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Case Report on Very Long Chain Acyl-Coa Dehydrogenase Deficiency in a Term Neonate

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Abstract

Background: Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is a rare autosomal recessive disorder affecting fatty acid β-oxidation, primarily caused by mutations in the ACADVL gene. This condition can manifest in neonates with severe symptoms, including hypoglycemia, cardiomyopathy, and sudden cardiac arrest, often leading to high mortality rates if not diagnosed early.

Case presentation: This article reports a case of neonatal-onset of VLCAD deficiency, a full-term infant with symptoms of hypoglycemia, arrhythmia, cardiac insufficiency, and respiratory and cardiac arrest. Whole exome sequencing of the family showed heterozygous mutations in the ACADVL gene.

Management: The current treatment is mainly based on dietary nutrition management and drug therapy, and the prognosis is related to the clinical symptoms and the severity of complications. The patient improved after treatment and was discharged from the hospital, with regular follow-up in the outpatient clinic.

Conclusion: This case highlights the critical need for early diagnosis and management of very long-chain acyl-CoA dehydrogenase deficiency, emphasizing the importance of genetic testing and multidisciplinary care to mitigate life-threatening complications. Timely dietary and pharmacological interventions are essential in improving prognosis and ensuring better outcomes for affected individuals.

Introduction

The early diagnosis and management of metabolic disorders, such as Very Long-Chain Acyl-Coa Dehydrogenase (VLCAD) deficiency, are critical in mitigating severe clinical outcomes. VLCAD deficiency, a rare autosomal recessive disorder, impairs fatty acid β-oxidation, resulting in life-threatening manifestations such as hypoglycemia, cardiomyopathy, and sudden cardiac arrest, particularly in neonates. Genetic mutations in the ACADVL gene are the underlying cause of this condition [1]. This case report details the clinical presentation and management of a full-term infant with neonatal-onset VLCAD deficiency, thus emphasizing the importance of multidisciplinary care and tailored dietary and pharmacological interventions in improving patient outcomes.

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Case presentation

Patient background: The patient was admitted to the hospital 2 days after birth due to "5 minutes of cardiac and respiratory arrest." The patient was the first child and the first delivery, with a gestational age of 39 weeks and a birth weight of 3150 g. There was no abnormality in the birth history. After birth, the mother and baby were in the same room and breastfed. 48 hours after birth, the parents found that the child had a poor response and transferred him to the neonatal department. The mother had regular prenatal checkups during pregnancy; a non-invasive DNA test showed low risk; and a systematic B-ultrasound examination showed increased intestinal echo. There was also no abnormality in the prenatal diagnosis clinic.

Clinical findings

Physical examination upon admission: Bluish lips; no obvious breath sounds, or heart sounds were heard by auscultation; chest compression and endotracheal intubation were performed immediately; adrenaline was given intravenously; and saline was used for volume expansion.

Lab results: Emergency blood gas analysis: pH 7.08, PCO2 62 mmHg, PO2 41 mmHg, Na+ 137 mmol/L, K+ 6.6 mmol/L, Ca2+ 0.93 mmol/L, Glu 0.5 mmol/L, Lac 9.2 mmol/L; blood routine: WBC 21.63×109/L, NE% 72.2%, HGB 168.0 g/L, PLT 216×109/L; liver and kidney function: ALT 60.8 U/L, AST 384.2 U/L, LDH 2 062 U/L, CK 19 448 U/L, HDL-C 0.43 mmol/L, LDL-C 0.49 mmol/L, TP 36.9 g/L, ALB 22.9 g/L, Glu 0.02 mmol/L, UA 558 μmol/L, K+ 7.9 mmol/L; blood ammonia: 83.2 μmol/L.

Post-lab treatments: Correction of acidosis, correction of hypoglycemia and electrolyte imbalance, and invasive ventilator-assisted ventilation.

Notable hospital events: 55 hours after birth, the patient suddenly developed ventricular fibrillation, and was immediately defibrillated with an asynchronous current of 5 J. After the sinus rhythm was restored, the blood gas analysis was repeated.

Subsequent blood gas analysis: pH 7.36, PCO2 18 mmHg, PO2 281 mmHg, Na+ 128 mmol/L, K+ 7.7 mmoml/L, Ca2+ 0.96 mmol/L, Glu 4.7 mmol/L, Lac 13.0 mmol/L.

Subsequent treatment course: Correction of acidosis and symptomatic potassium reduction were given. Because the patient's liver enzymes, creatine kinase and blood ammonia were abnormally elevated, the patient was sent for tandem mass spectrometry analysis and genetic testing 3 days after birth.

