201475

ACYL-CoA DEHYDROGENASE, VERY LONG-CHAIN, DEFICIENCY OF; ACADVLD

Alternative titles; symbols

VLCAD DEFICIENCY

SNOMEDCT: 237997005; **ORPHA:** 26793; **DO:** 0080155;

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
17p13.1	VLCAD deficiency	201475	Autosomal recessive	3	ACADVL	609575

TEXT

A number sign (#) is used with this entry because very long-chain acyl-CoA dehydrogenase deficiency is caused by homozygous or compound heterozygous mutation in the gene encoding very long-chain acyl-CoA dehydrogenase (ACADVL; 609575) on chromosome 17p13.

Description

Inborn errors of mitochondrial fatty acid beta-oxidation include medium-chain acyl-CoA dehydrogenase deficiency (201450), short-chain acyl-CoA dehydrogenase deficiency (201470), and very long-chain acyl-CoA dehydrogenase deficiency.

VLCAD deficiency can be classified clinically into 3 forms: a severe early-onset form with high incidence of cardiomyopathy and high mortality; an intermediate form with childhood onset, usually with hypoketotic hypoglycemia and more favorable outcome; and an adult-onset, myopathic form with isolated skeletal muscle involvement, rhabdomyolysis, and myoglobinuria after exercise or fasting (Andresen et al., 1999).

Patients reported with long-chain acyl-CoA dehydrogenase (LCAD) deficiency before VLCAD deficiency was defined were later found to have VLCAD deficiency (Strauss et al., 1995; Roe and Ding, 2001).

Clinical Features

Hale et al. (1985) reported 3 unrelated children who presented in early childhood with nonketotic hypoglycemia and episodes of cardiorespiratory arrest associated with fasting. Other features included hepatomegaly, cardiomegaly, and hypotonia. Total plasma carnitine concentration was low. The findings suggested a defect in mitochondrial fatty acid oxidation. Specific assays showed that the activity of long-chain acyl-CoA dehydrogenase was less than 10% of control values in fibroblasts, leukocytes, and liver. Activities of medium-chain, short-chain, and isovaleryl CoA dehydrogenases were normal. With cultured fibroblasts, CO2 evolution from medium-chain and short-chain fatty acids was normal and that from long-chain fatty acids was reduced. As in medium-chain acyl-CoA dehydrogenase deficiency, dicarboxylic acids in the urine and relatively low urinary beta-hydroxybutyrate levels were formed by omega-oxidation of fatty acids in the cytoplasm. The parents had intermediate levels of enzyme activity, suggesting autosomal recessive inheritance.

Hale et al. (1985) also demonstrated deficiency of the long-chain dehydrogenase in fibroblasts from 2 sibs reported by Naylor et al. (1980) with features similar to those in their 3 patients.

Treem et al. (1991) described an affected infant and compared the case with 7 previously published cases. The infant had hypotonia and marked cardiac enlargement as well as hypoglycemia.

Ribes et al. (1992) provided follow-up information on a patient described by Riudor et al. (1986). LCAD deficiency had been documented in the fibroblasts from the patient and treatment with frequent low-fat high-carbohydrate feedings, riboflavin, and carnitine reduced the frequency and intensity of crises. However, the patient developed progressive cardiomegaly and persistent hepatosplenomegaly. Following a crisis similar to those suffered previously, he went into cardiorespiratory arrest at the age of 4.5 years.

Bertrand et al. (1993) reported deficiency of very long-chain acyl-CoA dehydrogenase in a 2-year-old girl with a fatty acid oxidation defect.

Yamaguchi et al. (1993) identified VLCAD deficiency in 3 patients previously diagnosed with LCAD deficiency.

Aoyama et al. (1993) reported 2 male patients with VLCAD deficiency as evidenced by in vitro findings of very low palmitoyl-CoA dehydrogenase activity and lack of immunoreactivity to antibody against the VLCAD protein. One patient presented at age 3 months with hypoketotic hypoglycemia, hepatocellular disease, and cardiomyopathy. At autopsy, there was severe hepatocellular injury and marked lipid accumulation in many tissues. The other patient, reported by Tonsgard et al. (1991) as an instance of an unexplained defect of long-chain fatty

acid oxidation, presented at age 4 months with hypoglycemia, hepatocellular dysfunction, and cardiomyopathy. Laboratory testing revealed hyperammonemia and increased urinary levels of adipate and sebacate. Microscopic examination at autopsy showed lipid accumulation in many tissues.

