201450

ACYL-CoA DEHYDROGENASE, MEDIUM-CHAIN, DEFICIENCY OF; ACADMD

Alternative titles; symbols

ACADM DEFICIENCY
MCAD DEFICIENCY
MCADH DEFICIENCY
CARNITINE DEFICIENCY SECONDARY TO MEDIUM-CHAIN ACYL-CoA DEHYDROGENASE DEFICIENCY

SNOMEDCT: 128596003; **ICD10CM:** E71.311; **ORPHA:** 42; **DO:** 0080153;

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
1p31.1	Acyl-CoA dehydrogenase, medium chain, deficiency of	201450	Autosomal recessive	3	ACADM	607008

TEXT

A number sign (#) is used with this entry because medium-chain acyl-CoA dehydrogenase deficiency is caused by homozygous or compound heterozygous mutation in the medium-chain acyl-CoA dehydrogenase gene (ACADM; 607008) on chromosome 1p31.

Description

Inherited deficiency of medium-chain acyl-CoA dehydrogenase is characterized by intolerance to prolonged fasting, recurrent episodes of hypoglycemic coma with medium-chain dicarboxylic aciduria, impaired ketogenesis, and low plasma and tissue carnitine levels. The disorder may be severe, and even fatal, in young patients (Matsubara et al., 1986).

Clinical Features

Gregersen et al. (1976) first described MCADH deficiency in a patient who presented with unexplained episodes of lethargy and unconsciousness and C6-C10 dicarboxylic aciduria. Naylor et al. (1978) studied 2 early-adolescent sisters who suffered from intermittent hypoglycemia, lethargy, and coma associated with peripheral lobular fatty changes in the liver. During hypoglycemia, massive C6-C14 dicarboxylic aciduria was demonstrated by gas chromatography. Adipic and monounsaturated sebacic, seburic, ozeleic acids were among those elevated in urine and serum. The workers suggested that because of a defect in beta-oxidation of fatty acids of medium chain length, omega oxidation to dicarboxylic acids had occurred through an alternative pathway. Probably identical cases have been reported, although not in full detail.

Colle et al. (1983) reported 2 children with reversible episodes of hypoglycemia and 'Reye syndrome' who during the acute phases showed urinary excretion of dicarboxylic acids and psi-hydroxy fatty acids. Rhead et al. (1983) measured defective medium-chain acyl-CoA dehydrogenase in one of the patients of Colle et al. (1983), thus supporting the findings of Kolvraa et al. (1982) and Divry et al. (1983) that acyl-CoA dehydrogenase deficiency can be responsible for dicarboxylic aciduria.

In a Finnish family, Rasanen et al. (1971) reported 2 sibs with hepatic steatosis (228100). Studies of a subsequently born affected sib showed changes consistent with nonketotic C6-C10-dicarboxylic aciduria (Simila et al., 1984). Stanley et al. (1983) reported 3 children in 2 families who presented in early childhood with episodes of illness associated with fasting and resembling Reye syndrome: coma, hypoglycemia, hyperammonemia, and fatty liver. Deficiency of medium-chain acyl-CoA dehydrogenase was demonstrated. The authors concluded that the carnitine deficiency was a secondary phenomenon and suggested that other patients with 'systemic carnitine deficiency' (see 212140) who fail to respond to carnitine therapy may have defects in fatty acid oxidation of this type.

Roe et al. (1986) identified this defect in mitochondrial beta-oxidation in 2 asymptomatic sibs in a family in which 2 previous infant deaths had occurred: one attributed to sudden infant death syndrome and one to Reye syndrome. Recognition of MCAD deficiency in one of these infants and in a surviving sib was accomplished by detection of octanoylcarnitine.

Matsubara et al. (1986) stated that at least 24 cases of MCADH deficiency had been reported. Taubman et al. (1987) diagnosed MCADH deficiency in a 20-month-old girl with a history of 2 sibs who died of an encephalopathy diagnosed as Reye syndrome.

Biochemical Features

Amendt and Rhead (1985) studied the original patient described by Gregersen et al. (1976) and 7 others and found no biochemical heterogeneity. The patients showed elevated urinary excretion of straight-chain C6-C10-omega-dicarboxylic acids. These are formed by omega-oxidation of accumulated C10-C12-monocarboxylic acids, which are then shortened by beta-oxidation to medium-chain length. The isolated excretion of straight-chain C6-C10-dicarboxylic acids without associated ketosis is consistent with the defective mitochondrial beta-oxidation produced by MCADH deficiency.

