Rhabdomyolysis as a presenting manifestation of very long-chain acyl-coenzyme A dehydrogenase deficiency

Sara Freitas Oliveira,[1] Liliana Pinho,[2] Hugo Rocha,[3] Célia Nogueira,[3] Laura Vilarinho,[3] Maria José Dinis,[4] Conceição Silva[4]

[1]Vila Nova de Gaia/Espinho Hospital Center; [2]Porto Hospital Center; [3]Genetics Department, National Institute of Health Ricardo Jorge, Porto; [4]Póvoa de Varzim/Vila do Conde Hospital Center, Portugal

Abstract

Very long-chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency (MIM 201475) is a rare inherited disorder with three forms of clinical presentation: a severe early-onset form; an intermediate form with childhood onset; and an adult-onset form, of mild severity. During adolescence and adulthood, exercise intolerance, myalgia and recurrent episodes of rhabdomyolysis are the main clinical features. The authors present a case of a 13-year old female, with severe myalgia and dark urine after prolonged exercise. Analytical evaluation showed marked elevation plasma creatine kinase and myoglobin. The increased levels of tetradecenoyl carnitine in patient's dried blood spot suggested a VLCAD deficiency, which was confirmed by molecular study. Family history is remarkable for first grade consanguinity of parents and a 19-year old brother with records of repeated similar episodes after moderate intensity physical efforts which was subsequently also diagnosed with VLCAD deficiency. This is one of the first cases of late-onset of disease diagnosed in Portugal.

Introduction

Rhabdomyolysis is defined as a clinical and biochemical syndrome resulting from the lysis of skeletal muscle cells. It usually affects healthy individuals following excessive physical activity, trauma, infections, use of medications or illicit drugs and other toxic agent's consumption.[1,2]

Metabolic myopathies might be a rare cause of rhabdomyolysis. They result due to an inability of muscle cells to produce an adequate amount of energy for their needs because of underlying defects in glucose, glycogen, lipid or nucleoside metabolism.[3]

This heterogeneous group of inherited diseases include disorders of fatty acid oxidation (FAO) such as very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency. VLCAD is a key enzyme catalyzing the first reaction in the mitochondrial beta-oxidation of long-chain fatty acids with a chain length of 14 to 20 carbons. This autosomal recessive disorder has a prevalence of about 1:85,000,[4] and was first identified in 1992 by Izai *et al.*[5] The human *VLCAD* gene has been identified and located on the short arm of chromosome 17 between bands p11.2 and p11.13105.[6]

Since 2004, Portuguese Newborn Screening Program includes this disorder in its panel. Until the end of 2012 a total of 738,816 neonates were screened and eight VLCAD deficiency cases were identified (1:92,352). In this cohort, VLCAD deficiency is the second more prevalent FAO after medium-chain acyl-CoA dehydrogenase deficiency. The early detection avoids the morbility and mortality disease-associated.

There are three phenotypes described, according to the age at onset of clinical manifestations:[7-10] i) early infantile-onset cardiac type, a severe form that involves hyperthrophic cardiomyopathy and sometimes leads to sudden death in the early infantile period; ii) childhood-onset hypoglycemia type, of moderate-severity childhood onset, that usually presents as a hypoketotic hypoglycemia eventually with hepatomegaly which is induced by fasting or preceding infections; and iii) adolescent/adult-onset myopathic type, of mild severity and adolescent or adult onset, that occurs during situations of increased energy demand, *e.g.*, after physical exercise or fasting and mostly results in muscle weakness or muscle pain that can proceed to severe rhabdomyolysis with highly elevated creatine phosphokinase (CPK) concentrations.[11-15]

Here, we describe the clinical, biochemical and molecular findings of a female teen with the late-onset type of VLCAD deficiency.

Case Report

A 13-year old female was admitted for severe, generalized muscle pain and dark urine lasting less than one day. The day before, she underwent prolonged physical effort as a result of four soccer games. No history of recent infection or trauma neither intake of herbs, alcohol or other drugs. No history of previously similar episodes or other relevant medical history, such hypoglycemia, recurrent vomiting, liver disease or coma.

