

CASE REPORTS

BEYOND NEONATAL SEPSIS: VERY LONG-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY PRESENTING AT TWO MONTHS AS SEIZURES, RESPIRATORY DISTRESS, PERICARDIAL EFFUSION AND MIXED DILATED-HYPERTROPHIC CARDIOMYOPATHY

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ABSTRACT

Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is a rare autosomal recessive disorder of mitochondrial long-chain fatty acid β -oxidation caused by pathogenic variants in the ACADVL gene. The severe infantile phenotype is commonly associated with cardiomyopathy, arrhythmias, hypoketotic hypoglycaemia, and metabolic decompensation.¹⁻³

We report a 2-month-old infant who initially presented during the neonatal period with a sepsis-like illness and subsequently developed seizures, respiratory distress, severe hypertension, and cardiomyopathy. Evaluation for secondary causes of hypertension revealed mixed dilated-hypertrophic cardiomyopathy. Renal Doppler ultrasonography, abdominal ultrasonography, and evaluation of the aorta were normal. Whole exome sequencing identified a homozygous likely pathogenic frameshift variant in ACADVL (c.1006del; p.Ile336SerfsTer17), confirming VLCAD deficiency.

The infant was managed with medium-chain triglyceride supplementation, enalapril, avoidance of fasting, and parental counselling. This case highlights the importance of considering fatty acid oxidation disorders in infants presenting with unexplained cardiomyopathy and systemic manifestations.

Introduction

Very long-chain acyl-CoA dehydrogenase deficiency is an inherited disorder of mitochondrial fatty acid oxidation resulting from pathogenic variants in the ACADVL gene. VLCAD catalyses the initial dehydrogenation step of long-chain fatty acids within mitochondria and plays a critical role in energy production during fasting and physiological stress.¹

Clinical manifestations are heterogeneous and range from severe infantile disease with cardiomyopathy and metabolic crises to later-onset skeletal myopathy and exercise intolerance.² Infantile VLCAD deficiency carries significant morbidity and mortality owing to myocardial involvement and recurrent metabolic decompensation.³ Early diagnosis is essential because disease-specific nutritional interventions can substantially alter outcomes.⁴ We describe an infant whose diagnosis was established following evaluation for severe hypertension and mixed dilated-hypertrophic cardiomyopathy.

Case Report

A 2-month-old male infant born to non-consanguineous parents presented with respiratory distress, and gastroenteritis. During the neonatal period, he had experienced a sepsis-like illness with seizures, heart failure requiring hospitalisation and supportive

treatment including antiepileptic drugs, anti failure drugs, inotropes and antibiotics for 15 days later got discharged once he recovered.

At the current admission, blood pressure was 100/60 mmHg, exceeding the 99th percentile for age and weight as per IAP charts consistent with severe systemic hypertension. Evaluation for secondary causes of hypertension was undertaken.

Workup: Renal Doppler ultrasonography and abdominal ultrasonography were normal. Echocardiographic evaluation demonstrated dilated and hypertrophied cardiac chambers suggestive of mixed dilated-hypertrophic cardiomyopathy with pericardial effusion. These findings were considered significantly abnormal for a 2-month-old infant. No abnormalities of the aortic valve, aortic arch, or major vessels were identified.

The combination of early infantile cardiomyopathy, h/o neonatal seizures, respiratory distress, and unexplained hypertension prompted evaluation for an underlying genetic or metabolic disorder.

Whole exome sequencing identified a homozygous one-base pair deletion in exon 10 of the ACADVL. Based on the clinical phenotype and molecular findings, a diagnosis of VLCAD deficiency was established.

Management and outcome: The infant was managed symptomatically with probiotics, nebulization, oxygen and iv fluids during the acute illness, pig tail catheter drainage was done and child kept on anti-failure medication along with milrinone infusion, diuretics. Child was commenced on medium-chain triglyceride

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(MCT) oil supplementation. Enalapril was initiated for management of hypertension and cardiac remodelling. Parents were counselled regarding avoidance of prolonged fasting, maintenance of frequent feeds, prompt treatment of intercurrent illness, and prevention of hypoglycaemia. The child was discharged in stable condition with BP at 95th centile and good EF of heart and weight gain of 100 grams after 1 week of stay at hospital with planned metabolic and cardiology follow-up who succumbed to sudden cardiac arrest at home 3 weeks later.

Discussion

Fatty acid oxidation provides a major source of energy for the myocardium, particularly during periods of fasting and physiological stress. Consequently, defects in long-chain fatty acid oxidation frequently manifest with cardiac involvement.^{1,4}

Cardiomyopathy is among the most important manifestations of severe infantile VLCAD deficiency and may present as hypertrophic cardiomyopathy, dilated cardiomyopathy, or a mixed phenotype.^{2,5} In our patient, echocardiography demonstrated features of both ventricular hypertrophy and ventricular dilatation, suggesting advanced myocardial involvement.

Although cardiomyopathy is a recognised manifestation of VLCAD deficiency, hypertension is not commonly emphasised in published reports. In this infant, persistent hypertension triggered an extensive evaluation that ultimately led to identification of the underlying metabolic disorder. The absence of renovascular abnormalities, renal pathology, coarctation of the aorta, or structural aortic disease further strengthened the possibility of a systemic metabolic etiology.

The identified homozygous frameshift variants are generally associated with severe early-onset phenotypes characterised by cardiac manifestations and metabolic instability.^{1,2} Management of VLCAD deficiency focuses on preventing catabolism and providing alternative energy substrates. MCT supplementation bypasses the metabolic block and serves as an efficient source of energy.⁴ Strict avoidance of prolonged fasting remains one of the most important preventive measures.¹

More recently, Triheptanoin has emerged as a targeted therapy for long-chain fatty acid oxidation disorders. Unlike conventional MCT oil, triheptanoin provides both energy and anaplerotic substrates that replenish

tricarboxylic acid cycle intermediates. Clinical studies have demonstrated reductions in major metabolic events and improvements in cardiac and metabolic outcomes among patients with long-chain fatty acid oxidation disorders receiving triheptanoin therapy.^{6,7}

Conclusion

This case highlights the importance of considering fatty acid oxidation disorders in infants presenting with seizures, respiratory distress, unexplained hypertension, and mixed dilated-hypertrophic cardiomyopathy with pericardial effusion. Evaluation of severe hypertension in our patient led to recognition of cardiomyopathy and subsequent diagnosis of VLCAD deficiency through whole exome sequencing.

Early diagnosis permits institution of disease-specific nutritional therapy, avoidance of fasting, prevention of hypoglycaemia, cardiac surveillance, and family counselling. In addition, newer therapies such as triheptanoin offer promising opportunities to improve long-term metabolic and cardiac outcomes in patients with VLCAD deficiency and should be considered whenever available.^{6,7}

Compliance with Ethical Standards

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