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Case Report

Long-Chain Fatty Acid Oxidation Disorder Presenting with Metabolic Acidosis in a Preterm Infant

Dharmikkumar S. Patel[1], Keyur H. Madhu[1], Deepak R. Thakor[2], Meet D. Prajapati[1]

Department of Biochemistry,[1]Pramukhswami Medical College, Bhaikaka University, Karamsad. and [2]GMERS Medical College Gandhinagar

*** Correspondence:** Dr. Meet D. Prajapati (doctor.meetprajapati@gmail.com)

ABSTRACT

Long-chain fatty acid oxidation disorders (LC-FAODs) are rare autosomal recessive metabolic disorders caused by defects in mitochondrial β-oxidation. They often present in infancy with hypoketotic hypoglycaemia, cardiomyopathy, hepatic dysfunction or sudden metabolic decompensation. We report a 33.5-week gestation male neonate with birth weight 1.240 kg, born to non-consanguineous parents, who presented in the first days of life with persistent metabolic acidosis, hyperkalaemia and hypocalcaemia despite normal blood glucose. Newborn screening by tandem mass spectrometry showed marked elevations of long-chain acylcarnitines (C14, C14:1, C18) together with hydroxyacylcarnitines (C16-OH, C18-OH), a pattern suggestive of very-long-chain acyl-CoA dehydrogenase (VLCAD) or mitochondrial trifunctional protein (TFP) deficiency. Simultaneously, urine organic acid analysis revealed a 55-fold increase in 4-hydroxyphenyllactic acid (4-HPLA) and mild elevation of 4-hydroxyphenylpyruvic acid (4-HPPA), raising the possibility of concomitant tyrosinaemia or a mitochondrial disorder. Management with avoidance of fasting, continuous glucose infusion, and medium-chain triglyceride (MCT) supplementation led to gradual biochemical improvement. This case illustrates the diagnostic complexity of metabolic screening in preterm infants and underscores the importance of integrating clinical context with metabolic data. Early recognition and dietary intervention in LC-FAOD can significantly improve outcomes.

Keywords: Long-Chain Fatty Acid Oxidation Disorder, Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency, Newborn Screening, Tandem Mass Spectrometry, Preterm Infant.

INTRODUCTION

Long-chain fatty acid oxidation disorders (LC-FAODs) comprise a group of autosomal recessive disorders that impair mitochondrial β-oxidation of fatty acids[1]. Pathogenic mutations in the enzymes of this pathway prevent efficient energy production from fats, particularly during fasting or stress. Classically, LC-FAODs manifest with hypoketotic hypoglycaemia, liver dysfunction, cardiomyopathy and/or rhabdomyolysis[2]. With the expansion of newborn screening (NBS) by tandem mass spectrometry (TMS), many affected neonates are identified early, allowing prompt dietary and medical management to avert crises.[6,13]

In screening, certain acylcarnitine patterns point to specific LC-FAODs. For example, very-long-chain

acyl-CoA dehydrogenase (VLCAD) deficiency yields elevated C14 and C14:1 acylcarnitines[3], whereas deficiencies of long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) or TFP result in increased hydroxyacylcarnitines such as C16-OH and C18:1-OH[3]. However, overlapping profiles can occur (for instance, CPT II deficiency may also raise C16-OH) and factors like prematurity or illness can produce false positive screens. Transient catabolic states in neonates, such as postnatal starvation or stress, may mimic LC-FAOD acylcarnitine elevations[7]. Thus, interpretation requires clinical correlation.

Unexpected findings on urine organic acid analysis can provide additional clues. Elevated 4-hydroxyphenyllactic acid (4-HPLA) and 4-hydroxyphenylpyruvic acid (4-HPPA) are hallmark metabolites of tyrosine-catabolism disorders, particularly tyrosinaemia type III, but have also been reported in primary mitochondrial diseases such as Pearson syndrome[4]. Absence of succinylacetone (a pathognomonic marker of tyrosinaemia type I[5]) would argue against classical tyrosinaemia type I, prompting consideration of variant tyrosine metabolism defects or secondary changes due to mitochondrial dysfunction.

We describe a preterm neonate with a striking combination of elevated long-chain acylcarnitines and urinary tyrosine metabolites, a constellation rarely reported together. Tables 1 and 2 summarize his laboratory findings.

CASE HISTORY

A male infant was born at 33.5 weeks of gestation with a birth weight of 1.240 kg to healthy non-consanguineous parents via normal vaginal delivery. He was small-for-gestational age and had a Silverman-Anderson Score (SAS) of 5/10.. The neonate was admitted to the NICU for prematurity and mild respiratory distress. On examination, there were no dysmorphic features or organomegaly; muscle tone and reflexes were normal. The baby required minimal respiratory support with only mild tachypnoea attributable to prematurity.