She was the second of three children born to healthy first-degree cousins. Her 19-year old brother had a history of repeated similar episodes of muscle pain and dark urine after physical exertion of moderate intensity since the age of 17 and a hospitalization, one year ago, for rhabdomyolysis, but without further etiologic diagnosis.

On admission her temperature was normal. Except for tenderness in her muscles with mobilization difficulties, the physical and neurologic examinations were normal.

Blood sample analysis showed CPK 215,800 U/L (normal<167), lactate dehydrogenase 6000 U/L (normal 240-480), myoglobin 30,950 ng/mL (normal 25-58); and aspartate aminotransferase 4773 U/L (normal 10-50). Glucose, urea, creatinine, sodium, potassium, calcium and phosphorous levels were normal. Venous blood gas measurement revealed no abnormalities. Urinalysis was positive for blood by reagent testing and had 5-10 red blood cells per high-power field by microscopy. Influenza A and B, Epstein-Barr, herpes simplex, parainfluenza, coxsackie, echovirus, adenovirus, human immunodeficiency virus or cytomegalovirus were excluded based on serological studies.

Based on clinical presentation, family history and laboratory results, the diagnosis of

Correspondence: Sara Isabel Freitas de Oliveira, Department of Pediatrics, Vila Nova de Gaia/Espinho Hospital Center – Unit 2, Rua Dr. Francisco Sá Carneiro, 4400 Vila Nova de Gaia – Portugal.
Tel. +351.967804638.
E-mail: saraoliv83@hotmail.com

Key words: rhabdomyolysis, very long-chain acyl-coenzyme A dehydrogenase deficiency, metabolic myopathy.

Acknowledgements: we acknowledge to Helena Santos, physician at the Metabolic Diseases Unit of Vila Nova de Gaia/Espinho Hospital Center, for critical review of the manuscript.

Contributions: SFO, LP, manuscript drafting; SFO, LP, MJD, CS, clinical data collection; HR, CN, LV, genetic data collection and study; MJD, CS, HR, LV, manuscript critical revision. All authors approved the final version to be published.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 1 February 2013.
Revision received: 13 April 2013.
Accepted for publication: 29 April 2013.

Clinics and Practice 2013; 3:e22
doi:10.4081/cp.2013.e22

metabolic myopathy with rhabdomyolysis precipitated by exercise was suspected. For further clarification additional investigations revealed serum lactate 1.20 mmol/L (normal 0.63-2.44), pyruvate 77 µmol/L (normal 54.1-119.9), ammonia 77 µg/dL (normal 45-80) and free carnitine 15 µmol/L (normal 30-50). The urine organic acids profile showed 3-hydroxybutyric acid and acetoacetic acid. Acylcarnitine analysis by tandem mass spectrometry of the patient's dried blood spot disclosed elevated tetradecanoyl carnitine (C14) (0.26 µM, normal<0.24), tetradecenoyl carnitine (C14:1) (0.26 µM, normal<0.18) and tetradecadienoyl carnitine (C14:2) (0.13 µM, normal<0.08), suggesting VLCAD deficiency. This was confirmed on acyl-CoA dehydrogenase very long-chain (*ACADVL*) gene analysis, using standard polymerase chain reaction procedures, with in-house designed primers, to amplify from genomic DNA all exons and exon-intron boundaries of this gene. Sequence analysis was performed in an ABI Prism 3100xl genetic analyzer using the Big Dye terminator v3.1 Cycle Sequencing kit (Applied Biosystems, Inc., Foster City, CA, USA) and allowed the identification of a homozygous mutation, p.L500del (c.1500_1502delCCT), already described.[8] Echocardiography was performed and showed no signs of hypertrophy or cardiomyopathy.

Analgesic treatment with acetaminophen was started as well as aggressive intravenous hydration in order to avoid acute renal injury. Favorable clinical and biochemical evolution was noted, always with preserved renal function and no electrolytic abnormalities, and she was discharged after five days.

Despite having received advice on lifestyle and diet, a second episode of rhabdomyolysis occurred two months later, following a prolonged physical effort, a two hour long soccer game without hydration or food intake during the exercise. Between the two episodes she was asymptomatic with no laboratory abnormalities. Since the second episode, patient compliance has improved, and she remains asymptomatic when following a dietary regimen avoiding fasting for more than eight hours overnight, prolonged exercise and a high-carbohydrate, low-fat diet. She also started supplementation with medium-chain triglyceride oil before physical exercise.

