestive Findings, **Positive newborn screening**.

All causes of a Reye-like syndrome (i.e., acute noninflammatory encephalopathy with hyperammonemia, liver dysfunction, and fatty infiltration of the liver) need to be considered, including other disorders of fatty acid β-oxidation, defects in ketogenesis, urea cycle disorders, organic acidurias, respiratory chain defects, and inborn errors

of carbohydrate metabolism (e.g., hereditary fructose intolerance).

Although the same biochemical markers elevated in MCAD deficiency are also elevated in glutaric acidemia type II, the presence of one or more additional organic acids (glutaric acid, 2-hydroxy glutaric acid, ethylmalonic acid), C4 and C5 carnitine, and glycine esters [Millington et al 1992], and the normal excretion of phenylpropionylglycine [Rinaldo et al 1988] are important discriminators.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an **asymptomatic** individual diagnosed with medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency, the following evaluations are recommended:

- Plasma acylcarnitine analysis
- Plasma free and total carnitine measurement
- Urine acylglycine analysis
- Urine organic acid analysis
- MCAD activity assay in leukocytes (where available)

In a **symptomatic** individual diagnosed with MCAD deficiency the following additional laboratory studies should be considered:

- Blood glucose concentration
- Blood gas analysis
- Ammonia
- Lactic acid
- CBC with differential
- Electrolytes
- Liver function tests
- Blood cultures (in case of fever)

Although development is typically normal for individuals treated prospectively, those who experience metabolic decompensations requiring hospitalization often demonstrate developmental and neurologic disabilities. Neurodevelopmental assessments and intervention should therefore be considered for such individuals [Derks et al 2006].

Treatment of Manifestations

The most important aspect of treating symptomatic patients is reversal of catabolism and sustained anabolism by provision of simple carbohydrates by mouth (for example, glucose tablets, or sweetened, non-diet beverages) or IV if the patient is unable or unlikely to maintain or achieve anabolism through oral intake of food and fluids. IV administration of glucose should then be initiated immediately with a bolus of 2 mL/kg 25% dextrose, followed by 10% dextrose with appropriate electrolytes at a rate of 10-12 mg glucose/kg/minute and to achieve/maintain a blood glucose level higher than 5 mmol/L [Saudubray et al 1999].

All affected individuals should have 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 individual's metabolic specialist.

Prevention of Primary Manifestations

The mainstay in the treatment of MCAD deficiency is avoidance of fasting. Derks et al [2007] studied the length of time that MCAD-deficient but asymptomatic individuals should be able to fast. Based on their findings, they recommend maximum fasting times of:

- Up to eight hours in infants between ages six and 12 months
- Up to ten hours during the second year of life
- Up to 12 hours after age two years

To avoid excessive fasting:

- Infants require frequent feedings.
- Toddlers could receive 2 g/kg of uncooked cornstarch as a source of complex carbohydrates at bedtime to ensure sufficient glucose supply overnight. A relatively low-fat diet (e.g., <30% of total energy from fat) may be beneficial.

Additional consideration of the patient’s MCAD enzyme activity led Derks et al [2007] to suggest that when residual MCAD enzyme activity in leukocytes is greater than 10% of normal, prevention of fasting is not necessary for otherwise healthy individuals older than age six months [Touw et al 2013]. However, Sturm et al [2012] consider that residual MCAD enzyme activity lower than 30% requires treatment and follow up. Whether possible variability in MCAD enzyme activity assays plays a role in these different assessments is uncertain.

Prevention of Secondary Complications

Recent long-term outcome studies revealed that persons treated for MCAD deficiency are prone to excessive weight gain [Derks et al 2006]. Accordingly, follow up should include weight control measures such as regular education about proper nutrition and allowed physical exercise.

Surveillance

A metabolic specialist should be consulted immediately during intercurrent illness, especially when it involves fever and/or poor calorie in-/uptake.

During the first months of life, monthly visits should be considered to ensure that families understand and are comfortable with treatment while the infant is otherwise well. A dietician should be involved to ensure proper nutrition in terms of quality and quantity.

The frequency of routine follow-up visits is individualized based on comfort level of the patients, families, and health care providers.

Agents/Circumstances to Avoid

Hypoglycemia must be avoided by frequent feedings to avoid catabolism, if necessary by intravenous administration of glucose.

Infant formulas containing medium-chain triglycerides as the primary source of fat are contraindicated in MCAD deficiency.

Alcohol consumption, in particular acute alcohol intoxication (e.g., binge drinking), often elicits a metabolic decompensation in individuals with MCAD deficiency [Lang 2009].

Evaluation of Relatives at Risk

It is appropriate to evaluate the older and younger sibs and parents of a proband in order to identify as early as possible those who would benefit from institution of treatment and preventive measures [Leydiker et al 2011].

