DOI: 10.7860/JCDR/2015/13600.6560

Case Report

Paediatrics Section

Neonatal Carnitine Palmitoyltransferase II Deficiency: A Lethal Entity

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ABSTRACT

Carnitine palmitoyltransferase II (CPTII) deficiency is a rare disorder of mitochondrial fatty acid oxidation with autosomal recessive mode of inheritance. Three classic forms of CPT II deficiency have been described namely the lethal neonatal form, severe infantile hepatocardiomuscular form and the myopathic form. We present a three-day-old female child, admitted to us for lethargy, icterus, low sugars and convulsions. Persistent non ketotic hypoglycaemia, hyperammonemia, raised liver enzymes with hepatomegaly and cardiomyopathy led to the suspicion of fatty acid oxidation defect. Tandem mass spectrometry helped to clinch the diagnosis of CPT II Deficiency in the present case.

Keywords: CPT II gene, Fatty acid oxidation, Non ketotic hypoglycaemia, Tandem mass spectrometry

CASE REPORT

A full term 2135 grams female baby was born to a primigravida mother, by emergency caesarian section for oligohydramnios and meconium stained liquor. Baby was breastfeeding well and was in the postnatal ward with the mother. On day 3, baby was shifted to the neonatal intensive care unit for lethargy, icterus and seizures with low blood sugar. On examination, the baby had hepatomegaly and depressed tone and activity. Initial investigations showed high leukocyte count (21,260 /mm^3), low random blood sugar (28 mg/dl), normal arterial blood gases and raised serum aspartate transaminase (110 IU/l). With the above symptoms and investigations the initial differential diagnosis suspected were sepsis, galactosaemia and glycogen storage disorder. USG abdomen showed mild hepatosplenomegaly and gall bladder sludge with wall thickening. USG skull and 2D Echo were unremarkable. Inspite of treatment with appropriate glucose infusion rate (GIR), antibiotics and anticonvulsants the baby persistently had low sugars and seizures. Further investigations revealed high serum ammonia (289 mcg/dl), absent serum and urinary ketones and persistent non ketotic hypoglycaemia, which, led us to investigate for fatty acid oxidation defect. Second line investigations showed raised serum LDH (6860 U/l), CPK (460 IU/l) and CPK-MB (200 IU/l). Galactosaemia profile, total carnitine 119 µmol/l, free carnitine 47.7 µmol/l (range 24.6-66.6 µmol/l) plasma amino acids were all normal. Tandem mass spectrometry showing elevated levels of free fatty acids namely C16 -9.76 (cut-off value-6), C18- 3.30 (cut off 1.02) and C18:1- 4.84 (cut off 2.50) and thereby it clinched the diagnosis of Type I (lethal neonatal form) CPTII Deficiency.

Baby was managed with high GIR drip of 7-9 mg/kg/min, packed red blood cells, platelet transfusion and oral medium chain triglycerides. During the next ten days, the baby had a stormy course and developed evidence of liver cell failure and disseminated intravascular coagulation (anaemia, thrombocytopenia, prolonged prothrombin time, conjugated hyperbilirubinemia) and later developed respiratory failure and succumbed on day 19 despite our best efforts.

DISCUSSION

Fatty acid oxidation disorders (FAODs) are a group of rare inherited conditions that have varied presentations [1-3]. Carnitine palmitoyltransferase II (CPT II) deficiency is one of them in which the body is unable to oxidize fats for energy [4-6]. Tandem mass spectrometric (MS/MS) measurement of serum/plasma acylcarnitines is an important screening test to detect fatty acid oxidation defects [3,4,7]. Definitive diagnosis is usually made by detection of reduced CPT II enzyme activity and molecular genetic testing [8].

Neonatologists and health care providers should familiarize themselves with early manifestations of genetic metabolic defects in neonates [9]. The early red flag signs raising suspicion of inborn errors are persistent/unexplained lethargy, vomiting, poor feeding, seizures, altered sensorium and failure to gain weight [5]. During the last few decades, newer methods like tandem mass spectroscopy have been developed to screen neonates with fast and accurate yielding results and these have helped in averting morbidity and mortality in many cases [3-5,9].

Defects in the carnitine cycle are rare in neonates. Carnitine is required for transfer of long chain fatty acids from cytoplasm into the mitochondrial matrix for oxidation and energy production in the form of adenosine triphosphate (ATP) and provides acetyl – CoA for gluconeogenesis. The carnitine cycle defects include: a) primary carnitine deficiency; b) carnitine palmitoyltransferase I (CPT I) deficiency; c) carnitine-acylcarnitine translocase deficiency (CACT); and d) carnitine palmitoyltransferase II (CPTII) deficiency [6].

