

Disease Name:

**VERY LONG-CHAIN ACYL-CoA DEHYDROGENASE
DEFICIENCY
(VLCAD DEFICIENCY)**

Classification: Fatty acid oxidation disorder

Genetic **Inheritance:** Autosomal recessive

Information: **Population Incidence:** Unknown

Ethnic Incidence: No known population at increased risk

Gene & Location: ACADVL, VLCAD- 17p11.2-p11.1

Common Mutation: No common mutations seen.

OMIM # *201475

Disease **Symptom Onset:** Variable, depending on the phenotype, ranging from neonatal to adult
Information: onset.

Symptoms: Approximately 50% present as infants with nonketotic hypoglycemia, hepatic dysfunction and cardiomyopathy, and this has been generally lethal.
33% present in late infancy or childhood with episodes of nonketotic hypoglycemia and hepatic dysfunction, but no cardiac involvement. There is generally a mildly increased ammonemia, lactate, and creatine kinase.
Approximately 20% present as adolescents or adults with symptoms limited to muscle fatigue, rhabdomyolysis and myoglobinuria triggered by exercise or fasting. There is no hypoglycemia or cardiac involvement

Physical Findings: No particular dysmorphisms. Cardiomyopathy in infants.

Treatment: The mainstay of treatment is a high carbohydrate; low fat diet supplemented with MCT oil and strict avoidance of fasting and prolonged exercise. Aggressive support with calories and fluid is needed for intercurrent illnesses. Carnitine use is controversial.

Natural History without treatment: Patients with the infantile form of the disease usually die in the first year of life. The late infantile hepatic presentation children will die without treatment. The adult form can progress to renal failure if the myoglobinuria is not addressed.

Natural History with treatment: The infantile form is generally fatal, although there are now reports of survivors and complete resolution of cardiomyopathy with early diagnosis and treatment. The later onset patients can survive if treated appropriately. In general the outcome is believed to be good for patients who are identified presymptomatically.

Metabolic Information:

Missing Enzyme & Location: Defect in palmitoyl-CoA dehydrogenase. Responsible for reducing acyl-CoA's of chain lengths C14-C20. This is the first and rate-limiting step in the beta-oxidation of fatty acids by the mitochondria for energy metabolism.

MS/MS profile: C14:1 (tetradecenoyl carnitine)- elevated
C14:1/C12:1 ratio >3

Prenatal testing: Prenatal diagnosis is possible in families with a previously affected child.

Miscellaneous Information:

In the mouse model, there have been arrhythmias and death even in older mice. Confirmatory and diagnostic metabolic testing may be normal even in patients with a known VLCAD mutation.

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References:

1. Andresen SB, Olpin S, Kvittingen EA, Augoustides-Savvopoulou P, Lindhout D, Halley DJJ, Vianey-Saban C, Wanders RJA, IJlst L, Schroeder LD, Bolund L, Gregersen N. "DNA-based prenatal diagnosis for very-long-chain acyl-CoA dehydrogenase deficiency", *J Inher Metab Dis* 1999; 22: 281-285.
2. Andresen BS, Olpin S, Poorthuis BJ, Scholte HR, Vianey-Saban C, Wanders R, IJlst L, Morris A, Pourfarzam M, Bartlett K Baumgartner ER, deKlerk JB, Schroeder LD, Corydon TJ, Lund H, Winter V, Bross P, Bolund L, Gregersen N. "Clear Correlation of Genotype with Disease Phenotype in Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency", *Am J Hum Genet* 1999; 64(2): 479-494.
3. Bartlett K, Eaton S. "Mitochondrial beta-oxidation", *Eur J Biochem.* 2004 Feb;271(3):462-9.
4. Bonnet D, Martin D, deLonlay P, Villain E, Jouvet P, Rabier D, Brivet M, Saudubray JM. "Arrhythmias and Conduction Defects as Presenting Symptoms of Fatty Acid Oxidation Disorders in Children", *Circulation* 1999; 100(22): 2248-2253.
5. Brown-Harrison MC, Nada MA, Sprecher H, Vianey-Saban C, Farquhar J, Gilladoga AC, Roe CR. "Very Long Chain Acyl-CoA Dehydrogenase Deficiency: Successful Treatment of Acute Cardiomyopathy", *Biochem Molec Med* 1996; 58: 59-65.

