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Case Series

Paediatrics Section

A Clinical and Biochemical Camouflage-Carnitine Palmitoyltransferase-1 Deficiency: A Case Series

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ABSTRACT

Carnitine Palmitoyltransferase-1 (CPT-1) deficiency is a rare metabolic disorder of fatty acid oxidation. The presentation of this deficiency is a mixed bag of several clinical and biochemical manifestations which is determined by the tissue-specific isoforms of the enzyme. Presenting in one way, which can be lethal due to cardiac complications, another way that this disorder can come to a clinician's attention is when children manifests with increasing lethargy during intercurrent illnesses. Rarely, but not exclusively, a seizure may be the only presenting complaint along with severe metabolic acidosis. In this case series, we present a discussion of three cases with CPT1 deficiency presenting with a camouflage of various contrasting clinical and biochemical manifestations.

Keywords: Children, Encephalopathy, Metabolic

CASE 1

A 2.5-year-old boy was brought to outpatient of our Paediatric Department with complaints of increasing lethargy after an episode of loose stools lasting for the previous three days. There were similar episodes of lethargy during minor illnesses since, he turned 16 months. During one of these illnesses a random blood sugar performed was 22 mg/dL for which he was treated at 14 months of age in a primary care health centre. Birth history was unremarkable with age appropriate development and immunisation. There was consanguinity among parents. The sibling of this child was healthy and had an average acylcarnitine profile. On examination, he was underweight and stunted, the Glasgow Coma Scale was 15/15. Pulse-106/minutes, respiratory rate–22/minutes, BP-86/60 mmHg. Abdominal examination showed firm hepatomegaly of 6 cm with smooth margins. There was no splenomegaly. There were no signs of meningeal irritation. The cardiovascular and respiratory system examination were healthy. The investigations done are outlined in [Table/Fig-1]. He was treated with intravenous dextrose, and normal saline, vitamins B1, B2, and B6. He recovered after a week, but liver enzymes remained elevated ALT-110 IU/L, AST-167 IU/L. Parents were advised to initiate a carbohydrate-rich diet during intercurrent illnesses. The child remained underweight on follow up but otherwise was healthy.

CASE 2

A 3-month-old girl was seen in the emergency room for repeated vomiting of feeds and, fast breathing developing over three days. She had an acute respiratory illness 15 days prior and received outpatient treatment. Her birth history was unremarkable. She had attained partial head control and social smile and had no significant family history. On examination, pulse-170/minutes, BP: 84/58 mmHg, respiratory rate–68/minutes, Capillary Filling Time- >5 seconds, pulse poorly felt. The respiratory system showed intercostal and subcostal retractions and bilateral fine crackles. Cardiovascular system examination revealed apex in fifth intercostal space, and loud heart sounds with an audible S3. No murmurs were heard. Abdomen examination revealed a liver size of 6.5 cm below costal margin. The neurological systemic was normal. Investigations are outlined in [Table/Fig-1]. She was managed with oxygen and ventilator support, intravenous fluids, dextrose, inotropic support with dobutamine, adrenaline, and intravenous sodium bicarbonate. Oral Sildenafil at a dose of 3 mg/kg/day in three divided doses was given for pulmonary hypertension. She succumbed after five days of ICU care.

CASE 3

A 45-day-old boy was brought with persistent vomiting for two weeks and generalised seizures. He had cough and coryza a week before. The birth history was unremarkable. Maternal history showed one previous spontaneous abortion and one sibling death due to unexplained metabolic acidosis and ketonuria. On examination, he had tachycardia and tachypnoea. Neurological examination revealed a petulant child. There were no focal neurological deficits. Respiratory system and cardiovascular system examination were unremarkable. On palpation of the abdomen, liver measured 3.5 cm below the costal margin. Investigations are outlined in [Table/Fig-1]. He was managed in intensive care with intravenous dextrose, antiepileptics. Metabolic acidosis was corrected with intravenous sodium bicarbonate. During hospitalisation, he was ventilated due to uncontrolled seizures. He was started on carbohydrate rich diet, vitamins B1, B2, B6, and antiepileptics. At six month follow up, he was seizure free and developmentally normal. There was no history of exogenous carnitine supplementation in any of the above-described cases.

