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## Case Report

## The perioperative transition of serum biomarkers of a 1.5-year-old boy with very-long-chain acyl-CoA dehydrogenase deficiency

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## ABSTRACT

Very long-chain acyl-coenzyme A dehydrogenase deficiency (VLCADD, OMIM 201475) is a congenital fatty acid oxidation disorder. Individuals with VLCADD should avoid catabolic states, including strenuous exercise and long-term fasting; however, such conditions are required when undergoing surgery. The perioperative management of VLCADD in infants has rarely been reported and details regarding the transition of serum biomarkers reflecting catabolic status have not been disclosed. Herein, we present the perioperative clinical and biological data of cryptorchidism in a 1.5-year-old boy with VLCADD. The patient was diagnosed through newborn screening and his clinical course was very stable. Genetic testing of *ACADVL* revealed compound heterozygous variants c.506 T > C (p.Met169Thr) and c.606-609delC (p.L216\*). The enzyme activity of the patient with VLCAD was only 20% compared to that of healthy control. Left orchiopexy for the pediatric cryptorchidism was planned and performed at 1 and a half year of age. Induction anesthesia involved thiopental, fentanyl and rocuronium. The glucose infusion rate was maintained above 6.6 mg/kg/min starting the day before surgery until the operation was completed. Anesthesia was maintained with sevoflurane at approximately 2%. The serum concentration of tetradecenoylcarnitine were stable during the operation, ranging between 0.08 and 0.19  $\mu$ M (cutoff <0.2  $\mu$ M), and never deviated from the reference range. Concentration of other serum biomarkers including free fatty acid, 3-OH-butyrate, and creatine kinase, remained similarly unchanged. In this report, we describe the uneventful perioperative management of unilateral orchiopexy for left cryptorchidism in a 1.5-year-old boy with VLCADD using sufficient glucose infusion and volatile anesthesia.

## 1. Introduction

Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD, OMIM 201475) is a congenital fatty acid oxidation disorder with a prevalence of approximately 1:93,000 births in Japan [1]. Clinical symptoms for patients with VLCADD are provoked during catabolic conditions, such as infection, exercise, and fasting, and can include severe hypoketotic hypoglycemia, liver dysfunction, cardiac involvement, rhabdomyolysis due to the accumulation of long-chain acyl-CoA and acylcarnitines, and a shortage of energy [2,3]. Avoiding fasting and the consumption of a diet restricted in long-chain fatty acids, a diet rich in

middle chain triglycerides (MCT), like MCT milk, or oil are recommended as chronic therapy to prevent catabolic situations [4,5].

One concern for patients with VLCADD is the need for surgery for other medical conditions. Surgical procedures require perioperative management, including prolonged fasting, physical burden, and certain anesthetics that may include the use of lipid emulsions, which can lead to metabolic derangements [6]. Although there have been reports that focus on perioperative management of patients with VLCADD in adulthood [7,8], anesthesia of infant patients with VLCADD has rarely been reported [6,9]. Furthermore, the perioperative use of some medications is controversial. For instance, propofol, which includes lipid emulsions,

**Abbreviations:** 3-OHB, 3-hydroxybutyrate; CK, creatine kinase; FFA, free fatty acid; NBS, newborn screening; VLCADD, very long-chain acyl-coenzyme A dehydrogenase deficiency.

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has been reported to interfere with mitochondrial function [10] and volatile anesthesia may cause elevated free fatty acid (FFA) concentrations [6,8].

Long-chain acylcarnitines could be a reliable biomarker for metabolic status before any increase is detected in the concentrations of other biomarkers; however, immediate acylcarnitine analysis is not always available [11]. Therefore, it is recommended for many facilities that serum creatine kinase (CK) concentrations correlated with long-chain acylcarnitines should be used as biomarkers during the acute phase of fatty acid oxidation disorders [12,13]. However, changes in concentrations of these serum biomarkers during surgery has not been determined. As a result, inferring the extent of the burden that perioperative procedures may have on a patient remains impossible.