Ogilvie et al. (1994) reported a 21-year-old man with VLCAD who presented with a 5-year history of exercise-induced muscle pain and myoglobinuria. Residual enzyme activity was approximately 10% of control values. The patient was able to decrease the amount of pain if he ate a carbohydrate snack before or during the exercise.

Aoyama et al. (1995) used immunoblotting to analyze for VLCAD protein deficiency in skin fibroblasts from 26 patients suspected of having a disorder of mitochondrial beta-oxidation; 7 samples contained undetectable or trace levels of the VLCAD enzyme. Clinically, all patients with VLCAD deficiency exhibited cardiac disease, and at least 4 of them presented with hypertrophic cardiomyopathy. The biochemical work suggested a heterogeneity of mutations causing deficiency in the 7 patients. Six of the 7 patients studied by Aoyama et al. (1995) were North American Caucasians, and 1 was Asian. Clinical onset of abnormality was within 4 months after birth, 75% died within 2 months after onset, and all patients had liver dysfunction and cardiac disease.

Fukao et al. (2001) reported a 14-year-old Japanese girl who presented with recurrent myalgia and elevated serum creatine kinase after moderate exercise. She was diagnosed as having a myopathic form of VLCAD deficiency confirmed by genetic analysis (609575.0013; 609575.0014). Her first clinical symptom of the disease appeared at age 6. She had never had hypoglycemic attacks, hepatomegaly, or cardiomyopathy. In vitro functional expression studies showed that the mutant proteins were temperature-sensitive and retained residual activity at 30 degrees Celsius. Fukao et al. (2001) concluded that the temperature-sensitive mild mutations in both alleles resulted in this patient's very mild manifestations.

Brown et al. (2014) reported complete neuropsychologic assessment of 7 children with VLCAD deficiency, and 1 additional child with partial assessment. There were 2 females and 6 males in this group. IQs ranged from average to superior. No deficits were found in fine or gross motor skills. One patient had mild language deficit, and 2 had previously required speech therapy. Verbal memory, attention, and executive functioning skills were generally average or above average; visual memory scores were mostly above average. One child was identified as having social skills deficits, and 2 as having behavioral problems. One child rated high on an autism spectrum subscale, and another was formally diagnosed with ASD. Brown et al. (2014) concluded that VLCAD deficiency does not have significant impact on cognitive or motor skills.

Pena et al. (2016) retrospectively analyzed early outcomes for individuals who were diagnosed with VLCAD deficiency by newborn screening in the USA and described initial presentations, diagnosis, clinical outcomes, and treatment in a cohort of 52 individuals aged 1 to 18 years. Maternal prenatal symptoms were not reported, and most newborns remained asymptomatic. Cardiomyopathy was uncommon in the cohort, diagnosed in 2 of 52 cases. Elevations in creatine kinase were a common finding, and usually first occurred during the toddler period (1 to 3 years of age). Of the 14 subjects with elevated creatine kinase, 11 developed rhabdomyolysis. Diagnostic evaluations required several testing modalities, most commonly plasma acylcarnitine profiles and molecular testing. Functional testing, including fibroblast acylcarnitine profiling and white blood cell or fibroblast enzyme assay, is a useful diagnostic adjunct if uncharacterized mutations are identified.

Evans et al. (2016) reported on 22 patients with VLCAD deficiency identified by newborn screening in Victoria, Australia. Patients were treated with a low natural-fat diet which was relaxed at age 5 if the patients had been asymptomatic, but supplementation with medium-chain triglyceride (MCT) oil before and after physical activity was recommended to all. All patients were doing well with no episodes of encephalopathy or hypoglycemia, but 3 patients had episodes of muscle pain with or without rhabdomyolysis.

Biochemical Features

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, very long-chain, and multiple (MADD; 231680). 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 in these disorders are transported to the endoplasmic reticulum for esterification into neutral glycerolipids. The pattern of accumulation was characteristic for each disease, making 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.

Inheritance

Deficiency of very long-chain acyl-CoA dehydrogenase is an autosomal recessive disorder (Strauss et al., 1995).