6. Cairns AP, O'Donoghue PM, Patterson VH, Brown JH. "Very-long-chain acyl-coenzyme A dehydrogenase deficiency- a new cause of myoglobinuric acute renal failure", *Nephrol Dial Transplant* 2000; 15(8): 1232-4.
7. Costa CG, Dorland L, Tavares de Almeida I, Jakobs C, Duran m, Poll-The BT. "The effect of fasting, long-chain triglyceride load and carnitine loan on plasma long-chain acylcarnitine levels in mitochondrial very long-chain acyl-CoA dehydrogenase deficiency", *J Inherit Metab Dis* 1998; 21(4): 391-399.
8. Cox KB, Hamm DA, Millington DS, Matern D, Vockley J, Rinaldo P, Pinkert CA, Rhead WJ, Lindsey JR, Wood PA. "Gestational, pathologic and biochemical differences between very long-chain acyl-CoA dehydrogenase deficiency and long-chain acyl-CoA dehydrogenase deficiency in the mouse", *Hum Mol Genet* 2001; 10(19): 2069-2077.
9. Cox GF, Souri M, Aoyama T, Rockenmacher S, Varvogli L, Rohr F, Hashimoto T, Korson MS. "Reversal of severe hypertrophic cardiomyopathy and excellent neuropsychologic outcome in very-long-chain acyl-coenzyme A dehydrogenase deficiency", *J Pediatr* 1998; 133(2): 247-253.
10. Doi T, Abo W, Tateno m, Hayashi K, Hori T, Nakada T, Fukao T, Takahashi Y, Terada N. "Milder childhood form of very long-chain acyl-CoA dehydrogenase deficiency in a 6-year-old Japanese boy", *Eur J Pediatr* 2000; 159(12): 908-911.
11. Fukao, T, Watanabe H, Orii KE, Takahashi Y, Hirano A, Kondo T, Yamaguchi S, Aoyama T, Kondo N. "Myopathic Form of Very-Long Chain Acyl-CoA Dehydrogenase Deficiency: Evidence for Temperature-Sensitive Mild Mutations in Both Mutant Alleles in a Japanese Girl", *Ped Res* 2001; 49(2): 227-231.
12. Giak SK, Carpenter K, Hammond J, Christodoulou J, Wilcken B. "Quantitative fibroblast acylcarnitine profiles in mitochondrial fatty acid beta-oxidation defects: phenotype/metabolite correlations" *Mol Genet Metab* 2002; 76 (4): 327
13. Gregersen N, Andresen BS, Corydon MJ, Corydon TJ, Olsen RK, Bolund L, Bross P. "Mutation analysis in mitochondrial fatty acid oxidation defects: Exemplified by acyl-CoA dehydrogenase deficiencies, with special focus on genotype-phenotype relationship" *Hum Mutat* 2001; 18 (3): 169-189.
14. Gregersen N, Bross P, Andresen BS. "Genetic defects in fatty acid beta-oxidation and acyl-CoA dehydrogenases. Molecular pathogenesis and genotype-phenotype relationships", *Eur J Biochem.* 2004 Feb;271(3):470-82.
15. Guertl B, Noehammer C, Hoefler G. "Metabolic cardiomyopathies", *Int J Exp Pathol* 2000; 81(6): 349-372.
16. Hasegawa T, Hori N, Du W. "A case of impairment of mitochondrial fatty acid beta-oxidation", *Keio J Med* 2002; 51(2): 100-106.

