approved by the Institutional Review Board of the Japanese Red Cross Wakayama Medical Center (no. 816).

Acknowledgments

We express our sincere appreciation to the patient's parents and thank them for granting permission to publish. The authors would like to thank the Wakayama-City Health Center and Wakayama-City Institute of Public Health for conducting SARS-CoV-2 PCR tests.

Disclosure

The authors declare no conflicts of interest.

Author contribution

Dr Shinsuke Mizuno conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Dr Ken-ichiro Kobayashi, Kenji Kubo, and Nobuhiro Komiya designed the data-collection instruments, coordinated and supervised the data collection, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Very long-chain acyl-CoA dehydrogenase deficiency: No developmental delay after cardiopulmonary arrest

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Key words cardiopulmonary arrest, fatty acid oxidation, neonatal onset, VLCAD deficiency.

Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is an inherited disorder in which mitochondrial long-chain fatty acid oxidation (FAO) is impaired. Fatty acid oxidation is crucial for maintaining metabolic homeostasis, in particular during high energy demand conditions, such as fasting, illness, or exercise. Very long-chain acyl-CoA dehydrogenase deficiency can present as encephalopathy, myopathy, and sudden death. Herein, we present a case of neonatal-onset VLCAD deficiency that manifested as cardiopulmonary arrest (CPA) in a 2 day old without subsequent developmental delays. Consent was obtained from the parents.

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Received 18 March 2020; revised 9 February 2021; accepted 16 February 2021.
doi: 10.1111/ped.14666

Following an uneventful pregnancy, the boy was born at term via cesarian section due to premature rupture of the membranes and obstructed labor. His height was 49 cm (0 SD) and weight was 2,982 g (−0.2 SD) at birth. His parents were cousins with Pakistani backgrounds. He consumed 30–50 mL of milk every 3 h during day 1. However, by day 2 he vomited and turned pale after consuming 10 mL of milk. His mother made a nurse call, and the nurse found him in CPA and immediately started cardiopulmonary resuscitation (CPR). His heart was restarted within 20 min but he entered CPA again, requiring an additional 50 min of CPR. During this period, epinephrine (0.01 mg/kg) was administered six times, endotracheal intubation was performed, and glucose was injected because of hypoglycemia (13 mg/dL).

He was then transferred to our neonatal intensive care unit, where he arrived hypotonic with low blood pressure and poor reaction to pain. Laboratory results showed non-ketotic hypoglycemia (38 mg/dL), hyperammonemia (113 μmol/L) with

high creatine kinase (CK) levels (7,221 U/L) and metabolic acidosis (pH 7.146, CO_2 27.5 mmHg, HCO_3^- 9.1 mmol/L, BE –18.9 mmol/L, Lac 11.5 mmol/L). He had a seizure that was controlled with anti-epileptic medicines. We collected filter paper blood for newborn screening (NBS) and serum for acylcarnitine and amino acid analyses via tandem mass spectrometry. Urine samples were analyzed for organic acids. On day 5, elevation of C14:1 concentration (5.11 nmol/mL; cut-off <0.27) was revealed. Thus, the glucose infusion rate was increased to 8 mg/kg/min and medium-chain triglycerides (MCT) were administrated. On day 9, the VLCAD enzyme activity in leukocytes was revealed 3.5 pmol/min per 10^6 cells (control: 135.1 ± 47.6 pmol/min), 2% of the normal levels, and the deficiency was confirmed. *ACADVL* (acyl-CoA dehydrogenase, very long chain) gene analysis revealed homozygous mutations at p.E218K (c.652G>A); both parents were heterozygous carriers.

Post-diagnosis, the MCT formula was administered at a higher dose (140 kcal/kg/day), allowing the patient to gain weight with an average blood glucose level of 100 mg/dL. By day 57, his N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were 232 pg/mL, representing a marked reduction from the initial 160 000 pg/mL. He initially had a poor ejection fraction of 20%, which recovered to 70% by day 50, with no records of arrhythmia and with temporary mild thickening of the left ventricular wall. We considered that it was not a sign of dilated cardiomyopathy but only a temporary change after CPR. The brain MRI on day 33 showed no impairment resulting from the CPA episode, and he was discharged on day 65 (Fig. 1). The parents were instructed to feed him the MCT formula at least every 3–4 h and admit him to the hospital if he showed any signs of illness.

He attained 20 months with no developmental delays, according to the Revised Japanese Version of Denver Developmental Screening Test. He started walking without support at 14 months and understands what others say. Despite the MCT formula combined with baby food, his long-chained fatty acid intake remained limited to <10% of the total fat intake. Later on, he was hospitalized due to asymptomatic elevated CK (622 U/L), which was resolved with fluid replacement therapy. We have to follow him up carefully, to assess whether his language and cognitive development are impaired.

