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Very Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Synonyms: Very Long-Chain Acyl-CoA Dehydrogenase Deficiency, VLCAD Deficiency

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Summary

Clinical characteristics

Deficiency of very long-chain acyl-coenzyme A dehydrogenase (VLCAD), which catalyzes the initial step of mitochondrial beta-oxidation of long-chain fatty acids with a chain length of 14 to 20 carbons, is associated with three phenotypes. The severe early-onset cardiac and multiorgan failure form typically presents in the first months of life with hypertrophic or dilated cardiomyopathy, pericardial effusion, and arrhythmias, as well as hypotonia, hepatomegaly, and intermittent hypoglycemia. The hepatic or hypoketotic hypoglycemic form typically presents during early childhood with hypoketotic hypoglycemia and hepatomegaly, but without cardiomyopathy. The later-onset episodic myopathic form presents with intermittent rhabdomyolysis provoked by exercise, muscle cramps and/or pain, and/or exercise intolerance. Hypoglycemia typically is not present at the time of symptoms.

Diagnosis/testing

The diagnosis of VLCAD deficiency is established in a proband with a specific pattern of abnormal acylcarnitine levels on biochemical testing and/or by identification of biallelic pathogenic variants in *ACADVL* on molecular genetic testing. If one *ACADVL* pathogenic variant is found and suspicion of VLCAD deficiency is high, specialized biochemical testing using cultured fibroblasts or lymphocytes may be needed for confirmation of the diagnosis.

Management

Treatment of manifestations:

- **Routine daily treatment.** Low-fat formula or low long-chain fat / high medium-chain triglyceride (MCT) medical food, with 13%-39% of calories as total fat; total dietary protein above the dietary reference intake

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for age; MCT oil or triheptanoin supplementation; carnitine supplementation; consider supplementation with linoleic acid, arachidonic acid, alpha-linolenic acid, and docosahexaenoic acid; frequent feeding in infants and a bedtime snack high in complex carbohydrates in children and adults; nasogastric tube feeding for those with feeding issues; guided exercise and avoidance of severe exercise to address exercise intolerance in older individuals; standard treatment of cardiomyopathy; supportive developmental therapies as needed.

- **Emergency outpatient treatment.** Consider a trial outpatient treatment at home for up to 12 hours, including frequent high carbohydrate feedings, reduced fasting duration time, antipyretics, and antiemetics.
- **Acute inpatient treatment.** Administration of high-energy fluids (≥10% IV dextrose) with electrolytes at a rate of at least 1.5 times maintenance (minimum of 8 mg/kg/min of glucose) while avoiding the use of L-carnitine and IV lipids; standard treatment for cardiomyopathy / cardiac failure; ample hydration and alkalization of the urine for those with rhabdomyolysis.

Prevention of secondary complications: Acute rhabdomyolysis is treated with ample hydration and alkalization of the urine to protect kidney function and to prevent acute kidney failure secondary to myoglobinuria; if a surgery or procedure is required, notify designated metabolic center in advance of the procedure to discuss perioperative management with surgeons and anesthesiologists; some anesthetics may be contraindicated.

Surveillance: Measurement of growth parameters (including head circumference) and assessment of feeding skills (in infants/toddlers) at each visit; plasma carnitine panel, acylcarnitine profile, and creatine kinase level every three months for the first year of life, every three to six months for those between age one and seven years, and every six to 12 months for those older than age seven years; red blood cell or plasma essential fatty acids every six months for those on long-chain fat restriction; measurement of vitamins A, D, and E annually or as clinically indicated for those on long-chain fat restriction; echocardiogram at least annually or as clinically indicated; DXA scan every five years in adults; measurement of complete blood count, ferritin level, comprehensive metabolic panel, troponin, and B-type natriuretic protein as clinically indicated.

Agents/circumstances to avoid: Fasting; myocardial irritation; dehydration; high-fat diet; and volatile anesthetics and anesthetics that contain high doses of long-chain fatty acids such as propofol and etomidate.

Evaluation of relatives at risk: Evaluation of all at-risk sibs of any age is warranted to identify those who would benefit from treatment and preventive measures.

Pregnancy management: Labor and postpartum periods are catabolic states and place the mother at higher risk for rhabdomyolysis and subsequent myoglobinuria. A management plan for labor and delivery is necessary for the affected pregnant woman. In addition to regular assessment by a cardiologist and maternal fetal medicine specialist, the following are recommended: visit with a nutritionist familiar with VLCAD deficiency monthly or at least in each trimester; measurement of plasma carnitine panel (total, free, esters) and creatine kinase level at each visit; plasma acylcarnitine profile weekly to monthly; red blood cell or plasma essential fatty acids (for those on long-chain fat restriction) at least once during pregnancy; echocardiogram either prior to conception or as soon as a pregnancy is recognized; measurement of vitamins A, D, and E (for those on long-chain fat restriction), complete blood count, ferritin level, and metabolic panel as a baseline or as clinically indicated.

Genetic counseling

VLCAD deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ACADVL* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. Molecular genetic carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible if the pathogenic variants in the family are known.

GeneReview Scope

Very Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency: Included Phenotypes [1]
• Severe early-onset cardiac and multiorgan failure • Hepatic or hypoketotic hypoglycemia • Later-onset episodic myopathy with intermittent rhabdomyolysis

1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

Very long-chain acyl-coenzyme A dehydrogenase (VLCAD) catalyzes the initial step of mitochondrial beta-oxidation of long-chain fatty acids with a chain length of 14 to 20 carbons.

Suggestive Findings

Scenario 1: Abnormal Newborn Screening (NBS) Result

NBS for VLCAD deficiency is primarily based on quantification of various acylcarnitine levels (C14:1, C14:2, C14, and C12:1) and ratios of acylcarnitine levels (C14:1/C2, C14:1/C16) on dried blood spots.

Acylcarnitine values and ratios above the cutoff reported by the screening laboratory are considered positive and require follow-up biochemical testing, which typically includes a confirmatory acylcarnitine profile.