17. He G, Yang BZ, Roe DS, Teramoto R, Aleck K, Grebe TA, Roe CR, Ding JH. "Identification of Two Novel Mutations in the Hypoglycemic Phenotype of Very Long Chain Acyl-CoA Dehydrogenase Deficiency", *Biochem Biophys Res Commun* 1999; 264(2): 483-487.
18. Kluge S, Kuhnelt P, Block A, Merkel M, Gocht A, Lukacs Z, Kohlschutter A, Kreymann G. "A young woman with persistent hypoglycemia, rhabdomyolysis, and coma: Recognizing fatty acid oxidation defects in adults", *Crit Care Med* 2003; 31(4): 1273-1276.
19. Martinez G, Jimenez-Sanchez G, Divry P, Vianey-Saban C, Riudor E, Rodes M, Briones P, Ribes A. "Plasma free fatty acids in mitochondrial fatty acid oxidation defects", *Clinica Chimica Acta* 1997; 267: 143-154.
20. Mathur A, Sims HF, Gopalakrishnan D, Gibson B, Rinaldo P, Vockley J, Hug G, Strauss AW. "Molecular Heterogeneity in Very-Long-Chain Acyl-CoA dehydrogenase Deficiency Causing Pediatric Cardiomyopathy and Sudden Death", *Circulation* 1999; 99: 1337-1343.
21. Merinero B, Pascual SIP, Perez-Cerda C, Gangoiti J, Castro M, Garcia MJ, Castroviejo IP, Vianey-Saban C, Andresen B, Gregersen N, Ugarte M. "Adolescent myopathic presentation in two sisters with very long-chain acyl-CoA dehydrogenase deficiency", *J Inherit Metab Dis* 1999; 22(7): 802-810.
22. Millington DS. "Interpretation and follow-up of abnormal newborn screening results from MS/MS", 2004 Newborn Screening & Genetics Testing Symposium, May 3, 2004, Atlanta, GA
23. Morris AA, Leonard JV. "Early recognition of metabolic decompensation", *Arch Dis Child*. 1997 Jun;76(6):555-6.
24. Morris AAM, Lenoard JV. "Improving the Outcome for Fatty Acid Oxidation Disorders", *J Pediatr Gastroenterol Nutr* 2000; 31(4): 367-370.
25. Morris AA, Turnbull DM. "Fatty acid oxidation defects in muscle", *Curr Opin Neurol*. 1998 Oct;11(5):485-90.
26. Nada MA, Vianey-Saban C, Roe CR, Ding J-H, Mathieu M, Wappner RS, Bialer MG, McGlynn JA, Mandon G. "Prenatal Diagnosis of Mitochondrial Fatty Acid oxidation Defects" *Prenatal Diagn* 1996; 16: 117-124.
27. Onkenhout W, Venizelos V, Scholte HR, DeKlerk JBC, Poorthuis BJHM. "Intermediates of unsaturated fatty acid oxidation are incorporated in triglycerides but no in phospholipids in tissues from patients with mitochondrial B-oxidation defects". *J Inherit Metab Dis* 2001; 24: 337-344.
28. OMIM- Online Mendelian Inheritance in Man; ACYL-CoA DEHYDROGENASE, VERY LONG-CHAIN, DEFICIENCY OF- *201475
29. Osorio JH, Lluch M, Ribes A. "Analysis of organic acids after incubation with (16-2H3)palmitic acid in fibroblasts from patients with mitochondrial beta-oxidation defects", *J Inherit Metab Dis*. 2003;26(8):795-803.

