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# A CASE REPORT OF PRIMARY CARNITINE DEFICIENCY, HOMOZYGOUS PATHOGENIC VARIANT IN SLC22A5, PRESENTING AS ACUTE HYPERAMMONEMIC ENCEPHALOPATHY

**Swetha Rampally** MD DM, Department of Pediatric neurology, KIMS Hospitals, Kurnool, Andhra Pradesh, India.

**Naveen Reddy G** MD DrNB, Department of Pediatric neurology, KIMS Hospitals, Kurnool, Andhra Pradesh, India.

**ABSTRACT** Beta-oxidation of fatty acids in mitochondria becomes an important source of energy during periods of increased metabolic demand. Carnitine transport across cell membranes is essential for the transfer of long-chain fatty acids into mitochondria for beta-oxidation. Carnitine deficiency impairs this process and leads to acute metabolic decompensation affecting various vital organ systems. We report a case of an 18-month-old girl who presented with acute febrile illness, severe hyperammonemia, and encephalopathy. She had a family history of sudden infantile deaths. Her plasma free carnitine was below the normal range. It is essential to rule out secondary causes of carnitine deficiency because primary carnitine deficiency (PCD) has a good prognosis when detected early and treated appropriately. Genetic evaluation revealed homozygous pathogenic variants in the SLC22A5 gene, confirming the diagnosis of PCD.

**KEYWORDS :** Inborn error of metabolism, Hyperammonemia, Carnitine, Sudden deaths

## INTRODUCTION:

Primary carnitine deficiency (PCD) is a type of inborn error of metabolism due to pathogenic variants in SLC22A5 gene that codes organic cation transporter novel 2 (OCTN2) protein. This transporter mediates transport of carnitine across plasma membrane into cells as well as reabsorption in renal tubules. Impaired functioning of OCTN2 leads to decreased concentration of carnitine intracellularly hampering mitochondrial fatty acid oxidation. Diagnosis is confirmed through biallelic pathogenic variants in SLC22A5 and/or decreased carnitine transporter activity in fibroblasts. Several past cases attributed PCD turned out to have secondary carnitine deficiency due to medium-chain-acyl-CoA dehydrogenase deficiency. Hence there is a need to reappraise these previous reports of PCD while determining the clinical spectrum[1,2]

## Case Report :

An 18-month-old girl, born to third-degree consanguineous parents, presented with a two-day history of fever, followed by multiple episodes of vomiting, drowsiness, reduced feeding, and seizures. Her developmental history was normal. There was a history of sudden infant deaths in the maternal family. On examination, the child was drowsy and poorly responsive to pain, with brisk deep tendon reflexes and no neck stiffness or hepatomegaly. She was intubated and mechanically ventilated.

Investigations revealed leukocytosis, elevated plasma ammonia (534 µmol/L), normal blood glucose (84 mg/dL), elevated blood lactate (3.4 mmol/L), and normal liver function tests including prothrombin time. Cultures and cerebrospinal fluid analysis were normal. Tandem mass spectrometry showed normal amino acids, organic acids, and urea cycle intermediates. However, her fatty acid oxidation profile revealed very low free carnitine (23 µmol/L; reference range typically 25–50 µmol/L). MRI brain was normal, and EEG showed moderate generalised nonspecific dysfunction. Cardiac evaluation was normal.

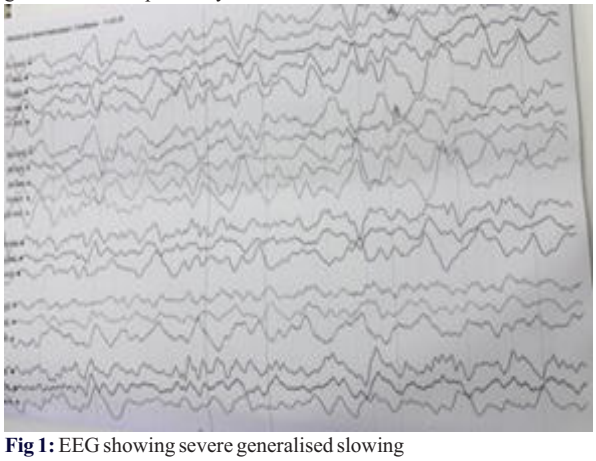
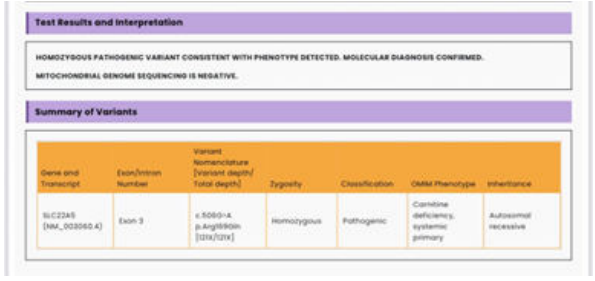