Recently, her brothers were also studied for VLCAD deficiency. The older brother revealed the same homozygous mutation on *ACADVL* gene analysis. Her younger brother, though asymptomatic, was studied through acylcarnitine analysis by tandem mass spectrometry of a dried blood spot specimen collected during a period of fasting that showed no alterations. *ACADVL* gene analysis was also performed and no mutation was identified.

Discussion

Episodes of exercise intolerance followed by dark urine as a result of rhabdomyolysis, and increased serum CPK activity are symptoms of skeletal muscle disease that can be acquired or inherited. Recognized heritable causes of rhabdomyolysis are defects in the glycogen metabolism and glycolysis, in the respiratory chain or in fatty acid oxidation. Within the group of disorders of fatty acid metabolism, carnitine palmitoyl-transferase II deficiency is the most frequently reported condition, but other defects, like VLCAD deficiency, have also been described.

For the present patient, common causes of rhabdomyolysis were excluded, including muscle injury, drugs, toxins or infections. A metabolic etiology, namely a fatty acid metabolism disorder, was suspected given the onset of symptoms after prolonged physical exercise and the suggestive family history, such as parent's consanguinity and brother's similar symptoms. Studies were conducted to confirm this diagnosis and exclude other above mentioned metabolic disorders, also associated to this presentation.

The key biochemical test which allowed an accurate diagnosis of VLCAD deficiency was the measurement of blood spotted onto filter paper acylcarnitines by tandem mass spectometry that revealed accumulation of tetradecenoyl carnitine (C14:1).[7] These biochemical results were sufficiently characteristic to proceed directly to mutation analysis of *ACADVL*, the only gene known to be associated with this disorder.[6] The molecular basis of VLCAD deficiency is very diverse with more than 80 mutations reported in the literature.[9,11,14,16] In fact, no prevalent mutation has yet been detected.

In this particular case we report a known mutation,[8] first described in 2006 which results in deletion of leucine at position 501 of the mature VLCAD protein, and are associated with the same phenotype *i.e.*, the myopathic type. Both parents were found to be heterozygous for this mutation.

Several studies have addressed the question whether or not it is possible to correlate genotype and phenotype in VLCAD deficiency. In fact the only established relations are the presence of null mutations in severe and early phenotypes and missense mutations in milder and later phenotypes.[11,14,16] In patients with two null mutations, the complete absence of VLCAD activity will affect many tissues, including the heart and liver, resulting in cardiomyopathy, hepatomegaly, and recurrent episodes of metabolic decompensation. Patients with missense mutations or single-amino acid deletion mutations may have sufficient residual VLCAD activity, when receiving adequate nourishment, to avoid liver and cardiac symptoms, and may not undertake sufficient sustained exercise, in childhood, to precipitate severe muscle symptoms. The late onset of disease in adolescent/adult patients could simply be the result of their avoidance to metabolic stress during childhood. Alternatively, it is possible that they have mutations with higher residual enzyme activity than that observed in patients with the mild childhood phenotype, resulting in a difference in tolerance of metabolic stress between the two groups of patients.[11]

Although VLCAD deficiency may present with severe cardiac involvement during childhood, almost all patients with later presentation, including the case presented here, did not have symptomatic cardiac abnormalities.

Treatment of VLCAD deficiency is based on dietary modification, with avoidance of long-chain fatty acids and eventually supplementation with medium chain triglycerides (MCT), so that the enzyme-deficient step can be bypassed.[17] Such diet should reverse most symptoms, although during periods of stress, like exercise, the MCT dosage may need to be raised in order to supply the extra energy, thus helping to prevent mobilization of long-chain fatty acids from the adipose tissue. Fasting needs to be avoided for similar reasons.[18]

The diagnosis of the older brother through family screening, stresses the need to consider this group of disorders in similar cases of extreme exercise intolerance and rhabdomyolysis.