- Although cutoff/abnormal values vary by age, method of collection, and laboratory, a C14:1 level greater than 1 µmol/L [Miller et al 2015] on an initial NBS test strongly suggests VLCAD deficiency. Individuals with this level or higher should be assumed to have VLCAD deficiency.
- Levels of C14:1 greater than 0.8 µmol/L suggest VLCAD deficiency but may also occur in carriers and some healthy individuals having no *ACADVL* pathogenic variants.
- Postanalytic tools, such as those developed by the Region 4 Stork (R4S/CLIR) collaborative, may contribute to refinement of NBS cutoffs and inform clinicians regarding the likelihood of a true positive diagnosis of VLCAD deficiency in individual newborns [Hall et al 2014, Merritt et al 2014]. In Georgia, postanalytic tools have been used to triage abnormal NBS results for follow up. For example, when a case on the dual scatter plot is in the "indeterminate" quadrant or the "affected" quadrant, the child is referred for testing, including sequence analysis, while other cases are referred for repeat screens [Hall et al 2020].
- A significant number of individuals with an abnormal NBS result have one *ACADVL* pathogenic variant and are likely heterozygotes (i.e., carriers) who have been detected because of the low specificity of the initial NBS acylcarnitine screening assay unless multiple marker calculations are applied [Diekman et al 2016].
- If the follow-up biochemical testing supports the likelihood of VLCAD deficiency, additional testing is required to establish the diagnosis (see Establishing the Diagnosis).
- Note: (1) Diagnostic abnormalities may no longer be present if an individual has been fed or has been treated with an IV glucose infusion, or if the episode prompting concern has resolved. (2) NBS data have affirmed that acylcarnitine analysis during periods of physiologic wellness often fails to identify affected individuals who have the milder phenotypes. (3) Severe body weight loss at the sampling day of NBS could cause false positive elevation of C14:1 and C14:1/C2.

The following **medical interventions** need to begin immediately on receipt of an abnormal NBS result while additional testing is performed to determine whether it is a true positive NBS result and to establish the diagnosis of VLCAD deficiency definitively:

- Evaluation of the newborn to ascertain clinical status

- Education of the caregivers to avoid prolonged fasting and to monitor for decreased oral intake, vomiting, or lethargy
- Immediate intervention (to be considered if the newborn is not doing well clinically) possibly including:
  - Admission to the hospital
  - Fluid resuscitation
  - Infusion of IV glucose
  - Nutritional evaluation
  - Institution of enteral nutrition with supplementation of medium-chain fat
  - Cardiac evaluation

  See also Management.

Scenario 2: Symptomatic Individual

A symptomatic individual may have either: findings associated with later-onset VLCAD deficiency; or untreated infantile-onset VLCAD deficiency resulting from any of the following: NBS not performed, false negative NBS result, or caregivers not adherent to recommended treatment following a positive NBS result.

Supportive – but nonspecific– clinical findings by age and preliminary laboratory findings can include the following.

Clinical findings

- Newborn/infant:
  - Severe hypertrophic or dilated cardiomyopathy
  - Pericardial effusion
  - Arrhythmias
  - Hypotonia
  - Hepatomegaly
  - Multiorgan failure
- Older child / adult:
  - Myopathy associated with exercise intolerance
  - Muscle cramps and/or pain
  - Episodic intermittent rhabdomyolysis provoked by strenuous exercise, fasting, cold exposure, or fever

Preliminary laboratory findings

- Newborn/infant:
  - Hypoglycemia out of proportion to the duration of fasting and/or unaccompanied by large ketones in the urine
  - Elevated liver transaminases
  - Altered hepatic synthetic liver function
- Older child / adult: intermittent elevations in creatine phosphokinase with return to normal between episodes

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of VLCAD deficiency **is established** in a proband with a specific pattern of abnormal acylcarnitine levels on biochemical testing and/or biallelic pathogenic (or likely pathogenic) variants in *ACADVL* identified

on molecular genetic testing (see Table 1). If one *ACADVL* pathogenic variant is found and suspicion of VLCAD deficiency is high, specialized biochemical testing using cultured fibroblasts or lymphocytes may be needed for confirmation of the diagnosis.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *ACADVL* variants of uncertain significance (or of one known *ACADVL* pathogenic variant and one *ACADVL* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular Genetic Testing

Scenario 1: Abnormal NBS result. When NBS results and other laboratory findings suggest the diagnosis of VLCAD deficiency, molecular genetic testing approaches typically include **single-gene testing**. Sequence analysis of *ACADVL* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Scenario 2: Genetic testing options for a symptomatic individual who has atypical findings associated with later-onset VLCAD deficiency or untreated infantile-onset VLCAD deficiency (resulting from NBS not performed or false negative NBS result) typically include a **multigene panel** or, less commonly, **comprehensive genomic testing**:

- **A fatty acid oxidation or rhabdomyolysis multigene panel** that includes *ACADVL* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- When the diagnosis of VLCAD deficiency has not been considered, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in VLCAD Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
ACADVL	Sequence analysis [3]	95%-97% [4]
	Gene-targeted deletion/duplication analysis [5]	Rare; 1 reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Liebig et al [2006], Merritt et al [2014], Evans et al [2016], Pena et al [2016], and Hesse et al [2018] report a total of 307 individuals with clinically diagnosed VLCAD, most ascertained by newborn screening. The number of observed vs expected sequence variants across the entire group is 97%. However, only Hesse et al [2018] performed systematic enzyme assays in their entire study population of 108 individuals. For the 55 individuals with enzyme activity that was 0%-24% of control, all pathogenic variants were identified through sequence analysis. For the smaller group, which was designated as an overlap affected/carrier group (n=7) with enzyme activity 25%-27% of control, only 57% had two variants identified through sequence analysis. In this table, the 95% reflects only the data reported by Hesse et al [2018], calculated across both subgroups. Note: The Hesse et al [2018] article does not state that all individuals in the overlap group are affected; that is, some individuals may have only one pathogenic variant, not biallelic pathogenic variants.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Pervaiz et al [2011], Miller et al [2015]

Specialized Biochemical Testing

Specialized biochemical testing may be used to clarify the diagnosis, particularly when molecular testing reveals only one pathogenic variant.