- If the *ACADM* pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the *ACADM* pathogenic variants in the family are not known, plasma acylcarnitine and urine acylglycine analysis can be used to clarify the disease status of at-risk sibs.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnant women who have MCAD deficiency must avoid catabolism. This is supported by several case reports describing carnitine deficiency, acute liver failure, and HELLP syndrome in pregnant women with MCAD deficiency [Nelson et al 2000, Santos et al 2007, Leydiker et al 2011].

Therapies Under Investigation

The need for reduction of dietary fat to less than 20% of total calories and the need for L-carnitine supplementation or increase of the L-carnitine dose during metabolic stress are controversial.

- Several authors recommend oral supplementation with 100 mg/kg/day of carnitine to correct the frequently observed secondary carnitine deficiency and to enhance the elimination of toxic metabolites [Roe & Ding 2001].
- Two exercise studies of persons with MCAD deficiency before and after L-carnitine supplementation suggested improved exercise tolerance with supplementation of 100 mg/kg/day [Lee et al 2005] and statistically insignificant benefit with supplementation of 50 mg/kg/day [Huidekoper et al 2006]. More recently, low-intensity exercise for one hour on a cycle ergometer showed reduced fatty acid oxidation rates in patients vs. controls that were not improved by carnitine administration (100 mg/kg/day), while carnitine concentrations in muscle and plasma increased among those receiving carnitine supplementation [Madsen et al 2013].
- Carnitine-mediated detoxification of medium-chain fatty acids, assessed by urinary excretion of medium-chain acylcarnitines, is quantitatively negligible in individuals who are MCAD deficient [Rinaldo et al 1993]; carnitine supplementation does not under controlled circumstances improve the response to a fasting challenge [Treem et al 1989].
  Note: The cost of long-term supplementation with carnitine could be significant. Furthermore, while no severe untoward effects of L-carnitine have been reported in individuals with MCAD deficiency [Potter et al 2012], some patients have complained about nausea, diarrhea, abdominal pain, and a fishy odor when treated with 100 mg/kg/day of L-carnitine [Madsen et al 2013].
- Gene therapy has been suggested; however, aside from promising studies in fibroblast cultures of a patient with MCAD deficiency gene therapy has not been attempted in vivo [Schowalter et al 2005].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of a child affected with MCAD deficiency are obligate heterozygotes and, accordingly, are both carriers of a pathogenic variant in *ACADM*.
- Carriers are asymptomatic.
- Since "asymptomatic" parents of children with MCAD deficiency have been reported to have biallelic *ACADM* pathogenic variants [Duran et al 1986, Kelly et al 1990, Andresen et al 1997, Bodman et al 2001], biochemical testing and/or molecular genetic testing should be offered to both parents.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Given that a clear genotype-phenotype correlation does not exist for MCAD deficiency and that individuals may remain asymptomatic until late adulthood, apparently unaffected sibs should be tested for MCAD deficiency [Roe et al 1986, Rinaldo et al 1999]. See Management, Evaluation of Relatives at Risk.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.

Offspring of a proband

- The offspring of an individual with MCAD deficiency inherit a *ACADM* pathogenic variant from their affected parent.
- The risk that the reproductive partner of an individual with MCAD deficiency is heterozygous for an *ACADM* pathogenic variant may be as high as 1/40. Thus, the risk to the offspring of an affected individual and reproductive partner of northern European origin of having MCAD deficiency is about 1/80.
- It is appropriate to test the offspring of an individual with MCAD deficiency for the disorder.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Options for carrier testing are molecular genetic testing and measurement of MCAD enzymatic activity in various tissues.

- Molecular genetic testing is possible if both *ACADM* pathogenic variants have been identified in an affected family member.
- MCAD enzymatic activity is, on average, 49% of normal MCAD enzymatic activity [Hale et al 1990, Sturm et al 2012].

Note: Biochemical screening tests such as acylcarnitine, organic acid, or acylglycine analyses are not useful in determining carrier status.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Note: States store leftover dried blood spot samples for variable lengths of time following newborn screening testing. These samples may be retrievable with parent/patient consent for retrospective biochemical or molecular genetic testing. See genes-r-us.uthscsa.edu for state-by-state newborn screening laboratory contact information.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once both *ACADM* pathogenic variants have been identified in an affected family member, prenatal testing and preimplantation genetic diagnosis for a pregnancy at increased risk for MCAD are possible options.

Biochemical testing. Prenatal diagnosis for pregnancies at increased risk is also possible by assay of MCAD enzymatic activity in CVS or amniocyte cultures. Amniocyte cultures can also be used for analysis of fatty acid β-oxidation as is done in fibroblast cultures (see Confirmatory Testing, **Biochemical testing**, **Analysis of fatty acid β-oxidation**).

