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PERINATAL/NEONATAL CASE PRESENTATION

Clinical and biochemical improvement of very long-chain acyl-CoA dehydrogenase deficiency in pregnancy

H Mendez-Figueroa[1], OA Shchelochkov[2,6], A Shaibani[3,4], K Aagaard-Tillery[1] and MS Shinawi[5]

[1]Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX, USA; [2]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA; [3]Department of Medicine, Baylor College of Medicine, Houston, TX, USA; [4]Nerve and Muscle Center of Texas, Houston, TX, USA and [5]Division of Genetics and Genomic Medicine, Department of Pediatrics, Washington University School of Medicine, St Louis, MO, USA

Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is an enzymatic defect of the fatty acid (FA) beta oxidation pathway. In catabolic states, such as labor and early postpartum period, patients are potentially prone to metabolic decompensation and subsequent rhabdomyolysis with increased risk for myoglobinuria and renal insufficiency. We report a 21-year-old primigravida with a previously characterized VLCAD deficiency, who experienced frequent and unprovoked episodes of rhabdomyolysis before pregnancy. As there was no published experience to guide her management, a detailed multidisciplinary care plan was established to minimize the potential morbidity. Although there is little known about the antenatal course of gravidae affected by VLCAD, we predicted that placental and fetal β-oxidation in an unaffected pregnancy may temporize or even improve maternal FA β-oxidation. Consistent with our prediction, we observed a significant clinical and biochemical improvement throughout her pregnancy, and she delivered vaginally with an uncomplicated postpartum course. We conclude that although VLCAD deficiency can present a therapeutic challenge during pregnancy, the beneficial placento-maternal metabolic interactions and the implementation of a proper peripartum management reassure a successful antenatal and perinatal outcome.
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Introduction

Fatty acids (FAs) are integral components of cellular membranes, hormones and enzymes, as well as an energy source. They are released from lipids and enter the mitochondrial outer membrane through transporter proteins, where they are converted into fatty acyl-CoA esters by a long-chain acyl-CoA synthetase.[1–3] After conjugation with carnitine, the long-chain acyl-CoA esters are converted to acylcarnitine esters, which are then transported into the mitochondrial matrix. After their import, acylcarnitine esters are converted back to acyl-CoA esters and subsequently enter FA β-oxidation.[2] Inherited defects in mitochondrial β-oxidation comprise a group of at least 20 disorders characterized by enzyme or transporter deficiencies along this pathway.[1–4]

Membrane-associated very long-chain acyl-CoA dehydrogenase (VLCAD), encoded by *ACADVL* on 17p13.1, is an enzyme that interacts in the earliest steps of the sequential 2-carbon shortening of FA in the β-oxidation spiral. The enzymatic deficiency has an autosomal recessive inheritance pattern, with an estimated incidence ranging from 1:31 500 to 1:125 000 live births.[5,6]

Mitochondrial β-oxidation deficiencies such as VLCAD deficiency present as a wide spectrum of phenotypes that are more pronounced during periods of metabolic stress, such as exercise, fasting and other intercurrent illnesses.[2,3] These variants reflect the variable tissue-specific energy requirements, gene expression, and perhaps complex epigenetic interactions in a developing organism. For example, in its most severe forms, the VLCAD deficiencies present with neonatal cardiomyopathy and hypoglycemia. The more common clinical presentation in early adulthood is myalgia and exercise intolerance with rhabdomyolysis. The biochemical hallmark of the disease is elevation of C14:1-carnitine; however acylcarnitine moieties with chain length between C12 to C18 are also frequently elevated. Regardless of the variant, management should include the administration of high-carbohydrate, low long-chain fat diet, with medium-chain triglyceride supplementation and replenishment of carnitine deficits.[1–4]