30. Parini R, Menni F, Garavaglia B, Fesslova V, Melotti D, Massone ML, Lamantea E, Rimoldi M, Vizziello P, Gatti R. "Acute, severe cardiomyopathy as main symptom of late-onset very long-chain acyl-coenzyme A dehydrogenase deficiency", *Eur J Pediatr* 1998; 157: 992-995.
31. Pons R, Cavadini P, Baratta S, Invernizzi F, Lamantea E, Garavaglia B, Taroni F. "Clinical and Molecular Heterogeneity in Very-Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency", *Pediatr Neurol* 2000; 22(2): 98-105.
32. Rinaldo P, Matern D. "Disorders of fatty acid transport and mitochondrial oxidation: challenges and dilemmas of metabolic evaluation", *Genet Med* 2000; 2(6): 338-44.
33. Rinaldo P, Matern D, Bennett MJ. "Fatty Acid Oxidation Disorders", *Annu Rev Physiol* 2002; 64: 477-502.
34. Roe CR. "Inherited disorders of mitochondrial fatty acid oxidation: a new responsibility for the neonatologist", *Semin Neonatol* 2002; 7: 37-47.
35. Roe CR, Ding J. Mitochondrial fatty acid oxidation disorders. In: C. Scriver, A.L. Beaudet, W. Sly and D. Valle, Editors, *The Metabolic and Molecular Basis of Inherited Disease* (eighth ed.), McGraw-Hill, New York (2001), pp. 2297-2326.
36. Roe CR, Sweetman L, Roe DS, David F, Brunengraber H. "Treatment of cardiomyopathy and rhabdomyolysis in long-chain fat oxidation disorders using an anaplerotic odd-chain triglyceride", *J Clin Invest* 2002; 110(2): 259-269.
37. Roe CR, Wiltse HE, Sweetman L, Alvarado LL. "Death caused by perioperative fasting and sedation in a child with unrecognized very long chain acyl-coenzyme A dehydrogenase deficiency", *J Pediatr* 2000; 136(3): 397-399.
38. Roe DS, Vianey-Saban C, Sharma S, Zobot MT, Roe CR. "Oxidation of unsaturated fatty acids by human fibroblasts with very-long-chain acyl-CoA dehydrogenase deficiency: aspects of substrate specificity and correlation with clinical phenotype",
39. Ruiz-Sanz JI, Aldamiz-Echevarria L, Arrizabalaga J, Aquino L, Jimeno P, Perez-Nanclares G, Sanjurjo P. "Polyunsaturated fatty acid deficiency during dietary treatment of very long-chain acyl-CoA dehydrogenase deficiency. Rescue with soybean oil", *J Inherit Metab Dis* 2001; 24(4): 493-503.
40. Scholte HR, VanCoster RNA, deJonge PC, Poorthuis BJHM, Jeneson JAL, Andresen BS, Gregersen N, deKlerk JBC, Busch HFM. "Myopathy in very-long-chain acyl-CoA dehydrogenase deficiency: clinical and biochemical differences with the fatal cardiac phenotype", *Neuromuscul Disord* 1999; 9(5): 313-319.
41. Sim KG, Hammond J, Wilcken B. "Strategies for the diagnosis of mitochondrial fatty acid β -oxidation disorders", *Clin Chim Acta* 2002; 323: 37-58.

42. Skladal D, Sass JO, Geiger H, Geiger R, Mann C, Vreken P, Wanders RJA, Trawogger R. "Complications in Early Diagnosis and Treatment of Two Infants With Long-Chain Fatty Acid β -Oxidation Defects", *J Pediatr Gastroenterol Nutr* 2000; 31(4): 448-452.
43. Sluysmans T, Tuerlinckx D, Hubinont C, Verellen-Dumoulin C, Brivet M, Vianey-Saban C. "Very long chain acyl-coenzyme A dehydrogenase deficiency in two sibling: Evolution after prenatal diagnosis and prompt management", *J Pediatr* 1997; 131(3): 444-446.
44. Solis JO, Singh RH. "Management of fatty acid oxidation disorders: A survey of current treatment strategies", *J Am Diet Assoc* 2002; 102(12): 1800-1803.
45. Souri M, Aoyama T, Yamaguchi S, Hashimoto T. "Relationship between structure and substrate-chain-length specificity of mitochondrial very-long-chain acyl-coenzyme A dehydrogenase", *Eur J Biochem* 1998; 257(3): 592-598.
46. Sovik O. "Inborn errors of amino acid and fatty acid metabolism with hypoglycemia as a major clinical manifestation", *Acta Paediatr Scand*. 1989 Mar;78(2):161-70.
47. Spiekerkötter U, Schwahn B, Korall H, Trefz FK, Andresen BS, Wendel U. "Very-long-chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency: monitoring of treatment by carnitine/acylcarnitine analysis in blood spots", *Acta Paediatr* 2000; 89: 492-495.
48. Spiekerkötter U, Sun B, Zytkovicz T, Wanders R, Strauss AW, Wendel U. "MS/MS-based newborn and family screening detects asymptomatic patients with very-long-chain acyl-CoA dehydrogenase deficiency", *J Pediatr*. 2003 Sep;143(3):335-42.
49. Spiekerkötter U, Tenenbaum T, Heusch A, Wendel U. "Cardiomyopathy and Pericardial Effusion in Infancy Point to a Fatty Acid β -Oxidation Defect After Exclusion of an Underlying Infection", *Pediatr Cardiol* 2002; 4: epub.
50. Strauss AW, Powell CK, Hale DE, Anderson MM, Ahuja A, Brackett JC, Sims HF. "Molecular basis of human mitochondrial very-long-chain acyl-CoA dehydrogenase deficiency causing cardiomyopathy and sudden death in childhood", *Proc Natl Acad Sci USA* 1995; 92: 10496-10500.
51. Strauss AW, Spiekerkötter U, Ding L, Tokunaga C, Zykovitz T, Marsden D, Rinaldo P, Bennett M. "The changing spectrum of fatty acid oxidation disorders post-newborn screening", *Mol Genet and Metab* 2004; 81: 156-7.
52. Straussberg R, Harel L, Varsano I, Elpeleg ON, Shamir R, Amir J. "Recurrent Myoglobinuria as a Presenting Manifestation of Very Long Chain Acyl Coenzyme A Dehydrogenase Deficiency", *Pediatrics* 1997; 99(6): 894-896.
53. Straussberg R, Strauss AW. "A Novel Mutation of Late-Onset Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency", *Pediatr Neurol* 2002; 27(2): 136-137.