Prenatal diagnosis, with its inherent risks, offers no advantage to timely postnatal measurement of plasma acylcarnitines and urine acylglycines. Prompt postnatal testing and consultation with a biochemical geneticist are indicated.

Requests for prenatal testing for conditions which (like MCAD deficiency) do not affect intellect and have effective treatment available are not common. Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries

for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Medical Home Portal**
  MCADD-Description
- **My46 Trait Profile**
  Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency
- **National Library of Medicine Genetics Home Reference**
  Medium-chain acyl-coenzyme A dehydrogenase deficiency
- **FOD Family Support Group (Fatty Oxidation Disorder)**
  PO Box 54
  Okemos MI 48805-0054
  Phone: 517-381-1940
  Fax: 866-290-5206 (toll-free)
  Email: deb@fodsupport.org; fodgroup@gmail.com
  www.fodsupport.org
- **Organic Acidemia Association**
  Phone: 763-559-1797
  Fax: 866-539-4060 (toll-free)
  Email: kstagni@oaanews.org; menta@oaanews.org
  www.oaanews.org
- **United Mitochondrial Disease Foundation (UMDF)**
  8085 Saltsburg Road
  Suite 201
  Pittsburg PA 15239
  Phone: 888-317-8633 (toll-free); 412-793-8077
  Fax: 412-793-6477
  Email: info@umdf.org
  www.umdf.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.

Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ACADM	1p31.1	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial	CCHMC - Human Genetics Mutation Database (ACADM)	ACADM	ACADM

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B.

OMIM Entries for Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency (View All in OMIM)

201450	ACYL-CoA DEHYDROGENASE, MEDIUM-CHAIN, DEFICIENCY OF; ACADMD
607008	ACYL-CoA DEHYDROGENASE, MEDIUM-CHAIN; ACADM

Gene structure. *ACADM*, a nuclear gene, comprises 12 exons that span more than 44 kb and encode a precursor monomer of 421 amino acids. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. More than 150 pathogenic variants have been described to date [HGMD, Smith et al 2010]. Among the 156 pathogenic variants listed in the HGMD database are 114 pathogenic missense and nonsense variants, 19 splicing variants, 13 small deletions, six small insertions, one small indel, and three large deletions.

The pathogenic variant 985A>G (located in exon 11), which causes an amino acid change from lysine to glutamate at residue 304 (p.Lys304Glu) of the mature MCAD protein, accounts for 67% of alleles in individuals with MCAD deficiency based on newborn screening and clinical testing results in diverse populations [Waddell et al 2006, Hsu et al 2008, Nichols et al 2008, Smith et al 2010, Anderson et al 2012, Andresen et al 2012, Prasad et al 2012, Purevsuren et al 2012, Sturm et al 2012, Thodi et al 2012, Touw et al 2012, Catarzi et al 2013, Chien et al 2013].

The pathogenic variant p.Lys304Glu was independently described by four groups [Kelly et al 1990, Matsubara et al 1990, Yokota et al 1990, Gregersen et al 1991]. In early estimates (based on retrospective clinical studies) the frequency of p.Lys304Glu was close to 90% of all alleles investigated [Yokota et al 1992]; however, with more regions in the world adopting newborn screening for MCAD deficiency this frequency is continuously declining as additional pathogenic variants are identified, particularly in non-northern European populations [Ziadeh et al 1995, Smith et al 2010, Purevsuren et al 2012, Ensenauer et al 2005].

To determine disease risk associated with presumably mild pathogenic variants, detailed investigations could be considered, including carefully executed fasting challenges that have been conducted for persons with "severe" pathogenic variants [Derks et al 2007]. For several presumably mild pathogenic variants identified only presymptomatically through newborn screening, expression studies that may aid in risk assessment have also been conducted to evaluate the effect of the variant on protein folding, temperature sensitivity, and enzyme activity [Jank et al 2014, Koster et al 2014].

Normal gene product. The mature MCAD protein is a homotetramer encoded by a nuclear gene; it is active within the mitochondria. The leading 25 amino acids of the precursor protein are cleaved off once the MCAD protein has reached the mitochondria. Heat shock protein 60 (Hsp60) then aids in the folding of the monomer (42.5 kd). The assembled, mature homotetramer is flavin dependent, with each subunit containing one flavin adenine dinucleotide (FAD) molecule. Electron transfer flavoprotein (ETF) functions as the enzyme's electron acceptor, which explains why MCAD metabolites are also present in individuals with glutaric acidemia type II.

Abnormal gene product. The known *ACADM* pathogenic variants represent primarily missense variants, followed by deletions, nonsense variants, and splicing variants. The common pathogenic variant p.Lys304Glu is a missense variant that leads to reduced production of an unstable protein but does not impair the enzyme's active site.

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Chapter Notes

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