Very little is known about the course of VLCAD deficiency during pregnancy. To our knowledge (Ovid and PubMed, 1966 to the present), only few cases have been reported in the literature[1,7] providing scattered details on the perinatal management in this condition. For example, Laforêt *et al*.,[7] reported that a total of nine pregnancies occurred in five women with the myopathic form of VLCAD deficiency but the course of the disease during pregnancy

Correspondence: Dr MS Shinawi, Division of Genetics and Genomic Medicine, Department of Pediatrics, Washington University School of Medicine, One Children's Place, Campus Box 8116, Northwest Tower, 9132, St Louis, MO 63110, USA.
E-mail: Shinawi_M@kids.wustl.edu
[6]Current address: Division of Genetics, Department of Pediatrics, University of Iowa Hospitals and Clinics, Iowa City, IA, USA.
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was not addressed. Therefore, we report our experience of the perinatal course and management of VLCAD deficiency in a primigravid patient whose clinical presentation and molecular defect has been previously described.[4] We observed an almost complete clinical and biochemical normalization during pregnancy with the return of symptoms ~8 weeks postpartum. We also offer our recommendations on the intrapartum management, which was developed by a multidisciplinary team.

Case

A 21-year-old G_1P_0 patient, followed by the Metabolic Genetics service, was seen in consultation by the Maternal-Fetal medicine team for peripartum management. She was diagnosed with VLCAD deficiency at the age of 20 years, when she presented with recurrent, mostly unprovoked, episodes of muscle weakness, chronic myalgia, rhabdomyolysis and elevated plasma creatine kinase (CK). These episodes appeared 14 months before her initial presentation and recurred every 2–3 months. Her family history was noncontributory.[4] Sequence analysis of the *ACADVL* gene revealed a recurrent c.848T>C mutation (p.V283A) alongside a novel heterozygous splicing mutation (c.879-8T>A), which disrupts transcription as previously reported.[4]

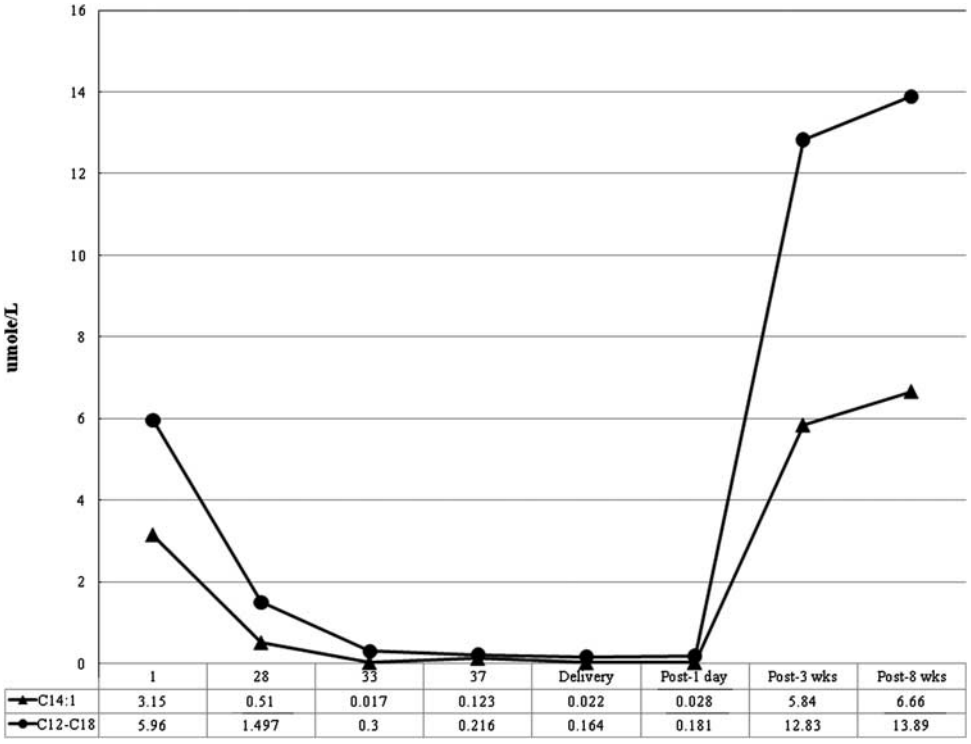
Her past medical history was significant for hypoketotic hypoglycemia in infancy and complex partial seizures since late childhood, which were treated with lamotrigine and levetiracetam. These anticonvulsive medications were discontinued 2 years before pregnancy due to side effects and lack of response. She had multiple hospital admissions for recurrent rhabdomyolysis that were partially controlled with high-carbohydrate diet supplemented with medium-chain triglyceride oil and Levocarnitine supplementation ($50\,mg\,kg^{-1}\,day^{-1}$). Between episodes of rhabdomyolysis before pregnancy, the baseline plasma CK levels never normalized and her acylcarnitine profile exhibited typical findings of VLCAD deficiency. The relatively severe course of disease in our patient was attributed to the lack of compliance to medium-chain triglycerides and to the presence of a splice site mutation.[4]