In the current study, we performed a surgical course to treat cryptorchidism in a 1.5-year-old boy with VLCADD. Detailed perioperative clinical and biological findings regarding long-chain acylcarnitines and other serum biomarkers were clarified. The findings were helpful in the perioperative management of VLCADD.

## 2. Material and methods

### 2.1. Case details

A 1-year 6-month-old Japanese boy diagnosed with VLCADD was enrolled in the current study. He was the second child of non-consanguineous parents born at 39-weeks 5-days of gestation, weighing 3440 g, and had a healthy elder sister. Elevated concentrations of tetradecenoyl carnitine (C14:1) (0.46  $\mu\text{M}$ ; cutoff,  $<0.27 \mu\text{M}$ ) and C14:1/ acetylcarnitine (C2) ratio (0.019; cutoff,  $<0.013$ ) were detected during newborn screening (NBS). Serum acylcarnitine analysis also suggested the elevation of C14:1 at 0.35  $\mu\text{M}$  (cutoff  $<0.2 \mu\text{M}$ ) 9 days after birth. Genetic testing of *ACADVL*, the gene encoding VLCAD, revealed compound heterozygous c.506 T > C (p.Met169Thr) and c.606-609delC (p. L216\*) variants, the former of which was a novel variant. The enzyme activity of VLCAD was only 20% compared to that of healthy control. Ultimately, the patient was diagnosed with VLCADD at the preclinical stage. After the diagnosis, no obvious clinical symptoms or laboratory abnormalities were shown except for the elevation of C14:1. MCT-supplemented medical formula was administered only during the acute phase of upper respiratory infections, but L-carnitine treatment was not started as his free carnitine concentrations were within the normal range.

Cryptorchidism of the left testis was identified at the one-month medical check-up. Left orchiopexy for the cryptorchidism was planned and then performed at 1 year 6 months of age. Informed consent was obtained from the parents of the patient.

### 2.2. Monitoring of laboratory data

We collected a total of five blood samples, including a preoperative sample, a post-induction sample, and samples 30 min, 60 min, and one day after surgery. Blood samples were taken using an arterial line to reduce the effects of hemolysis. The results of plasma glucose and biological tests, including serum concentrations of CK, 3-hydroxybutyrate (3-OHB), and FFA were also measured at the same timing. The plasma glucose, CK, 3-OHB, and FFA were measured using ADAMS Glucose GA-1171 (Arkray, Inc. Kyoto, Japan), Cygnus Auto CK (Shino-Test Corporation, Tokyo, Japan), 3HB-L (Kainos Laboratories, Tokyo, Japan), and NEFA-HR (FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan), respectively. Serum acylcarnitine concentrations during surgery were analyzed via tandem mass spectrometry (MS/MS) using non-derivatized acylcarnitine analysis kit (NeoSMAAT®AC; Sekisui Medical Corporation, Tokyo, Japan).

### 2.3. Enzyme assay

The residual VLCAD enzyme activity was measured using fibroblasts or lymphocytes, as reported previously [14].

## 3. Results

The milk and food intake was stopped 6 h before surgery. Glucose infusion rates were maintained above 6.6 mg/kg/min from the day before surgery until the operation was completed. No abnormalities were detected on echocardiography or electrocardiography before general anesthesia.

