International Journal of Contemporary Pediatrics
Ramachandran HP et al. Int J Contemp Pediatr. 2022 May;9(5):487-490
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20221008

Case Report

Pre-symptomatically detected novel variant of CPT1A deficiency: a case report

Hari Prasath Ramachandran*, Ramkumaar U.

Department of Neonatology, Cloudnine Hospital, Chennai, Tamil Nadu, India

Received: 13 March 2022
Accepted: 28 March 2022

***Correspondence:**
Dr. Hari Prasath Ramachandran,
E-mail: drrhariprasath@gmail.com

ABSTRACT

CPT1A enzyme deficiency is a rare metabolic disorder of mitochondrial fatty acid oxidation, with late manifestations during infancy or childhood, including hypoketotic hypoglycemia and hepatic encephalopathy. Newborn screening in several countries include pre-symptomatic detection of CPT1A deficiency, which helps in early diagnosis and better management of the disorder. We report here a case of CPT1A deficiency, detected pre-symptomatically with newborn screening, which was confirmed by exome sequencing to be a novel c. 232G>A variant in exon 3 of CPT1A gene. This is a rare variant of uncertain significance which has not been reported in literature.

Keywords: CPT1A deficiency, Hypoketotic hypoglycemia, Fatty acid oxidation, Newborn screening, Novel mutation

INTRODUCTION

Carnitine palmitoyltransferase 1A (CPT1A) is an enzyme which plays a role in hepatic mitochondrial fatty acid oxidation (FAO).[1] CPT1A deficiency (OMIM ID #255120) is a rare autosomal recessive disorder (as low as 1:750,000 to 1:2,000,000) with impaired mitochondrial long-chain fatty acid beta-oxidation, resulting in accumulation of high levels of long chain fatty acids in the liver. Impaired mitochondrial FAO leads to typical presentations of hypoketotic hypoglycemia and hepatic encephalopathy.[2,3] However, patients with CPT1A deficiency do not present with symptoms until there is increased energy demands as noted in fasting or febrile illness, thus increasing the chances of delayed diagnosis and management.[4] However, it can be detected pre symptomatically by tandem mass spectrometry.[2,5] Hence, to detect pre-symptomatically and start early treatment, CPT1A is included in newborn screening programs in several countries. In this report, we present a case of pre-symptomatic CPT1A deficiency with a novel c.232G>A variant of uncertain significance, detected through newborn screening and later confirmed by exome sequencing. This emphasizes importance of pre-symptomatic detection of CPT enzyme deficiency through newborn screening. Evaluation, clinical assessment and management of disorder has been discussed.

CASE REPORT

Conceived naturally after 5 years of married life, by parents who had 3rd degree consanguinity. Born to primi gravida with gestational diabetes mellitus and was delivered by emergency caesarean section (Indication: Meconium-stained liquor/fetal distress) at 36 weeks and 3 days (Late preterm) with a birth weight of 3.17 kilograms (Appropriate for gestational age). Baby cried immediately after birth. APGAR score was 7/10 and 8/10 at 1st and 5th minute respectively. She was treated in NICU for transient tachypnea of newborn. However, baby had lability in oxygen saturation and required prolonged oxygen support by nasal prongs with minimal FiO_2 requirement until 3 days of life. Echocardiogram ruled out persistent pulmonary hypertension. Baby received antibiotics empirically which were discontinued as septic work up including blood culture was negative. Baby received nutrition through IV fluids until distress subsided and later switched to exclusive breastfeeding. Sugar monitoring was done which was normal