The patient was counseled regarding her recurrence risk for VLCAD deficiency. The estimation of VLCAD deficiency prevalence today is ~1/31 000.[6] This would translate into a carrier frequency of ~1/90 ($q^2 = 1/31\,000$; $q = 1/180$; $2pq = 1/90$, where $p = \sim 1$). In this particular situation, the possibility that the fetus would have been affected by VLCAD deficiency is 1/1 (mother's chance of allele transmission) × 1/90 (carrier frequency) × 1/2 (father's chance of transmitting the affected allele) = 1/180. This number would drop to 1/350 if we use the prevalence of 1/125 000 as some sources suggest.[6] After discussing these calculated risks with the patient and her husband, they elected not to proceed with parental testing. The patient was also counseled regarding the theoretical possibility of developing acute fatty liver of pregnancy and hemolysis, elevated liver enzymes and low platelets syndrome, as these pathologies have been seen in other FA β-oxidation disorders.[8,9]

Her prenatal laboratories and fetal sonographic examination in midgestation were unremarkable. Maternal serum acylcarnitine profile (Figure 1), liver enzymes, urine organic acids and plasma CK levels were followed up the throughout pregnancy. Her acylcarnitine profile showed a trend toward improvement during the second trimester and complete normalization during third trimester. In parallel with the improvement in her acylcarnitine profile, we observed normalization of her muscle enzymes accompanied by complete resolution of myalgia and muscle weakness.

Given the limited literature available on this disorder in pregnancy,[1,7] an individualized plan of care was established in close collaboration with her team of maternal–fetal medicine, anesthesia, pharmacy, neonatology and metabolic specialists. Our primary goal was to prevent acute metabolic decompensation and precipitation of rhabdomyolysis. In our decision regarding the mode of delivery, we weighed a theoretical concern for rhabdomyolysis triggered by maternal exertion during labor and delivery versus the risks of anesthesia and surgical intervention related to a scheduled cesarean delivery. The patient elected to attempt vaginal delivery with an assisted second stage. Given concerns over prolonged fasting and risk of cesarean section with a scheduled induction, spontaneous labor was preferred. The outlined plan of care detailed for the patient additionally included *a priori* discussions with the critical care team and pharmacy to assure the availability of 10% dextrose fluids and intravenous (i.v.) carnitine. Before delivery, discussions with the obstetrical anesthesia team were also undertaken with the aims to enable the potential need for an epidural analgesia to deliver sympathetic blockade and to avoid the use of inhaled anesthetics, potentially capable of triggering rhabdomyolysis.[10] Prior arrangements were made to allow for the ongoing consumption of carbohydrate-enriched liquids; fasting was contraindicated.

