Case Report

Mitochondrial Complex I Deficiency Masquerading as Stroke-Like Episode Clinically and as Alexander Disease Radiologically Following Chicken Pox

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Abstract

Mitochondrial disorders are a group of metabolic disorders with variable presentation and usually affect organs with high energy requirements like the brain, eye, and heart. Seventeen-month-old girl child presented with right hemiparesis and regression of milestones following chicken pox. Investigations showed elevated lactate, white matter signal changes in both periventricular and subcortical white matter with frontal predominance in the MRI of the brain, cardiomyopathy in the echocardiography, with complex I deficiency in respiratory enzyme assay in the muscle biopsy. A homozygous missense variant c.304C>T (p. Arg102Cys) in exon 5 of NDUFS8 gene (chr11:67800682C>T; NM_002496.4) was detected on whole exome sequencing with positive parental Sanger for the same gene. The child was started on a mitochondrial cocktail, ramipril, and frusemide. Mitochondrial complex deficiency should be considered in cases with stroke-like episodes, and predominant white matter involvement on imaging mimicking classical genetic leukodystrophy like Alexander disease.

Keywords: Alexander disease, India, mitochondrial disorder, *NDUFS8* gene, stroke-like episodes

Introduction

Leukodystrophy encompasses uncommon genetic disorders involving the central nervous system white matter and affecting various age groups. Each subtype has a unique genetic origin.[1,2] The occurrence of mitochondrial disorder as leukodystrophy accounts for 5%–10%.[3,4] The mitochondrial disorder is known to present stroke-like episodes in mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) but is not described in mitochondrial complex deficiencies. Here, we report mitochondrial complex deficiency due to *NDUFS8* mutation presenting as stroke-like episodes and mimicking Alexander leukodystrophy radiologically.

Case

A 17-month-old girl child born to second-degree consanguineous marriage with normal birth history, presented with fever with a rash suggestive of chicken pox about 40 days back and a recent onset right-sided weakness and lethargy for five days. During febrile illness, she was dull with poor oral intake, reduced playfulness, and preferred to stay in bed. The weakness of the right side was insidious onset, and gradually progressed over a period of five days with maximal weakness of inability to sit independently and inability to lift right side limbs against gravity, however, was able to move her right arm and right leg sideways. No facial deviation/vomiting/seizures/trauma. At seventeen months of age, she was able to stand independently and walk a few steps with support, used to scribble, was able to speak two words with meaning, and was able to indicate a few body parts. Following the febrile illness at 17 months, her milestones regressed – she was unable to sit, reach out to objects, or grasp objects, stopped recognizing her parents, and stopped vocalizing. On examination her weight was 7.5 kg (WHO 0 to −2 Z score), length was 69 cm (WHO 0 to −2 Z score), and head circumference was 44.5 cm (−1 to −2 Z score). The child was irritable with poor response, power on the right side was 2/5 [Figure 1a], and hypotonia (right more than left) with brisk deep tendon reflexes and bilateral extensor plantar response. Significant improvement in the power on the right side was noted one month after discharge [Figure 1b].

On investigation, arterial blood gas showed pH-7.367, pO_2-82, pCO_2-32.6 and HCO_3:18.4 suggestive of mild metabolic acidosis, elevated serum lactate: 56.27 mg/dl (normal: 4.5–19.8). Serum Creatine phosphokinase (CPK) was normal (25.7 U/L). Magnetic resonance imaging (MRI) brain showed hyperintensities in bilateral periventricular, subcortical white matter, subcortical U fibers with frontal predominance in T2WI and hypointense on T1W sequences

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with diffusion restriction in corresponding areas in diffusion weighted imaging (DWI) [Figure 2a-c]. There was only minimal apparent diffusion coefficient (ADC) mismatch and the involvement of non-vascular territories suggests stroke-like episodes rather than stroke. There was left ventricular septal hypertrophy on cardiac evaluation with mild left ventricular systolic dysfunction (EF: 45%–50%). A muscle biopsy was done on suspicion of mitochondrial disease which showed diffuse type 2 fiber atrophy, no fiber type disproportion, and no Cytochrome C Oxidase (COX) deficient fibers. Mitochondrial respiratory chain assay showed complex I activity of less than 30%. Whole exome sequencing showed a homozygous missense variant c.304C>T (p. Arg102Cys) in exon 5 of *NDUFS8* gene (chr11:67800682C>T; NM_002496.4) and parental Sanger showed heterozygous carrier state in both parents for the same mutation. Functional evidence of complex I deficiency was also proven in muscle tissue. According to the above findings; the variant is classified as likely pathogenic as per American College of Medical Genetics and Genomics (ACMG) classification.