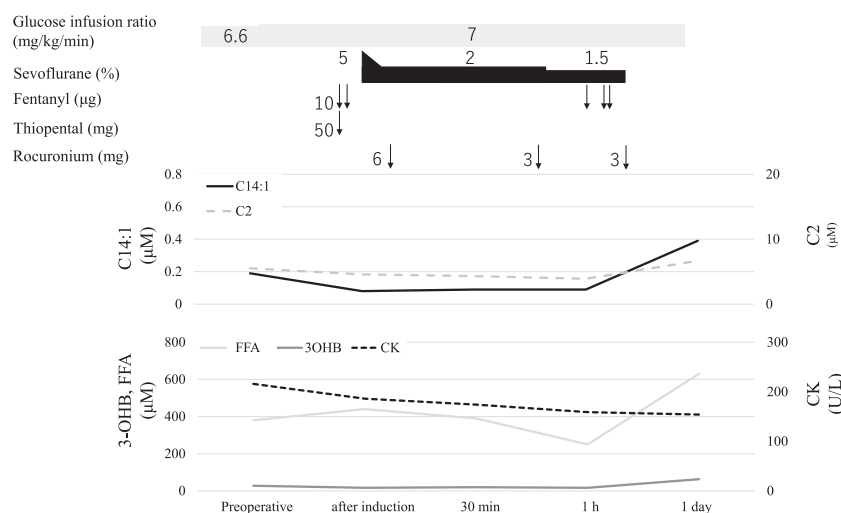
Induction of anesthesia at the start of the operation included thiopental (5 mg/kg), fentanyl and rocuronium as shown in Fig. 1. Anesthesia was maintained with approximately 2% sevoflurane. Careful monitoring of electrocardiography and frequent monitoring of glucose and serum biomarkers, such as CK, 3-OHB, FFA, and serum acylcarnitines, were performed before and every 30 min after the surgery. Hydration including glucose was continued post-surgery until normal oral intake was observed. Plasma glucose levels were stable, ranging between 5.3 and 7.1 mM (reference value, 4.0–6.0 mM). As shown in Fig. 1, CK concentrations were 159–216 U/L (reference value 59–248 U/L), FFA concentrations were 250–380  $\mu\text{M}$  (reference value 100–810  $\mu\text{M}$ ), and 3-OHB concentrations were 17–28  $\mu\text{M}$  (reference value 28–120  $\mu\text{M}$ ), all of which were within normal ranges. Similarly, serum C14:1 concentration was stable during the operation, ranging between 0.08 and 0.19  $\mu\text{M}$  (cutoff  $<0.2 \mu\text{M}$ ) and never deviating from the reference range. Induction and maintenance of anesthesia did not elevate C14:1 concentration. The total length of surgery was 67 min and the duration of anesthesia was 152 min. The preoperative and postoperative course was uneventful with no abnormal biological findings or clinical symptoms during glucose infusion and strict monitoring. The day after the operation, C14:1 concentration was relatively high (0.39  $\mu\text{M}$ ), but the patient was able to leave the hospital without any problems.

## 4. Discussion

In the current study, we describe the successful perioperative management of unilateral orchiopexy for left cryptorchidism in a 1.5-year-old boy with VLCADD using sufficient glucose infusion and volatile anesthesia. This is the first report showing the detailed transition of serum biomarkers under general anesthesia, including acylcarnitines, CK, 3-OHB, and FFA.

During the operation, we performed strict monitoring of the biological markers of VLCADD at the preclinical stage. In the past, when NBS for VLCADD did not exist, postoperative death of a patient with undiagnosed VLCADD was reported [15]. Subsequently, VLCADD has been commonly diagnosed during the pre-symptomatic stage through NBS, making it possible to closely monitor these patients during surgical procedures. However, it remains difficult for attending physicians to determine whether surgical stress causes a metabolic decompensation in patients with pre-symptomatic VLCADD. Due to the shortage of evidence on the perioperative management of VLCADD, extreme caution is required when performing surgery, even if it is over-managed.

In this study, we determined the concentrations of C14:1 as a reflection of catabolic status and found that they remained unchanged during surgery under sufficient glucose infusion. Similarly, concentrations of other serum biomarkers, including CK, FFA, and 3-OHB, were within normal ranges and remained stable. This suggested that sufficient glucose infusion and close monitoring could prevent metabolic derangement, even in infants with VLCADD. Elevation of C14:1 and CK concentrations were observed the day following the surgery, probably because we stopped hydration with glucose after assuring a normal meal intake. Previous studies have shown that catabolic situations are not limited to the day of the surgery [6,16]. Accordingly, it is important for attending physicians to focus on catabolic status even after surgery.