CPT I enzyme is bound to the outer mitochondrial membrane and its deficiency usually presents in infants and children with recurrent attacks of hypoketotic hypoglycaemia with sparing of heart and muscle involvement. However, CPT II is located on the inner mitochondrial membrane. CPT II gene provides instructions for making an enzyme called CPT II which acts to convert long chain acylcarnitine substrates that are transported across the outer mitochondrial membrane to acyl-CoA for subsequent β oxidation. Thus, long chain acylcarnitines accumulate inside mitochondria and plasma in patients with carnitine palmitoyltransferase II (CPT II) deficiency [2]. CPT II is not required for metabolism of medium and short chain fatty acids and these are metabolized normally in the body [8].

Lethal neonatal form, severe infantile hepatocardiomuscular form, and myopathic form are the three clinical forms of CPT II deficiency. Myopathic type is usually mild and manifests anytime from infancy to adulthood. In the lethal neonatal form there is a profound deficiency of the enzyme CPT II. It presents within the first few days of life and invariably leads to early infantile death. This neonatal form presents with episodes of liver failure, hypoketotic hypoglycaemia, respiratory distress, cardiomyopathy, cardiac arrhythmias, seizures, lethargy, coma (precipitated by infections and fasting). Our patient too had hypoketotic hypoglycaemia, seizures, cardiomyopathy

and hepatomegaly. Additionally, some of the neonates have facial abnormalities and structural malformations (like cystic renal dysplasia and neuronal migration defects) [2].

In contrast to the lethal neonatal form, the severe infantile hepatocardiomuscular form usually has an onset in the first year of life. These infants present with liver failure, hypoketotic hypoglycaemia, cardiomyopathy, seizures, peripheral myopathy and attacks of abdominal pain and headaches. This form clinically closely mimics CACT deficiency and MS/MS studies can help to differentiate one from the other. The myopathic form of CPT II deficiency is the most common disorder of lipid metabolism affecting skeletal muscle and is the most frequent cause of hereditary myoglobinuria. Males are more likely to be affected than females and this form has a variable onset from the first to sixth decade. It is characterized by recurrent attacks of myalgia accompanied by myoglobinuria precipitated by prolonged exercise, cold exposure or stress. Weakness can occur during the attacks and the patient is asymptomatic in between attacks [2].

An initial screening test for diagnosis can be done by measurement of serum/plasma acylcarnitines by Tandem Mass Spectrometry. However, definitive diagnosis can be established by detection of decreased CPT enzyme activity in cultured fibroblasts and skeletal muscle [8]. An additional non invasive, rapid and specific diagnostic test is provided by molecular genetic testing of CPTII gene (which is the only gene known to be associated with CPT II deficiency). Various mutations seen in at least one copy of S113L, P50H, or Q413fs-F448L genes have been reported [8,10]. Morbidity and mortality can be reduced by molecular genetic testing of at-risk relatives. Prenatal diagnosis for at risk pregnancies is possible either by molecular genetic testing of CPT II or by CPTII enzyme activity assay in cultured amniocytes. Brain or renal abnormalities on fetal USG in mid trimester of pregnancy and pre-implantation genetic diagnosis (PGD) can be supportive [8].

Treatment is primarily conservative for the infantile and the myopathic forms with high carbohydrate (70%) and low fat (<20%) diet, infusions of glucose, frequent meals, avoiding extended fasting and prolonged exercise, providing adequate hydration during an attack of rhabdomyolysis and myoglobinuria to prevent renal failure. Medium chain triglyceride oil may be beneficial for all patients, because it bypasses the need for CPT II activity. Evaluation of relatives at risk and genetic counseling of families is essential in the management of such cases [2,6,8].

CONCLUSION

Neonates presenting with unexplained seizures, respiratory distress, cardiac rhythm abnormalities, liver failure and hypoketotic hypoglycemia should be thoroughly worked up to rule out inborn errors of metabolism especially fatty acid oxidation defects. Tandem mass spectrometry, enzyme assays and molecular genetic studies help to clinch the diagnosis in these infants.

ACKNOWLEDGEMENT

The authors wish to acknowledge the support given by Dr. Anil B Jalan, Chief Scientific Research Officer, of Navi Mumbai Institute of Research in Mental and Neurological Handicap for performing the IEM screening tests and tandem mass spectrometry for our patient.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Feb 18, 2015**
Date of Peer Review: **May 24, 2015**
Date of Acceptance: **Jul 08, 2015**
Date of Publishing: **Oct 01, 2015**