throughout the hospital stay. Baby required repeated double surface phototherapy for neonatal hyperbilirubinemia (O-A setting). Baby was discharged on day 7 of life. The diagnosis was arrived at through newborn screening done on day 4 of life, when the baby was stable and on direct breastfeeding, showed 'slightly high' concentration of free carnitine (C0) in the plasma sample (85.55 µmol/L; ref range 18.5-71.15 µmol/L) with normal C0/C16+C18 ratio. As per American college of Medical Genetics guidelines, clinical exome sequencing was done on DNA extracted from blood.[6] Clinically relevant mutations were annotated using published variants in literature and a set of diseases databases-ClinVar, OMIM, GWAS, HGMD (v2020.2) and SwissVar. Common variants are filtered based on allele frequency in 1000genome phase 3, gnomAD (v2.1), EVS, dbSNP (v151), 1000 Japanese genome and internal Indian population database. Only non-synonymous and splice site variants consisting of 6120 genes were used for clinical interpretation. Silent variations that do not result in any change in amino acid in the coding region were excluded. In this case, A homozygous missense variation in exon 3 of the CPT1A gene (chr11:g.68812486C>T; depth: 152x) that results in the amino acid substitution of asparagine for aspartic acid at codon 78 (p.Asp78Asn; ENST00000265641.10) was detected, which is a novel c.232G>A variant of uncertain significance.

Further plan of action as per American college of medical genetics recommendation (ACT sheet) was initiated.[6] Family was informed and counselled, baby's clinical status ascertained, and a management strategy formulated. Enzyme activity assays, sequencing of variants in parents and periodic follow up of child to assess clinically for appearance of any related or new symptoms are recommended to ascertain clinical significance of this variant. Baby has been on periodical follow up and has remained asymptomatic on exclusive breastfeeds. Family screening of these mutations for patient's parents was not performed yet, as the child has remained asymptomatic thus far. Genetic counseling through family screening of identified mutations is necessary if the parents want to have another baby.

DISCUSSION

The CPT1 enzyme has three tissue specific isoforms: the liver isoform (CPT1A), the muscle isoform (CPT1B), and the brain isoform (CPT1C) which are encoded by different genes. Mutations in the CPT1A gene (11q13.1-q13.2) results in deficiency of the liver isoform of carnitine palmitoyl transferase 1A. The CPT1A enzyme is located in the outer mitochondrial membrane where it converts the long chain fatty acyl-CoA molecules to their respective acyl-carnitine molecules. The carnitine acylcarnitine translocase system then transports these fatty acyl co-A molecules, across the inner mitochondrial membrane into the mitochondria to undergo beta-oxidation.[7] In the absence of this system, long chain fatty acids cannot be transported into mitochondria. Hepatic mitochondrial fatty acid oxidation is an important alternative source of energy when glycogen reserves are used up during phases of increased energy demands like fasting or a febrile illness. The reduced ability to utilize long-chain fatty acids for ketogenesis leads to clinical presentation of hepatomegaly and hypoketotic hypoglycaemia, which can lead to seizures and coma.[8]

To reduce the risk of neurological damage and sequelae, one must prevent hypoglycemia. Hence, it is important to diagnose these patients early. CPT1A deficiency has been included in newborn screening programs using tandem mass spectrometry to detect an abnormal carnitine profile.[3,5,9] TMS usually uses a few indicators such as C0 level, C16 level, C18 level, or C0/ (C16+C18) ratio to diagnose CPT 1A deficiency. In a Japanese report of pre-symptomatic detection of CPT1A deficiency by TMS newborn screening, the patient did not show hypoglycemia or jaundice.[10] However, elevation of free carnitine level (C0) was noticed by newborn screening. Fingerhut et al reported 2 false negative cases in the method using C16 level.[5] Although, some consider C0/ (C16+C18) ratio to be a very reliable diagnostic marker for CPT1A deficiency, even when patient is stable, a vice versa of C0 / (C16+C18) being in normal range in patients has also been observed.[5,9] In fact, in our case the C0/C16 + C18 ratios were low as opposed to studies which reported 6-60 fold increase.[5] The data is attributable to variant of unknown significance with possible lesser clinical severity as reflected in a case report by Borch et al.[11]