No immediate life-saving interventions were needed initially. Over the first 48 hours, the infant remained euglycaemic under maintenance glucose infusion (to prevent catabolism) and had no seizures or hypoglycaemic episodes. Routine monitoring revealed progressive metabolic acidosis and electrolyte disturbances. By day 1 of life, arterial blood gas showed pH 7.25 and base excess –10.1 (Table 1), with concurrent hyperkalaemia (5.6 mEq/L) and hypocalcaemia (0.89 mmol/L). Serum C-reactive protein (CRP) was not elevated at that time. Based on these findings, empiric antibiotics were started for presumed sepsis; however, blood cultures remained negative, and CRP began to rise by day 4, suggesting a systemic response but no identifiable source. Hematocrit and platelet counts remained normal throughout.

Given persistent metabolic acidosis with normal glucose and electrolyte imbalance, an inborn error of metabolism was suspected. The screening and diagnostic work-up were expanded accordingly. Laboratory investigations on admission (Day 1) are shown in Table 1. The infant had an anion-gap metabolic acidosis (pH 7.25, bicarbonate 17.1 mmol/L, base excess –10.1) with elevated serum potassium (5.6 mEq/L) and low ionized calcium (0.89 mmol/L).

Table 1: Day-wise summary of key laboratory findings.

Parameter	Day 1 (Apr 9)	Day 4 (Apr 12)	Day 6 (Apr 14)	Day 10 (Apr 18)
Glucose (mg/dL)	72	147	51	65
Lactate (mmol/L)	7.2	7.8	11.6	11.8
pH	7.25	7.11	7.15	7.20
Bicarbonate (mmol/L)	17.1	11.2	13.8	12.9
Base excess (mEq/L)	–10.1	–18.5	–12.6	–15.1
CRP (mg/L)	–	25.7	47.0	70.6
Na^+ (mEq/L)	127	133	138	132
K^+ (mEq/L)	5.6	5.9	3.8	4.1
Ca^{2+} (mmol/L)	0.89	0.99	1.12	1.15
S. Creatinine (mg/dL)	–	0.24	–	0.49

Renal function (serum creatinine) and liver enzymes were essentially normal, and ammonia was only mildly elevated. In the setting of prematurity and an otherwise unremarkable physical examination, the combination of metabolic acidosis, hyperkalaemia and normoglycaemia prompted urgent metabolic testing.

Over the next few days, despite supportive care, metabolic acidosis persisted (day 4 pH 7.11, base excess –18.5) and CRP rose to 25.7 mg/L (Table 1). Broad-spectrum antibiotics were continued empirically for suspected sepsis, but repeat cultures remained sterile. Because the infant remained clinically stable (no seizures, no progressive organ failure), attention focused on metabolic causes. On day 6 of life, plasma and urine samples were sent for detailed metabolic screening, including tandem mass spectrometry (TMS) of acylcarnitines and urine organic acid analysis by gas chromatography–mass spectrometry (GC–MS).

Normal reference ranges: pH 7.38–7.44; HCO_3^- 22–28 mmol/L; base excess –3 to +3 mEq/L; CRP <3 mg/L; Na^+ 136–145 mEq/L; K^+ 3.8–5.2 mEq/L; Ca^{2+} 1.12–1.25 mmol/L; Creatinine 0.20–0.40 mg/dL.

Metabolic Investigations

Results of the metabolic screen (Table 2) were remarkable. Plasma acylcarnitine profiling revealed a distinctive pattern of multiple elevated long-chain species. Specifically, C14 (tetradecanoyl carnitine), C14:1, and C18 acylcarnitines were all above the normal range, as were the hydroxy-acylcarnitines C16-OH and C18-OH. This broad pattern of elevations is characteristic of LC-FAODs[3]. For example, VLCAD deficiency typically produces high C14 and C14:1, while LCHAD/TFP defects raise C16-OH and C18:1-OH[3]. Our patient's profile (with

concurrent elevations in C14 through C18 and in multiple hydroxyacylcarnitines) suggested a severe long-chain β-oxidation defect. A mitochondrial trifunctional protein deficiency

(which combines LCHAD activity) was considered most consistent with these findings.

