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Case Report

Paediatrics Section

Carnitine Cycle Defect in Newborn: A Rare Case Report

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ABSTRACT

Carnitine Acylcarnitine Translocase (CACT) deficiency and Carnitine Palmitoyl Transferase (CPT I and II) deficiency comes under a group of disorders called mitochondrial fatty acid oxidation disorders, due to defects in the carnitine cycle. The CPT and CACT enzymes play a pivotal role in the transfer of Long Chain Fatty Acids (LCFA) from the cytoplasm to the mitochondrial matrix, where β-oxidation take place. In the present case, a male baby presented on day 2 of life with chief complaints of respiratory distress, apnoea, lethargy and seizures. The baby had multiple episodes of hypoglycaemia and seizures after admission. Diagnosis was made with the help of extended newborn screening using Tandem Mass Spectrometry (TMS) showing accumulation of hexadecanoyl carnitine due to CACT/CPT II deficiency. Echocardiography showed features of cardiomyopathy with cardiomegaly. Liver Function Test (LFT) and Prothrombin Time-International Normalisation Ratio (PT-INR) of the child was also deranged, with hypotonia of all muscles. Early detection along with carnitine supplementation and further prevention of fasting episodes resulted in generalised improvement of the baby. So, a high degree of suspicion of Inborn Error of Metabolism (IEM) and timely diagnosis can save the baby.

Keywords: Cardiomyopathy, Gene analysis, Hypoglycaemia, Newborn screening, Tandem mass spectrometry

CASE REPORT

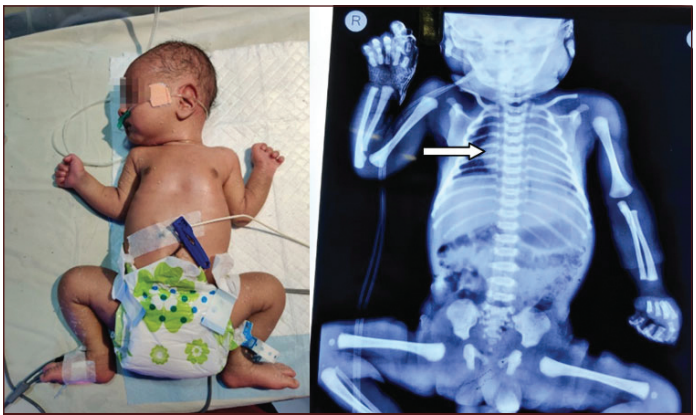
A two-day-old male baby was referred to the Paediatric Special Newborn Care Unit of a tertiary care hospital, with chief complaints of respiratory distress, apnoea, lethargy and seizures. Baby was born term (39 weeks+6 days) and was Appropriate for his Gestational Age (AGA).

Baby was born out of a primi mother by normal vaginal delivery. Baby cried immediately after birth. The Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores at one and five minutes were 8 and 9, respectively. The child developed respiratory distress around five to six hours after birth. Around 12 hours after birth, child had two episodes of apnoea and bradycardia, improved with bag and mask ventilation and also had one episode of hypoglycaemia {Random Blood Sugar (RBS) 42 mg/dL} prior to admission.

The baby was born out of non consanguineous marriage. The mother spontaneously conceived after marriage. No significant habit or morbidity was seen in the mother during antenatal period. There was no history of any significant illness running in the family.

On admission, baby was in active seizure with low oxygen saturation (85% in room air). Cry and activity was very poor and baby was in comatose state [Table/Fig-1]. Physical examination revealed no facial dysmorphism. Systemic examination revealed enlarged liver and spleen. His Random Blood Sugar (RBS) was 37 mg/dL. Baby was given 10% dextrose bolus followed by glucose infusion at 6 mg/kg/minute Glucose Infusion Rate (GIR 6). On day 3, blood gas analysis revealed a low calcium level (ionised calcium=0.46 mmol/L) and no other derangements was evident.

