



Triheptanoin use for severe neonatal cardiomyopathy secondary to mitochondrial trifunctional protein deficiency: a first report

Brief Report

Cite this article: Coppola J-A, Boothe M, McGuinness A, Yau YL, Blanchette H, Brock MA, Bleiweis MS, Jacobs JP, Peek GJ, and Gupta D (2025). Triheptanoin use for severe neonatal cardiomyopathy secondary to mitochondrial trifunctional protein deficiency: a first report. *Cardiology in the Young*, page 1 of 3. doi: [10.1017/S1047951124026386](https://doi.org/10.1017/S1047951124026386)

Received: 28 May 2024

Revised: 1 August 2024

Accepted: 25 August 2024

Keywords:

Cardiomyopathy; newborn screen; trifunctional protein deficiency; triheptanoin; long-chain fatty acid oxidation disorder; ECMO

Corresponding author:

John-Anthony Coppola;
Email: jcoppola@ufl.edu

John-Anthony Coppola and Megan Boothe are co-first authors (contributed equally to this work).

John-Anthony Coppola¹ , Megan Boothe², Anna McGuinness², Yuen Lo Yau¹, Haley Blanchette¹, Michael A. Brock¹ , Mark S. Bleiweis³ , Jeffrey P. Jacobs³ , Giles J. Peek³ and Dipankar Gupta¹

¹Congenital Heart Center, Division of Pediatric Cardiology, Departments of Pediatrics, University of Florida, Gainesville, FL, USA; ²Division of Genetics and Metabolism, Department of Pediatrics, University of Florida, Gainesville, FL, USA and ³Congenital Heart Center, Division of Cardiovascular Surgery, Departments of Surgery and Pediatrics, University of Florida, Gainesville, FL, USA

Abstract

Mitochondrial trifunctional protein deficiency is a long-chain fatty acid disorder that may include manifestations of severe cardiomyopathy and arrhythmias. The pathophysiology for the severe presentation is unclear but is an indicator for worse outcomes. Triheptanoin, a synthetic medium chain triglyceride, has been reported to reverse cardiomyopathy in some individuals, but there is limited literature in severe cases. We describe a neonatal onset of severe disease whose clinical course was not improved despite mechanical support and triheptanoin.

Introduction

Long-chain fatty acid disorders are a group of autosomal recessive inborn errors of metabolism that lead to incomplete oxidation of fatty acids during periods of fasting or physiologic stress, which leads to an energy deficit affecting the heart, skeletal muscle, brain, and liver. The incidence of long-chain fatty acid disorders is less than <1 per 100,000 in the USA, with some variation among countries worldwide.¹ Mitochondrial trifunctional protein deficiency is a long-chain fatty acid disorder caused by deficiency of mitochondrial trifunctional protein, a multienzyme complex that catalyses the last three steps of mitochondrial long-chain fatty acid β -oxidation.² Clinical symptoms of mitochondrial trifunctional protein deficiency range from neonatal onset with severe dilated cardiomyopathy, hypoketotic hypoglycaemia, and liver dysfunction to a later-onset presentation with myopathy, episodic rhabdomyolysis, cardiomyopathy, peripheral neuropathy, and pigmentary retinopathy.² Despite newborn screening for these disorders, morbidity and mortality remain high for the neonatal-onset presentations with most infants reported deceased in the first months of life.³

Treatment of long-chain fatty acid disorders including mitochondrial trifunctional protein deficiency is supportive and includes avoidance of fasting, implementation of diet high in carbohydrates and low in long-chain fatty acids, and supplementation with medium-chain fatty acids. Historically, supplementation has consisted of medium-chain triglycerides, which is comprised of predominantly eight and 10 carbon triglycerides that can bypass the enzymatic defect and provide three molecules of acetyl-CoA for the Krebs cycle.⁴

Triheptanoin (Dojolvi[®]) is a synthetic odd-carbon (C7) medium-chain triglyceride composed of three heptanoate (seven carbon fatty acids) molecules linked to a glycerol backbone that has been trialled for use in long-chain fatty acid disorders.⁵ Triheptanoin is metabolised into two molecules of acetyl-CoA and one of propionyl-CoA, thus helping to replenish depleted anaplerotic substrates for the Krebs cycle.⁵ Triheptanoin has been shown to decrease episodes of recurrent rhabdomyolysis, hypoglycaemia, and reverse cardiomyopathy in patients with long-chain fatty acid disorders leading to FDA approval for use in these disorders in 2020.⁶

Given the rarity of these disorders, information regarding its use in improving outcomes for neonatal-onset mitochondrial trifunctional protein deficiency has not been published to date. We present a case of neonatal-onset severe mitochondrial trifunctional protein deficiency who presented with acute decompensation with metabolic derangements and severe dilated cardiomyopathy immediately after birth. Triheptanoin was initiated swiftly after diagnosis without significant resolution of dilated cardiomyopathy, suggesting that the efficacy of triheptanoin in such early and severe cases needs to be further investigated.