The reliability of urine organic acids is also debatable. Studies have reported that C12 dicarboxylic acids and 3-OH glutaric acids are elevated in acute cases of CPT1A deficiency.[12-15] However, a few studies have also reported urine organic acids to be normal when the patient is stable.[8,10]

American college of medical genetics recommends timely confirmatory testing. Molecular genetic analysis for the CPT1A gene is the confirmative test for diagnosis Targeted gene sequencing is a cost-effective approach to detect variants present in multiple/large genes in an individual, in which selective capture and sequencing of the protein coding regions of the genome/genes is performed. Approximately 30 kinds of mutations have been reported till date (the Human Gene Mutation Database, ttp://www.hgmd.cf.ac.uk). Some well-known founder mutations include c.1436C＞T (p.Pro479Leu) in Inuit population and c.2129G＞A (p.Gly710Glu) in Hutterite populations.[16-18] In our case, a homozygous missense variation in exon 3 of the CPT1A gene that results in the amino acid substitution of Asparagine for Aspartic Acid at codon 78 (p.Asp78Asn; ENST00000265641.10) was detected. The p.Asp78Asn variant has not been reported in the 1000 genomes database and has a minor allele frequency of 0.0006% and 0.002% in the gnomAD and Indian database

respectively, making it a novel variant of uncertain significance (difficult to classify as either pathogenic (disease causing) or benign (non-disease causing) based on current available scientific evidence).[19-22]

CPT1 deficiency can have a variable presentation. Newborns may appear asymptomatic but can progress to fasting hypoketotic hypoglycemia, lethargy, hepatomegaly, elevated transaminases, elevated creatine kinase and cardiac rhythm disturbances and seizures, usually precipitated by fasting or acute illness. Critical hypoketotic hypoglycemia is a common presentation with most patients having recurrent hypoglycemic events as the first manifestation especially in the event of prolonged fasting or infection where glycogen reserves are exhausted soon.[23] However, in the present case, the patient did not demonstrate any hypoglycemic events before diagnosis. After diagnosis, infant did not show symptoms such as hypoglycemia and encephalopathy and showed a normal weight gain pattern during follow up.

Atypical presentations in published literature include hepatosplenomegaly, nephromegaly and cholestatic jaundice as the first manifestation of CPT1A deficiency.[24,25]

In the case report of a patient with cholestatic jaundice along with CPT1A deficiency, it is postulated that cholestatic jaundice is due to impaired adenosine triphosphate (ATP)-dependent bile acid secretion from lack of energy.[26] However milder forms of CPT1A deficiency might be able to supply glucose through mitochondrial FAO.[27] Early diagnosis is difficult in these patients before progression of hepatic dysfunction. Hence in any patient showing an unusual course of jaundice, screening for metabolic disorders including TMS analysis and carnitine assay should be considered. No features were suggestive of cholestasis jaundice in our case.

Renal tubular acidosis in CPT1A deficient patients has been reported.[28] The kidney is rich in mitochondria with fatty acids being an important source of energy. Therefore, RTA can be due to lack of energy for the kidney from impaired fatty acid oxidation, which can be treated with medium chain triglyceride supplement. A study also reported nephromegaly with significant proteinuria due to accumulation of long chain fatty acid and dyslipidemic changes in kidney.[24] No symptoms or clinical findings were suggestive if RTA or nephromegaly in our case.

Key to management is in prevention of hypoglycemia. A sufficient level of glucose should be constantly supplied to patients with CPT1A deficiency during long time of fasting. Higher glucose infusion rates are essential in CPT1A deficient patients along with mandatory blood glucose level monitoring during stressful conditions including major operation and severe infection.[23] The long-term treatment is to provide a steady diet which is low in fat, high in carbohydrate and a supply of medium-chain fatty acids. Fasting periods should be minimalized and avoided.

