Muscle Biopsy: A Boon for Diagnosis of Mitochondrial Parkinsonism in Developing Countries

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Abstract

Mitochondrial dysfunction plays an important role in the pathogenesis of Parkinson's disease. Primary genetic abnormalities in the mitochondrial DNA or nuclear DNA can cause parkinsonism. Mitochondrial parkinsonism presents with classical features of parkinsonism along with multisystem involvement. Genetic analysis is essential in reaching the diagnosis which is not always possible, especially in developing countries. Muscle biopsy can be a boon in this setting as exemplified in our report of two siblings where a diagnosis of mitochondrial parkinsonism was made on the basis of muscle biopsy.

Keywords: Dystonia, mitochondria, muscle biopsy, Parkinsonism

Introduction

Parkinsonism with onset in childhood has a wide spectrum of differential diagnosis, ranging from treatable causes like Wilson's disease to neurodegenerative disorders like juvenile-onset Huntington's disease. In addition, primary genetic abnormalities in the mitochondrial DNA (mDNA) or nuclear DNA (nDNA) can lead to Parkinson's disease. Clue to the diagnosis of mitochondrial parkinsonism rests on multisystem involvement in the form of ptosis, myopathy, and neuropathy, with classical features of parkinsonism. Dystonia has also been seen with defects in the mitochondrial oxidative phosphorylation system exemplified typically by striatal necrosis in Leigh's disease. We report two siblings who presented with a similar phenotype of parkinsonism, dystonia, and peripheral neuropathy and were found to have mitochondrial cytopathy on histopathological examination.

Case Report

A 16-year-old boy born out of a nonconsanguineous marriage with normal birth and developmental milestones presented with slowness of daily activities since 7 years of age. He would freeze while walking and gradually started using support to walk. Subsequently, over the next 2 years, he developed weakness of both lower limbs in the form of slippage of slippers followed by difficulty in getting up from ground. Past history was suggestive of seizures at 1 year of age with poor scholastic performance. His elder sister was also suffering from similar illness with more severity [Video 1]. Examination revealed mini-mental score examination of 29/30, mask-like facies with decreased blink rate. Speech was extrapyramidal with both hypophonic and dystonic quality. There was symmetrical parkinsonism with bradykinesia and cogwheel rigidity in both the upper limbs. There was also evidence of action dystonia in bilateral feet [Video 2]. Other neurological examination showed bilateral pes cavus with hammer toes, foot drop, wasting, and weakness of distal muscles in both the upper and lower limbs (power of 5/5 in bilateral shoulders, elbow, wrist, hip, and knee; 4-/5 in bilateral ankle dorsiflexion; and 4+/5 in bilateral ankle plantar flexion, weak small muscles of hands) with absent knee and ankle jerks [Figure 1]. Fundus examination and extraocular movements were normal. Gait dysfunction was multifactorial due to extrapyramidal involvement and lower motor neuron type of weakness. Magnetic resonance imaging of brain including susceptibility weighted imaging was unremarkable with no evidence of iron deposition [Figure 2a and b]. Nerve conduction studies and electromyography were suggestive of sensorimotor axonal neuropathy [Figure 3a-c]. Serum lactate (1.6), creatine kinase (234 U/L), ferritin, ceruloplasmin, and parathyroid hormone were within normal limits. Bone marrow biopsy did not reveal any abnormal cells suggestive of storage disorder. Finally, muscle biopsy was done which revealed evidence of mitochondrial cytopathy in the form of ragged red fibers in Gomori trichrome stain, confirmed on succinate dehydrogenase (SDH) and cytochrome c oxidase COX staining [Figure 4a-d]. Genomic DNA sequencing of

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DOI: 10.4103/aian.AIAN_436_17

polymerase gamma (POLG) gene did not show any mutations. Mutational analysis for other specific mitochondrial syndromes could not be done because of financial constraints. The patient had only a marginal improvement with levodopa.

