CASE REPORT

A case report of Carnitine Palmitoyltransferase deficiency type II

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SUMMARY

Carnitine Palmitoyltransferase deficiency type II (CPT II) is a rare metabolic disorder of fatty acid oxidation with an autosomal recessive mode of inheritance. The outcome is usually severe with most of the patients typically passing away in the newborn period. In this report, we share our experience in managing a case of CPT II in a one-day-old term female baby who was delivered at Hospital Sultan Abdul Halim.

INTRODUCTION

Carnitine enzyme is required for the transport of long-chain fatty acids into the mitochondria for the β-oxidation cycle. Four types of carnitine defects have been detected. The four defects are; Carnitine transport defect, Carnitine Palmitoyltransferase deficiency type IA (CPT I), Carnitine Acylcarnitine translocase deficiency (CACT), and Carnitine Palmitoyltransferase deficiency type II (CPT II).[1]

The CPT II enzyme converts long-chain acylcarnitine to long-chain acylCoAs for β-oxidation. This CPT II deficiency is an autosomal recessive disorder and there are 3 main phenotypes in this deficiency: lethal neonatal form, severe infantile hepatocardiomuscular form, and the myopathic form.[1]

We present a one-day-old term female infant, admitted at NICU, Hospital Sultan Abdul Halim for lethargy, low sugars, and cyanosis. The presence, as well as persistent non-ketotic hypoglycemia, hyperammonemia, and cardiomyopathy, led to the suspicion of fatty acid oxidation defect.

CASE REPORT

A term female baby was delivered at Hospital Sultan Abdul Halim with a birth weight of 2760 grams via spontaneous vaginal delivery with an APGAR score of 9 in 1 minute and 10 in 5 minutes. At 25 hours of life, she was referred for unresponsiveness and hypoglycemia (0.8mmol/L). On examination, we noted a non-dysmorphic baby girl, encephalopathic with poor breathing effort and bradycardic. The hypoglycemia was treated accordingly, and she was transferred to neonatal intensive care (NICU) for further management.

She was ventilated, and the initial blood investigation showed a slightly raised leukocyte count (20,800), a respiratory alkalosis blood gas with an anion gap of 21.3. Given the above clinical findings and investigations, she was initially treated for meningitis. However, the cerebral spinal fluid (CSF) biochemistry was normal, and the CSF culture did not yield any growth. In addition to the above investigation, an Inborn Errors of Metabolism (IEM) panel was sent which resulted in a raised ammonia (144mmol/L), raised lactate (3mmol/L), and raised creatinine kinase (3414 units/L). The plasma amino acid resulted in an elevation of methionine and tyrosine levels, suggesting liver dysfunction and urine organic acid was non-diagnostic. The blood spot resulted in an elevation of the C16 with moderate elevation of C18 with mild to moderate elevation of C12, C14, C16:1, and CIB:1. The free carnitine levels were lowish (C0) with a moderate elevation of C16+CLB:11C2 ratio. This profile is very suggestive of long-chain fatty acid oxidation either CACT or CPT 2 deficiency.

Bedside echocardiography revealed cardiomyopathy with both the ultrasonography brain and abdomen resulting in a normal study. Given the cardiomyopathy and a general edematous appearance, she was started on oral furosemide.

Feeding was introduced slowly, and she achieved full feeds by day 5 of life. Unfortunately, the following day she went into metabolic crisis. An Anti-hyperammonemia cocktail was administered and the refractory hypoglycemia was stabilized with GIR ranging between 18 – 20 mg/kg/min. We aimed to maintain a calorie intake of 120kcal/kg/day.

The case was discussed with the metabolic team and based on the clinical findings and the initial IEM panel a differential diagnosis of CPT II and CALT was put forward. We also repeated the IEM blood spot and urine organic acid test. In addition, serum carnitine and parents' DNA extraction were also sent. The IEM blood spot test resulted in elevated C12, C160H, and C1b with persistently raised C16+C18:1/C2 ratio with lowish free carnitine and C2. The serum carnitine levels resulted in a mildly increased acyl: free carnitine ratio. The urine organic acid resulted in a non-diagnostic profile. The parents' DNA extraction revealed in both parents were carriers of the mutation in the patient.

We increased her calorie intake to 140 – 190kcal/kg/day initially with a mixture of IV maintenance and fortified expressed breast milk. As she showed improvement in both her dexterity as well as her ammonia levels (75 – 140 umol/L) we were able to shift all her calorie intake to oral feeds.

During the following 3 weeks, she had a stormy course. Unfortunately, she contracted nosocomial pneumonia subsequently followed with MRSA sepsis. In both conditions,

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the inflammatory markers were raised, and she was covered with IV antibiotics. Despite our best efforts, on day 29th she developed respiratory failure secondary to sepsis and cardiomyopathy and succumbed to her illness.

DISCUSSION

CPT II is a fatty acid oxidation (FAODs) group. These groups are a rare inherited disorder in which the body is unable to oxidize fats for energy. A definitive diagnosis is usually made by detection of reduced CPT II enzyme activity and molecular genetic testing. As stated earlier the 3 clinical presentations are the lethal neonatal form, severe infantile hepatocardiomuscular form, and the myopathic form.[2] Among the 3 forms, the myopathic form is the most encountered with the highest numbers seen in males.