The x-ray done on day 3, showed cardiomegaly with Cardiothoracic (CT) ratio >60% [Table/Fig-2]. A neonatal screening Echo was done on day 3 of life which revealed Patent Foramen Ovale (PFO) with moderate Tricuspid Regurgitation (TR) and TR jet through PFO (Right to Left shunt), with Patent Ductus Arteriosus (PDA) with left to right shunt. There was biventricular hypertrophy with echogenicity seen in both myocardium and endocardium with cardiomyopathy. A diagnosis of infiltrative lesion, possibly storage disorder was made, with differential diagnosis of glycogen storage disorder, fatty acid oxidation defects, galactosemia, disorders of gluconeogenesis, carnitine cycle defects were considered. Following first Echo scan, empirically carnitine syrup was started.

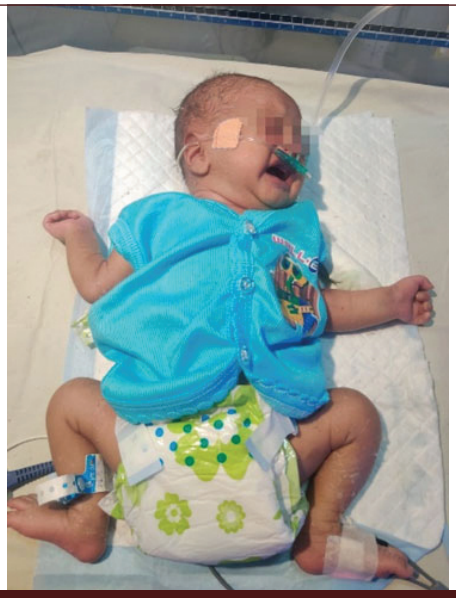


[Table/Fig-1]: Showing baby on day 3 of life, in comatose stage.
[Table/Fig-2]: Initial x-ray on day 3 of life, showing cardiomegaly. (Images from left to right)

Child was started on L-carnitine syrup empirically on day 3, at a dose of 200 mg/kg/day. Feeding gradually increased and child weaned off from GDR 6 on day 4. On day 7 of life, [Table/Fig-3] child had one episode of hypoglycaemia. Baby was restarted on GDR 6 and extended newborn screening panel (TMS) was sent. Other investigations like Complete Blood Count (CBC), serum electrolytes, Renal Function Test (RFT) were normal.

By 2nd week of life, symptoms improved, cry was present, baby was taking Katori Spoon Feeding (KSF) from mother, was responding to loud sounds but child remained hypotonic with diminished moro reflex, palmar and plantar grasp with saturation maintained around 90% with oxygen. Extended newborn screening revealed elevated hexadecanoyl carnitine suggestive of CPT II deficiency or CACT

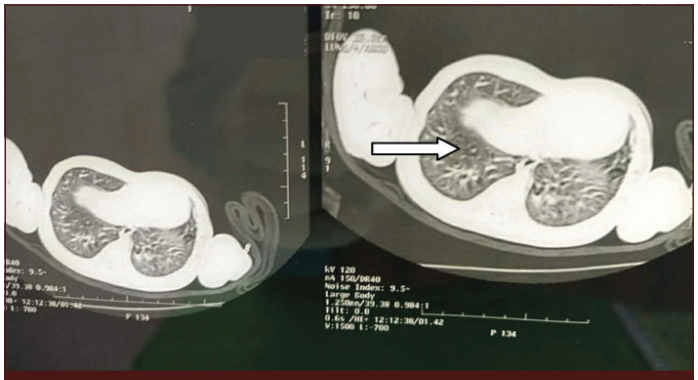
deficiency [Table/Fig-4]. High Resolution CT (HRCT) Thorax [Table/Fig-5] and Contrast Enhanced CT (CECT) brain [Table/Fig-6] revealed features of pneumonia and Hypoxic Ischaemic Encephalopathy (HIE) changes, respectively.



[Table/Fig-3]: Baby on day 7 of life, during episode of hypoglycaemia.