54. Takusa Y, Fukao T, Kimura M, Uchiyama A, Abo W, Tsuboi Y, Hirose S, Fujioka H, Kondo N, Yamaguchi S. "Identification and Characterization of Temperature-Sensitive Mild Mutations in Three Japanese Patients with Nonsevere Forms of Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency", *Mol Genet Metab* 2002; 75(3): 227-234.
55. Tamaoki Y, Kimura M, Hasegawa Y, Iga M, Inoue M, Yamaguchi S. "A survey of Japanese patients with mitochondrial fatty acid β -oxidation and related disorders as detected from 1985 to 2000", *Brain Dev* 2002; 24: 675-680.
56. Touma EH, Rashed MS, Vianey-Saban C, Sakr A, Divry P, Gregersen N, Andresen BS. "A severe genotype with favourable outcome in very long chain acyl-CoA dehydrogenase deficiency", *Arch Dis Child* 2001; 84(1) 58-60.
57. Vianey-Saban C, Divry P, Brivet M, Nada M, Zobot M-T, Mathieu M, Roe C. "Mitochondrial very-long-chain acyl-coenzyme A dehydrogenase deficiency: clinical characteristics and diagnostic considerations in 30 patients", *Clin Chim Acta* 1998; 269: 43-62.
58. Watanabe H, Orii KE, Fukao T, Song X-Q, Aoyama T, IJlst L, Ruitter J, Wanders RJA, Kondo N. "Molecular Basis of Very Long Chain Acyl-CoA Dehydrogenase Deficiency in Three Israeli Patients: Identification of a Complex Mutant Allele With P65L and K247Q Mutations, the Former Being an Exonic Mutation Causing Exon 3 Skipping", *Hum Mutat* 2000; 15(5) 430-438.
59. Wood JC, Magera MJ, Rinaldo P, Seashore MR, Strauss AW, Friedman A. "Diagnosis of Very Long Chain Acyl-Dehydrogenase Deficiency From an Infant's newborn Screening Card", *Pediatrics* 2001; 108(1): e19.
60. Yoon HR, Strauss AW, Yoo HW. "Sudden death in a Korean infant with very long-chain acyl-CoA dehydrogenase deficiency", *J Inherit Metab Dis* 2001; 24: 407-408.
61. Zhang LF, Ding JH, Yang BZ, He GC, Roe C. "Characterization of the bidirectional promoter region between the human genes encoding VLCAD and PSD-95", *Genomics*. 2003 Dec;82(6):660-8.