www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2022;11(2):e110209
doi: 10.7363/110209
Received: 2021 May 03; revised: 2021 Jul 29; accepted: 2021 Aug 12; published online: 2022 Oct 12

Case report

NDUFB8 mutation in a neonate with Leigh's disease

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Abstract

The *NDUFB8* gene, located at 10q24.31, encodes a nuclear-encoded accessory subunit that is essential for the stability and activity of the mitochondrial complex. In this report, we describe a novel homozygous mutation in the *NDUFB8* gene that was associated with mitochondrial complex I deficiency in a neonate with Leigh's disease. The neonate, born at term to consanguineous parents, suffered from seizures, depressed sensorium, and failure to gain weight at 3 weeks of age. The child was ventilator-dependent and had progressive encephalopathy. His blood and cerebrospinal fluid lactate levels were elevated. Magnetic resonance imaging of the brain showed diffusion restriction in the medulla, basal ganglia, and pericentral cortex. He developed cerebral edema and irreversible brain injury, despite medical treatment for congenital lactic acidosis.

Keywords

NDUFB8, novel homozygous mutation, mitochondrial complex I deficiency, Leigh's disease, neonate.

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How to cite

Arumugam SK, Manickam V. *NDUFB8* mutation in a neonate with Leigh's disease. J Pediatr Neonat Individual Med. 2022;11(2):e110209. doi: 10.7363/110209.

Introduction

Mitochondrial complex I deficiency is the commonest biochemical defect in childhood mitochondrial disorders. Mammalian complex I is composed of 45 different subunits, including 38 nuclear-encoded and 7 mitochondrial

subunits that assemble together into a structure of ~1 MDa [1]. The *NDUFB8* subunit is one of the nuclear-encoded accessory subunits essential for the stability of the complex.

Mutations in *NDUFB8* were recently reported in 2 infants [2]. We identified a novel homozygous mutation in exon 4 of the *NDUFB8* gene, located at 10q24.31 in a neonate who presented with encephalopathy and failure to thrive, fulfilling the criteria for Leigh's disease.

Case presentation

A 1-month-old infant was referred to our hospital with encephalopathy and seizures after a week of ventilation at a peripheral health center. He was born via cesarean section, with a birth weight of 2.5 kg. He was the product of a third-degree consanguineous marriage to a primigravida woman. The infant was breastfed for the first 2 weeks, and then formula-fed due to inadequate breast milk. The child showed reduced activity and feeding after the second week of life.

Upon admission, the infant was deeply comatose, responding only to painful stimuli, and both pupils reacted equally to light. He was edematous and weighed 2.5 kg. He experienced several episodes of intermittent generalized tonic convulsions, which subsided with anticonvulsants. Echocardiography showed normal cardiac function.

A complete blood count showed: hemoglobin 9.2 g/dL, white blood cell count of 15,300/mm^3, and platelet count of 3×10^5/mm^3. Blood tests showed: C-reactive protein 35 mg/L, sodium 141 mmol/L, potassium 3.5 mmol/L, chloride 104 mmol/L, and serum albumin 2.8 g/dL. His prothrombin time was 35 s (international normalized ratio 2.4) and his activated prothromboplastin time was 87 s. His blood gas at admission was suggestive of mild metabolic acidosis. After extubation, he developed respiratory acidosis (pH 7.23), PCO_2 61 mmHg, and bicarbonate 24 mEq/L. Cerebrospinal fluid (CSF) tests showed 7 cells/mm^3, protein 40 mg/dL, and glucose 65 mg/dL. An endotracheal secretion culture grew *Klebsiella spp.* The infant was treated for ventilator-associated pneumonia. He had copious endotracheal secretions and suffered repeated extubation failure because his respiratory drive was poor.