**Fig. 1.** Perioperative transition of serum biomarkers, including acylcarnitine concentrations. C14:1, tetradecenylcarnitine; C2, acetylcarnitine; 3-OHB, 3-hydroxybutyrate; FFA, free fatty acid; CK, creatine kinase.

Cryptorchidism is a relatively common condition in infants; therefore, it can occur as a complication in individuals with VLCAD deficiency. From the perspective of pediatric surgeons, surgical intervention for cryptorchidism is recommended at 6 months, and no later than 18 months, as delayed surgery may cause an irreversible pathological change [17,18]. As the current patient had VLCADD, the timing of the surgical intervention was delayed as much as possible. The stable clinical condition of the patient and concentration of the serum biomarkers during the procedure suggested that the surgery did not result in metabolic decompensation in this young patient. However, to confirm this finding as an expected outcome, more cases are needed.

In the current case, we selected sevoflurane for maintenance of anesthesia, and could ultimately perform an uneventful surgical intervention to treat cryptorchidism. Propofol includes lipid emulsions; and therefore, it can impair mitochondrial entry of long-chain fatty acids and inhibit the respiratory chain at several points [6,8]. However, there are case reports demonstrating the uneventful use of propofol in individuals with VLCADD and other fatty acid oxidation disorders [7,19]. This makes the use of propofol in patients with VLCADD controversial. Similarly, it has been reported that volatile anesthetics are associated with significant increases in FFA concentrations during the first phases of anesthesia, which in the past has resulted in the development of rhabdomyolysis [6]. Our results are consistent with the results of recent publications that reported relatively safe volatile agents [7,8].

The current study had a limitation. Our patient harbored a novel ACADVL mutation and his residual VLCAD enzyme activity was relatively high, suggesting his phenotype may have been asymptomatic or benign. Whether metabolic derangement occurs or not following anesthesia depends on several factors in addition to the ACADVL genotype, including the duration, the degree of surgical intervention, and surgical-related stress. Therefore, this strategy may not be well suited to manage the perioperative period for more severe cases of VLCADD or those involving more invasive surgery. More cases, including those with more diverse phenotypes or known genotypes are needed.

## 5. Conclusion

Adequate glucose infusion and careful monitoring can lead to uneventful surgical outcomes and stable biomarkers in patients with VLCADD, even in infants.

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## Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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## References

- [1] N. Shibata, Y. Hasegawa, K. Yamada, H. Kobayashi, J. Purevsuren, Y. Yang, et al., Diversity in the incidence and spectrum of organic acidemias, fatty acid oxidation disorders, and amino acid disorders in Asian countries: selective screening vs. expanded newborn screening, *Mol Genet Metab Rep.* 16 (2018) 5–10.
- [2] R. Bo, H. Awano, K. Nishida, K. Fujioka, A. Nishiyama, O. Miyake, K. Iijima, False positive cases of elevated tetradecenyl carnitine in newborn mass screening showed significant loss of body weight, *Mol Genet Metab Rep.* 24 (2020) 100634.
- [3] S. Yamaguchi, Y. Indo, P.M. Coates, T. Hashimoto, K. Tanaka, Identification of very-long-chain acyl-CoA dehydrogenase deficiency in three patients previously diagnosed with long-chain acyl-CoA dehydrogenase deficiency, *Pediatr. Res.* 34 (1) (1993) 111–113.
- [4] U. Spiekeroetter, M. Lindner, R. Santer, M. Grotzke, M.R. Baumgartner, H. Boehles, et al., Treatment recommendations in long-chain fatty acid oxidation defects: consensus from a workshop, *J. Inher. Metab. Dis.* 32 (4) (2009) 498–505.
- [5] K. Yamada, T. Taketani, Management and diagnosis of mitochondrial fatty acid oxidation disorders: focus on very-long-chain acyl-CoA dehydrogenase deficiency, *J. Hum. Genet.* 64 (2) (2019) 73–85.
- [6] P. Vellekoop, E.F. Diekman, I. van Tuijl, M.M. de Vries, P.M. van Hasselt, G. Visser, Perioperative measures in very long chain acyl-CoA dehydrogenase deficiency, *Mol. Genet. Metab.* 103 (1) (2011) 96–97.
- [7] M.M. Welsink-Karsies, J.A.W. Polderman, E.J. Nieveen van Dijkum, B. Preckel, W. S. Schlack, G. Visser, et al., Very long-chain acyl-coenzyme a dehydrogenase deficiency and perioperative management in adult patients, *JIMD Rep.* 34 (2017) 49–54.
- [8] C. Redshaw, C. Stewart, Anesthetic agents in patients with very long-chain acyl-coenzyme a dehydrogenase deficiency: a literature review, *Paediatr. Anaesth.* 24 (11) (2014) 1115–1119.
- [9] A.S. Hess, G.M. Rice, J.D. Jochman, B.L. Muldowney, Volatile anesthesia for a pediatric patient with very long-chain acyl-coenzyme a dehydrogenase deficiency: a case report, *Paediatr. Anaesth.* 28 (3) (2018) 296–297.