**Fig 1:** EEG showing severe generalised slowing

She was treated with peritoneal dialysis, intravenous fluids, antibiotics, and levocarnitine (150 mg/kg/day in divided doses). The child improved clinically, became seizure-free, and her sensorium normalised with normalised ammonia levels. Whole exome sequencing revealed homozygous pathogenic variants in SLC22A5 (c.506G>A), confirming PCD. She was discharged with regular follow-up and family members were advised genetic screening.



Test Results and Interpretation

HOMOZYGOUS PATHOGENIC VARIANT CONSISTENT WITH PHENOTYPE DETECTED. MOLECULAR DIAGNOSIS CONFIRMED.

MITOCHONDRIAL GENOME SEQUENCING IS NEGATIVE.

Summary of Variants

| Gene and Transcript | Exon/Intron Number | Variant Nomenclature (Variant depth/ Total depth) | Zygosity | Classification | OMIM Phenotype | Inheritance |
|---|---|---|---|---|---|---|
| SLC22A5 (NM_003060.4) | Exon 3 | c.506G>A p.Arg169Gln (121X/121X) | Homozygous | Pathogenic | Carnitine deficiency, systemic primary | Autosomal recessive |

**Fig 2:** Whole exome sequencing report

**Fig 3-A :** Child during acutely ill stage with Peritoneal dialysis port in situ. **Fig 3-B:** Child recovered and became clinically stable prior to discharge.

## Case Discussion:

The incidence of Primary Carnitine deficiency varies based on ethnicity. It is approximately 1 in 1,42,000 based on newborn screening. In Japan, the incidence is 1 in 40,000. Some of them have mild symptoms or remain asymptomatic as many women were diagnosed soon after giving birth, after their infants being detected with low carnitine levels during newborn screening.[3,4]

PCD due to carnitine transport defect is an autosomal recessive genetic disorder affecting the OCTN2 protein encoded by SLC22A5 gene. PCD is characterised by low plasma carnitine levels, decreased intracellular carnitine, increased urinary loss. Carnitine is transported via OCTN2 intracellularly and is expressed predominantly in kidneys, cardiac muscles, skeletal muscles. Fatty acids remain the main source of energy during fasting under normal physiological conditions. But in carnitine deficient states long chain fatty acids cannot be transported into mitochondria for beta oxidation. Improper utilisation of fatty acids

impairs gluconeogenesis, krebs cycle, amino acid metabolism, ketone body production. Unstable energy and altered metabolic pathways can impair brain function causing encephalopathy, seizures. Abnormal accumulation of fat alters the function of heart, and skeletal muscle leading to cardiomyopathy, arrhythmia, sudden cardiac deaths and myopathy respectively. Metabolic complications include hypoglycemia, hyperammonemia, metabolic acidosis. Rarely hyperammonemia without hypoglycaemia is reported.[1,2,5]

Majority of the symptomatic patients experienced their first symptom with a median age of 1 year. Sudden deaths are reported from the age of one year till twenty years. C 95A>G variant is reported to have strong association with sudden deaths. Majorly, patients are at risk for developing cardiomyopathy. Neurological, hepatic, muscular and metabolic complications occurred in approximately 10% of patients [1,6]

Metabolic complications, cardiac and skeletal muscle function improve with 100-200 mg/kg/day of oral levocarnitine if it is started before any irreversible damage has occurred. Routine management includes prevention of hypoglycaemia with frequent feeding, avoid prolonged fasting, notifying in advance prior to medical or surgical procedure. Child has be kept under regular surveillance with frequent monitoring of plasma carnitine levels.

## CONCLUSION:

PCD has a favorable prognosis when diagnosed early and managed with L-carnitine. Delayed diagnosis or poor control may lead to severe complications, including sudden death. Secondary causes of carnitine deficiency, such as fatty acid oxidation disorders or organic acidurias, tend to involve more severe organ damage when compared to PCD.[7,8] Further research is needed to identify markers that predict symptomatic versus asymptomatic cases.

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