Diagnosis

Costa et al. (1996) described 2 patients with celiac disease and prolonged malnourishment whose urinary organic acid profile during a crisis of metabolic decompensation was similar to those frequently observed in long-chain fatty acid oxidation disorders. The first patient was a girl with a history of vomiting and poor weight gain since the introduction of solid food at the age of 3 months. Clinically she had failure to thrive, hypotonia, and motor retardation. Metabolic screening at the age of 12 months revealed normal amino acids, purines, pyrimidines, and mono- and oligosaccharides. Urinary organic acid analysis revealed an increased excretion of dicarboxylic (DC) and 3-hydroxydicarboxylic (3OHDC) acids without ketonuria. Celiac disease was suspected because of gastrointestinal problems. On a gluten-free diet, the organic acid profile normalized completely. The second patient, a girl, presented with a similar clinical history. Organic acid analysis from the urine collected at 12 months of age revealed hypoketotic dicarboxylic aciduria. After the diagnosis of celiac disease and the introduction of a gluten-free diet, the organic acid profile normalized completely. Costa et al. (1996) showed that neither the demonstration of hypoketotic dicarboxylic aciduria nor the analysis of the ratios between urinary DC and 3OHDC acids was sufficient grounds to prove a reliable diagnosis of a potential fatty acid oxidation defect.

Ohashi et al. (2004) identified 13 patients with the myopathic form of VLCAD deficiency by using immunohistochemistry to analyze the VLCAD protein in skeletal muscle biopsies. Biochemical analysis confirmed that all 13 patients had low enzymatic activity and reduced amounts of VLCAD protein. Genetic analysis confirmed that they all had mutations in the ACADVL gene. Ohashi et al. (2004) concluded that the immunohistochemical technique was an effective diagnostic tool for VLCAD deficiency.

Clinical Management

Cox et al. (1998) described a 5-year-old girl with VLCAD deficiency confirmed by genetic analysis (see, e.g., 609575.0012). She was first seen at 5 months of age with severe hypertrophic cardiomyopathy, hepatomegaly, encephalopathy, and hypotonia. After initial treatment with intravenous glucose and carnitine, the patient thrived on a low-fat diet supplemented with medium-chain triglyceride oil and carnitine and avoidance of fasting. Her ventricular hypertrophy resolved significantly over 1 year, and cognitively, she was in the superior range for age. Cox et al. (1998) emphasized that clinical recognition of VLCAD deficiency is important because it is one of the few directly treatable causes of cardiomyopathy in children.

Parini et al. (1998) described a 5-year-old boy with VLCAD deficiency who presented at the age of 5 years with acute severe cardiac and skeletal muscle damage, gross myoglobinuria, and normoglycemia. He was admitted to hospital with severe acute diarrhea, having previously been healthy. Over the next 6 years, he responded well to treatment with 5 meals per day, with medium-chain triglycerides as the main source of lipids, and with raw cornstarch after the last meal of the day. At the time of first presentation in 1992, the patient had been thought to have long-chain acyl-CoA deficiency.

Djouadi et al. (2003, 2005) found that pharmacologic enhancement of a deficient enzyme could be achieved in cells carrying mild mutations of the CPT2 gene (600650), which underlies CPT2 deficiency. This was achieved through cell exposure to bezafibrate, a drug widely used for its hypolipidemic action and acting as an agonist of the peroxisomal proliferator-activated receptors (PPARs). Upon pharmacologic activation, PPARs trigger an upregulation of CTP2 gene expression, which results in an increase in CPT2 residual enzyme activity and thereby correction of fatty-acid oxidation (FAO) flux in treated cells. It was thought that this approach might be extended to other FAO defects, since the PPAR signaling pathway controls many different enzymes in the beta-oxidation pathway. Djouadi et al. (2005) found a beneficial effect of bezafibrate in a small series of VLCAD-deficient fibroblast cell lines.

Gobin-Limballe et al. (2007) investigated response to bezafibrate as a function of genotype in 33 VLCAD-deficient fibroblast cell lines representing 45 mutations. Their results showed that, despite the great diversity of possible consequences of missense mutations for enzyme synthesis, activity, or steady-state level, pharmacologic stimulation of mutant VLCAD gene expression improved the beta-oxidation capacities in a relatively large panel of genotypes.

In 2 unrelated adult men with VLCAD deficiency, Orngreen et al. (2007) found that neither intravenous glucose nor oral medium-chain triglycerides had a beneficial effect on exercise tolerance.

Molecular Genetics

In cultured fibroblasts of 2 patients with VLCAD deficiency, Aoyama et al. (1995) identified a 105-bp deletion in the ACADVL gene (609575.0001).