The intrapartum and postpartum management was optimized with i.v. hydration using 10% dextrose in normal saline (rate of $175\,ml\,h^{-1}$; $2.5\,ml\,kg^{-1}\,h^{-1}$) to prevent catabolism, rhabdomyolysis and ensuing renal complications. Renal function was monitored with serial blood pressures, measured urine output, and blood chemistry including CK every 4 h. Nephrology was notified about the potential need for dialysis if creatinine or CK became critically elevated. If metabolic acidosis were to develop, the use of bicarbonate would be implemented. Hepatic transaminases and glucose levels were drawn on admission and every 8 h to evaluate for the deteriorating hepatic function. Given the placement of epidural and concern over potential inability to assess subjective muscle weakness, biochemical markers of rhabdomyolysis were objectively assessed using serum CK-MB fractions, aldolase and urine myoglobin on admission and repeated



	1	28	33	37	Delivery	Post-1 day	Post-3 wks	Post-8 wks
C14:1	3.15	0.51	0.017	0.123	0.022	0.028	5.84	6.66
C12-C18	5.96	1.497	0.3	0.216	0.164	0.181	12.83	13.89

Figure 1 The change of acylcarnitine profile during pregnancy (1–37 weeks), delivery and after delivery (1 day, 3 and 8 weeks). The plasma concentration ($\mu mol\,l^{-1}$) of C14:1 (the curve with triangles) and C12–C18 (the curve with circles). Note the significant decrease of acylcarnitines during the second trimester, their normalization during the third trimester and the recurrence of the abnormalities after delivery.

every 8 h. Similarly, acylcarnitine, carnitine and urine organic acids levels were followed intrapartum and postpartum with a contingency plan for initiation of i.v. carnitine at 1000 mg three times a day if deficits were detected.

The patient went into spontaneous labor at 39 weeks gestation, and on admission, the outlined plan of care was initiated. She was allowed to consume fruit juices and light snacks during her labor course following successful placement of epidural analgesia. Oxytocin was administered for augmentation of labor and she progressed in an adequate manner. A 3485 g male infant was delivered through a low-forceps-assisted vaginal delivery with APGAR scores of 9 and 9 at 1 and 5 min. His expanded newborn screen was normal. No significant complications developed in her intrapartum or postpartum course and all laboratory values remained stable, with the sole exception of a mild increase in her CK to 437 units l^{-1}. This resolved with continuous i.v. hydration using 10% dextrose-containing solutions. She was discharged home on postpartum day 4 after counseling regarding the importance of adequate hydration and the increased caloric needs of 800 to 1000 kcal per day while breastfeeding.

The patient was evaluated by her Metabolic Genetics team on weeks 3 and 8 postpartum, and was found to have recurrence of pre-pregnancy symptoms of myalgia and muscle weakness in the latter visit. Remarkably, the long-chain acylcarnitine moieties (especially the C14:1) were disturbed and returned to their abnormal levels observed before pregnancy (Figure 1).

Discussion

VLCAD deficiency presents as a spectrum of clinical phenotypes.[3,7] On the basis of our patient's clinical profile of adult-onset myopathic form of VLCAD deficiency and her history of unprovoked recurrent rhabdomyolysis, we had significant concerns regarding her ability to tolerate any acute intrapartum changes in the metabolic demands. However, given the potential substitutive function of the placental and fetal β-oxidation,[8] we predicted that the mother could experience improvement in her biochemical phenotype. The patient's myalgia and muscle weakness temporally dissipated antepartum with noted significant nadirs of her biochemical markers in the second trimester and completely normalized in latter stages of gestation (Figure 1). In addition, she experienced a relatively uncomplicated labor and postpartum course.