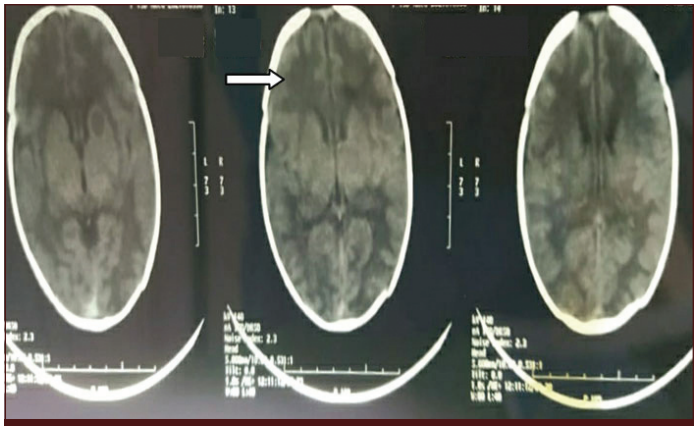
Acylcarnitines	Results in µmole/L	Reference in µmole/L
Acetyl carnitine C2	50.50	8-150
Propionyl carnitine C3	4.90	<5.65
Malonyl carnitine\3 Hydroxy butyryl carnitine	0.17	<0.41
Butyryl carnitine C4	0.75	<1.5
Methylmalonyl\3 Hydroxy isovaleryl carnitine	0.15	<0.8
Isovaleryl carnitine C5	0.20	<1.5
Glutaryl carnitine\3 hydroxyhexanoylcarnitine	0.24	<0.82
Tiglylcarnitine C5:1	0.02	<0.21
Hexanoylcarnitine C6	0.46	<0.5
Octanoylcarnitine C8	0.37	<0.5
Decanoylcarnitine C10	0.32	<0.40
Decenoylcarnitine C10:1	0.18	<0.30
Decadienoylcarnitine C10:2	0.03	<0.15
Dodecanoylcarnitine C12	0.23	<0.71
Tetradecanoylcarnitine C14	0.64	<0.70
Tetradecenoylcarnitine C14:1	0.15	<0.6
Hexadecanoylcarnitine C16	11.98	<8.9

[Table/Fig-4]: Extended newborn screening report.



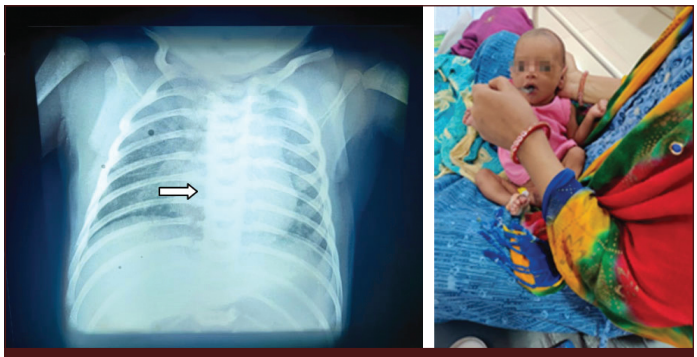
[Table/Fig-5]: HRCT thorax showing pneumonia.

On day 15 of life, CBC with LFT and PT-INR were sent. The baby's INR was 2.64 with elevated liver enzymes, with conjugated



[Table/Fig-6]: CECT brain showing Hypoxic Ischaemic Encephalopathy (HIE) changes.

hyperbilirubinaemia. Baby was started on vitamin K and Fresh Frozen Plasma (FFP). Investigations repeated on day 23 of life, showed normal LFT and PT-INR. Repeat echocardiography and chest x-ray [Table/Fig-7] were done on day 26 of life. Echo revealed Acyanotic Congenital Heart Disease (ACHD), moderate Atrial Septal Defect (ASD) with trivial TR with echogenic infiltration in endocardium and myocardium. Based on the Echo report, L-carnitine was continued. Cardiothoracic (CT) ratio decreased. General well-being of the baby improved, euglycaemia was maintained, oxygen saturation was maintained at room air, the baby was taking KSF and the sensorium improved [Table/Fig-8]. Baby was discharged with advice to follow-up. Gene analysis was not done in view of economic constraints.



[Table/Fig-7]: X-ray on day 26, showing decreased Cardiothoracic (CT) ratio. **[Table/Fig-8]:** Baby on day 26, taking Katori Spoon Feed (KSF). (Images from left to right)

The baby was followed-up monthly for three months after discharge. The baby was doing well, social smile was achieved. Counselling to parents was given with special emphasis to prevent hypoglycaemia.