Echocardiogram results: The scan was done 5 days after birth and showed left ventricular myocardial thickening, decreased cardiac function, patent foramen ovale, mild tricuspid regurgitation, and neonatal pulmonary hypertension. Aod 8mm, LAD 11mm, LVDd20mm, LVDs14mm, VS 5mm, LVPW4mm, RAD-15mm, RVDd12mm, FS30%, EF60.3%, PASP 30mmHg, Simpson method estimated LVEF54%.

Tandem mass spectrometry results: A significant increase in blood myristoylcarnitine (C14:1) and urine organic acid gas phase mass spectrometry adipic acid and pimelic acid on day 6 after birth was reported.

Whole exome sequencing results: The sequencing was done on day 12 after birth. The patient's ACADVL gene had two heterozygous mutations. Specifically, the c.1843C>T (p.Arg615Ter) mutation was originated from the mother and was a reported pathogenic mutation. This variant genotype was also reported in a 5-month-old Korean child diagnosed with VLCADD in 1999 with symptoms of lethargy and cardiomyopathy [2]. The patient's second heterozygous mutation was c.436G>A (p.Val146Met), which was originated from the father and was not reported in the Cinvar database. According to the ACMG guidelines, the mutation was preliminarily determined to be of unknown clinical significance (PP3+PM2+PM3).

Diagnosis: From the results of tandem mass spectrometry and genetic testing, the patient was diagnosed with VLCADD.

Plan after diagnosis: L-carnitine, adenosine disodium triphosphate tablets, and coenzyme Q10 were taken orally, and medium-chain triglycerides (MCT) formula milk powders were fed. The milk intake reached 150 ml/(kg·d) on 14 days after birth, about 150 kcal/(kg·d). The patient was discharged smoothly after 21 days of hospital treatment.

Post-discharge events: Echocardiograms were repeated at 3 months and 12 months of age. First re-examination showed no obvious abnormality in cardiac structure and cardiac function; Aod 10mm, LAD 12mm, LVDd 23mm, LVDs 13mm, VS 4mm, LVPW 3mm, RAD 14mm, RVDd 11mm, FS435%, EF77.1%, PASP Normal (Figure 1; Charts A & B). The second re-examination also showed no obvious abnormality in cardiac structure and cardiac function; Aod 11mm, LAD 14mm, LVDd 25mm, LMDs 16mm, VS 4mm, LVPW 3mm, RAD18mm, RVDd16mm, FS36%, EF67.9%, PASP Normal (Figure 1; Charts C & D). Neurobehavioral assessment was 39 points (out of 40 points). Blood ammonia: 15.2 μmol/L; liver enzymes were normal. Oral L-carnitine was discontinued.

At 4 months old, the patient's height was 66 cm (P50-P75), his weight was 7.1 kg (P25-P50), and his head circumference was 41 cm (P25-50). He was mainly fed with MCT milk powder, along with complementary food. The patient's Alberta Infant Motor Scale score was at the 10th percentile (less than 25% of children who have gross motor function and are in the bottom 25 of 100 children of the same age, requiring active functional training).

At 5 months old, his height was 68 cm (P50-P75), his weight was 7.8 kg (P25-P50), with a head circumference of 41.5 cm. The patient's Alberta Infant Motor Scale score was at the 25th percentile.

At 8 months old, his height was 72 cm (P50-P75), weight was 8.7 kg (P25-P50), with a head circumference of 43.5 cm (P25-50). The patient's Developmental Quotient in the Child Development Behavior Assessment Scale was 92 points.

At 20 months old, the patient was 88 cm tall and weighed 13.6 kg, and there were no special differences in language and gross motor development between him and children of the same age in community physical examination. He had 2 complementary foods and a total milk intake of 860 ml per day. The C14:1 indexes of the child by tandem mass spectrometry were 5.053 μmol/L, 0.589 μmol/L, 0.475 μmol/L, 0.342 μmol/L, and 0.192 μmol/L at 3 days, 21 days, 2 months, 3 months, and 5 months after birth, respectively. Recent re-examination results showed that myristoylcarnitine and various long-chain acylcarnitines had returned to normal.

