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Donna Raval

Kristina Cusmano-Ozog
George Washington University

Omar Ayyub

Callie Jenevein

Laura Kofman

See next page for additional authors

Authors
Donna Raval, Kristina Cusmano-Ozog, Omar Ayyub, Callie Jenevein, Laura Kofman, Brendan Lanpher, Natalie Hauser, and Debra Regier

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Donna B. Raval [a], Kristina P. Cusmano-Ozog [b], Omar Ayyub [b], Callie Jenevein [c], Laura H. Kofman [d], Brendan Lanpher [e], Natalie Hauser [c], Debra S. Regier [b,*]

[a] Maryland Perinatal Associates, Takoma Park, MD, USA
[b] Genetics and Metabolism, Children's National Health System, Washington, DC,USA
[c] Inova Translational Medicine Institute, Division of Medical Genomics, Falls Church, VA, USA
[d] Department of Medical Genetics, Kaiser Permanente Mid-Atlantic States, McLean, VA USA
[e] Department of Medical Genetics, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

Trifunctional protein deficiency/Long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHAD/TFP) deficiency is a disorder of fatty acid oxidation and ketogenesis. Severe neonatal lactic acidosis, cardiomyopathy, and hepatic dysfunction are caused by the accumulation of toxic long-chain acylcarnitines. The feasibility of umbilical cord blood use in screening for acylcarnitine analysis and free carnitine has been hypothesized but not reported in LCHAD/TFP neonates.

We present a 4 week old female who was at risk of inheriting LCHAD/TFP deficiency and was diagnosed at the time of delivery using umbilical cord blood. Umbilical cord blood was collected at delivery and sent for acylcarnitine analysis. Treatment was started immediately. Acylcarnitine analysis demonstrated findings that are consistent with a biochemical diagnosis of LCHAD/TFP deficiency.

Patients with LCHAD/TFP deficiency should have treatment initiated as early as possible to avoid acute decompensation and minimize the long-term complications of the disorder including cardiomyopathy. In pregnancies at risk of having a child with LCHAD/TFP deficiency, umbilical cord blood sample is an efficient method to diagnose an inborn error of metabolism such as LCHAD/TFP deficiency.

1. Objective

To describe the diagnosis of Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency using umbilical cord blood at the time of delivery in an at-risk pregnancy.

2. Introduction

Long-chain hydroxyacyl-CoA dehydrogenase deficiency is a disorder of fatty acid oxidation and ketogenesis. Accumulation of toxic long-chain acylcarnitines in LCHAD deficiency may cause severe neonatal lactic acidosis, cardiomyopathy, and hepatic dysfunction. Patients may also manifest chronic weakness, pain, as well as recurrent rhabdomyolysis. Patients may have acute decompensations with episodes of illness, decreased oral intake, prolonged fasting episodes, surgery, etc. Mothers of affected fetuses can present with acute fatty liver of pregnancy or HELLP syndrome [1].

"Mitochondrial trifunctional protein is composed of four alpha-subunits and four beta-subunits; the alpha-subunit has long-chain enoyl-CoA hydratase (LCEH) and LCHAD activities, and the beta-subunit has long-chain ketoacyl-CoA thiolase (LCKAT) activity" [1]. Isolated LCHAD deficiency typically presents with hypoglycemia as well as liver dysfunction, lactic acidosis, and cardiomyopathy. As the patients age, they can also develop feeding difficulties, rhabdomyolysis, hypoparathyroidism, and retinopathy [1]. Mitochondrial Trifunctional Protein deficiency is a more heterogeneous condition, which can range from milder to severe [1]. The milder phenotype can consist of exercise induced rhabdomyolysis and/or peripheral neuropathy to a more severe phenotype similar to isolated LCHAD deficiency [1].

Patients can be identified through newborn screening with initiation of appropriate interventions. The confirmatory testing for the diagnosis is acylcarnitine profile analysis. Patients affected with LCHAD deficiency have increased hydroxycompounds C14-OH, C16-OH, C18-OH, and C18:1-OH. Urine organic acids demonstrate C6-C14 hydroxydicarboxylic acids. Although patients identified presymptomatically and treated can have a milder course, patients with LCHAD deficiency can still develop chronic complications including cardiomyopathy.

* Corresponding author at: Department of Genetics and Metabolism, Children's National Health System, 111 Michigan Ave NW, Washington, DC 20010, USA.
E-mail address: DRegier@childrensnational.org (D.S. Regier).

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Treatment consists of limiting dietary fat and providing other essential nutrients in the formula and fasting avoidance. Due to increased renal excretion of bound acylcarnitines, patients may develop a secondary carnitine deficiency. Carnitine can be provided if the patient is found to be deficient [2]. Aggressive treatment of cardiomyopathy, rhabdomyolysis, and retinopathy are essential for optimal quality of life.