Analysis of fatty acid beta-oxidation in cultured fibroblasts. In vitro incubation of cultured fibroblasts with C13-palmitate or unlabeled palmitate and carnitine may provide indirect evidence of impaired beta-oxidation. Individuals with severe VLCAD deficiency typically accumulate excess tetradecanoyl (C14) carnitine, whereas individuals with less severe phenotypes may shift accumulation toward dodecanoyl (C12) carnitine. This test is often called the "in vitro probe study" and is available clinically.

Analysis of VLCAD enzyme activity. Measurement of VLCAD enzyme activity in leukocytes, cultured fibroblasts, liver, heart, skeletal muscle, or amniocytes by the electron transfer flavoprotein or ferricineum reduction assay can be used to confirm the diagnosis of VLCAD deficiency. Better specificity has been noted when the products are separated and quantitated by high-performance liquid chromatography or tandem mass spectrometry (MS/MS). The clinical availability of this assay has varied with time.

Clinical Characteristics

Clinical Description

Depending on the severity of very long-chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency, individuals can present with hypoketotic hypoglycemia, hepatomegaly, cardiomyopathy, and myopathy with recurrent rhabdomyolysis, triggered by a catabolic state. Therefore, the condition has been divided into three clinical subgroups, including a severe early-onset cardiac and multiorgan failure form, a hepatic or hypoketotic hypoglycemic form, and a later-onset myopathic form [Andresen et al 1999]. Most affected individuals identified by newborn screening (NBS) are asymptomatic at the time of diagnosis [Spiekerkoetter 2010, Baruteau et al 2013].

Scenario 1: Abnormal NBS result and prompt initiation of appropriate management in neonatal period. With early intensive supportive care and diet modification (see Management), normal cognitive outcome has been reported.

- Developmental and intelligence quotient (IQ) scores were similar to those seen in the general population (developmental quotient / IQ ≥85) [Brown et al 2014, Landau et al 2017].
- However, motor and speech delays were reported [Waisbren et al 2013].

Both Pena et al [2016] and Vockley et al [2016] reported individuals who developed cardiomyopathy while being treated with a medium-chain triglyceride oil-based diet.

Bleeker et al [2019] and Marsden et al [2021] reported that NBS results in prevention of hypoglycemic events in those with some residual enzyme activity, but not prevention of hypoglycemia or cardiac complications in affected individuals with very low residual enzyme activity.

Scenario 2: Symptomatic individual associated with later-onset VLCAD deficiency or untreated infantile-onset VLCAD deficiency (resulting from NBS not performed or false negative NBS result)

- **Severe early-onset cardiac and multiorgan failure VLCAD deficiency** typically presents in the first months of life with hypertrophic or dilated cardiomyopathy, pericardial effusion, and arrhythmias, as well as hypotonia, hepatomegaly, and intermittent hypoglycemia.
  - Cardiomyopathy and arrhythmias are often lethal. Ventricular tachycardia, ventricular fibrillation, and atrioventricular block have been reported [Bonnet et al 1999].
  - Although the morbidity resulting from cardiomyopathy may be severe, cardiac dysfunction may be reversible with early intensive supportive care and diet modification.
  - Cox et al [1998] reported normal cognitive outcome at age four years in an affected individual diagnosed clinically with VLCAD deficiency who had severe hypertrophic cardiomyopathy at age five months.
- **Hepatic or hypoketotic hypoglycemic VLCAD deficiency** typically presents during early childhood with hypoketotic hypoglycemia and hepatomegaly (similar to medium-chain acyl-coenzyme A dehydrogenase deficiency) but without cardiomyopathy. Hypoglycemia and poor feeding during the newborn period have been reported in neonates who were later diagnosed with VLCAD deficiency [Pena et al 2016].
- **Later-onset episodic myopathic VLCAD deficiency,** probably the most common phenotype, presents with intermittent rhabdomyolysis provoked by exercise, muscle cramps and/or pain, and/or exercise intolerance. Hypoglycemia typically is not present at the time of symptom onset in these individuals. Ascertainment in adulthood has been reported [Hoffman et al 2006].

Genotype-Phenotype Correlations

As a general rule, strong genotype-phenotype correlations exist in VLCAD deficiency [Andresen et al 1999]:

- Severe disease is associated with no residual enzyme activity, often resulting from null variants. Approximately 81% of pathogenic truncating variants in *ACADVL* are associated with the severe early-onset form [Andresen et al 1999].
- A specific homozygous missense pathogenic variant (c.709T>C;p.Cys237Arg) leading to low long-chain fatty acid oxidation flux may also be associated with cardiac disease [Diekman et al 2015].
- Milder childhood and adult forms are often associated with residual enzyme activity. The common p.Val283Ala variant, in both homozygous and compound heterozygous genotypes, is typically associated with the non-cardiac phenotypes [Spiekerkoetter et al 2009, Diekman et al 2015, Miller et al 2015].

Prevalence

Complete ascertainment by NBS is not assured, but the incidence of VLCAD deficiency is now estimated at 1:30,000 to 1:100,000 births.

NBS has demonstrated that VLCAD deficiency is more prevalent than previously suspected; however, the majority of children ascertained by NBS are asymptomatic during the first few years of observation, suggesting that these individuals may have gone undiagnosed prior to the advent of population-based screening.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ACADVL*.

Differential Diagnosis

Infantile cardiomyopathy with evidence of abnormal fatty acid oxidation may be seen in the autosomal recessive disorders summarized in Table 2 [Roe et al 2006].

