Carnitine palmitoyl transferase 1A deficiency: A disease in disguise - a case report

Sumera Janvekar, Ramesh Pol, Raghavendra Vanaki, Bhuvaneshwari Yelamali

Department of Pediatrics, S. N. Medical College, Bagalkot, Karnataka, India

Abstract

Carnitine palmitoyl transferase type 1A (CPT 1A) deficiency is a rare metabolic disorder of fatty acid oxidation. The deficiency does not allow the breakdown of stored fat into energy especially during an intercurrent illness and periods of fasting, leading to a series of symptoms that mimics various other inborn errors of metabolism and liver diseases. The affected child lands in metabolic crisis, having hypoketotic hypoglycaemia, gradual loss of consciousness, hepatomegaly usually following a gastrointestinal illness. We studied a 2-year-old boy coming with such complaints with increased free carnitine levels. Tandem Mass Spectrometry was suggestive of CPT 1A deficiency. This case report focuses on such Inborn Errors of Metabolism to spread awareness among pediatricians across the globe.

Keywords: Carnitine palmitoyltransferase type 1A deficiency, Primary carnitine deficiency

Introduction

Carnitine palmitoyl transferase type 1A (CPT 1A) deficiency is a disorder of long chain fatty acid oxidation. It is a rare treatable form of Inborn Errors of Metabolism (IEM) that is autosomal recessively inherited, with fewer than 60 cases reported worldwide. Mutation in CPT 1A gene causes Carnitine palmitoyl transferase deficiency[1]. It was first described by Bougneres and colleagues and first reported in 1981[3]. The usual age of presentation is during first 2 years of life[4,5]. The event is triggered either by an intercurrent illness or periods of fasting. The typical features include altered consciousness, acute liver failure with hepatomegaly. Life threatening attacks of hypoketotic hypoglycaemia and coma usually precedes a gastrointestinal illness.

CPT 1A deficiency is common in Hatrurite & Inuit population. Although the exact prevalence of CPT deficiency is not known, CPT 1 deficiency accounts for 5% fatty acid oxidation defects according to a study done in 2013 by a tertiary care centre in Delhi[6]. Cases from India are also coming into light recently. This study reports such a case from Bagalkot district of Karnataka state.

Case report:

A 2 year old boy, resident of Bagalkot district of Karnataka, was brought to the Pediatric intensive care unit of our hospital with complaints of loose stools, vomiting and fever since 5-6 days, followed by sudden loss of consciousness and up rolling of eyeballs; was unresponsive since then. He was then taken to a private hospital, where he was suspected to have meningoencephalitis. CSF analysis was inconclusive. He was treated with IV antibiotics and anticonvulsants. He was referred to our hospital. The child presented to emergency department with GCS of 9/15, random blood sugar was 60mg/dl, was in hypovolemic shock. IV fluid correction was given using crystalloids. There was no improvement in hemodynamic status, but worsening sensorium and shallow respiration. Child was intubated and started on inotropes. Meanwhile child had two episodes of hypoglycaemia. Corrected the same and kept continuous dextrose infusion with GIR of 6-8mg/kg/min. Wilsons disease and other hepatotropic viral markers were negative. With this sudden deterioration of apparently healthy child, we suspected him to have IEM. Workup for the same was done. IEM work up was done, Tandem Mass Spectrometry (TMS) was done. Meanwhile measures were taken to eliminate the toxic ammonia.

Address for Correspondence:

Dr. Ramesh Pol

Department of Pediatrics, S. N. Medical College, Bagalkot, Karnataka, India

E-mail: rameshpol@ymail.com

Treated with intravenous **L-ornithine and L-aspartate** (hepamerz). It stimulates urea cycle resulting in loss of ammonia[7]. **Oral lactulose** that acidifies the intestinal contents and favours conversion of toxic ammonia [NH3] to ammonium [NH4][8] and **Metronidazole** that inhibits ammonia producing bacteria in the gut. Supplemented with IV **carnitine** (200mg/kg/day in 2 divided doses)[9]. **Sodium benzoate** that acts by acylation using exogenous organic acids with endogenous amino acids to form nontoxic compound with high renal clearances. In addition to this, child received IV antibiotics and anticonvulsants, hypertonic saline and MVI.

