Successful management of pregnancy with very-long-chain acyl-coenzyme A dehydrogenase deficiency

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Abstract

Very-long-chain acyl-coenzyme A dehydrogenase deficiency (VLCADD) is a rare and life-threatening disease characterized by an enzymatic defect in the fatty acid β-oxidation pathway. A nulliparous woman with VLCADD showed improvements in serum levels of the long-chain acylcarnitine moiety (C14:1) during pregnancy and successfully delivered a healthy infant vaginally. Pregnancy and vaginal delivery can be successfully completed in patients with VLCADD with careful management.

Key words: placenta, pregnancy, very-long-chain acyl-coenzyme A dehydrogenase deficiency.

Introduction

β-oxidation of fatty acids (FA) plays a crucial role in energy production and involves a variety of FA oxidation enzymes. Very-long-chain acyl-coenzyme A dehydrogenase deficiency (VLCADD), a mitochondrial β-oxidation deficiency, presents with neonatal cardiomyopathy and hypoglycemia in its severe early-onset form, or with myalgia and exercise-induced rhabdomyolysis in later-onset episodic myopathic form.¹⁻³ This enzymatic deficiency shows an autosomal recessive inheritance pattern with an estimated incidence ranging from 1 in 13 500 to 1 in 125 000 live births.⁴⁻⁵ We report the case of a woman with myopathic-form VLCADD who successfully completed a pregnancy without major complications, and discuss the clinical course and obstetric management of this disease with reference to previous reports.

Case Report

The patient was referred to our hospital at 12 years old because of generalized myalgia and recurrent elevation of plasma levels of creatine kinase (CK). Her medical and family histories were non-contributory and her intelligence developed normally. The diagnosis of VLCADD was made based on findings of elevated C14:1. Palmitoyl-coenzyme A oxidation was used to test VLCADD activity in lymphocytes (assay performed at Hiroshima University, Tajima, Japan). Palmitoyl-coenzyme A dehydrogenase level in lymphocytes was low (3.6 pmol/min/10⁶ lymphocytes; reference value, 59.5 ± 12.8 pmol/min/10⁶ lymphocytes) and sequence analysis of the ACADVL gene revealed a novel c.696C>G (Pro266Ala) mutation and a known pathogenic c.1153C>T (Arg385Trp) mutation.⁵ Her free carnitine level was low (19 μM) at diagnosis and carnitine...
supplementation was initiated. Free carnitine level subsequently remained stable within the range of 27–42 μM during pregnancy. She was treated with carnitine and a low-fat diet supplemented with medium chain triglyceride formula. She had only been able to attend high school 2–3 days a week in the year before she became pregnant due to severe myalgia.

With a complaint of amenorrhea at 17 years old, she visited an obstetrician, and 25 weeks’ gestation was confirmed according to fetal size measured on ultrasonography. The fetus showed no abnormalities. The patient suffered severe myalgia and rhabdomyolysis with elevated plasma CK levels (3250 U/L) in the first trimester, which resolved with bed rest and continuous i.v. infusion using 5% glucose-containing solutions. She was admitted to hospital in gestational week 28, after a short uterine cervix was recognized. We decided against using tocolytic agents, and bed rest was maintained until gestational week 35, allowing slow walks around the ward and showers. The day after discharge during gestational week 35, she again complained of myalgia, and elevated CK levels (3388 U/L) were seen, allowing slow walks around the ward and showers. The day after discharge during gestational week 35, she again complained of myalgia, and elevated CK levels (3388 U/L) were seen, so she remained in hospital until delivery. During gestational week 38, labor was induced with i.v. administration of oxytocin under epidural anesthesia using levobupivacaine hydrochloride. A healthy female infant weighing 3070 g was delivered. During labor and delivery, the patient was given access to drinks and food (∼1700 kcal/day) with medium chain triglyceride formula (360 kcal/day) as desired. In addition, we provided i.v. glucose-containing solutions as a supplemental energy source (400 kcal/day), continuing for 1 week after delivery. She stopped breastfeeding, and her course and that of her baby remained uneventful until the follow-up visit 1 month later. Episodic myalgia and rhabdomyolysis, however, started after the visit. Serum C14:1 level decreased during pregnancy, then again increased from 2 weeks after delivery (Fig. 1). During late pregnancy, basal serum CK levels were normalized (30 U/L) for the first time since she was first diagnosed with VLCADD, but returned to the increased level after the delivery in the same manner as for C14:1 (data not shown). Although C16 and C18:1 levels were elevated before pregnancy and had normalized by the time of delivery, other acylcarnitine moieties remained within normal ranges throughout the clinical course.

Discussion

Two major concerns arise in women with VLCADD. The first is whether pregnancy can be risked with this life-threatening disease, and the second is how and when to make the decision to deliver the baby. Laforêt et al. reported long-term follow-up of 13 patients with VLCADD.6 A total of five women delivered nine newborns, with cesarean section performed for two. Three women suffered from delayed myalgia after the first delivery, with elevated levels of CK or myoglobinuria, but renal function remained normal. Although Laforêt et al. did not mention indications or strategies underlying the choice of vaginal delivery or cesarean section, mode of delivery did not seem to severely impact maternal or neonatal outcomes in those cases.

Mendez-Figueroa et al. described a case of VLCADD in which the patient showed clinical and biochemical improvement during pregnancy.7 They speculated that VLCAD activity within the placenta metabolized the maternal FA and resulted in a transient decrease in C14:1, with a return to abnormal levels after delivery. In fact, VLCAD has been found to be highly expressed in the human placenta from early gestation.4 Our case likewise showed improved serum concentrations of C14:1 after the identification of pregnancy. However, as seen in the first trimester of this case, emesis or loss of appetite could lead to a catabolic condition triggering rhabdomyolysis. Caution is also warranted after delivery and during puerperium. Previously, three of five patients with VCLADD were reported to experience myoglobinuria after their first delivery.7 Cardiac failure during the postpartum period has also been reported.9 In our case, myalgia started around the same time that she stopped breastfeeding and/or started menses. Hormonal changes during puerperium may thus represent a risk factor for exacerbation of the disease condition.
In conclusion, pregnancy and vaginal delivery seem to be acceptable with careful management in women with VLCADD. Epidural anesthesia can reduce fatigue during labor. Cesarean section should be considered only based on obstetric indications, and perioperative fasting could present a risk for the disease. This case report might provide encouraging information for patients wishing to bear children, and further cases should be accumulated to establish protocols of pregnancy management for this disease.

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Disclosure

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References