Table 2. Disorders in the Differential Diagnosis of Severe Early-Onset VLCAD

Gene	Disorder	Biochemical Phenotype
CPT2	Carnitine palmitoyltransferase (CPT) II deficiency – severe infantile hepatocardiomuscular form	↓ CPT enzyme activity in muscles
ETFA *ETFB* *ETFDH*	Severe forms of multiple acyl-coenzyme A dehydrogenase deficiency	↑ multiple acylcarnitine species of different length size in blood in combination w/↑ excretion of multiple organic acids in urine
HADHA *HADHB*	Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) / trifunctional protein deficiency	↑ C16OH, C18OH, C18:1OH
SLC22A5	Systemic primary carnitine deficiency	Extremely ↓ plasma free carnitine (C0) levels
SLC25A20	Carnitine-acylcarnitine translocase deficiency	↑ C16, C16:1, C18, & C18:1
TANGO2	*TANGO2*-related metabolic encephalopathy & arrhythmias	Recurrent episodes of acute metabolic crises (hypoglycemia, ↑ lactate, mild hyperammonemia)

The hepatic hypoglycemic form of VLCAD deficiency may have clinical features similar to medium-chain acyl coenzyme A dehydrogenase (MCAD) deficiency, or to the electron transfer flavoprotein (ETF) / ETF ubiquinone (coenzyme Q) oxidoreductase defects that produce multiple acyl-coenzyme A dehydrogenase deficiencies; however, the biochemical phenotypes are distinct.

Intermittent rhabdomyolysis is a feature of glycogen storage disease type V (McArdle disease), carnitine palmitoyltransferase (CPT) II deficiency, some primary myopathies, and trifunctional protein deficiency (see Table 3). Rhabdomyolysis is also seen in LPIN1 deficiency, though often at younger ages than in VLCAD deficiency and typically provoked by illness rather than exercise.

Table 3. Selected Metabolic Myopathies in the Differential Diagnosis of Later-Onset Episodic Myopathic VLCAD Deficiency

Disorder Type	Selected Examples	Gene(s)	Clinical Characteristics
Fatty acid oxidation disorders	Multiple acyl-coenzyme A dehydrogenase deficiency	*ETFA* *ETFB* *ETFDH*	Manifest w/endurance-type activity or under fasting or other metabolically stressful conditions
	Carnitine palmitoyltransferase (CPT) II deficiency	*CPT2*	
	Systemic primary carnitine deficiency	*SLC22A5*	
	Trifunctional protein deficiency	*HADHB*	
	Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency	*HADHA*	
Glycogen storage disorders (GSD)	GSD V (McArdle disease)	*PYGM*	Muscular hypotonia, muscle weakness w/limb girdle distribution, high-intensity exercise intolerance
	GSD II (Pompe disease)	*GAA*	
	GSD III	*AGL*	
	GSD IV	*GBE1*	
Lipid metabolism disorders	LPIN1 deficiency (OMIM 268200)	*LPIN1*	Episodic rhabdomyolysis triggered by fasting, infection/fever, or prolonged exercise
Mitochondrial myopathies	*TK2*-related mitochondrial DNA maintenance defect, myopathic form	*TK2*	Impaired use of available oxygen assoc w/muscle fatigue & lactic acidosis at low levels of physical activity
	SUCLA2-related mitochondrial DNA depletion syndrome, encephalomyopathic form w/ methylmalonic aciduria	*SUCLA2*	

Management

Clinical guidelines for the nutritional management of very long-chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency at various ages have been published [Van Calcar et al 2020] (full text). Guidelines can be accessed from the Genetic Metabolic Dietitians International and Southeast Regional Genetics Network websites.

When VLCAD deficiency is suspected during the diagnostic evaluation – for example, as a result of a suggestive acylcarnitine profile (see Suggestive Findings) – fasting precautions should be implemented immediately. In asymptomatic neonates, maternal breast milk without supplemental medium-chain triglycerides can continue as long as fasting precautions are taken [Van Calcar et al 2020].

Development and evaluation of treatment plans, training and education of affected individuals and their families, and avoidance of side effects of dietary treatment (e.g., malnutrition, growth failure) require a multidisciplinary approach including multiple subspecialists, with oversight and expertise from a specialized metabolic center.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with VLCAD deficiency, the evaluations summarized in Tables 4 or 5 (depending on the age at diagnosis) are recommended, if not previously performed as part of the evaluation that led to the diagnosis.

Table 4. Recommended Evaluations Following Initial Diagnosis of VLCAD Deficiency in a Neonate or Infant

Evaluation	Comment
Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian [1]	• Transfer to specialist center w/experience in mgmt of inherited metabolic diseases is strongly recommended. • Consider short hospitalization at center of expertise for inherited metabolic conditions to provide caregivers w/detailed education (natural history, maintenance & emergency treatment, prognosis, & risks for crises).
Baseline laboratory studies	To incl serum creatine kinase concentration, liver transaminases, & blood glucose concentrations
Electrocardiogram	To assess for arrhythmias
Echocardiogram	To assess for cardiomyopathy & cardiac dysfunction
Nutrition / feeding team eval	To incl eval of feeding skills, anthropometric measures, & nutritional status
Consultation w/psychologist &/or social worker	To ensure understanding of diagnosis & assess parental / affected person's coping skills & resources
Genetic counseling by genetics professionals [2]	To inform affected persons & families re nature, MOI, & implications of VLCAD deficiency to facilitate medical & personal decision making

MOI = mode of inheritance
1. After a new diagnosis of VLCAD deficiency in a neonate or infant, the closest hospital and local pediatrician should also be informed.
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Table 5. Recommended Evaluations Following Initial Diagnosis of VLCAD Deficiency in an Older Child or Adult

Evaluation	Comment
Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian	Transfer to specialist center w/experience in mgmt of inherited metabolic diseases is strongly recommended.
Baseline laboratory studies	To incl serum creatine kinase concentration & liver transaminases
Physical exam of abdomen	To assess for hepatomegaly
Developmental assessment	Routine neurodevelopmental assessment
Consultation w/psychologist &/or social worker	To ensure understanding of diagnosis & assess parental / affected person's coping skills & resources
Genetic counseling by genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of VLCAD deficiency to facilitate medical & personal decision making

MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Frequently updated, succinct emergency care plans should detail the typical clinical issues (either those already experienced by the affected individual or those anticipated based on the diagnosis) and the importance of early management (e.g., use of IV glucose as an energy source, monitoring for cardiac rhythm disturbance, and monitoring of rhabdomyolysis) and avoidance of triggers (fasting, long-chain fats, and irritation of the myocardium) [Arnold et al 2009].