Little is known about pregnancy complicated by FA oxidation enzyme deficiencies in general and VLCAD deficiency in particular. Theoretically, pregnancy could serve as a trigger for an acute decompensation and rhabdomyolysis. The hepatic long-chain FA oxidation capacity is reduced in the mother due to VLCAD

deficiency and the maternal reliance on fat as a source of energy increases during the later stages of gestation. In addition, maternal triglyceride levels rise two- to threefold during the catabolic latter third of gestation, thereby increasing the need for FAs uptake and metabolism. However, as the human placenta expresses the enzymes involved in the FA β-oxidation in levels similar or higher to those seen in normal liver,[8] an affected mother carrying an unaffected fetus might improve clinically as the placental mass grows and enables efficient FA oxidation. Lipoprotein lipase, an enzyme that hydrolyzes plasma triacylglycerol, is highly expressed on the maternal surface of the placenta.[11] This enzyme activity increases the liberation of free FAs and makes them available for uptake by the placenta. The organic cation/carnitine, sodium-dependent transporter (OCTN2) is also highly expressed in the placental tissue and mediates active carnitine transport across the placenta.[12] All these data indicate that FAs undergo extensive mitochondrial β-oxidation in the placenta and offer a theoretical explanation to the observed normalization of biochemical markers in the third trimester. Furthermore, studies on fetal tissues, such as the liver and heart, showed strong expression and enzyme activity of VLCAD and other FA oxidation enzymes, emphasizing the role of β-oxidation during early human development.[13,14]

This beneficial effect of the placento-maternal metabolic interactions was observed in our patient, as evidenced by improvement of her acylcarnitine profiles in the second and third trimester (Figure 1). This observation also suggests that the toxicity of the accumulated acylcarnitine moieties has a more significant role in eliciting the myopathic manifestations than the energy deficits associated with underutilization of FAs. However, these complex interactions can occasionally be deleterious as seen in women carrying fetuses with long-chain 3-hydroxy acyl-CoA dehydrogenase deficiencies bear an increased risk for hemolysis, elevated liver enzymes and low platelets syndrome and acute fatty liver of pregnancy.[9] It is hypothesized that this results from relative carnitine deficiency secondary to increased consumption and accumulation of harmful acylcarnitine intermediates from the developing fetus.[9]

The need and frequency for attainment of metabolic profiling in β-oxidation defects during pregnancy is unknown. As rising acylcarnitine and urinary medium and long-chain dicarboxylic acid profiles generally are associated with acute metabolic decompensation,[2] we reasoned that interval follow-up of profiles could be used for the prediction and management of our patient, as it can change as pregnancy progresses. We do not recommend performing acylcarnitine profile and urinary organic acids in the intrapartum setting, and instead, total and free carnitine should be measured 1–2 weeks before delivery and deficits should be corrected. We observed in this single case report that our patient maintained low values of abnormal acylcarnitines consistent with her uncomplicated clinical course (Figure 1).

On the basis of our experience, we recommend a trial of labor with an assisted vaginal delivery in patients with VLCAD deficiency. We believe that cesarean delivery in VLCAD subjects should be reserved for (1) obstetrical indications, or (2) clear maternal or fetal benefit. Given that cesarean delivery would, by definition, encompass a surgery, separation of the abdominal rectus and a uterine hysterotomy, we alternately reasoned that a trial of spontaneous labor and anticipated vaginal birth would serve as the most appropriate delivery route for the patient. By encompassing an assisted second stage into our mode of delivery, it was our secondary aim to minimize maternal energy expenditures and diminish risk of rhabdomyolysis with ensuing risk of renal compromise.

In conclusion, the management of defects in FA oxidation in pregnancy poses a significant challenge in the maternal–fetal medicine. Our experience serves as an initial report that this condition can be safely managed during pregnancy and in the instances of an unaffected fetus, affected mother may benefit from the placental-mediated β-oxidation of FAs. However, this is merely a single case report and without further substantiating experiences patients and clinicians alike should be alerted to potential complications and individualize a comprehensive and multidisciplinary plan of care based on the patient's clinical course, genotype and nonpregnant phenotype.

Conflict of interest

The authors declare no conflict of interest.

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