Magnetic resonance imaging (MRI) of the brain showed bilateral symmetric diffusion restriction in the ventral medulla, basal ganglia, and pericentral cortex (**Figures 1-3**). Electroencephalography

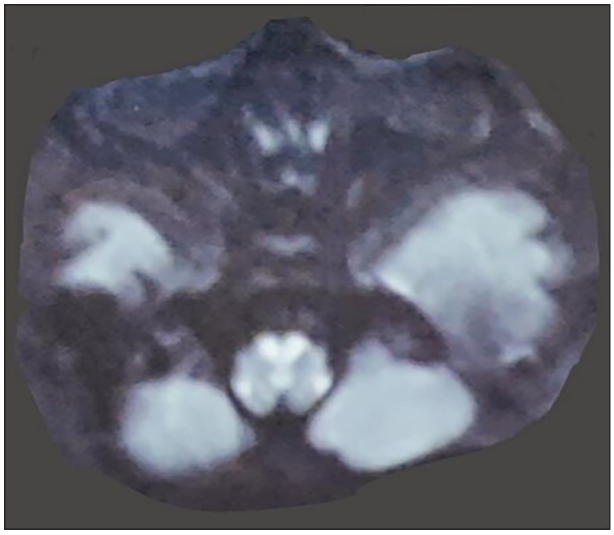

Figure 1. Diffusion restriction in the ventral medulla.

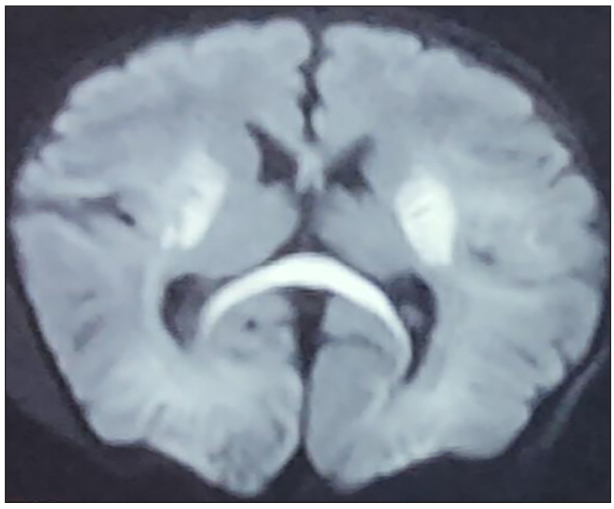

Figure 2. Diffusion restriction in the lentiform nucleus.

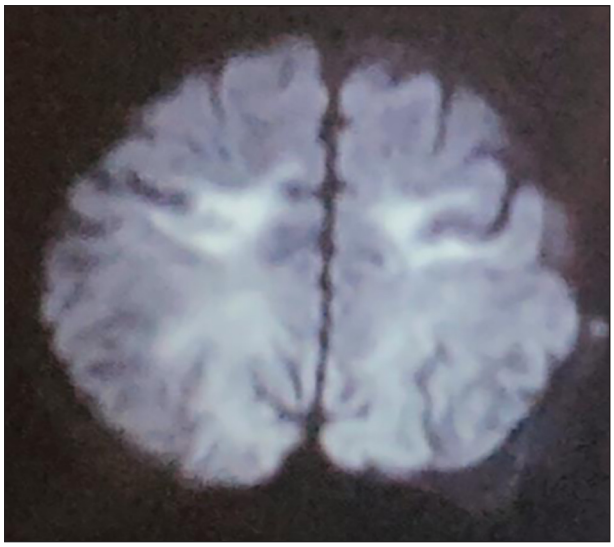

Figure 3. Diffusion restriction in the pericentral cortex.

showed intermittent epileptiform discharges with normal background activity. An ophthalmologic examination showed a normal fundus.

The infant's progressive encephalopathy against the background of a consanguineous marriage suggested an inborn error of metabolism. Tandem mass spectroscopy findings were negative. The child's blood ammonia was 54.6 µmol/L (reference level 64-107 µmol/L), creatine phosphokinase 175 IU/L (20-200 IU/L), blood lactate 6.2 mmol/L (0.5-2.2 mmol/L), and plasma glycine 82.82 µmol/L (< 740 µmol/L). His CSF glycine was 7 µmol/L (< 38 µmol/L) and his CSF lactate was 16.9 mmol/L (0.9-2.5 mmol/L).

Leigh's disease was diagnosed based on the criteria described by Rahman et al. The infant did not respond to cocktail therapy (thiamine, riboflavin, coenzyme Q, and L-carnitine) and suffered progressive encephalopathy, with no brainstem reflex. Life support was discontinued after parental consent was given.