Cardiac dysfunction may be reversible with early, intensive supportive care (occasionally including extracorporeal membrane oxygenation) and diet modification.

Triheptanoin (C7). This odd medium-chain fatty acid was approved by the FDA in June 2020 for the treatment of pediatric and adult individuals with VLCAD deficiency.

- The use of triheptanoin is based on its action as an anaplerotic molecule that can correct the secondary depletion of TCA cycle intermediates occurring in these disorders.
- Benefits include decrease in total days of hospitalization per year and reduction in episodes of rhabdomyolysis [Roe & Brunengraber 2015, Zöggeler et al 2021]. Improvement in cardiomyopathy, hepatomegaly, and hypoglycemia was reported in those treated with triheptanoin compared to pretreatment [Roe & Brunengraber 2015, Vockley et al 2015, Vockley et al 2016, Gillingham et al 2017, Vockley et al 2017, Calvert et al 2018].
- Triheptanoin was less effective in reducing rhabdomyolysis post treatment compared to its effect on other symptoms of VLCAD deficiency, suggesting a role for other pathophysiologic mechanisms and demonstrating the need for additional therapies (see Therapies Under Investigation) [Sklirou et al 2021].
- Adverse events in all of the clinical trials were similar for C7 and C8 treatment and predominantly consisted of gastrointestinal symptoms (abdominal pain, diarrhea) [Sklirou et al 2021, Zöggeler et al 2021].

Table 6. Routine Daily Treatment in Individuals with VLCAD Deficiency

Principle/ Manifestation	Treatment	Considerations/Other
Restriction of long-chain fats in persons w/severe disease [1]	Low-fat formula [2, 3] or low long-chain fat / high MCT medical food	Ranging from 13% to 39% of calories as total fat (See Table 7.)
	MCT oil OR triheptanoin (Dojolvi®) supplementation [4, 5]	• For MCT oil: to provide an addl 15%-18% of calories (See Table 7.) • For triheptanoin: to provide 30% of daily caloric intake [6]
	Total dietary protein at or above the DRI for age	
	The Institute of Medicine EER calculation for physical activity & age can be used to predict energy needs. [7]	In infants & children who are gaining weight & are otherwise healthy
	Consider supplementation w/: • LA (3%-4% of total energy) • ARA (0.5%-1.2% of total energy) • ALA (0.5% of total energy) • DHA (infants/toddlers: 60 mg/day; older persons: 100 mg/day)	For those requiring long-chain fat restriction
Prevention of catabolism from overnight fasting	Frequent feeding, incl awakening an infant for feeding or overnight enteral feeding if necessary	In infants
	Consider bedtime snack high in complex carbohydrates.	For children & adults
Exercise intolerance in older persons	• MCT oil at 0.5 g/kg lean body weight 20 min prior to exercise [8] • Exercise guided by affected person's tolerance level	
	Avoidance of severe exercise (e.g., military training)	Which may unmask symptoms in previously asymptomatic adults [9] (See Agents/Circumstances to Avoid.)

Table 6. continued from previous page.

Principle/ Manifestation	Treatment	Considerations/Other
Secondary carnitine deficiency	• Initial oral dosage of 10-25 mg L-carnitine/kg/day divided into 3-4 doses is typical. • Dose is adjusted on an individual basis to maintain plasma free L-carnitine concentration w/in normal age-appropriate reference range.	Supplemental carnitine may not be required but should be considered in those w/free carnitine concentration <10 µmol/L.
Cardiomyopathy	Standard treatment per cardiologist	W/appropriate dietary modification & cardiac support (incl use of ECMO when appropriate), cardiac dysfunction may be reversible.
↑ energy/caloric demands	Nasogastric tube feeding to address feeding issues	Adequate provision of info & education to parents, affected persons, & caregivers
Speech / gross motor delay	• Speech therapy • Physical therapy • Rehab therapy	

ALA = alpha-linolenic acid; ARA = arachidonic acid; DHA = docosahexaenoic acid; DRI = dietary reference intake; ECMO = extracorporeal membrane oxygenation; EER = estimated energy requirement; LA = linoleic acid; MCT = medium-chain triglycerides

1. Solis & Singh [2002], Van Calcar et al [2020]

2. Breast-feeding (or using expressed breast milk) without MCT oil supplements may be considered in asymptomatic neonates predicted to have mild VLCAD deficiency who are growing well, as long as fasting precautions are followed.

3. In asymptomatic infants with moderate VLCAD deficiency, breast-feeding (or using expressed breast milk) can be used with consideration of supplementation with a low long-chain fat / high MCT medical food [Van Calcar et al 2020].

4. Triheptanoin, a synthetic seven odd medium-chain fatty acid triglyceride, was approved by the FDA in June 2020 [Sklirou et al 2021, Zöggeler et al 2021].

5. The FDA recommends discontinuing MCT products prior to initiation of triheptanoin therapy. In the retrospective study by Zöggeler et al [2021], affected individuals were given parallel administration of MCT oil and triheptanoin.