DISCUSSION

The CACT deficiency and CPT I & II deficiency comes under a group of disorders called mitochondrial fatty acid oxidation disorders, due to defects in the carnitine cycle [1]. The LCFAs needs to be transferred from the cytosolic compartment to the mitochondrial matrix for the process of beta oxidation. The CPT enzyme along with CACT enzyme and CoA synthetase plays a crucial role in this process [2].

As per literature three types of CPT I deficiency are there. The most severe one is the neonatal presentation having profound enzyme deficiency and early death which is associated with dysplastic kidneys, cerebral malformations and mild facial anomalies. The adult form is a minor one with episodic rhabdomyolysis. Hypoglycaemia has not been described. Attacks are frequently precipitated by prolonged exercise. The third intermediate form presents in infancy or

early childhood with fasting induced hepatic failure, cardiomyopathy, and skeletal myopathy with hypoketotic hypoglycaemia [1]. The Carnitine Acylcarnitine Translocase Deficiency (CACTD) is an autosomal recessive disorder of LCFA oxidation. The incidence of CACT deficiency has been reported to be as low as 1:750,000 to 1:20,00,000 in Caucasians [3] and approximately 1:60,000 in Hong Kong neonatal populations [4].

The CACTD results from variations of the solute carrier family 25 member 20 (SLC25A20) gene. In Asia, the c.199-10T>G splice site variation is the most frequently reported variant [5]. The clinical features of this entity reflect a combination of energy deprivation and endogenous toxicity due to accumulation of long chain acylcarnitines predominantly in brain, heart, skeletal muscle and liver [5]. The most commonly described initial symptoms include enlarged liver, arrhythmias and/or bradycardia and respiratory distress. Hypoketotic hypoglycaemia and hyperammonaemia were the most frequent laboratory findings [6]. The only specific clue to the diagnosis may be the finding of inappropriately low concentrations of plasma or urinary ketones in an infant who has hypoglycaemia [1].

The abnormal blood acylcarnitine profile can be detected by TMS (MS-MS) allows early detection in neonatal period [7]. Patients were identified by high levels of plasma long chain acylcarnitines (C 16:0, C18:0, C18:1 and C18:2) and hypocarnitinemia. This profile is indistinguishable for both CPT I and CACT deficiencies. The C6-C10 dicarboxylic acidurias might also be present during decompensation episodes [6]. Diagnosis can also be made by enzyme detection in fibroblast [8]. The final diagnosis can be achieved by SLC25A20 gene analysis located on chromosome 3p21.31 which was not done in this case.

Acute presentation of this condition can be a differential diagnosis of Reye's syndrome. If fatal, can be misdiagnosed as a sudden infant death syndrome [1]. Other differential diagnosis includes glycogen storage disorders, fatty acid oxidation defects and galactosemia [9]. Mortality rate is very high. The long term prognosis is extremely poor [10]. A low LCFA oxidation rates in cultured fibroblasts and presence of heart disease indicates a poor prognosis. Genotype, residual activity of the enzyme, prompt medical intervention during the acute episode and the duration and type of long-term treatment used are the major prognostic indicators of CACTD [6].

Intravenous glucose is proved to be a fruitful treatment regime during acute episodes due to its suppressive action on fatty acid oxidation and fat mobilisation. Avoidance of long chain fatty acids with supplementation of MCT oil, high carbohydrate intake and frequent regular meals to avoid fasting are the long-term dietary strategies of this disorder. Medium chain fatty acids in the form of MCT oil, which is commonly used for malnutrition and easily available in low resource settings can bypass the carnitine cycle and enter the mitochondrial matrix where β-oxidation takes place. Pharmacological doses of oral carnitine (100-200 mg/kg/day) can be tried [11]. In the present case, patient improved with oral carnitine.

A very commonly used drug in paediatrics for neonatal seizures, valproic acid is contraindicated in CPT I deficiency as it triggers acute rhabdomyolysis [12].

CONCLUSION(S)

To conclude, high index of suspicion of IEM and timely diagnosis by extended newborn screening can save a baby. Dietary interventions to prevent hypoglycemia, avoidance of fasting and early therapeautic intervention improve long term clinical outcome.

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