Clinical exome sequencing revealed a homozygous mutation in exon 4 of the *NDUFB8* gene, c.319T>G (chr10:g.100526548A>C; depth: 183x), resulting in an amino acid substitution that replaced tryptophan with glycine at codon 107. Mitochondrial gene sequencing detected no mutations.

Discussion

The oxidation of carbohydrates, fatty acids, and amino acids generates reducing equivalents in the mitochondria. The 4 large protein complexes that constitute the respiratory chain are embedded in the inner mitochondrial membrane. The respiratory chain and oxidative phosphorylation system transfer electrons from reduced NADH to coenzyme Q10 and pump protons to maintain the electrochemical gradient across the inner mitochondrial membrane. This proton motive force drives the synthesis of ATP from ADP and inorganic phosphate by ATP synthase [3].

Complex I (NADH:ubiquinone oxidoreductase) is the first and largest enzyme in the respiratory chain. It is an L-shaped structure consisting of 3 functional modules: the peripheral arm includes an N module (for NADH oxidation) and a Q module (for ubiquinone reduction), and the membrane arm has a proton translocase P module [4]. The 7 nuclear-encoded core subunits are located in the peripheral arm and the 7 mitochondrially encoded core subunits are located in the P module. Approximately 30 nuclear-encoded accessory subunits are essential for the stability of the complex [5-7].

Isolated complex I deficiency is the commonest biochemical defect in childhood mitochondrial diseases, accounting for 20-30% of cases [8, 9]. It involves nuclear and mitochondrial genomes, and leads to clinical and genetic heterogeneity. It affects neonates to adults with varying severity, and involves one or more organs.

The clinical presentation includes fatal neonatal lactic acidosis, Leigh's syndrome, and childhood-onset mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Isolated cardiomyopathy and Leber's hereditary optic neuropathy are also associated with complex I deficiency [10].

Thorburn et al. used the following criteria for a diagnosis of Leigh's disease [11]:

i. progressive neurological disease with motor and intellectual developmental delay;
ii. clinical features of brainstem and/or basal ganglia disease;
iii. high lactate levels in the blood and/or CSF;
iv. the presence of one or more of the following:
    - typical neuroimaging (computed tomographic scan or MRI);
    - typical neuropathology;
    - typical neuropathology in a similarly affected sibling.

Nuclear-gene-encoded Leigh's disease can be diagnosed either by identifying a mutation in the proband's nuclear DNA or by excluding the presence of a mutation in the mitochondrial DNA [12].

The most common brain MRI findings in patients with complex I deficiency are brainstem and basal ganglion involvement, particularly the putamina. The defects appear as bilateral and symmetric hyperintensity on T2 and fluid-attenuated inversion recovery (FLAIR) sequences and as hypointensity on T1 images [13, 14].

NDUFB8 mutations causing childhood mitochondrial diseases have recently been reported in 2 individuals from unrelated families. The first symptoms in both children were failure to thrive, depressed sensorium, hypotonia, and seizures. The outcomes were poor; one child died at 15 months old and the other was completely dependent on a respirator. Compound heterozygous *NDUFB8* mutations were identified in both families [2].

Our patient presented with failure to thrive, depressed sensorium, and seizure at 3 weeks of age. He was ventilator-dependent and suffered

progressive encephalopathy. Brain MRI revealed symmetric involvement of the medulla, basal ganglia, and pericentral cortex.

Clinical exome sequencing and mitochondrial gene sequencing revealed a homozygous missense mutation in exon 4 of the *NDUFB8* gene (chr10:g.100526548A>C), resulting in the amino acid substitution of tryptophan with glycine at codon 107 (c.319T>G [p.Try107Gly]).

Conclusions

A homozygous mutation in the *NDUFB8* gene is associated with mitochondrial complex I deficiency. Failure to thrive, seizure, ventilator-dependence, and progressive encephalopathy were the clinical features observed in our patient.

Brain stem and basal ganglion involvement are typical of mitochondrial diseases. Elevated blood and CSF lactate levels, together with typical neuroimaging findings, are also suggestive of mitochondrial disease, which can be confirmed with targeted genetic testing.

Acknowledgements

We thank Dr. Kiruthika, clinical geneticist, and Dr. Raeshmi, consultant pediatrician, at Ramalingam Hospital, Salem, India, for their assistance with diagnosis and patient management.

Declaration of interest

The Authors declare that there is no conflict of interest.

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