6. Calvert et al [2018], Vockley et al [2019]

7. Van Calcar et al [2020]

8. Gillingham et al [2006], Behrend et al [2012]

9. Hoffman et al [2006], Laforêt et al [2009]

Table 7. Baseline [1] Recommended Total, Long-Chain, and Medium-Chain Fat Intake and Estimated Energy Requirement By Age and Pregnancy/Lactation Status in Individuals with VLCAD Deficiency

Age	Disease Severity	% of Total Energy			Method of Calculating Energy Requirement
		From Total Fat	From Long-Chain Fat	From Medium-Chain Fat	
0-6 mos	Severe	40-55	10-15	30-45	EER [2]
	Moderate		15-30	10-30	
	Mild		30-55	0-20	
7-12 mos	Severe	35-45	10-15	25-30	
	Moderate		15-30	10-25	
	Mild		30-40	0-10	
1-3 yrs	Severe	30-40	10-15	10-30	
	Moderate		20-30	10-20	
	Mild		20-40	0-10	

Table 7. continued from previous page.

Age	Disease Severity	% of Total Energy			Method of Calculating Energy Requirement
		From Total Fat	From Long-Chain Fat	From Medium-Chain Fat	
4-18 yrs	Severe	25-35	10	15-25	EER w/PAL
	Moderate		15-25	10-20	
	Mild		20-35	0-10	
>19 yrs	Severe	20-35	10	10-25	
	Moderate		15-20	10-20	
	Mild		20-35	0-10	
Pregnancy	Severe	20-35	10	10-25	EER per trimester
	Moderate		15-20	10-20	
	Mild		20-35	0-10	
Lactation	Severe	20-35	10	10-25	EER
	Moderate		15-25	10-20	
	Mild		20-35	0-10	

Adapted from Van Calcar et al [2020] Table 2
EER = estimated energy requirement; PAL = physical activity level
1. When an affected individual is clinically well.
2. The estimated energy requirement calculated based on age or pregnancy trimester was published by the Institute of Medicine [2005].

Table 8. Emergency Outpatient Treatment in Individuals with VLCAD Deficiency

Manifestation	Treatment	Considerations/Other
Mildly ↑ catabolism [1]	• Frequent high-carbohydrate feedings [2] • Fasting duration time should be ↓ compared to when person is well.	• Trial of outpatient treatment at home for up to 12 hrs • Reassessment frequently for clinical changes
Fever	Administer antipyretics (acetaminophen, ibuprofen) if temperature >38.5 °C.	
Occasional vomiting	Antiemetics [3]	

1. Fever <38.5 °C (101 °F); enteral feeding is tolerated without recurrent vomiting or diarrhea; absence of neurologic symptoms (altered consciousness, irritability)
2. Focusing on foods that will provide glucose polymers, or simple or complex carbohydrates [Van Calcar et al 2020]
3. Some classes of antiemetics can be used safely on an occasional basis to temporarily improve enteral tolerance of food and beverages at home or during transfer to a hospital.

Table 9. Acute Inpatient Treatment in Individuals with VLCAD Deficiency [1]

Manifestation	Treatment	Consideration/Other
↑ catabolism (due to fever, perioperative/ peri-interventional fasting periods, repeated vomiting/diarrhea)	Administer high-energy fluids (at least 10% IV dextrose) w/electrolytes at rate of ≥1.5x maintenance (minimum of 8 mg/kg/min of glucose). [2]	• Avoid use of L-carnitine during acute illness. • Avoid use of IV lipids. • A source of essential fatty acids should be provided after 7 days.
Cardiomyopathy / Cardiac failure	Standard treatment	Fluid amounts may require adjustment based on cardiac status w/o compromising caloric provisions.

Table 9. continued from previous page.

Manifestation	Treatment	Consideration/Other
Rhabdomyolysis	Ample hydration & alkalization of urine	To protect kidney function & prevent acute kidney failure secondary to myoglobinuria

Adapted from Van Calcar et al [2020]
1. Inpatient emergency treatment should (1) take place at the closest medical facility, (2) be started without delay, and (3) be supervised by physicians and specialist dieticians at the responsible metabolic center, who should be contacted without delay.
2. Total fluid volumes may need to be adjusted if the affected individual has cardiomyopathy; however, caloric provision should not be compromised. If necessary, decreasing IV fluid rates and increasing dextrose concentration (with supplemental insulin, if necessary, to avoid acute hyperglycemia) is required.

Transitional care from pediatric to adult-centered multidisciplinary care settings. As a lifelong disorder with varying implications according to age, smooth transition of care from the pediatric setting is essential for long-term management and should be organized as a well-planned, continuous, multidisciplinary process integrating resources of all relevant subspecialties. Standardized procedures for transitional care do not exist for VLCAD deficiency because of the absence of multidisciplinary outpatient departments.

- Transitional care concepts have been developed in which adult internal medicine specialists initially see individuals with VLCAD deficiency together with pediatric metabolic experts, dietitians, psychologists, and social workers.
- As the long-term course of pediatric metabolic diseases in this age group is not yet fully characterized, continuous supervision by a center of expertise with metabolic diseases with sufficient resources is essential.

Prevention of Primary Manifestations

See Management, Treatment of Manifestations, Table 6.

Prevention of Secondary Complications

One of the most important components of management (as it relates to prevention of secondary complications) is education of parents and caregivers such that diligent observation results in management that can be administered expediently in the setting of intercurrent illness or other catabolic stressors.

Table 10. Prevention of Secondary Manifestations in Individuals with VLCAD Deficiency

Manifestation/ Situation	Prevention	Considerations/Other
Acute decompensation / Rhabdomyolysis	• Intense & ongoing education of affected persons & caregivers re natural history, maintenance & emergency treatment, prognosis, & risks of acute decompensation / rhabdomyolysis • Treatment protocols & provision of emergency letters or cards to incl guidance for care in event of illness while away from home • Medical alert bracelets/pendants, or car seat stickers	• Written protocols for maintenance & emergency treatment should be provided to parents & primary care providers/ pediatricians, & to teachers & school staff. [1, 2] • Emergency letters/cards should be provided summarizing key info & principles of emergency treatment for VLCAD deficiency & containing contact info for primary treating metabolic center. • For any planned travel or vacations, consider contacting a center of expertise near destination prior to travel dates.

Table 10. continued from previous page.