Urine organic acid analysis by GC–MS (Table 2) showed an extreme elevation of 4-hydroxyphenyllactic acid (4-HPLA) (over 55-fold above normal) and a mild increase in 4-hydroxyphenylpyruvic acid (4-HPPA). Lactic acid was also slightly elevated. Notably, succinylacetone (the diagnostic marker of tyrosinaemia type I) was undetectable. This combination – isolated urinary tyrosine metabolites without succinylacetone – is not typical of classic tyrosinaemia type I[5]. It can occur in milder tyrosinaemia variants (such as type III, due to 4-hydroxyphenylpyruvate dioxygenase deficiency) or as a secondary effect of mitochondrial dysfunction. Given the infant's profound acylcarnitine abnormalities, we prioritized a primary LC-FAOD diagnosis (particularly a TFP/LCHAD defect) and considered the abnormal tyrosine metabolites as either a coincidental finding or secondary phenomenon. The combination of long-chain acylcarnitines with elevated 4-HPLA has been described in mitochondrial disorders such as Pearson syndrome[4], underscoring the diagnostic overlap. Definitive molecular or enzyme testing would be needed for confirmation.

Management

Initial treatment focused on halting catabolism and correcting metabolic derangements. The infant was kept nil per os and started on high-rate intravenous dextrose (10% glucose solution) to correct acidosis and suppress lipolysis, with careful monitoring of blood glucose and electrolytes. Once stabilized, feeds were re-introduced using a high-calorie, low-long-chain-fat formula enriched with MCT oil. Dietary fat intake was restricted primarily to medium-chain triglycerides, while long-chain fats were minimized[8,9]. Frequent feeding schedules were enforced to prevent fasting. After confirming low plasma free carnitine levels, supplemental L-carnitine was given to support fatty acid transport. Electrolyte abnormalities were addressed (e.g. intravenous calcium gluconate for hypocalcaemia) and bicarbonate was administered as needed to gradually normalize blood pH.

This management strategy follows published recommendations for LC-FAODs[8,9]. Guidelines emphasize avoidance of prolonged fasting and excess long-chain fat, with provision of alternative energy sources (glucose, carbohydrates and MCT) that bypass the metabolic block[8,9]. In our patient, these measures led to gradual improvement: over several days, blood gas parameters (pH and bicarbonate) and electrolytes began to normalize. The infant remained hemodynamically stable without organ dysfunction.

The family was advised on "sick-day" protocols (e.g. rapid glucose supplementation during illness), and later patient took discharge against medical advice (DAMA).

DISCUSSION

This case highlights the diagnostic and management challenges of LC-FAOD in a preterm neonate. The detection of multiple elevated long-chain acylcarnitines on TMS strongly pointed to an LC-FAOD. The classic combination of high C14, C14:1

Table 2: Metabolic screening results: key abnormal analytes on tandem mass spectrometry (acylcarnitines) and urine organic acids (GC–MS).

Metabolite	Patient Result	Reference/ Normal Range	Interpretation
Tandem Mass Spectrometry (Acylcarnitines)			
C14 (tetradecanoyl carnitine)	1.42 (Elevated)	<0.70 µmol/L	Suggests LC-FAOD (e.g. VLCAD)
C14:1 (tetradecenoyl carnitine)	1.03 (Critical)	<0.6 µmol/L	Consistent with LC-FAOD
C18 (octadecanoyl carnitine)	3.16 (Elevated)	<2.4 µmol/L	LC-FAOD marker
C16-OH (3-hydroxyhexadecanoyl Cn)	5.77 (Critical)	<0.13 µmol/L	LCHAD/TFP marker
C18-OH (3-hydroxyoctadecanoyl Cn)	2.14 (Elevated)	<0.1 µmol/L	LCHAD/TFP marker
Urine GC–MS (Organic Acids)			
4-Hydroxyphenyllactic acid	373.40% (Markedly elevated)	0–4.7%	55.73-fold rise; seen in tyrosinaemia or mitochondrial disease
4-Hydroxyphenylpyruvic acid	8.03% (Mildly elevated)	< 6.7%	As above (tyrosinaemia)
Lactic acid	7.44% (Mildly elevated)	0.0–4.7%	Non-specific; supports possible mitochondrial dysfunction
5-Hydroxy-2-furoic acid	30.47% (Elevated)	< 9.02%	Non-specific; may indicate hepatic dysfunction

Reference ranges are from newborn screening laboratories.

All listed analytes were increased above normal

and C18 is most often associated with VLCAD deficiency[3], while the concurrent elevation of C16-OH and C18-OH implicates the LCHAD/TFP enzyme complex[3]. An infant with mitochondrial trifunctional protein deficiency can exhibit all these acylcarnitine elevations, as reported by recent genetic and clinical studies.[8,9,10] For example, CPT II deficiency or severe metabolic stress may also raise long-chain hydroxyacylcarnitines. Critically, prematurity and neonatal illness themselves can cause false positive results, and have been reported in assosciation with complication such as necrotising enterocolitis in preterms.[11] As reported in a recent study, transient neonatal starvation (e.g. from inadequate feeding) can elevate a broad range of acylcarnitines and mimic VLCAD profiles. Our patient's prematurity and NICU admission could have contributed to partial fasting states, though the magnitude of abnormalities was far beyond mild false-positives. Nevertheless, all results must be interpreted in a clinical context[6,7].