She was started on a mitochondrial cocktail, consisting of thiamine 100 mg given once daily (tablet thiamine 100 mg), carnitine 100 mg/kg/day in two divided doses (syrup carnitine 500 mg/5 ml), riboflavin 200 mg once daily (tablet riboflavin 200 mg), Co-enzyme Q 10 mg/kg/day in two divided doses, and was also given tablet ramipril at 1.25 mg half daily (tablet Ramipril 1.25 mg) along with frusemide at 1 mg/kg/day (syrup frusemide 10 mg/1 ml) for cardiac failure.

Figure 1: A clinical photograph of a child at the time of admission shows right upper limb weakness and a sick-looking appearance (a). After one-month, significant improvement in the power on the right was noted with improvement in the child's activity (b)

Discussion

A 17-month-old Indian female born to a second-degree consanguineous marriage presented with right-sided weakness with encephalopathy with regression, white matter disease, and cardiomyopathy. The differentials considered in the current case were post-chicken-pox vasculopathy/vasculitis, stroke/stroke-like episode, demyelinating disorder, and neurometabolic disease. Post chicken pox vasculopathy and demyelination were ruled as MRI is not suggestive of either of them. The neuroimaging, in this case, had frontal predominant white matter involvement, which could be seen in Alexander's disease; however, there was no involvement of basal ganglia or thalamus. Metachromatic leukodystrophy was ruled out as onset was acute and no long-tract involvement in the brainstem of MRI of the brain.[5] Vanishing white matter disease can be differential, however, the signal intensity of affected white matter is not like cerebrospinal fluid (CSF) on T1, T2, Fluid attenuated inversion recovery (FLAIR), and proton density-weighted imaging with vermis predominant cerebellar involvement with atrophy.[6]

Human nicotinamide adenine dinucleotide (NADH) ubiquinone oxidoreductase also known as complex I is 1 MDa in size with 45 subunits. All are encoded by nuclear genes except the seven subunits, namely, *ND1-ND4, ND4L, ND5*, and *ND6*. The *NDUFS8* also known as *TYKY* is a nuclear-encoded complex subunit well-documented in humans.[7] Phenotypic variability exists in *NDUFS8*-related disorders. Procaccio V and Wallace DC[8] reported a patient with mild phenotype and later onset of Leigh syndrome with MRI features suggestive of Leigh syndrome and partial enzyme defect with the compound heterozygous variant. Loeffen J *et al*.[9] reported a compound heterozygous mutation in the *NDUFS8* gene leading to severe metabolic crisis and cardiomyopathy with MRI showing features of Leigh syndrome where the child died at eleven weeks due to cardiopulmonary arrest.

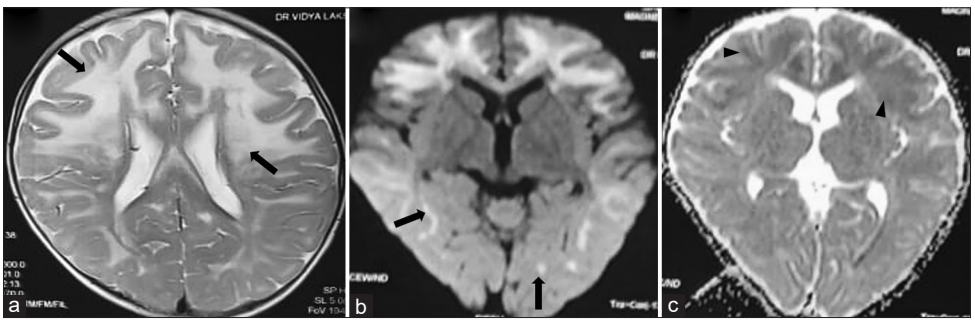

Figure 2: Axial MRI brain T2 weighted (a), diffusion weighted (b), and attenuated diffusion coefficient (c) images showing hyperintense on T2 and diffusion-weighted images (Black arrow) in bilateral cerebral subcortical and deep white matter and corona radiata regions with restricted diffusion on ADC (Black arrowhead), more prominent in the frontal region compare to occipital region

Nagappa M *et al*.[10] reported a seventeen-year-old male with juvenile-onset Leigh syndrome with compound heterozygous variation in *NDUFS8* gene presenting with features of ataxia, perioral dyskinesia, generalized dystonia with neuroimaging showing hyperintensities in the inferior olivary nucleus and with lesions in Guillain-Mollaret triangle and around it. This is the only reported case of the gene from India. The present case has a different presentation both clinically and molecularly.

Conclusion

Mitochondrial complex deficiency should be considered in cases with stroke-like episodes, predominant white matter involvement on imaging masquerading as leukodystrophy, and in addition to the classical presentation of cavitating leukodystrophy. Multi-modal integrated diagnostic approach encompassing biochemical assays, neuro-imaging, and genetic analysis is useful for accurate diagnosis and management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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