There are several studies including the one by Neto, et al. that demonstrate the feasibility of umbilical cord blood use in screening for acylcarnitine and free carnitine [3]. These studies used umbilical cord blood that was placed on filter paper for analysis. In comparison to regularly timed newborn screening, the earlier screening using umbilical cord blood could potentially miss some diagnoses that require ingestion of breast milk or formula before the values start rising. There is one abstract reporting clinical utility of umbilical cord blood in diagnosis of high-risk neonates with isovaleric acidemia and medium-chain acyl-coenzyme A dehydrogenase deficiency [4].

To date, there are no published cases of LCHAD/TFP deficiency diagnosed using umbilical cord blood.

3. Clinical case

3.1. Clinical presentation

Our patient is a 4 week-old female with LCHAD deficiency diagnosed at the time of delivery using umbilical cord blood. Concern for the diagnosis of LCHAD deficiency was suspected due to an affected older sibling diagnosed through routine newborn screening. Her older sister was found to have one pathogenic change in HADHB and no changes in other genes associated with LCHAD deficiency; thus, she was diagnosed with LCHAD deficiency secondary to trifunctional protein (TFP) deficiency. Our patient is a 4 week-old female with LCHAD deficiency diagnosed at the time of delivery using umbilical cord blood. Concern for the diagnosis of LCHAD deficiency was suspected due to an affected older sibling diagnosed through routine newborn screening. Her older sister was found to have one pathogenic change in HADHB and no changes in other genes associated with LCHAD deficiency; thus, she was diagnosed with LCHAD deficiency secondary to trifunctional protein (TFP) deficiency. The older sibling had a complex neonatal course due to feeding intolerance and lactic acidosis before discharge from the birth. Her lactic acidosis led to a prolonged neonatal intensive care unit hospitalization. Her newborn screen was notable for elevations concerning for LCHAD deficiency and this was confirmed using acylcarnitine profile testing. Her cardiac evaluation was normal. Due to the complex neonatal course and feeding intolerance, a gastric tube (G-tube) was placed prior to her discharge from the birth hospital. Her first year of life was notable with feeding intolerance requiring G-tube feeds. Her first hospitalization with creatinine kinase elevation in the setting of mild illness was at 12 months of age. Her cardiac evaluation remained normal.

Her mother was counseled on invasive prenatal testing; however, due to the limited information that could be obtained prenatally, the testing was declined. Pregnancy was complicated by late pregnancy swelling, hypertension, and elevated liver function levels both before and after delivery, suggestive of a diagnosis of HELLP syndrome.

The neonate was delivered at 37 weeks gestation. Umbilical cord blood was collected at delivery and sent for acylcarnitine analysis. Treatment was started immediately at delivery, including dextrose-containing fluids and Lipistart formula, a low long chain fat, high medium chain fat formula.

3.2. Laboratory findings

Acylcarnitine analysis from the umbilical cord blood was significant for C14-OH 0.14 nmol/mL (normal <0.04 nmol/mL), C16-OH 0.50 (normal <0.10), C18:2-OH 0.23 (normal <0.04), and C18:1-OH 0.39 (normal <0.03). These findings are consistent with a biochemical diagnosis of LCHAD/TFP deficiency. Acylcarnitine analysis from the umbilical cord blood was significant for C14-OH 0.14 nmol/mL (normal <0.04 nmol/mL), C16-OH 0.50 (normal <0.10), C18:2-OH 0.23 (normal <0.04), and C18:1-OH 0.39 (normal <0.03). These findings are diagnostic for LCHAD deficiency. The newborn screen performed at 1 h of life from a heel stick showed C16-OH 0.88 μmol/L (<0.10) and C18:1-OH 0.39 μmol/L (<0.11). Repeat newborn screen at day 7 of life after initiation of formula containing high medium chain and low long chain fat flagged as abnormal for the following: C16-OH 0.29 μmL/L, C18:1-OH 0.48 μmol/L, and C10 0.55 μmol/L (<0.10). Plasma acylcarnitine profile performed at 4 weeks of life showed similar elevations with C16-OH 0.53 μmol/L (<0.06) and C18:1-OH 0.28 μmol/L (<0.03).

Creatine kinase remained elevated throughout her 17 day stay in the intensive care unit with maximum noted on 2 days of life at 363 unit/L (29–168) and improved prior to discharge.

Molecular testing was performed to identify any genetic changes in the genes associated with LCHAD deficiency. Both siblings were found to have a single change in the *HADHB* gene, c.1059delT, a likely pathogenic variant identified in one previous publically reported database. A follow-up microarray analysis did not indicate an exon deletion in the HADHB gene. Gene sequencing of the other causative genes in fatty acid oxidation disorders were also performed to ensure that an alternate diagnosis was not the cause of the sibling's biochemical diagnosis. These genes included ACAD9, ACADVL, AGA, AP3B1, BLNK, CASP10, CD40, CD79A, CXCR4, ELANE, FMO3, G6PC3, GATA1, GATA2, FGI1, GSS, HADHA, HAX1, ICOS, IGHM, PIK3R1, PNP, RFX5, RFXANK, RFXAP, RMRP, RPS19, SDBS, SLC35A1, SMARCAL1, STK4, STX11, VPS13B, WAS.