DISCUSSION

Carnitine palmitoyltransferase-1 deficiency is a rare disorder of oxidation of fatty acids [1]. Three isoforms of CPT-1 have been described–CPT1a; associated with activity predominantly in the liver, CPT1b; muscle specific isoenzyme, CPT1c; brain-specific activity [2-4]. The Hutterite population distributed across the United States and Canada is known to be associated with this rare, autosomal recessive disorder [5,6]. The clinical presentations of reduced enzyme activity predominantly involve hepatic, muscle and neurological systems. Hepatic manifestations due to deficiency of CPT1a are usually seen between birth to 18 months of age, where affected children develop lethargy and hypoglycaemia, following antecedent illnesses. The evaluation shows elevated liver enzymes and fatty acids [7]. A case of CPT1 deficiency which manifested in an adolescent boy has been reported in India which presented with hepatic encephalopathy [8]. Though, the exact prevalence of CPT deficiency is not knwn, CPT1 deficiency accounts for 5% of fatty acid oxidation defects according to a study done in 2013 by a tertiary care centre in Delhi [9]. The first case in our series manifested similarly along with a metabolic acidosis with an anion gap of 18. The muscle isoform CPT1b is predominantly expressed in the heart CPT1b deficiency is known to cause lipotoxicity in the heart during

Clinical features	Case 1	Case 1	Case 1
Presenting feature	Drowsiness, unconsciousness, lethargy, seizures, hypoglycaemia with concurrent illnesses since 1.5 years of age	Vomiting, lethargy and fast breathing for three days	Vomiting, irritability, seizures
Maternal history	Hypertensive mother, developmental delay, consanguinity,	Primigravida, no antenatal complications	History of one abortion and one sibling death
Birth weight in kg	Three	3.2	2.75
Presented at	2.5 years	Three months	1.5 months
Preceding illness	Acute gastroenteritis	Cough, cold and coryza 15 days before admission	Cough and nasal discharge
Laboratory investigations with normal values			
Creatinine (0.5–0.9 mg/dL)	0.3	0.6	0.4
Sodium (135-145 mEq/L)	132	128	128
Potassium (3.5-5.5 mEq/L)	4	>7	5.8
Calcium (9-11 mg/dL)	9.7	9.5	9.4
Ammonia (11-35 µg/dL)	96	95	183
Lactate (5-21 mg/dL)	15.6	14	134
Pyruvate (0.7-1.4 mg/dL)	0.59	0.7	0.7
[1]AST (10-45 IU/L)	151	69	31
[2]ALT (12-45 IU/L)	135	25	21
[3]ALP (145-420 IU/L)	268	254	238
[4]CRP (0-10 mg/L)	0.3	0.9	6
[5]RBS (<200 mg/dL)	22	118	95
[6]CSF examination	Not done	Not done	Normal
Haemoglobin (10.5-15 mg/dL)	8.3	8.4	12.7
Total white cell count (4.0-14.0*10.3 cells/mm^3)	15000	15,100	6600
Platelet (150-400*10.3 cells/mm^3)	356000	533000	695000
Urea (7-18 mg/dL)	12	12	18
Direct bilirubin (<1 mg/dL)	3.3	0.5	0.3
Indirect bilirubin (mg/dL)	0.5	0.3	0.4
Serum albumin (3.5-5.0 mg/dL)	4.78	3.42	3.7
Triglycerides (<150 mg/dL)	83	76	56
Prothrombin time (9.5-13.5 seconds)	13.9	15.9	16.8
Activated partial prothrombin time (30-40 seconds)	23.6	20.8	22
[7]INR (<1.1)	1.3	1.6	1.2
Chloride (98-106 mEq/L)	98	83.2	104
Creatine phosphokinase 5-130 (IU/L)	33	338	108
Urine protein	Negative	Negative	+1
Urine sugar (mg/dL)	Negative	Negative	+1
Urine ketone	+1	Negative	+1
pH	7.4	6.89	6.82
pCO_2 mm of Hg	24.7	23.3	15.9
pO_2 mm of Hg	124	106	138
SO_2	99%	99%	95%
HCO_2 (mEq/L)	19.5	5.7	4.3
Base excess	6	14	28.3
Anion gap	18.5	24.2	27.7
Chest X-ray	Normal	Cardiomegaly, clear lung fields	Normal
Ultrasound Abdomen	Hepatomegaly with coarse echotexture	Normal	Normal
2D Echo test	Normal	Severe PAH, right ventricular dysfunction and dilatation.	Normal
C0/(C16+C18) ratio	1510.3	238.2	230.4
Total carnitine (normal–20-87.7)	239.7	308.69	555.1
Free carnitine (normal–24.7-66.6)	211.44	235.82	536.7
Methyl malonic acid	Not detected	Not detected	Not detected
Urinary orotic acid	Not detected	Not detected	Not detected
Treatment	Intravenous dextrose, rehydration therapy	Intravenous fluids, Dextrose, dobutamine, adrenaline, carnitine, milrinone	Bicarbonate, dopamine, cephalosporin, antiepileptic, multivitamins-B1,B2,B6 ventilation