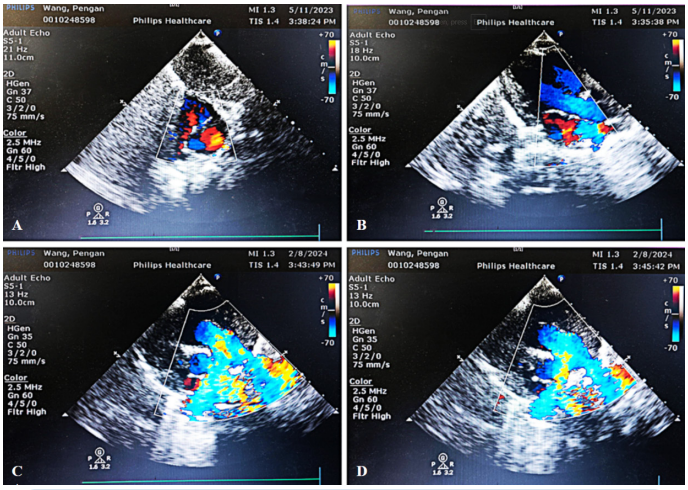

Figure 1: Echocardiograms for the patient at 3 months of age (Charts A & B) and at 12 months of age (Charts C & D).

Discussion

This case presents multifaceted challenges in managing VLCADD, a metabolic disorder resulting from mutations in the ACADVL gene [3]. VLCADD disrupts mitochondrial fatty acid oxidation, manifesting in severe phenotypes such as cardiomyopathy, hypoglycemia, and arrhythmia, as illustrated by the neonatal cardiac arrest described earlier. Unlike other metabolic conditions, VLCADD presents a unique interplay between biochemical markers and clinical outcomes, necessitating precise diagnostic and therapeutic approaches [4]. The diagnostic process emphasizes the indispensable role of tandem mass spectrometry, which facilitates the early detection of elevated acylcarnitine markers, particularly C14:1 [5]. This biomarker, widely recognized as a sentinel indicator of VLCADD, enables timely intervention even before overt symptoms arise [6]. However, this case also highlights the intricacies of genetic diagnosis, as illustrated by the novel c.436G>A (p.Val146Met) mutation of uncertain clinical significance. Such findings call for continuous updates to variant databases and refined diagnostic algorithms.

The management strategy in VLCADD showcases a tailored approach, anchored by nutritional interventions. Consistent with emerging guidelines, symptomatic neonates benefit from medium-chain triglycerides (MCT)-enriched formulas to circumvent the metabolic stress caused by long-chain fatty acids [7,8]. Triheptanoin, a novel anaplerotic therapy, has been reported to improve left ventricular ejection fraction and stabilize cardiac function, offering a promising alternative for patients with pronounced cardiomyopathy [9,10]. This patient's gradual recovery and post-discharge stability exemplify the importance of such targeted interventions. However, controversies surrounding adjunct therapies like L-carnitine and bezafibrate persist, further research into their efficacy and safety is needed.

A notable aspect of VLCADD management lies in its preventive focus. This case reiterates the value of genetic counseling and prenatal diagnostics for at-risk families. Comprehensive prenatal screening empowers prospective parents with actionable insights, ensuring preparedness for potential neonatal complications [11]. Post-discharge follow-up reflects another critical dimension of VLCADD care, bridging metabolic control with developmental outcomes [12]. Regular echocardiograms, metabolic monitoring, and neurodevelopmental assessments ensure the early detection of residual complications [13]. In this case, consistent follow-up enabled timely functional interventions, supporting the patient's motor development and overall growth trajectory. This integrative model emphasizes the importance of acute management along with long-term developmental care.

Emerging treatment modalities, such as gene therapy, offer a valuable insight into the future of VLCADD management. Preliminary studies suggest the potential for long-term enzymatic correction, heralding a paradigm shift from symptomatic to curative therapies [14-16]. Although still in experimental phases, these advances showcase the relentless evolution of therapeutic options for rare genetic disorders. By integrating advanced diagnostics, tailored nutrition, and multidisciplinary care, clinicians can significantly improve outcomes for affected individuals, transforming the prognosis of this once-lethal condition.

Conclusion

VLCADD is a preventable and treatable genetic metabolic disease. Most children who receive standardized treatment in the early stage have normal growth and development, and very few have brain damage due to severe hypoglycemia or energy metabolism disorders. Therefore, tandem mass spectrometry and genetic testing should be prioritized and emphasized in newborns with unexplained metabolic problems in the early stage to clarify the diagnosis, thereby avoiding complications and irreversible damage to the functions of various organs in children. Future healthcare strategies should prioritize newborn screening and prenatal counseling to prevent complications and improve the quality of life for affected families.

Conflict of interest: The authors declare that there is no conflict of interest.

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