Conclusions

In a patient with rhabdomyolysis, and after more common causes are excluded, it is important to consider the possibility of a metabolic disease, in order to provide a quick and adequate diagnosis. In this particular case, the history of parent's consanguinity and a brother with similar symptoms help us to have a high index of suspicion of this disorder. After the diagnosis, adjustments in life-style and diet are crucial in the prevention of recurrent episodes of metabolic decompensation.

References

1. Guis S, Mattei JP, Cozzone PJ, Bendahan D. Pathophysiology and clinical presentations of rhabdomyolysis. Joint Bone Spine 2005;72:382-91.
2. Warren JD, Blumbergs PC, Thompson PD. Rhabdomyolysis: a review. Muscle Nerve 2002;25:332-47.
3. Vanholder R, Sever MS, Erek E, Lameire N. Rhabdomyolysis. J Am Soc Nephrol 2000; 11:1553-61.

4. Lindner M, Hoffmann GF, Matern D. Newborn screening for disorders of fatty-acid oxidation: experience and recommendations from an expert meeting. J Inherit Metab Dis 2010;33:521-6.
5. Izai K, Uchida Y, Orii T, et al. Novel fatty acid beta-oxidation enzymes in rat liver mitochondria. I. Purification and properties of very-long-chain acyl-coenzyme A dehydrogenase. J Biol Chem 1992;267: 1027-33.
6. Andresen BS, Bross P, Vianey-Saban C, et al. Cloning and characterization of human very-long-chain acyl-CoA dehydrogenase cDNA, chromosomal assignment of the gene and identification in four patients of nine different mutations within the VLCAD gene. Hum Mol Genet 1996;5:461-72.
7. Laforet P, Acquaviva-Bourdain C, Rigal O, et al. Diagnostic assessment and long-term follow-up of 13 patients with Very Long-Chain Acyl-Coenzyme A dehydrogenase (VLCAD) deficiency. Neuromuscul Disord 2009;19:324-9.
8. Boneh A, Andresen BS, Gregersen N, et al. VLCAD deficiency: pitfalls in newborn screening and confirmation of diagnosis by mutation analysis. Mol Genet Metab 2006;88:166-70.
9. Pons R, Cavadini P, Baratta S, et al. Clinical and molecular heterogeneity in very-long-chain acyl-coenzyme A dehydrogenase deficiency. Pediatr Neurol 2000;22 98-105.
10. Arnold GL, Van Hove J, Freedenberg D, et al. A Delphi clinical practice protocol for the management of very long chain acyl-CoA dehydrogenase deficiency. Mol Genet Metab 2009;96:85-90.
11. Andresen BS, Olpin S, Poorthuis BJ, et al. Clear correlation of genotype with disease phenotype in very-long-chain acyl-CoA dehydrogenase deficiency. Am J Hum Genet 1999;64:479-94.
12. Andresen BS, Vianey-Saban C, Bross P, et al. The mutational spectrum in very long-chain acyl-CoA dehydrogenase deficiency. J Inherit Metab Dis 1996;19:169-72.
13. Vianey-Saban C, Divry P, Brivet M, et al. Mitochondrial very-long-chain acyl-coenzyme A dehydrogenase deficiency: clinical characteristics and diagnostic considerations in 30 patients. Clin Chim Acta 1998; 269:43-62.
14. Gregersen N, Andresen BS, Corydon MJ, et al. Mutation analysis in mitochondrial fatty acid oxidation defects: Exemplified by acyl-CoA dehydrogenase deficiencies, with special focus on genotype-phenotype relationship. Hum Mutat 2001;18:169-89.
15. Hoffmann L, Haussmann U, Mueller M, Spiekerkoetter U. VLCAD enzyme activity determinations in newborns identified by screening: a valuable tool for risk assessment. J Inherit Metab Dis 2012;35:269-77.
16. Mathur A, Sims HF, Gopalakrishnan D, et al. Molecular heterogeneity in very-long-chain acyl-CoA dehydrogenase deficiency causing pediatric cardiomyopathy and sudden death. Circulation 1999;99:1337-43.
17. Cox GF, Souri M, Aoyama T, et al. Reversal of severe hypertrophic cardiomyopathy and excellent neuropsychologic outcome in very-long-chain acyl-coenzyme A dehydrogenase deficiency. J Pediatr 1998;133: 247-53.
18. 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;136:397-9.