[Table/Fig-1]: Comparative features of the cases in our series.
[1]Aspartate transaminase, [2]Alanine transaminase, [3]Alkaline phosphatase, [4]C-reactive Protein, [5]Random blood sugar, [6]Cerebrospinal fluid, [7]International Normalized Ratio

pathological stress, aggravating underlying cardiac pathology [4]. In line with this, the patient in case second presented similarly with cardiogenic shock, dilatation of ventricles and severe metabolic acidosis and elevated total/free carnitine ratio and acylcarnitine. The neuronal isoform of CPT1c is localised in the hypothalamus, amygdala, and hippocampus [10]. A reduced function of this isotype has been, observed in recent studies in mice, shown to be associated with motor impairment and hypoactivity [3]. The third case in this series manifested with lethargy, poor suck, seizures and encephalopathy similar to that described in the deficient isoform CPT1c but on the other hand, these features may not be exclusive to the disease in question.

The diagnosis of a disorder of fatty acid oxidation in the above clinical settings is usually entertained when certain pointers are present in the blood metabolic work up like metabolic acidosis with a high anion gap, with either an elevated or normal ammonia levels as described in our cases. Tandem mass spectroscopy for acylcarnitine profile is highly specific for fatty acid disorders [11]. In CPT-1 deficiency, elevated free carnitine concentrations and low acylcarnitine concentrations are diagnostic findings [12]. An elevated C0/(C16+C18) ratio >100 has been described in CPT-1 deficiency and is specific as outlined by the referenced studies [13]. Likewise, the most sensitive indicator to diagnose CPT-2 deficiency is an elevated (C16+C18:1)/C2 ratio [13,14]. In the cases described in our series, there is an elevation of the C0/(C16+C18) ratio of 1510.3, 238.2 and 230.4 in cases first, second and third, respectively, which is greater than the typical cut-offs. Several mutations in the CPT1 gene are described till date, and mutational analysis is recommended for the definitive diagnosis [6,15]. Alternatively, the enzyme activity of CPT1 assayed by tandem mass spectroscopy in cultured fibroblasts can be implemented to confirm the diagnosis [16]. In the three described cases in our series, a mutational analysis was not possible in one case as the child died very early during the treatment despite our best efforts. The other two children described were offered the mutation analysis but was not done due to financial constraints and limited resource settings.

Treatment for deficiency of CPT1 entails a low-fat diet augmented with medium-chain triglycerides, carnitine supplements, and avoidance of fasting and sustained exercise [7]. Prenatal diagnosis is offered to families along with newborn screening with tandem mass spectroscopy [17]. The outcome of this disorder is lethal in many cases causing sudden deaths, arrhythmias, and failure to thrive in children [18]. In our experience with these cases, two children have survived but remained underweight, though developmentally appropriate. One child expired due to cardiac and renal complications. The sibling screen for one child was healthy. Prenatal screening was offered to the parents of all the cases.

CONCLUSION

Carnitine Palmitoyltransferase-1 deficiency is a rare disorder presenting as a camouflage of varying manifestations clinically and biochemically. Tandem mass spectroscopy for C0/(C16+C18) ratios in cases with a high-index of suspicion is precise and can be used to identify these cases. Treatment is supportive, and prenatal diagnosis can be offered to families with affected children.

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