Case report

The patient was born at 36^{4/7} weeks gestation following a pregnancy complicated by preeclampsia. On the first day of life, the patient developed recurrent hypoglycaemia and

© The Author(s), 2025. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

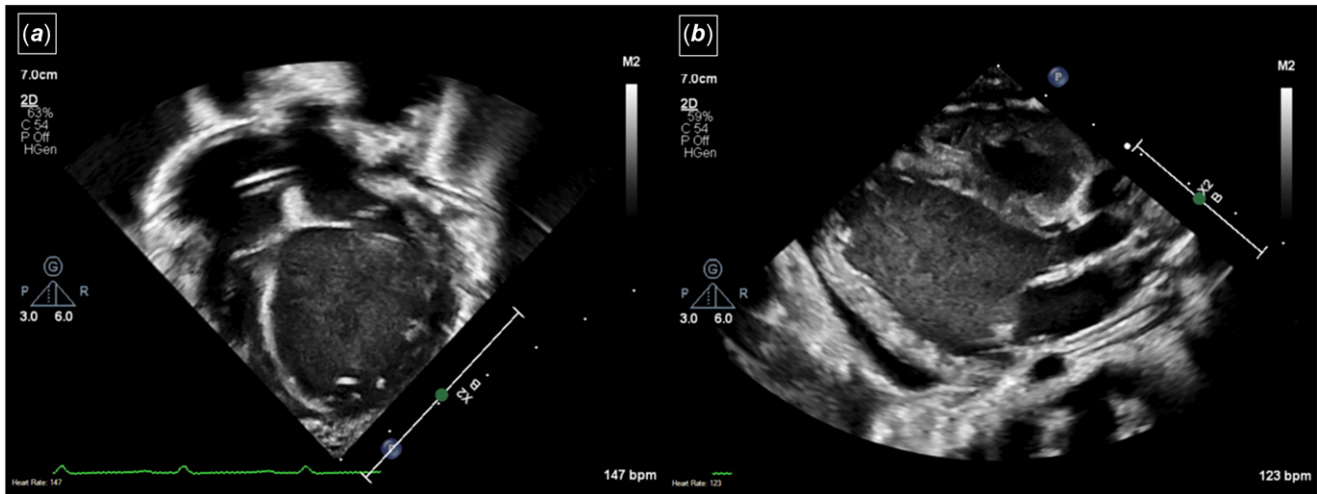


Figure 1. Transthoracic echocardiogram showing severely dilated left ventricle on the apical four chamber (a) as well as on the parasternal long axis view (b) during extracorporeal membrane oxygenation wean trial.

increased work of breathing. Chest X-ray revealed cardiomegaly and echocardiography showed severely reduced biventricular function. The patient was intubated, and inotropic support was initiated. The patient deteriorated and was transferred on inotropes to an extracorporeal membrane oxygenation centre where cannulation via the right neck for veno-arterial support was initiated. The patient was transferred on day five of life to our institution for cardiac transplantation evaluation.

Newborn screen collected at 29 h of life resulted on day five of life revealing elevations of long-chain hydroxyacylcarnitines C16:OH 0.94 (RR < 0.16 $\mu\text{mol/L}$), C16:1-OH 0.28 (RR < 0.26 $\mu\text{mol/L}$), C18:OH 0.39 (RR < 0.13 $\mu\text{mol/L}$), and C18:1-OH 0.74 (RR < 0.10 $\mu\text{mol/L}$), concerning for mitochondrial trifunctional protein deficiency. Plasma acylcarnitines demonstrated markedly elevated concentrations of long-chain 3-hydroxyacylcarnitines despite very low free carnitine and milder elevations of long-chain acylcarnitines, consistent with mitochondrial trifunctional protein. Rapid exome sequencing trio obtained through GeneDx identified a homozygous pathogenic variant c.989del (p.G330Vfs*) in *HADHB* arising from a uniparental disomy of chromosome 2, confirming the diagnosis of mitochondrial trifunctional protein deficiency.

Treatment was then initiated, including high dextrose intravenous fluids (GIR 13 mg/kg/min), TrophAmine®, and MCT oil at 0.5 mL/hr. Medium-chain triglyceride oil was slowly titrated up to a goal of 30% daily caloric intake. Carnitine was briefly initiated at 20mg/kg but discontinued due to ventricular arrhythmias. After approval, triheptanoin was initiated on day nine of life and titrated to goal dosing of 35% total energy.⁶ Continuous enteral feeds via a nasogastric tube, with a small amount of Enfamil™ infant and Vivonex®, were initiated along with triheptanoin.

The patient developed intractable ventricular arrhythmias on day six of life, and balloon atrial septostomy for left atrial decompression was performed. The patient remained on extracorporeal support while receiving triheptanoin and feeds for more than 3 weeks. A wean trial was performed while on inotropic support, which ultimately did not show significant improvement in cardiac function despite adequate nutritional interventions and maximising triheptanoin dosing (Figure 1). Ultimately, the patient

was not considered a candidate for ventricular assist device or cardiac transplantation due to the severity of illness and underlying metabolic disease with multi-organ dysfunction. The patient's multidisciplinary team and parents elected comfort care and discontinued life-sustaining therapies at five weeks of life.