Onkenhout et al. (2001) determined the fatty acid composition of liver, skeletal muscle, and heart obtained postmortem from patients with deficiency of 1 of 3 types of acyl-CoA dehydrogenase: medium-chain, multiple (MADD; 231680), and very long-chain (VLCADD; 201475). Increased amounts of multiple unsaturated fatty acids were found exclusively in the triglyceride fraction. They could not be detected in the free fatty acid or phospholipid fractions. Onkenhout et al. (2001) concluded that intermediates of unsaturated fatty acid oxidation that accumulate as a consequence of MCAD, MADD, and VLCADD are transported to the endoplasmic reticulum for esterification into neutral glycerolipids. The pattern of accumulation is characteristic for each disease, which makes fatty acid analysis of total lipid of postmortem tissues a useful tool in the detection of mitochondrial fatty acid oxidation defects in patients who have died unexpectedly.

Diagnosis

Rinaldo et al. (1988) found that measurement of urinary hexanoylglycine and phenylpropionylglycine by a method of stable-isotope dilution is a fast and reliable method for diagnosis of MCAD deficiency. It can be applied to random urine specimens without pretreatment such as fasting.

Bennett et al. (1990) identified urinary metabolites useful in detecting MCAD deficiency in the newborn period. They suggested that this would be useful in the screening of later-born sibs of cases of the following: proven MCAD deficiency, Reye syndrome (deceased and not tested for MCAD deficiency), sudden infant death syndrome under 1 year of age, sudden unexpected death between ages 1 and 4, and hypoglycemia of unknown origin. Two of the 5 patients studied by von Dobeln et al. (1990) had elder sibs who had died unexpectedly in early infancy. In 3 of the 5 patients and in both deceased sibs, stored filter paper blood samples obtained from the patients and their deceased sibs for purposes of neonatal screening showed elevated levels of 3-hydroxy fatty acids.

Santer et al. (1990) suggested that there are distinctive mitochondrial abnormalities on electron microscopy that rule out Reye syndrome and are suggestive of a disorder of mitochondrial fatty acid oxidation: in addition to large-droplet steatosis, there are an electron-dense mitochondrial matrix and a widened space of inner mitochondrial membranes.

Van Hove et al. (1993) demonstrated that the diagnosis of MCAD deficiency, including presymptomatic neonatal recognition, can be made reliably through the analysis of acylcarnitines in blood. Tandem mass spectrometry is a convenient method for fast and accurate determination.

Iafolla et al. (1994) suggested that MCAD deficiency satisfies the criteria for newborn population screening. The authors collated medical data on 120 patients with MCAD deficiency referred to Duke University Medical Center for biochemical testing. They found that 88% were initially referred because of clinical illness or sudden death. Viral infections precipitated the illness in 85% of cases. Only 12% were initially suspected of having MCAD deficiency. Other initial diagnoses included Reye syndrome, SIDS, idiopathic hypoglycemia, and carnitine deficiency. There were 55 male and 65 female patients ranging from birth to 19 years of age; 118 were white. Twenty-three children died before the diagnosis was made, indicating that unidentified patients with this disorder have a risk of sudden death in early childhood. Furthermore, they found that survivors have a risk of developmental disability, chronic muscle weakness, failure to thrive, and 'cerebral palsy.' Among the sibs of the patients, 23 living sibs were found to be affected on screening and 14 had died. Five carrier parents had been symptomatic in childhood.

Ziadeh et al. (1995) reported the findings in a prospective neonatal screening program in Pennsylvania using tandem mass spectrometry. From the first 80,371 newborns screened, they found 9 babies with MCAD (1/8930), plus 2 additional newborns, screened because of a previously known family history. Molecular analysis showed that 56% of the patients were compound heterozygotes for the 985A-G mutation (K304E; 607008.0001), commonly referred to as G985, and a second mutation.

Clayton et al. (1998) reported their experience in diagnosing MCAD deficiency using the technique of electrospray ionization tandem mass spectrometry (ESI-MS/MS) analysis of butylated carnitine species from dried blood spots. The authors concluded that if neonatal screening was undertaken at 7 to 10 days of age, this technique was both sensitive and specific and would therefore be suitable for a national neonatal screening program.

Prenatal Diagnosis

Bennett et al. (1987) succeeded in prenatal diagnosis by demonstration of marked reduction in octanoate oxidation in cultured amniotic cells. The diagnosis was confirmed by enzyme assay of skin fibroblasts from the aborted fetus.

Clinical Management

In the family reported by Roe et al. (1986), early treatment with L-carnitine was important to the survivors. Breast feeding may be protective in MCAD deficiency. Treem et al. (1989) found that supplementation with carnitine was ineffective. They stressed that avoidance of fasting and prompt institution of glucose supplementation in situations when oral intake is interrupted remain the mainstays of therapy.