In 2 unrelated patients with VLCAD deficiency, Strauss et al. (1995) identified mutations in the ACADVL gene (609575.0002-609575.0004). Both patients had originally been diagnosed with long-chain acyl-CoA deficiency (Hale et al., 1985).

Mathur et al. (1999) identified 21 different mutations in the ACADVL gene in 18 of 37 children with cardiomyopathy, nonketotic hypoglycemia and hepatic dysfunction, skeletal myopathy, or sudden death in infancy with hepatic steatosis. Sixty-seven percent of children had severe dilated or hypertrophic cardiomyopathy at presentation. In 7 patients, only 1 mutation was found despite direct sequencing of all exons. Missense, frameshift, and splice consensus sequence mutations were seen, as well as in-frame deletions. Eighty percent of these mutations were associated with cardiomyopathy. The authors concluded that infantile cardiomyopathy is the most common clinical phenotype for VLCAD deficiency and highlighted the marked allelic heterogeneity in this disorder.

Of the 52 patients with VLCAD deficiency reported by Pena et al. (2016), molecular testing was available for 46. Two mutations were identified in 44 of these while only 1 mutation was identified in the remaining 2. Most (38 of 46, 83%) were compound heterozygous, and of the 50 different alleles reported, 26 were novel. Evans et al. (2016) reported 5 novel mutations among 22 patients with VLCAD deficiency identified in Victoria, Australia.

Genotype/Phenotype Correlations

Andresen et al. (1999) studied 54 patients with VLCAD, several of whom had been previously reported. Twenty-five patients had the severe childhood form, 75% of whom had onset within the first 3 days of life. These patients had cardiomyopathy (92%), hepatomegaly (80%), hypotonia (52%), and early death (80%). Twenty-one patients had a milder childhood form with onset by 4 years of age. Clinical features in this group included cardiomyopathy (19%), hepatomegaly (62%), rhabdomyolysis or myoglobinuria (14%), hypotonia (62%), and hypoketotic hypoglycemia (76%). Eight patients had a myopathic adult form, with onset after age 13 years. All of these patients had rhabdomyolysis or myoglobinuria, whereas only 13% had cardiomyopathy and 13% had hypotonia. Genotype analysis identified 58 different ACADVL mutations among the whole group. In patients with the severe childhood form of VLCAD, the majority (71%) of mutant alleles were null, whereas in patients with the milder childhood and adult forms of VLCAD, the majority of alleles (82% and 93%, respectively) were predicted to result in some residual enzyme activity.

Gregersen et al. (2001) reviewed current 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.

History

In an abstract, Kelly et al. (1991) reported the identification of a mutation in the ACADL gene (gln303-to-lys; Q303K) in 3 unrelated patients with LCAD deficiency. No follow-up on this abstract was reported.

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carol : 07/09/2016
alopez : 1/20/2015
carol : 4/27/2011
carol : 4/22/2011
wwang : 12/7/2007
ckniffin : 12/4/2007
alopez : 11/30/2007
alopez : 11/29/2007
alopez : 11/29/2007
carol : 9/22/2005
ckniffin : 9/14/2005
carol : 3/17/2004
tkritzer : 3/11/2004
tkritzer : 3/10/2004
carol : 12/29/2003
ckniffin : 6/13/2002
carol : 4/30/2002
cwells : 2/18/2002
cwells : 2/7/2002
carol : 10/4/2001
mcapotos : 10/1/2001
terry : 9/26/2001
cwells : 9/14/2001
cwells : 9/14/2001
cwells : 9/4/2001
terry : 8/29/2001
cwells : 5/22/2001
cwells : 5/9/2001
cwells : 5/7/2001
terry : 4/23/2001
alopez : 7/3/2000
mcapotos : 6/5/2000
mcapotos : 5/26/2000
carol : 5/22/2000
terry : 5/22/2000
terry : 6/9/1999
terry : 2/19/1999
carol : 11/25/1998
terry : 11/6/1998
carol : 10/5/1998
terry : 10/1/1998
terry : 6/4/1998
alopez : 12/15/1997
alopez : 12/15/1997
dholmes : 12/4/1997
carol : 7/13/1996
mark : 5/31/1996
mark : 5/31/1996
mark : 5/31/1996

carol : 5/22/1996
mark : 5/6/1996
carol : 5/4/1996
mark : 4/23/1996
mark : 1/25/1996
terry : 1/23/1996
mark : 12/6/1995
mark : 12/6/1995
mark : 8/30/1995
jason : 6/27/1994
mimadm : 3/11/1994
carol : 5/27/1993