4. Discussion

Patients with LCHAD/TFP deficiency should have treatment initiated as early as possible to avoid or minimize the long-term complications of the disorder including cardiomyopathy. Standard newborn screening using a dried blood spot is performed after 24 h of life and mailed to the state laboratory. This delay in recognition and treatment of this disorder can result in irreversible damage.

Walter et al. (2009) [5] and Neto et al. [3] have demonstrated acylcarnitine analysis using umbilical cord blood spots to be technically feasible but they were not able to justify its use clinically. Although the studies by Walter et al. were positively able to identify affected newborns with umbilical cord blood spot analysis, there were some patients who had a negative screen who subsequently were diagnosed with a metabolic condition [5].

The role of the maternal environment leading to abnormal newborn screening results has been hypothesized. Multiple groups have shown complex prenatal, transition, and early infancy carnitine fluctuations [6–9]. This case shows that even as early as delivery, the neonatal metabolism of carnitine species is markedly abnormal from normal ranges. In the case presented here, whole umbilical cord blood, newborn screening at time of delivery, newborn screening at seven days of life, and plasma acylcarnitine analysis at 4 weeks of life. Although umbilical cord blood has been demonstrated to be reliable in diagnosis in some conditions, other conditions require time outside of the maternal environment to accumulate metabolites therefore traditional newborn screening cannot be currently replaced by umbilical cord blood sampling.

5. Conclusions

In pregnancies at risk of having a child with LCHAD deficiency due to TFP deficiency, umbilical cord blood sample is an efficient method to diagnose an inborn error of metabolism when other prenatal mechanisms are not available or reliable for a family.

Author roles

Donna B Raval evaluated and managed the patient, wrote the manuscript.

Kristina Cusmano-Ozog evaluated and managed the patient and performed the molecular data described.

Omar Ayyub assisted in evaluation of the testing results, writing of the manuscript.

Callie Jenevein evaluated and managed the patient, edited the manuscript.

Laura H Kofman evaluated and managed the patient, edited the manuscript.

Brendan Lanpher evaluated and managed the patient, edited the manuscript.

Natalie Hauser evaluated and managed the patient, edited the manuscript.

Debra S. Regier evaluated and managed the patient, assisted in writing and editing the manuscript.

Guarantor: Debra S. Regier.

Conflict of interest

The authors have nothing to declare.

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Ethics approval was not required for this study.

Parental guardian has given consent for the publication of this report.

References

[1] J.M. Saudubray, G. van den Bergher, J.H. Waler, Inborn Metabolic Diseases, fifth ed. Springer-Verlag, Berlin Heidelberg, 2012 205.

[2] I. De Biase, K.S. Viau, A. Liu, T. Yuzyuk, L.D. Botto, M. Pasquali, N. Longo, Diagnossis, treatment, and clinical outcome of patients with mitochondrial trifunctional protein/long-chain 3-Hydroxy acyl-CoA dehydrogenase deficiency, JIMD Reports DOI (2016)http://dx.doi.org/10.1007/8904_2016_558.

[3] E.V. Neto, A.A. Fonseca, R.F. Almeida, M.P. Figueiredo, M.A.S. Porto, M.G. Ribeiro, Analysis of acylcarnitine profiles in umbilical cord blood and during the early neonatal period by electrospray ionization tandem mass spectrometry, Braz. J. Med. Biol. Res. 45 (2012) 546–556.

[4] AL Patterson, M Pourfarzam, MJ Henderson. (2000) The utility of cord blood analysis in the diagnosis of organic acidaemias. J. Inherit. Metab. Dis. 23 (Suppl 1): 84 (Abstract).

[5] J.H. Walter, A. Patterson, J. Till, G.T. Besley, G. Fleming, M.J. Henderson, Bloodspot acylcarnitine and amino acid analysis in cord blood samples: efficacy and reference data from a large cohort study, J. Inherit. Metab. Dis. 32 (2009) 95–101.

[6] C.T. Cavedon, P. Bourdoux, K. Mertens, H.V. Van Thi, N. Herremans, C. de Laet, P. Goyens, Age-related variations in acylcarnitine and free carnitine concentrations measured by tandem mass spectrometry, Clin. Chem. 51 (2005) 745–752.

[7] J. Meyburg, A. Schulze, D. Kohlmueller, O. Linderkamp, E. Mayatepek, Postnatal changes in neonatal acylcarnitine profile, Pediatr. Res. 49 (2001) 125–129.

[8] G.C. Talián, K. Komlósi, T. Decsi, B. Koletzko, B. Melegh, Determination of carnitine ester patterns during the second half of pregnancy, at delivery, and in neonatal cord blood by tandem mass spectrometry: complex and dynamic involvement of carnitine in the intermediary metabolism, Pediatr. Res. 62 (2007) 88–92.

[9] D.H. Chace, R. Pons, C.A. Chiriboga, D.J. McMahon, I. Tein, E.W. Naylor, D.C. De Vivo, Neonatal blood carnitine concentrations: normative data by electrospray tandem mass spectometry, Pediatr. Res. 53 (2003) 823–829.