An essential component of neonatal screening for inherited diseases is to have a diagnostic algorithm for each disorder to be able to establish accuracy of diagnosis. In cases of variant of unknown significance, the diagnostic or management algorithm from American College of Medical genetics can be followed. Enzyme activity assays, sequencing of variants in parents and periodic follow up of child to assess clinically for appearance of any related or new symptoms are recommended to ascertain clinical significance of this variant and plan management accordingly. More such reports can be encouraging to detect the prevalence of such disorders in Indian population which remains largely undiscovered. Careful follow-up programs and evaluation of new genetic variants are required to strike a balance between the psychosocial risks and the clinical benefits of screening.

CONCLUSION

We conclude that Newborn screening is essential to detect CPT1A deficiency. Exome sequencing was helpful in clinching the diagnosis in this case pre-symptomatically and institute management for the same in a timely manner.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Carnitine palmitoyl transferase I deficiency. Genetics Home Reference. 2014. Available at http://ghr.nlm.nih.gov/condition=carnitinepalmitoyltransferaseideficiency. Accessed on 11 November 2016
2. Fatty acid oxidation disorders. STAR-G Screening, Technology and Research in Genetics. 2/28/2016; Available at: http://www.newbornscreening.info/Parents/fattyaciddisorders/CPT1.html#3. Accessed on 11 November 2016
3. Lindner M, Hoffmann GF, Matern D. Newborn screening for disorders of fatty-acid oxidation: experience and recommendations from an expert meeting. J Inherit Metab Dis. 2010;33(5):521-6.
4. Bennett MJ, Santani AB. Carnitine Palmitoyltransferase 1A Deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle. 2005;1993-2022.
5. Fingerhut R, Röschinger W, Muntau AC, Dame T, Kreischer J, Arnecke R et al. Hepatic carnitine palmitoyltransferase I deficiency: acylcarnitine profiles in blood spots are highly specific. Clin Chem. 2001;47(10):1763-8.