Manifestation/ Situation	Prevention	Considerations/Other
Surgery or procedure (incl dental procedures)	• Notify designated metabolic center in advance of procedure to discuss perioperative mgmt w/ surgeons & anesthesiologists. [3] • Emergency surgeries/procedures require planning input from physicians w/expertise in inherited metabolic diseases (w/respect to perioperative fluid & nutritional mgmt). • Some anesthetics may be contraindicated (see Agents/Circumstances to Avoid).	Consider placing a "flag" in affected person's medical record so that all care providers are aware of diagnosis & need to solicit opinions & guidance from designated metabolic specialists in setting of certain procedures.

1. Essential information including written treatment protocols should be provided *before* inpatient emergency treatment may be necessary.
2. Parents or local hospitals should immediately inform the designated metabolic center if (1) temperature rises above 38.5 °C, (2) vomiting/diarrhea or other symptoms of intercurrent illness develop, or (3) new neurologic symptoms occur.
3. For affected individuals deemed to be high risk for perioperative complications, perioperative/perianesthetic management precautions may include an evaluation at a specialty anesthetic clinic.

Surveillance

In addition to regular evaluations by a metabolic specialist and metabolic dietician, the surveillance evaluations summarized in Table 11 are recommended.

Table 11. Recommended Surveillance for Individuals with VLCAD Deficiency

Manifestation	Evaluation	Frequency/Comment
Abnormal growth / Assessment of nutritional deficiencies / Feeding issues	• Measurement of growth (w/special attention to obesity) [1] & head circumference • Assessment of feeding skills in infants/ toddlers	At each visit
Abnormal biochemical laboratory parameters	Plasma carnitine panel (total, free, esters)	• Every 3 mos for 1st yr of life • Every 6-12 mos for those age >1 yr
	Plasma acylcarnitine profile	• Every 3 mos for 1st yr of life • Every 3-6 mos for those age 1-7 yrs • Every 6-12 mos for those age >7 yrs
	Creatine kinase level	
	RBC or plasma essential fatty acids (for persons on long-chain fat restriction)	Every 6 mos
	Vitamins A, D, & E (for persons on long-chain fat restriction)	Annually or as clinically indicated
	CBC, ferritin level, comprehensive metabolic panel [2]	As clinically indicated
Cardiomyopathy	Echocardiogram	At least annually or as clinically indicated [3]
	Measurement of troponin & BNP	As clinically indicated

Table 11. continued from previous page.

Manifestation	Evaluation	Frequency/Comment
↓ bone mineral density	DXA scan	Every 5 yrs in adults [4]

Adapted from Van Calcar et al [2020]
BNP = B-type natriuretic protein; CBC = complete blood count; DXA = dual-energy x-ray absorptiometry; RBC = red blood cell
1. Obesity can become a significant problem, and is not easy to remedy in individuals with exercise intolerance and requirement for active management of fasting.
2. To include electrolytes, kidney function, liver function, and glucose
3. Particularly in individuals with previous cardiac dysfunction or those with significant exercise intolerance
4. Decreased bone mineral density is not a primary feature of VLCAD deficiency but can occur in those who have nutritional deficiencies, such as low total 25-hydroxyvitamine D concentrations.

Agents/Circumstances to Avoid

Avoid the following:

- Fasting, including periods of preparation and recovery from planned surgery or sedation [Vellekoop et al 2011]
- Myocardial irritation (e.g., cardiac catheterization)
- Dehydration (risk for acute tubular necrosis)
- High-fat diet (long-chain fats) including ketogenic or carbohydrate-restricted diets for the purpose of weight loss. Careful weight reduction has been accomplished by restricting long-chain fats and calories, supplementing with calories provided through medium-chain triglycerides, and limiting overnight catabolism with uncooked cornstarch [Zweers et al 2012].
- Volatile anesthetics and anesthetics that contain high doses of long-chain fatty acids such as propofol and etomidate [Vellekoop et al 2011]. However, the use of propofol for short-duration procedures has been evaluated in individuals with long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency and was not found to cause adverse events [Martin et al 2014].

Evaluation of Relatives at Risk

Testing of all at-risk sibs of any age is warranted to identify as early as possible those who would benefit from institution of treatment and preventive measures (see Management, Treatment of Manifestations).

- If the pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known, plasma or dried blood spot acylcarnitine analysis may not be sufficiently sensitive, and direct VLCAD assay of lymphocytes or fatty acid oxidation probe studies of cultured fibroblasts may be required.

For at-risk newborn sibs when prenatal testing was not performed: in parallel with newborn screening either test for the familial *ACADVL* pathogenic variants or measure an acylcarnitine profile.

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

Pregnancy Management

During pregnancy, placental and fetal beta-oxidation may temporize or even improve maternal fatty acid beta-oxidation [Mendez-Figueroa et al 2010]. However, labor and postpartum periods are catabolic states and place the mother at higher risk for rhabdomyolysis and subsequent myoglobinuria. A management plan for labor and delivery has been proposed by Mendez-Figueroa et al [2010].

Energy needs and fat intake recommendations for women who are pregnant or lactating are listed in Table 7.

Table 12. Recommended Surveillance for Pregnant and Lactating Women with VLCAD Deficiency

Manifestation	Evaluation	Frequency/Comment
Nutritional deficiencies	Formal visit w/nutritionist familiar w/ VLCAD deficiency	Monthly or at least in each trimester
Abnormal biochemical laboratory parameters	Plasma carnitine panel (total, free, esters)	At each visit
	Creatine kinase level	
	Plasma acylcarnitine profile	• Weekly to monthly in pregnant women • At every clinic visit in lactating women
	RBC or plasma essential fatty acids (for persons on long-chain fat restriction)	At least once during pregnancy
	Vitamins A, [1] D, & E (for persons on long-chain fat restriction)	As baseline during pregnancy or as clinically indicated
	CBC, ferritin level, comprehensive metabolic panel [2]	As clinically indicated
Cardiomyopathy	Echocardiogram	As baseline either prior to conception or as soon as pregnancy is recognized
	Assessment by cardiologist & maternal fetal medicine specialist	Regularly, if affected person has known cardiac issue

Adapted from Van Calcar et al [2020]
CBC = complete blood count; RBC = red blood cell
1. Vitamin A excess can be harmful to the developing fetus. Therefore, women who are pregnant or who are planning to become pregnant should reduce their vitamin A supplement dose by 50%. Additionally, close monitoring of serum vitamin A levels throughout pregnancy is recommended. Because vitamin A is an essential vitamin, however, vitamin A supplementation for affected women should not be discontinued during pregnancy. Vitamin A deficiency can lead to maternal morbidity.
2. To include electrolytes, kidney function, liver function, and glucose

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Bezafibrates. Small clinical trials have demonstrated controversial results.