Discussion

Mitochondrial cytopathies have a varied presentation albeit their multisystem involvement. They can result from either mutation in mtDNA or nDNA. nDNA encodes proteins necessary for proper functioning of mitochondrial DNA, elctron transport chain and other processes such as trafficking.[1-3] Mitochondrial diseases which result from mutations in mtDNA are maternally inherited, while those due to nDNA mutations follow classic Mendelian pattern of inheritance such as POLG, Twinkle helicase, ANT1, and OPA1. nDNA mutations are usually autosomal recessive and, however, may also show autosomal dominant pattern. Movement disorders in mitochondrial cytopathies are not uncommon and range from dystonia, tremors, ataxia, myoclonus, and rarely chorea.[4,5] Parkinsonism has been reported rarely in the case reports and case series only because of which the exact prevalence of mitochondrial disease with parkinsonism is not known. Autosomal recessive POLG mutation presents with progressive external ophthalmoplegia (PEO), ataxia, neuropathy, epilepsy, and myopathy, while autosomal dominant forms manifest with parkinsonism along with PEO and neuropathy.[6] Point mutations in mDNA causing parkinsonism have been reported rarely as a part of known mitochondrial syndromes such as MELAS and MERRF. Levodopa responsive parkinsonism has been described in a patient with classic A8344G mutation in the tRNA gene who had no other classical features of MERRF such as epilepsy and myoclonus.[7] Other nonspecific mitochondrial mutations have also been reported to present with parkinsonism. Point mutation in 12SrRNA (T1095C) presents with peripheral neuropathy and deafness along with parkinsonism,[8] and mitochondrial deletions are usually associated with myopathy and parkinsonism.[9] Progressive hypokinetic rigid syndrome phenotype has been seen as a part of adult-onset Leigh syndrome due to missense mutation in m. 14487T>C[10] and also due to base pair deletions in the mitochondrial cytochrome b gene, leading to parkinsonism along with features of classic mitochondrial cytopathies (stroke-like episodes, epilepsy, and optic atrophy).[11] Leber's "plus" disease is known to present with parkinsonism, cervical dystonia, optic neuropathy, and supranuclear ophthalmoplegia.[12] mtDNA gene coding for mtDNA helicase Twinkle has also been reported with familial parkinsonism with other features like PEO.[13,14] There is an ample growing evidence to suggest the role of mitochondrial dysfunction in the pathophysiology of idiopathic Parkinson's disease. There are many genes which have been implicated

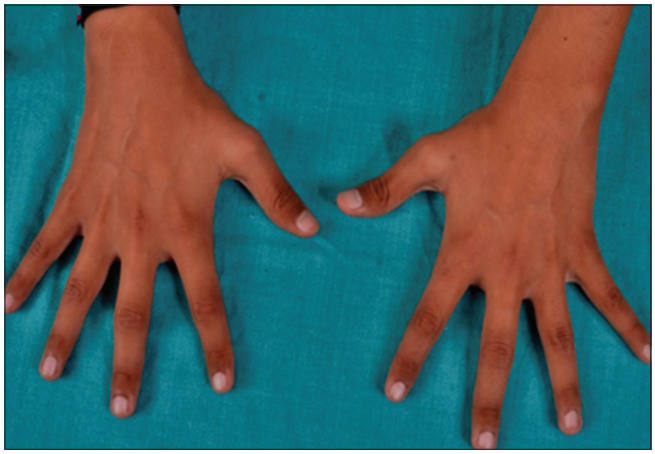

Figure 1: Atrophy of first dorsal interossei

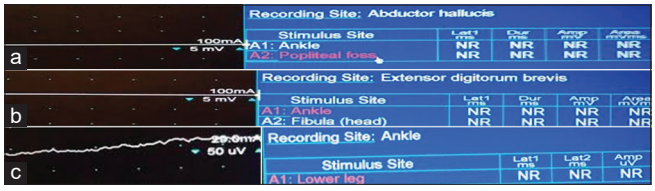

Figure 3: (a-c) Nonrecordable compound muscle action potential of right tibial, peroneal, and sensory nerve action potential of sural nerve