Clinically, the presentation of lethal neonatal form and severe infantile hepatocardiomuscular have almost similar systemic involvement. The lethal neonatal form presents with liver failure, hypoketotic hypoglycemia, cardiomyopathy, respiratory distress, and/or cardiac arrhythmias. It has been reported that in this form there is a neuronal migration defect leading to cystic dysplasia of the basal ganglia. Patients with lethal neonatal form can have nervous system involvement; hydrocephalus, cerebellar vermian hypoplasia, polymicrogyria, pachygyria, cerebral calcification, cystic dysplasia of the brain, and agenesis of the corpus callosum. Some cases have also reported the presence of polycystic kidneys.[2]

The severe infantile hepatocardiomuscular form is characterized by hypoketotic hypoglycemia, liver failure, cardiomyopathy, and peripheral myopathy. The myopathic form is due to lipid metabolism affecting skeletal muscle and is the most frequent cause of hereditary myoglobinuria.[2]

In our patient, the clinical manifestations, as well as the investigations, led to a diagnosis of CPT II with the lethal neonatal form variant. In this form, the presentations are seen within the first few days of life and invariably lead to early infantile death. Certain red flag signs raised suspicion of inborn error of metabolisms such as persistent/unexplained lethargy, vomiting, poor feeding, seizure, altered sensorium, and failure to gain weight should be familiar with health care providers particularly those in a NICU setup. Acylcarnitine analysis using tandem mass spectrometry helps in the diagnosis of CPT II deficiency. The activity of the CPT II enzyme can be demonstrated by carnitine levels, serum creatinine kinase levels, and transaminase levels. However, a definitive diagnosis can be obtained by sequencing the CPT II gene for mutation analysis.[1]

Prenatal diagnosis for risky pregnancies is possible either by molecular genetic testing of CPT II or CPT II enzyme activity assay in cultured amniocytes. Radiological evidence of brain or renal abnormalities in the mid-trimester of pregnancy can be supportive.[1]

Management of CPT II is by reducing dietary fat intake and at the same time increasing carbohydrate mainly to reduce the abnormal accumulation of both long-chain acyl-coenzyme A (CoA) and acylcarnitine intermediates. In acute cases, glucose infusion has been suggested to reduce lipid mobilization and a large volume of fluid alkalinization to enhance renal excretions of myoglobin.[3]

The current treatment approach to a case of CPT II is avoidance of known triggers and reduction in the amount of long-chain dietary fat while covering essential fatty acids. Patients should also be given carnitine to convert potentially long-chain acyl-CoAs to acylcarnitine. A large portion of the patient's calories should be obtained from carbohydrates which in turn reduces body fat utilization and prevents hypoglycemia. At least 1/3 of the calories should be obtained from even-chain medium-chain triglycerides (MCT). Metabolism of the eight to ten carbon fatty acids in medium-chain triglycerides oil, for example, is independent of CPT I, carnitine/acylcarnitine translocase, CPT II, very-long-chain-acyl-CoA dehydrogenase (VLCAD), trifunctional protein, and long-chain hydroxyl-acyl-CoA dehydrogenase deficiency (LCHAD) enzyme activities.[3]

The anaplerotic diet with triheptanoin provides an alternate route to produce acetyl-CoA and oxaloacetate to allow for citrate synthesis which in turn results in increased ATP formation via the respiratory chain. The trihepatonin is readily taken up by the mitochondria of the liver without needing the transport via CPT I, carnitine-acylcarnitine translocase, or CPT II. Once within the liver mitochondria, the trihepatonin undergoes β-oxidation leading to the formation of acetyl-CoA and pentanoyl-CoA.[3]

Oxidation of Pentanoyl-CoA leads to the formation of acetyl-CoA and propionyl-CoA. The propionyl-CoA enters the citric acid cycle forming oxaloacetate. The acetyl-CoA along with β-ketopentanoyl-CoA (BKP-CoA) forms the ketone bodies via the β-hydroxy- β-methylglutaryl-CoA pathway. This ketone body is used by the peripheral organs, more importantly, the brain.3The presence of acetyl-CoA and oxaloacetate allows for citrate synthesis resulting in increased ATP formation via the respiratory chain.

Triheptanoin is available as over a counter product. The recommended total daily dose is administered in milliliters (ml) using the formula:

- Patient DCL (kcal) x target % dose of DCL divided by 8.3kcal/mL
- The total dose is then given at least 4 times per day in equal doses
- When initiating, begin with 10% of the calculated dose in 4 individual doses
- The dosage is slowly titrated up to the maximum dose over a 2-to-3-week period

For patients switching from another medium-chain triglycerides product

- Discontinue previous medium-chain triglycerides before therapy initiation
- Initiate at last tolerated medium-chain triglycerides dose divided into at least 4 individual doses
- Increase total daily dosage by approximately 5% DCI every 2 to 3 days until target dosage is achieved

Certain appropriate measures to prevent primary manifestations include:

- Infusion of glucose during intercurrent infection to prevent catabolism
- High-carbohydrate (70%) and low-fat (<20%) diet to provide fuel for glycolysis
- Frequent meals and avoidance of extended fasting
- Avoidance of prolonged exercise

The most important complication that tends to arise in individuals with CPT II deficiency is renal failure which usually is secondary to an episode of rhabdomyolysis and myoglobinuria. To avoid this, sufficient hydration and if necessary dialysis must be performed immediately.

CONCLUSIONS

There has not been any case report published regarding CPT II deficiency in Malaysia. The initiation of investigation towards a case of CPT II deficiency requires a high degree of suspicion. In this publication, we intend to highlight persistent and unexplained lethargy, vomiting, poor feeding, seizure, altered sensorium, and failure to gain weight are some red flags for CPT II deficiency.

The diagnosis, investigation, and management in the case of CPT II deficiency have not been fully established. We share our limited experience in the management and treatment of such a case.

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