Few reports have described neonatal-onset VLCAD deficiency due to its non-specific symptoms and insufficient laboratory data. It has been suggested that VLCAD deficiency-related deaths are often classified as sudden infant death syndrome. In Japan, the only patient who was reported as having VLCAD deficiency and who survived the neonatal crisis died

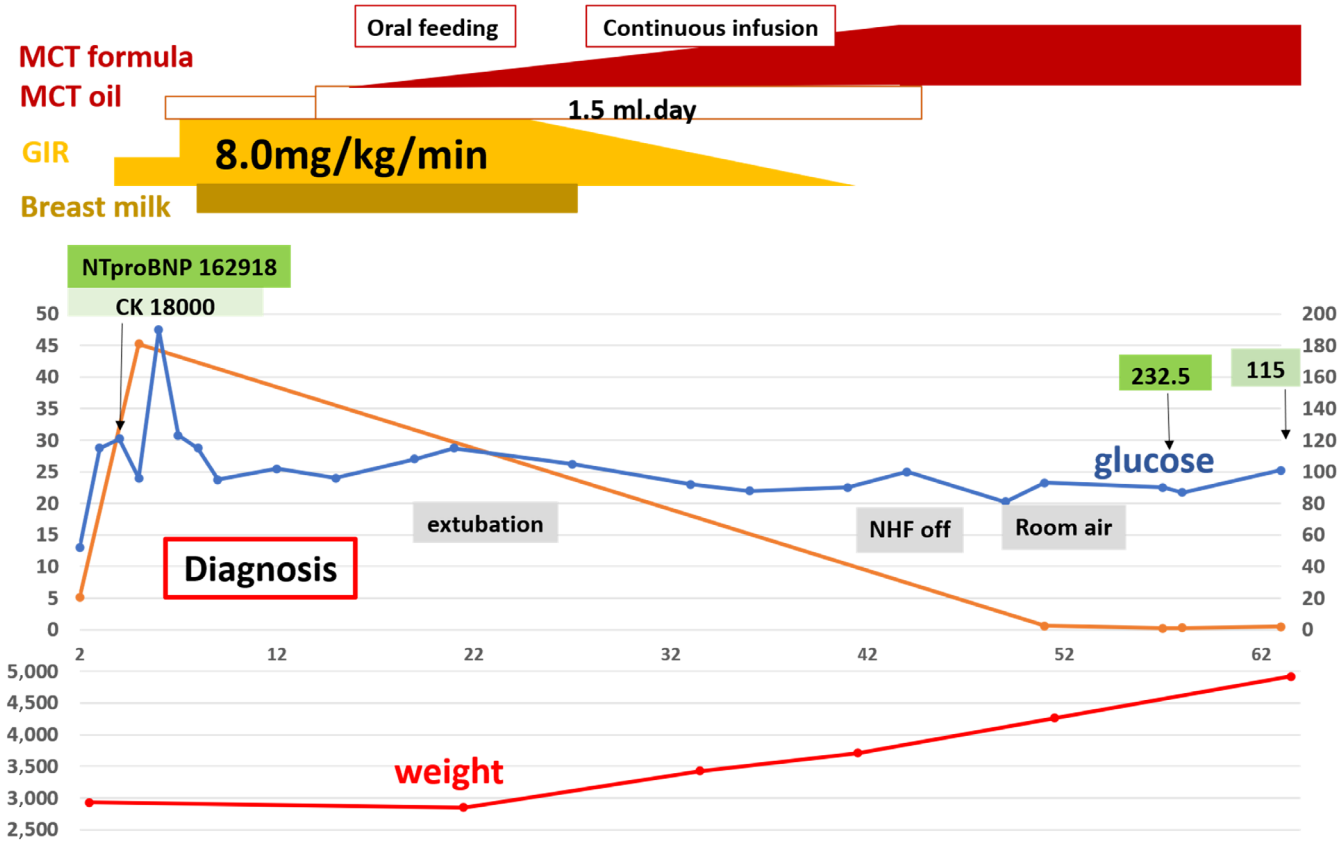

Fig. 1 Clinical course of the patient with VLCAD deficiency. After starting high-concentration glucose infusion and medium-chain triglycerides (MCT) formula, the blood glucose level was stabilized around 100 mg/dL. The patient gained good weight after taking 140 kcal/kg/day of MCT formula. GIR, glucose infusion rate; NHF, nasal high flow.

from an infection at age 2.[1] His VLCAD enzyme activity was 0.8% and he visited the emergency department only a few hours before his death. The enzyme activity level of our patient was higher than this previously reported case, but lower than in VLCAD deficiency asymptomatic cases. Although disease onset was severe, he may not have been the most severe type. He did not show signs of cardiomyopathy, possessed a homozygous missense mutation, and the enzyme activity was not null. Thus, the phenotype of his homozygous mutations is elusive. Andresen *et al.* reported that most severe phenotypes are associated with null alleles, whereas mild phenotypes were linked to various mutations that cause different levels of residual enzyme activity.[2] Increased awareness to diagnose this disorder is still required to gather further knowledge on this genotype-phenotype relationship. Additionally, many cases are diagnosed after NBS; however, in our patient, the crisis occurred before the screening results were available.[3] Even if the phenotype is not the most severe and the patient is fed every 3 h with adequate milk, the crisis can present as CPA and it could occur before the NBS.

Pediatricians must be familiar with VLCAD deficiency and its different presenting manifestations to provide adequate care, especially when high amounts of energy are required, thereby preventing unidentified deaths.

Acknowledgments

We thank the family for participating in this study. We also thank Dr Go Tajima (National Center for Child Health and Development) for measuring the VLCAD enzyme activity in leukocytes, and Dr Keiichi Hara (National Hospital Organization, Kure Medical Center) for the *ACADVL* gene analysis.

Disclosure

The authors declare no conflict of interest.

Author contributions

Nao Takizaki wrote the manuscript. Nao Takizaki and Koji Muroya revised the manuscript. Junko Hanakawa and Yasuhiro Hirano were the attending pediatricians and collected the clinical information. Reiko Iwano performed the acylcarnitine analysis. All authors read and approved the final manuscript.

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