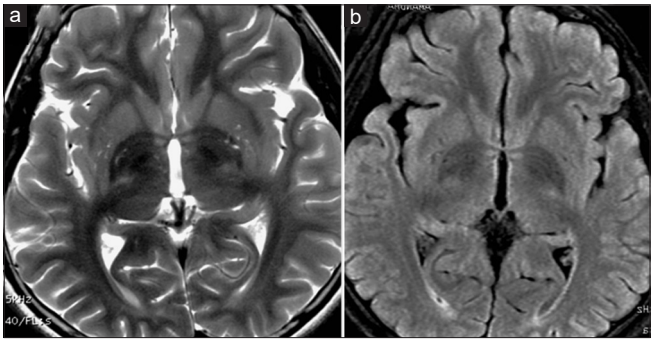

Figure 2: (a and b) Magnetic resonance imaging brain (T2-weighted sequence and FLAIR) shows prominence of Virchow–Robin spaces and T2 hyperintensities in bilateral basal ganglia

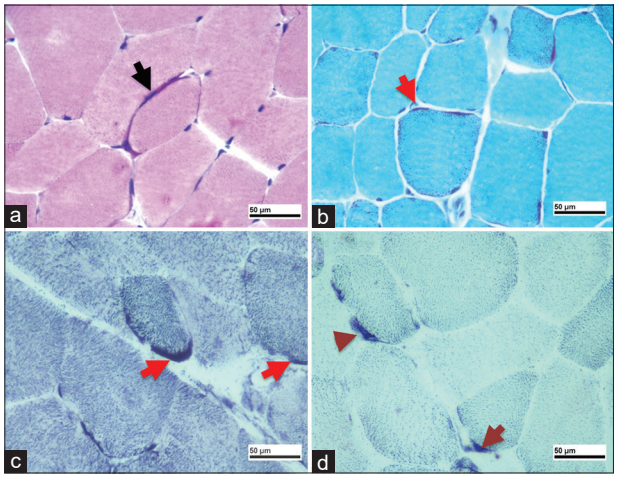

Figure 4: (a) Hematoxylin and eosin-stained snap frozen section shows muscle fibers with subtle subsarcolemmal amphophilic density (black arrow). These abnormal fibers are highlighted by (b) modified Gomori trichrome stain (red arrow), (c) nicotinamide adenine dinucleotide stain (red arrows), and (d) succinate dehydrogenase stain (brown arrows)

in mitochondrial dysfunction because they are responsible for encoding specific proteins needed for proper functioning of mitochondrion, for example, DJ-1, parkin, and PINK1.[15]

Histopathology also plays a significant role in the diagnosis of mitochondrial diseases because genetic tests are not widely available. The classical muscle biopsy findings include the presence of ragged red fibers, COX or SDH fibers, and abnormal aggregates of mitochondria containing paracrystalline inclusions on electron microscopy. In a study, clinical, histological, and biochemical data were collected from 68 patients carrying the homozygous p. Ala467Thr mutation. Muscle histology revealed ragged red fibers or cytochrome c oxidase–deficient fibers in 91% of the patients, a mitochondrial respiratory chain defect in 54%, and multiple mDNA deletions in 60%, whereas mDNA depletion was present in only 13% of the patients.[16] This study shows that the most sensitive investigation among all is histopathology although histological, biochemical, and genetic analysis of skeletal muscle did not show any correlation with the disease activity.

To summarize, we report two siblings who presented with levodopa unresponsive parkinsonism, dystonia and peripheral neuropathy where a diagnosis of mitochondrial cytopathy was confirmed with the aid of muscle biopsy

Conclusion

Mitochondrial parkinsonism should be added to the list of young-onset parkinsonism and must be suspected especially if there is a multisystem involvement with positive family history. Muscle biopsy plays an important role in diagnosis particularly in developing countries, where mutation analysis could not be done for many patients because of financial constraints.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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