Molecular Genetics

In 9 patients with MCAD deficiency, Matsubara et al. (1990) found a 985A-G transition which resulted in a lys304-to-glu substitution (K304E; 607008.0001) in the mature protein. These patients were unrelated, suggesting a high incidence of this abnormality among Caucasian patients. The change was not found in 20 healthy Caucasian and 6 healthy Japanese subjects. Matsubara et al. (1990) found this point mutation in 31 of 34 (91%) mutant MCAD alleles. Yokota et al. (1992) estimated that 90% of MCAD cases involve the same mutation.

Andresen et al. (1997) determined the frequency of 14 known and 7 previously unknown non-G985 mutations in 52 families with MCAD deficiency not caused by homozygosity for the prevalent G985 mutation. They showed that none of the non-G985 mutations is prevalent. In 14 families in which they identified both disease-causing mutations, they correlated the mutations with clinical/biochemical data and found that a genotype/phenotype correlation in MCAD deficiency is not straightforward.

Zschocke et al. (2001) characterized the molecular defect in 4 patients with mild MCAD deficiency. In routine neonatal screening on the fifth day of life, they had been found to have abnormal acylcarnitine profiles indicative of MCAD deficiency. Two were of German origin and the other 2 were born to different consanguineous Turkish parents. In all 4, the clinical course and routine laboratory investigations up to the age of 6 months were unremarkable. Enzyme studies showed residual MCAD activities between those with classic MCAD deficiency and heterozygotes. In 2 cases, ACADM gene analysis revealed compound heterozygosity for the common K304E mutation (607008.0001) and the 199T-C mutation (Y42H; 607008.0011), which they designated Y67H. In the 2 children of consanguineous parents, homozygosity was found for the gly267-to-arg mutation (G267R; 607008.0003) and the S220L mutation (607008.0012), respectively. As in other metabolic disorders, the distinction between 'normal' and 'disease' in MCAD deficiency is blurred into a spectrum of enzyme deficiency states caused by different mutations in the ACADM gene potentially influenced by factors affecting intracellular protein processing.

Genotype/Phenotype Correlations

Gregersen et al. (2001) reviewed the understanding of genotype-phenotype relationships in VLCAD, MCAD, and SCAD. They discussed both the structural implications of mutation type and the modulating effect of the mitochondrial protein quality control systems, composed of molecular chaperones and intracellular proteases. The realization that the effect of the monogene, such as disease-causing mutations in these 3 genes, may be modified by variations in other genes presages the need for profile analyses of additional genetic variations. They stated that the rapid development of mutation detection systems, such as chip technologies, made such profile analyses feasible.

Population Genetics

Pollitt and Leonard (1998) reported the findings of a prospective clinical study of MCAD deficiency in the UK. Between 1994 and 1996 there were 62 reported cases in 54 families, giving a minimum incidence of 4.5 in 100,000. In 46 cases, diagnosis followed an acute illness: 39 after a single episode, 6 after a second, and 1 after his third episode at the age of 12 years. The authors commented that the mortality and morbidity associated with MCAD deficiency remained high. Most patients have their first acute manifestation after the age of 3 months; this, the authors argued, supported the case for the introduction of a national neonatal screening program in the UK.

In a prospective tandem mass spectrometry screening of 930,078 blood spots from neonates in the U.S. population, Andresen et al. (2001) determined the frequency of MCAD deficiency to be 1 in 15,001. Mutation analysis showed that the MS/MS-based method is excellent for detection of MCAD deficiency. The frequency of the 985A-G (607008.0001) mutant allele in newborns with a positive acylcarnitine profile is much lower than that observed in clinically affected patients. They identified a new mutation, 199T-C (607008.0011), which had never been observed in patients with clinically manifest disease but was present in a large proportion of the acylcarnitine-positive samples. Overexpression experiments showed that 199T-C is a mild folding mutation that exhibits decreased levels of enzyme activity only under stringent conditions. A carrier frequency of 1 in 500 in the general population made the 199T-C mutation 1 of the 3 most prevalent mutations in the enzymes of fatty acid oxidation.

In a meta-regression analysis of 43 studies reporting the frequency of the c.985A-G mutation in over 10 million individuals, Leal et al. (2014) found significant variation in the frequency of the mutation across regions. The proportion of individuals homozygous for the mutation was highest in western Europe (4.1 per 100,000), followed by the New World, including the United States, Canada, and Australia (3.2), southern Europe (1.2), and eastern Europe (0.9). No cases with the mutation were identified in Asia or the Middle East. The findings were consistent with a founder effect originating in northern Europe.

See Also:

Coates et al. (1985); Duran et al. (1986)

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Creation Date:
Victor A. McKusick : 6/2/1986
Edit History:
carol : 10/24/2014
mcolton : 10/24/2014
ckniffin : 10/23/2014
carol : 4/22/2013
carol : 3/23/2012
carol : 4/22/2011
terry : 9/9/2010
ckniffin : 8/25/2006
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