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Case Report

A rare cause of combined floppy infant: Combined oxidative phosphorylation defect: 11 due to variant in RMND1

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ABSTRACT

Homozygous or compound heterozygous mutations in the required for meiotic nuclear division 1 homolog (RMND1) gene are reported to cause combined oxidative phosphorylation defect type 11. An 11-month-old boy presented with developmental delay, floppiness, and paucity of limb movements. On examination, the child had failure to thrive, dysmorphism, and a floppy. Investigations showed elevated creatinine, hyponatremia, hyperkalaemia, and metabolic acidosis. Whole exome sequencing revealed a homozygous variant known as c.1349G>C in the RMND1 gene. The child is currently on dialysis and has a mitochondrial cocktail. For any child presenting with failure to thrive, renal involvement, and myopathy an oxidative phosphorylation defect needs to be suspected.

Keywords: Renal failure, Oxidative phosphorylation, RMND1, Lactic acidosis, Floppy infant

INTRODUCTION

Mitochondrial deoxyribonucleic acid (DNA) biogenesis and maintenance are dependent on nuclear genes, and the nuclear deoxyribonucleic acid (nDNA)-encoded genes are required for replication, transcription and translation. Mutations in these genes cause mitochondrial complex deficiency and cause defects in intergenomic communication.[1] Renal dysfunction might be seen in many oxidative phosphorylation (OXPHOS) defects but is associated more commonly with *RMND1* mutations. The other features include lactic acidosis, deafness and severe muscle involvement.[2] Here, we present an Indian child with this rare disorder.

CASE REPORT

An 11-month-old boy born to a third-degree consanguineous marriage with a normal birth history presented with developmental delay, floppy limbs and a paucity of limb movements. Developmentally, the child has no neck control, with stranger anxiety being present and using monosyllables to speak. There was a history of the paucity of movements noted in all limbs. At 10 months, the child developed vomiting and lethargy and was admitted for encephalopathy. On examination, the child weighs 5.5 kg (−4.01 World Health Organization [WHO] Z), has a length of 66.5 cm (−2.91 WHO Z) and a head size of 43 cm (−1.39 WHO

Z). The child had myopathic facies, hypotonia in all limbs, head lag and power of 1/5 in all limbs with absent deep tendon reflexes. No hepatosplenomegaly is seen. Fundus examination was normal.

A complete hemogram was normal. Other investigations revealed elevated serum urea: 78 mg/dL (normal: 12–24 mg/dL), creatinine: 0.63 mg/dL, and serum potassium is 8.33 mEq/L. Serum sodium was 126 mEq/L, blood glucose was 75.6 mg/dL, lactate levels were 20.7 mg/dL, Ph: 7.277, bicarbonate was 21.5 mEq/L, base excess −2.0 and partial pressure of carbon dioxide (pCO2) is 31.6. Serum Creatine phosphokinase (CPK): 570 mcg/L (Normal: 100–200) was increased. Ultrasound abdomen showed mildly echogenic kidneys, and the magnetic resonance imaging brain was normal. Light microscopy examination of the muscle was normal. Electron microscopy showed an altered cristae pattern and the presence of electron-dense linear inclusions. Several fibres show abnormal pleomorphic mitochondria in subsarcolemmal and myofibrillar regions. Electrocardiogram (ECG) and 2D Echo, hearing assessment, renin levels and aldosterone levels were normal. Whole exome sequencing identified a known pathogenic homozygous variant c.1349G>C: p.Ter450SerextTer31 in the *RMND1* gene with the variant segregating with the disease in the family. We treated with a mitochondrial cocktail consisting of Thiamine-20 mg/kg/day, Riboflavin-15 mg/kg/day, Biotin-5/kg/day, CoQ10–10 mg/kg/day and Carnitine-100 mg/kg/day in three divided doses, Vitamin B12–1000 micrograms per day. The child was on regular dialysis, expired after 18 months of starting treatment due to pneumonia.

DISCUSSION

This is the report of an Indian child with severe myopathy, hypotonia, lactic acidosis and renal failure due to a homozygous *RMND1* mutation. *RMND1* is an integral membrane protein localising to mitochondria with an exact function unknown. The protein is essential in the biogenesis of OXPHOS complexes by forming a homopolymeric complex of 240 kDa. Patients with this disorder present as a severe condition in the neonatal period (oldest is 18 months at presentation), with a fatal course in 5/9 (age at death varies from 5 months to 10 years).[3-5] Experiments on *RMND1* suggest the role in the stabilisation or anchoring of mitochondrial ribosomes to the subdomains of mitochondria which ultimately results in spatial coupling of post-transcriptional handling and subsequent translation.[6]

A homozygous stop loss variation c.1349G>C in the exon 12 of the *RMND1* gene was detected. This variation causes loss of termination in the amino acid chain at position 450: p.Ter450SerextTer31. This variation has been reported at 0.002% in the gnomAD and 0.001 exome aggregation consortium (ExAC) population database. The multiple *in silico* predictions of this variation show a damaging effect. ClinVar reports this variant as pathogenic (VCV000143051.4).

Ng *et al.* reported the same variant in 8 families (7 Pakistani and 1 Bangladeshi family) and have reported it as a South Asian founder variant. This variant was associated with bradycardia in seven cases, two of which required cardiac pacing. Clinical variability was seen in the form of three patients who expired before 12 months, and the oldest surviving patient was 6 years. The reason for the variability was not known.[7] Taylor *et al.* reported five independent families from Pakistani with the same *RMND1* mutation, and the homogeneous haplotype flanking the mutation showed a founder effect.[5]

Nagappa *et al*. reported an Indian patient with the same mutation. Clinical phenotypes include regression of acquired milestones, failure to thrive, sensory neural hearing loss, hypotonia with areflexia and heart block with neuroimaging showing mild frontotemporal atrophy and delayed myelination.[8] Vinu *et al*. reported a 10-month-old Indian girl with developmental delay, hypotonia, poor feeding, hyperaldosteronism and long QT but no deafness with the same variant.[9]

The current case also showed the same South Asian variant with overlapping features. The current case adds to the phenotypic variability associated with the South Asian variant and needs further studies at the cellular level.

CONCLUSION

Any child with multi-system involvement of both the central nervous system and peripheral nervous system, like a floppy child and renal disease, *RMND1-related* mitochondrial disorder needs to be considered. Renal function needs to be monitored.

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