Child showed improvement following the treatment. Diagnosis of CPT 1A deficiency was confirmed by TMS. Child was discharged with dietary advice and carnitine supplementation. As the mother was pregnant, parents were counselled regarding foetus being affected in 25% cases and need for prenatal check-up of further pregnancies[1]. We followed up the boy for 1 year and is doing well, however the younger sibling expired at 3 months of age due to febrile illness.

Discussion

CPT 1A deficiency is very rare in general population, gets easily missed leading to mortality.

3 isoforms of CPT 1 have been identified in various tissues of the body[10]. Viz,

- Liver type [LCPT 1 or CPT 1A]
- Muscle type [MCPT 1 or CPT 1B]
- Brain type [CPT 1C]

CPT 1A is the only isoform for which human deficiency has been recognised. In contrast to most other inborn errors of fatty acid oxidation, free carnitine concentration is increased rather than decreased in CPT 1A deficiency.

Table 1: Laboratory findings of the case

Laboratory investigations with normal values	Values
Complete blood count	
Haemoglobin(13-18gm/dl)	7.1 g/dl
Total WBC count(4000-11000cells/cumm)	20,700 cells/cumm
Platelet(150000-400000 cells/cumm)	5,22,000 cells/cumm
RBC count	3.25 millions/cumm
ESR (0-20mm/ hour)	30mm
Sodium(135-153meq/L)	135 mEq/L
Potassium(3.5-5.5meq/L)	3.2 mEq/L
Chloride(95-105meq/L)	110 mEq/L
Magnesium(1.9-2.9mg/dl)	2.1 mg/dl
Calcium(8.5-11mg%)	10.1 mg%
Urea(15-39mg/dL)	17 mg/dl
Creatinine(0.6-1.2mg%)	0.5 mg/dl
Liver function tests	
Direct bilirubin(0.1-0.4mg%)	0.4 mg%
Indirect bilirubin(0.1-0.6mg%)	0.6 mg%
Total protein(5.5-8.2gm%)	6.6 g%
Albumin(3.5-5g/dL)	3 g/dl
AST(upto 40U/L)	127.4 IU/L
ALT(upto 41U/L)	91.4 IU/L
ALP (145-420 IU/L)	125.9 IU/L
Prothrombin time (12-15sec)	25.5 sec
Activated partial prothrombin time(21-28sec)	Not clotted
INR (<1.1)	2.4
Creatine phosphokinase (CPK)-total(0-226u/l)	315 IU/L
LDH(132-228U/L)	650.7 IU/L
Ferritin(25-350ng/ml)	11.24 ng/ml
HIV	Non-reactive
HbsAg, HCV	Negative
RBS (60-105mg/dL)	23mg/dl
Urine for ketone bodies	Negative
ABG	Wide anion gap metabolic acidosis
Plasma ammonia	>500
Urine routine	5-6 pus cells
Stool routine	Normal
Lipid profile	
Triglycerides(<150mg/dL)	2418.6mg/dl
Total cholesterol(<200mg/dL)	286.8mg/dl
HDL(<50mg/dL)	30.8
Uric acid	12.6
Total carnitine	307mmol/l
Culture sensitivity	
Blood/stool/urine/CSF	No growth

Molecular mechanism of CPT 1A deficiency

CPT 1 is a mitochondrial membrane protein that converts long chain fatty acyl CoA molecules to their corresponding acyl carnitine, molecules. The resulting acyl carnitines are then available for transport into the mitochondrial matrix where they can undergo fatty acid oxidation. Mitochondrial fatty acid oxidation by the liver provides an alternative source of fuel when glycogen stores are significantly reduced, most often due to fasting or intercurrent illness. The pathway fuels ketogenesis for metabolism in the peripheral tissues that cannot oxidize fatty acids.