- [10] C. Allen, R. Perkins, B. Schwahn, A retrospective review of anesthesia and perioperative care in children with medium-chain acyl-CoA dehydrogenase deficiency, *Paediatr. Anaesth.* 27 (1) (2017) 60–65.
- [11] R. Bo, I. Musha, K. Yamada, H. Kobayashi, Y. Hasegawa, H. Awano, et al., Need for strict clinical management of patients with carnitine palmitoyltransferase II deficiency: experience with two cases detected by expanded newborn screening, *Mol Genet Metab Rep.* 24 (2020) 100611.
- [12] A.M. Lund, F. Skovby, H. Vestergaard, M. Christensen, E. Christensen, Clinical and biochemical monitoring of patients with fatty acid oxidation disorders, *J. Inherit. Metab. Dis.* 33 (5) (2010) 495–500.
- [13] U. Spiekerkötter, B. Schwahn, H. Korall, F.K. Trefz, B.S. Andresen, U. Wendel, Very-long-chain acyl-coenzyme a dehydrogenase (VLCAD) deficiency: monitoring of treatment by carnitine/acylcarnitine analysis in blood spots, *Acta Paediatr.* 89 (4) (2000) 492–495.
- [14] G. Tajima, N. Sakura, K. Shirao, S. Okada, M. Tsumura, Y. Nishimura, et al., Development of a new enzymatic diagnosis method for very-long-chain acyl-CoA dehydrogenase deficiency by detecting 2-hexadecenoyl-CoA production and its application in tandem mass spectrometry-based selective screening and newborn screening in Japan, *Pediatr. Res.* 64 (6) (2008) 667–672.
- [15] C.R. Roe, H.E. Wiltse, L. Sweetman, L.L. Alvarado, Death caused by perioperative fasting and sedation in a child with unrecognized very long chain acyl-coenzyme a dehydrogenase deficiency, *J. Pediatr.* 136 (3) (2000) 397–399.
- [16] K. Iwata, K. Tanabe, Y. Sugiyama, M. Tanaka, M. Takenaka, H. Iida, Anesthetic management for a patient with very-long-chain acyl-coenzyme a dehydrogenase deficiency, *J. Anesth.* 26 (6) (2012) 957–958.
- [17] K.H. Park, J.H. Lee, J.J. Han, S.D. Lee, S.Y. Song, Histological evidences suggest recommending orchiopexy within the first year of life for children with unilateral inguinal cryptorchid testis, *Int. J. Urol.* 14 (7) (2007) 616–621.
- [18] C. Radmayr, H.S. Dogan, P. Hoebeke, R. Kocvara, R. Nijman, S. Silay, et al., Management of undescended testes: European Association of Urology/European Society for Paediatric Urology Guidelines, *J. Pediatr. Urol.* 12 (6) (2016) 335–343.
- [19] J.M. Martin, M.B. Gillingham, C.O. Harding, Use of propofol for short duration procedures in children with long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) or trifunctional protein (TFP) deficiencies, *Mol. Genet. Metab.* 112 (2) (2014) 139–142.