Discussion

Morbidity and mortality in mitochondrial trifunctional protein deficiency remains high, despite early identification in many patients by newborn screening.¹ Severe disease may present before newborn screen results return, as in our patient.³ Additionally, newborn screens may miss individuals with long-chain fatty acid disorders.³ Clinicians should have a low threshold for evaluating newborns and older individuals with cardiomyopathy for these disorders.

In addition to supportive measures and dietary interventions, studies have shown an increased benefit of triheptanoin over the traditional supplementation of medium-chain triglyceride oil in these disorders.⁵ Currently, published studies regarding triheptanoin therapy have shown improvement or reversal of cardiomyopathy in older individuals with long-chain fatty acid disorders, but to our knowledge, there has been no published data regarding initiation of triheptanoin in the neonatal period in patients with severe disease.⁵ While there are rare reports of individuals with mitochondrial trifunctional protein deficiency undergoing cardiac transplantation, they developed cardiomyopathy at older ages and had a less severe disease course than our case.⁷

We highlight that despite improvements in therapy and early detection of long-chain fatty acid disorders, mortality and morbidity remain high for these individuals. Our case highlights that the efficacy of triheptanoin in improving the disease course of severe neonatal presentations of long-chain fatty acid disorders needs to be studied further. One potential area of study would be whether earlier implementation of treatment could improve outcomes. In some instances, prenatal diagnosis may be possible either due to known family history or in utero diagnosis of cardiomyopathy, which could present with an opportunity to initiate therapy prior to diagnosis by newborn screening.^{8,9} Another area of potential study is ketone body supplementation,

as ketone bodies can serve as an alternative source of energy during periods of impaired fatty acid metabolism.¹⁰ The use of D,L-3-hydroxybutyrate (D,L-3-HB) has been shown to improve cardiac function in patients with multiple acyl-CoA dehydrogenase deficiency and may be a therapy worth investigating further for other fatty acid oxidation disorders.¹⁰

Acknowledgements. We would like to acknowledge the expert care given by the Pediatric Team at St. Joseph's Children's Hospital and the University of Florida ECMO Team, including Mr. Andrew Jaudon, RRT.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Competing interests. None.

References

1. Marsden D, Bedrosian CL, Vockley J. Impact of newborn screening on the reported incidence and clinical outcomes associated with medium- and long-chain fatty acid oxidation disorders. *Genet Med* 2021; 23: 816–829.
2. den Boer ME, Dionisi-Vici C, Chakrapani A, van Thuijl AO, Wanders RJ, Wijburg FA. Mitochondrial trifunctional protein deficiency: a severe fatty acid oxidation disorder with cardiac and neurologic involvement. *J Pediatr* 2003; 142: 684–689.
3. Schwantje M, Fuchs SA, de Boer L et al. Genetic, biochemical, and clinical spectrum of patients with mitochondrial trifunctional protein deficiency identified after the introduction of newborn screening in the Netherlands. *J Inher Metab Dis* 2022; 45: 804–818.
4. De Biase I, Viau KS, Liu A et al. Diagnosis, treatment, and clinical outcome of patients with mitochondrial trifunctional protein/long-chain 3-hydroxy acyl-coA dehydrogenase deficiency. *JIMD Rep* 2017; 31: 63–71.
5. Vockley J, Enns GM, Ramirez AN et al. Response to triheptanoin therapy in critically ill patients with LC-FAOD: report of patients treated through an expanded access program. *Mol Genet Metab* 2022; 136: 152–162.
6. Norris MK, Scott AI, Sullivan S et al. Tutorial: triheptanoin and nutrition management for treatment of long-chain fatty acid oxidation disorders. *JPEN J Parenter Enteral Nutr* 2021; 45: 230–238.
7. Bursle C, Weintraub R, Ward C, Justo R, Cardinal J, Coman D. Mitochondrial trifunctional protein deficiency: severe cardiomyopathy and cardiac transplantation. *JIMD Rep* 2018; 40: 91–95.
8. Spiekerkoetter U, Mueller M, Cloppenburg E et al. Intrauterine cardiomyopathy and cardiac mitochondrial proliferation in mitochondrial trifunctional protein (TFP) deficiency. *Mol Genet Metab* 2008; 94: 428–430.
9. Bo R, Hasegawa Y, Yamada K et al. A fetus with mitochondrial trifunctional protein deficiency: elevation of 3-OH-acylcarnitines in amniotic fluid functionally assured the genetic diagnosis. *Mol Genet Metab Rep* 2016; 6: 1–4.
10. van Rijt WJ, Jager EA, DPallersma et al. Efficacy and safety of D,L-3-hydroxybutyrate (D,L-3-HB) treatment in multiple acyl-CoA dehydrogenase deficiency. *Genet Med* 2020; 22: 908–916.