CPT 1A deficiency is characterized by episodes of hypoketotic hypoglycaemia beginning in early childhood usually associated with fasting or illness[6]. In this case, a 2-year-old boy born out of 3-degree consanguineous marriage belonging to a Muslim family presented with typical features of LCPT 1 deficiency, triggered by irregular food intake during the fasting periods of Ramzan festival. Clinically suspected IEM was confirmed by TMS.

The treatment of CPT 1A deficiency entails a low-fat diet supplemented with medium chain triglycerides (MCT), lifelong carnitine supplementation [100-400mg/kg/day in divided doses][9], avoidance of fasting and sustained exercise. Prevention strategy includes a high carbohydrate diet (70% of calories) & low fat (20% of calories). MCT should constitute about 1/3rd of the calories during period of illness.

Older children should not fast for more than 12 hours and for a shorter time, if evidence of febrile or gastrointestinal illness exists[1]. In infants, frequent feeding with corn starch overnight is necessary to provide a constant source of slow release carbohydrate to prevent hypoglycaemia during sleep. Prenatal diagnosis is offered to families along with new born screening with TMS.

Conclusion: Amongst all inborn errors of metabolism, fatty acid oxidation disorders CPT 1A deficiency is relatively rare in Asian countries. It mimics other diseases like organic acidurias, urea cycle disorders and disorders of gluconeogenesis (glycogen storage disease type 1). Hence a high index of suspicion is required for diagnosis. Prompt sending of TMS, treatment and prevention of such further episodes and parental counselling remains main intension of this study.

References

1. *Bennet MJ, Santani AB. Carnitine palmitoyltransferase 1A deficiency. InGeneReviews[internet] 2016 Mar 17. University of Washington, Seattle.*
2. *Olpin SE, Allen J, Bonham JR, Clark S, Clayton PT, Calvin J, et al. Features of carnitine palmitoyltransferase type 1 deficiency. J inherit metab dis. 2001;24(1):35-42*
3. *Collins SA, Sinclair G, McIntosh S, bamforth F, Thompson R, sobol I, Osborne G, et al. Carnitine palmitoyltransferase 1A (CPT1A) P479L prevalence in live newborns in Yukon, Northwest territories, and Nunavut. Mol genet metab. 2010 oct 1;101(2-3);200-4*
4. *Naher N, Nahar LN, Sultana S, Matin A, Fakir MH, Islam MR. Carnitine palmitoyl transferase type 1 deficiency in fatty acid oxidation disorder: A case report. Journal of Shaheed Suhrawardy medical college. 2014;6(1)38-40*
5. *Korman SH, Waterhan HR, Gutman A, Jakobs C, Wanders RJ. Novel metabolic and molecular findings in hepatic carnitine palmitoyl transferase 1 deficiency. Mol Genet Metab 2005;86(3):337-43*
6. *Sood V, Rawat D, Khanna R, Sharma S, Gupta PK, AlamS et al. Study of prevalence of fatty acid oxidation defects in children and adults with acute liver failure. Significance of carnitine/acylcarnitine and amino acid profile. Journal of clinical and experimental hepatology. 2016(suppl 1):S1-S7*
7. *Aidrus F, Razzaque S, Siddiqui A, Kumar A, Ghaur MI. Therapeutic efficacy of l-ornithine l-aspartate in patients with hepatic encephalopathy. Pakistan journal of neurological sciences (PJNS). 2015;10(3):47-41*
8. *Bhatia V, Lodha R. Intensive care management of children with acute liver failure. The Indian journal of paediatrics. 2010 Nov 1;77(11):1288-95.*
9. *Fu L, Huang M, Chen S. Primary carnitine deficiency and cardiomyopathy. Korean Circ J. 2013; 43:785-92.*
10. *Price NT, Vander LFR, Jackson VN, Corstorphine CG, Thompson R, Sorensen A, et al. A novel brain expressed protein related to carnitine palmitoyl transferase I. Genomics. 2001; 80:433-442.*

Conflict of interest: Nil

Source of funding: Nil

Date received: November 13th 2019

Date accepted: December 6th 2019