- An open-label clinical trial showed continuously improving physical functioning as assessed through quality of life questionnaire scores in all affected individuals who participated [Shiraishi et al 2019].
- An in vitro study found that mitochondrial metabolic capacity and glutathione were affected by benzafibrate treatment [Lund et al 2021].

Dodecanedioic acid. In an in vitro study, dodecanedioic acid supplementation reduced levels of toxic very long-chain acylcarnitines [Radzikh et al 2021].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Very long-chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *ACADVL* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ACADVL* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *ACADVL* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has VLCAD deficiency or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ACADVL*.

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

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *ACADVL* pathogenic variants in the family.

Biochemical genetic testing. Measurement of acylcarnitines (an acylcarnitine profile), particularly in an unstressed individual, is not reliable for identifying heterozygotes. Functional testing of fibroblasts, using the various protocols of palmitate oxidation and incorporation into small acylcarnitine species, also does not typically identify carriers. A direct VLCAD enzyme assay may provide better evidence of a carrier state than the options described previously, but in most cases molecular genetic testing is preferred. In addition, the clinical availability of the VLCAD enzyme assay has varied with time.

Related Genetic Counseling Issues

The genetic status of full sibs should be determined since many individuals with VLCAD deficiency are not symptomatic during early childhood. See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis, treatment, and preventive measures.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *ACADVL* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Biochemical genetic testing. Prenatal diagnosis of VLCAD deficiency based on the pattern of incorporation of labeled carbons (ranging from palmitate into shorter-chain acylcarnitines) by cultured amniocytes (similar to the fibroblast in vitro acylcarnitine profile) has been described. Assay of VLCAD enzyme activity can distinguish between affected and unaffected cells. Absence of immunoreactive VLCAD on western blot analysis in those with severe VLCAD deficiency should provide additional information. As experience with and clinical availability of these assays is limited in the United States, molecular genetic testing is preferred for prenatal testing.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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**
  VLCADD
- **MedlinePlus**
  Very long-chain acyl-coenzyme A dehydrogenase deficiency
- **STAR-G (Screening, Technology and Research in Genetics)**
  Email: info@newbornscreening.info
  Very long chain acyl-coenzyme A dehydrogenase
- **FOD Family Support Group (Fatty Oxidation Disorder)**
  Phone: 517-381-1940

Email: deb@fodsupport.org; fodgroup@gmail.com
www.fodsupport.org

- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  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. Very Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ACADVL	17p13.1	Very long-chain specific acyl-CoA dehydrogenase, mitochondrial	CCHMC - Human Genetics Mutation Database (ACADVL)	ACADVL	ACADVL

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 Very Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency (View All in OMIM)

201475	ACYL-CoA DEHYDROGENASE, VERY LONG-CHAIN, DEFICIENCY OF; ACADVLD
609575	ACYL-CoA DEHYDROGENASE, VERY LONG-CHAIN; ACADVL

Molecular Pathogenesis

The fatty acid oxidation (FAO) spiral is a series of four reactions occurring in the mitochondrial matrix. Very long-chain acyl-coenzyme A dehydrogenase (VLCAD) catalyzes the initial step of mitochondrial beta-oxidation (β-oxidation) of long-chain fatty acids with a chain length of 14 to 20 carbons. There are a total of four highly homologous, straight-chain acyl-coenzyme A (CoA) dehydrogenases with differing, but overlapping, substrate specificities:

- Short (SCAD; uses C4-C6 fatty acyl-CoAs)
- Medium (MCAD; C6-C10 fatty acyl-CoAs)
- Long (LCAD; C10-C14 fatty acyl-CoAs)
- Very long (VLCAD; C14-C20 fatty acyl-CoAs)

SCAD, MCAD, and LCAD are homotetramers localized to the mitochondrial matrix; VLCAD is a homodimer associated with the inner mitochondrial membrane. These four homologs share about 40% amino acid identity or similarity within the catalytic domain; all use flavin adenine dinucleotide as the electron-accepting cofactor. Electrons are fed into the electron transport chain via ETF and ETF dehydrogenase.

With every turn of the β-oxidation spiral, the chain length is shortened by two carbon atoms. Reactions distal to the long-chain acyl-CoA dehydrogenase (LCAD) include those catalyzed by the long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) / trifunctional protein, including a hydratase step, dehydrogenase step, and thiolase step.

As one of the first enzymes in the FAO spiral, the enzyme VLCAD controls a critical point in the supply of electrons to the respiratory chain, and also provides a pathway permissive to the production of ketones. It would be expected that significant reduction at this step of fatty acid oxidation would impair the ability to transition successfully from fetal to neonatal life, maintain cardiac output, adapt to long fasting, and generate energy for exercise.

Mechanism of disease causation. Loss of function

Table 13. Notable *ACADVL* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_000018.4 NP_000009.1	c.709T>C	p.Cys237Arg (Cys215Arg)	Assoc w/cardiac disease [Diekman et al 2015]
	c.848T>C	p.Val283Ala (Val243Ala)	The most common pathogenic variant; accounts for ~10%-29% of all pathogenic alleles [Miller et al 2015, Pena et al 2016]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

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