6. American College of Medical Genetics, ACT sheet, 2009. Available at: https://rarediseases.info.nih.gov/diseases/1120/carnitine-palmitoyl-transferase-1a-deficiency. Accessed 11 November 2016.
7. Fraser F, Corstorphine CG, Zammit VA. Topology of carnitine palmitoyltransferase I in the mitochondrial outer membrane. Biochem J. 1997;323 (Pt 3):711-8.
8. Bennett MJ, Narayan SB, Santani AB. Carnitine palmitoyl transferase 1A deficiency. In Pagon RA, Bird TD, Dolan CR, editors. GeneReviews. Seattle (WA): University of Washington, Seattle. 2010;1993.
9. Sim KG, Wiley V, Carpenter K, Wilcken B. Carnitine palmitoyltransferase I deficiency in neonate identified by dried blood spot free carnitine and acylcarnitine profile. J Inherit Metab Dis. 2001;24(1):51-9.
10. Tsuburaya R, Sakamoto O, Arai N, Kobayashi H, Hasegawa Y, Yamaguchi S et al. Molecular analysis of apresymptomatic case of carnitine palmitoyl transferase I (CPT I) deficiency detected by tandem mass spectrometry newborn screening in Japan. Brain Dev. 2010;32(5):409-41.
11. Borch L, Lund AM, Wibrand F. Normal Levels of Plasma Free Carnitine and Acylcarnitines in Follow-Up Samples from a Presymptomatic Case of Carnitine Palmitoyl Transferase 1 (CPT1) Deficiency Detected Through Newborn Screening in Denmark. JIMD Rep. 2012;3:11-5.
12. Bennett MJ, Boriack RL, Narayan S, Rutledge SL, Raff ML. Novel mutations in CPT 1A define molecular heterogeneity of hepatic carnitine palmitoyltransferase I deficiency. Mol Genet Metab. 2004;82:59-63.
13. Brown NF, Mullur RS, Subramanian I, Esser V, Bennett MJ, Saudubray JM, et al., Molecular characterization of L-CPT I deficiency in six patients: insights into function of the native enzyme. J Lipid Res. 2001;42(7):1134-42.
14. Stoler JM, Sabry MA, Hanley C, Hoppel CL, Shih VE. Successful long-term treatment of hepatic carnitine palmitoyl transferase I deficiency and a novel mutation. J Inherit Metab Dis. 2004;27(5):679-84.
15. Korman SH, Waterham HR, Gutman A, Jakobs C, Wanders RJ.Novel metabolic and molecular findings in hepatic carnitine palmitoyltransferase I deficiency. Mol Genet Metab. 2005;86(3):337-43.
16. Collins SA, Sinclair G, McIntosh S, Bamforth F, Thompson R, Sobol I et al. Carnitine palmitoyl transferase 1A (CPT1A) P479L prevalence in live new borns in Yukon, Northwest Territories, and Nunavut. Mol Genet Metab. 2010;101:200-4.
17. Prasad C, Johnson JP, Bonnefont JP, Dilling LA, Innes AM, Haworth JC et al. Hepatic carnitine palmitoyl transferase 1 (CPT1 A) deficiency in North American Hutterites (Canadian and American): evidence for a founder effect and results of a pilot study on a DNA based newborn screening program. Mol Genet Metab. 2001;73:55-63.
18. Brown NF, Mullur RS, Subramanian I, Esser V, Bennett MJ, Saudubray JM et al. Molecular characterization of L-CPT I deficiency in six patients: insights in to function of the native enzyme. J Lipid Res. 2001;42:1134-42.
19. The 1000 Genomes Project Consortium. A global reference for human genetic variation. Nature. 2015;526(7571):68-74.
20. Exome Variant Server, NHLBI GO Exome Sequencing Project (ESP), Seattle, WA. Available at: http://evs.gs.washington.edu/EVS/. Accessed on 12 December 2021.
21. Nagasaki M. Rare variant discovery by deep whole-genome sequencing of 1,070 Japanese individuals. Nat Commun. 2015;6:8018.
22. Sherry ST, Ward MH, Kholodov M, Baker J, Phan L, Smigielski EM, Sirotkin K. dbSNP: the NCBI database of genetic variation. Nucleic Acids Res. 2001;29(1):308-11.
23. Bonnefont JP, Djouadi F, Prip-Buus C, Gobin S, Munnich A, Bastin J. Carnitine palmitoyltransferases 1 and 2: biochemical, molecular and medical aspects. Mol Aspects Med. 2004;25:495-520.
24. Lee BH, Kim YM, Kim JH, Kim GH, Kim JM, Kim JH et al. Atypical manifestation of carnitine palmitoyl ransferase 1A deficiency: hepatosplenomegaly and ne phromegaly. J Pediatr Gastroenterol Nutr. 2015;60:e19-22.
25. Choi JS, Yoo HW, Lee KJ, Ko JM, Moon JS, Ko JS. Novel Mutations in the CPT1A Gene Identified in the Patient Presenting Jaundice as the First Manifestation of Carnitine Palmitoyltransferase 1A Deficiency. Pediatr Gastroenterol Hepatol Nutr. 2016;19(1):76-81.
26. Morris AA, Olpin SE, Bennett MJ, Santani A, Stahl Schmidt J, McClean P. Cholestatic jaundice associated with carnitine palmitoyltransferase IA deficiency. JIMD Rep. 2013;7:27-9.
27. Greenberg CR, Dilling LA, Thompson GR, Seargeant LE, Haworth JC, Phillips S et al. The paradox of the carnitine palmitoyltransferase type Ia P479L variant in Canadian Aboriginal populations. Mol Genet Metab. 2009;96:201-7.
28. Falik-Borenstein ZC, Jordan SC, Saudubray JM, Brivet M, Demaugre F, Edmond J et al. Brief report: renal tubular acidosis in carnitine palmitoyltransferase type 1 deficiency N Engl J Med. 1992;327:24-7.

Cite this article as: Ramachandran HP, Ramkumaar U. Pre-symptomatically detected novel variant of CPT1A deficiency: a case report. Int J Contemp Pediatr 2022;9:487-90.