The urine organic acid findings added complexity. Elevated 4-HPLA and 4-HPPA are classical markers of tyrosine metabolism disorders. In tyrosinaemia type I, these would accompany high tyrosine and pathognomonic succinylacetone levels; their absence in our case makes classical type I very unlikely[5]. Instead, these metabolites can appear in tyrosinaemia type III (4-hydroxyphenylpyruvate dioxygenase deficiency) or other disorders. Importantly, 4-HPLA has also been documented in mitochondrial disorders such as Pearson syndrome[4]. The coincident lactic acidosis in our patient (seen in blood gas) further hinted at possible mitochondrial energy dysfunction. It is conceivable that severe metabolic stress from an LC-FAOD could secondarily impair other pathways. Published reports of TFP deficiency note overlapping biochemical features and frequent metabolic crises[4,6]. In sum, while the acylcarnitine profile favoured a primary LC-FAOD (specifically a TFP/LCHAD defect), we remained aware of other contributing factors. Genetic or enzymatic testing would ultimately be required for definitive diagnosis.

Treatment of LC-FAOD focuses on preventing catabolism. Consistent with expert guidelines, the infant was maintained on frequent feeds and continuous glucose support, initiated MCT-rich nutrition, and restricted long-chain fats[8,9]. These measures follow standard protocols for VLCAD and LCHAD/TFP.

CONCLUSION

This case of a moderate preterm neonate illustrates a complex metabolic phenotype with concurrent long-chain acylcarnitine elevations and urine tyrosine metabolites. Careful interpretation was required, considering both inherent screening pitfalls in prematurity and the overlap between disorders of fatty acid oxidation and tyrosine catabolism. Our experience underscores the need for a comprehensive, multidisciplinary approach: combining newborn screening results with detailed clinical assessment and further biochemical testing is essential. Early identification of LC-FAOD through NBS and prompt implementation of dietary therapy can be life-saving.[6,8,13] We recommend close follow-up and genetic analysis to confirm the diagnosis and refine management.

REFERENCES

1.Baker JJ, Burton BK. Diagnosis and clinical management of long-chain fatty-acid oxidation disorders: a review. *Eur Endocrinol.* 2021;17(2) :108.

2.Knottnerus SJG, Bleeker JC, Wijburg FA, Wanders RJ, Ferdinandusse S. Disorders of

mitochondrial long-chain fatty acid oxidation and the carnitine shuttle. *J Inherit Metab Dis.* 2018;41(4):637–646.

3.Baydakova GV, Iurieva EK, Savochkina OV, et al. New acylcarnitine ratio as an indicator of LCHAD deficiency. *Int J Neonatal Screen.* 2023;9(3):48.

4. Liu R, Mo GL, Song YZ. In-depth understanding of Pearson syndrome arising from a novel large mitochondrial DNA deletion in an infant case. *Transl Pediatr*. 2021;10(7):1972–1973.

5. de Jesús VR, Adam BW, Mandel D, Cuthbert CD, Matern D. Succinylacetone as primary marker to detect tyrosinemia type I in newborns. *Mol Genet Metab.* 2014;113(1–2):67–75.

6.Pickens CA, Petritis K. High-resolution MS newborn screening for acylcarnitines. *Anal Chim Acta.* 2020; 1120:85–96.

7.Morishima S, Shimada Y, Watanabe Y, Ihara K. Transient elevation of acylcarnitines in neonatal screening and neonatal weight loss. *Int J Neonatal Screen.* 2025;11(2):33.

8.Vatkar A, Makkar J, Andankar MH. Neuromyopathy due to mitochondrial trifunctional protein deficiency. *Indian J Child Health.* 2022;9(5):84–86.

9.Ishikawa R, Luo C, Vongkum S, et al. HADHB mutation causing mitochondrial trifunctional protein deficiency. *Front Neurol.* 2023; 14:1187822.

10.Nakama M, Mizuno S, Sano E, et al. Novel HADHB mutations in mitochondrial trifunctional protein deficiency. *Hum Genome Var.* 2020; 7:10.

11.Metzler M, Burns W, Mitchell C, Napolitano S, Chaudhari BP. Necrotising enterocolitis in a moderately preterm neonate with LCHADD. *Front Pediatr*. 2023; 11:1081802.

12. John JB, Kandasamy V, Shankar P, Devanbu VGC. Combined fatty acid oxidation disorder in a term infant. *Int J Contemp Pediatr*. 2022; 9:627–629.

13.Outcome of VLCAD deficiency in Indian newborns. *Somaiya-KJSSC Repository.* 2009;11(2): 99–104.

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