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Peripheral neuropathy in genetically characterized patients with mitochondrial disorders: A study from south India☆

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ABSTRACT

Background: There are relatively few studies, which focus on peripheral neuropathy in large cohorts of genetically characterized patients with mitochondrial disorders. This study sought to analyze the pattern of peripheral neuropathy in a cohort of patients with mitochondrial disorders.
Methods: The study subjects were derived from a cohort of 52 patients with a genetic diagnosis of mitochondrial disorders seen over a period of 8 years (2006–2013). All patients underwent nerve conduction studies and those patients with abnormalities suggestive of peripheral neuropathy were included in the study. Their phenotypic features, genotype, pattern of peripheral neuropathy and nerve conduction abnormalities were analyzed retrospectively.
Results: The study cohort included 18 patients (age range: 18 months–50 years, M:F- 1.2:1).The genotype included mitochondrial DNA point mutations (n = 11), *SURF1* mutations (n = 4) and *POLG1*(n = 3). Axonal neuropathy was noted in 12 patients (sensori-motor:n = 4; sensory:n = 4; motor:n = 4) and demyelinating neuropathy in 6. Phenotype-genotype correlations revealed predominant axonal neuropathy in mtDNA point mutations and demyelinating neuropathy in *SURF1*. Patients with *POLG* related disorders had both sensory ataxic neuropathy and axonal neuropathy.
Conclusion: A careful analysis of the family history, clinical presentation, biochemical, histochemical and structural analysis may help to bring out the mitochondrial etiology in patients with peripheral neuropathy and may facilitate targeted gene testing. Presence of demyelinating neuropathy in Leigh's syndrome may suggest underlying *SURF1* mutations. Sensory ataxic neuropathy with other mitochondrial signatures should raise the possibility of *POLG* related disorder.

1. Introduction

Mitochondria have a number of essential roles in neuronal growth, survival and function (Sheng, 2014). In addition to maintaining energy milieu within the cell body, dendrites and axons, mitochondrial ATP production also supports synapse assembly, generation of action potentials and synaptic transmission in peripheral nerves (Sheng & Cai, 2012). The peculiar morphological features of peripheral nerves such as small cell body, arborizing dendrites with elaborate anchors and thin long axons necessitate specialized mechanisms to efficiently distribute mitochondria to distal areas of nerves (Sheng, 2014). Mitochondria are concentrated on the nodes of Ranvier and nerve terminals and transmission of energy across long distances in peripheral nerves is facilitated by both

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anterograde and retrograde mitochondrial transport (Vital & Vital, 2012). This is regulated by a continuous process of mitochondrial fusion and fission referred to as mitochondrial 'dynamics'. Abnormalities in mitochondrial dynamics are being increasingly identified as a cause of peripheral nerve dysfunction and they form an important subgroup of mitochondrial neuropathies with a Charcot–Marie–Tooth (CMT) disease like phenotype (Milone & Benarroch, 2012). Given the important role of mitochondria in neuronal function, peripheral neuropathy is often seen in patients with mitochondrial disorders (Menezes & Ouvrier, 2012; Pareyson et al., 2013). Peripheral neuropathy is reported in one-third of patients with mitochondrial disorders, but is often under-recognized due to overwhelming involvement of the central nervous system (Finsterer, 2005). The severity of neuropathy varies from mild or subclinical, to severe and may be the main or only feature of a mitochondrial disorder (Bouillot et al., 2002).

Molecular genetic classification of peripheral neuropathies related to mitochondrial disorders is still evolving. Peripheral neuropathy is uncommon and a non-prominent feature of disorders arising from point mutations of mitochondrial DNA (mtDNA) (Vital & Vital, 2012; Bouillot et al., 2002; Karppa et al., 2003). However neuropathy is a predominant feature in neuropathy, ataxia, and retinitis pigmentosa (NARP) syndrome secondary to mutations in Mitochondrial Encoded ATP Synthase 6 (*MT-ATP6*) (Childs et al., 2007; Gelfand et al., 2011). Neuropathy is more frequently related to a defect in nuclear DNA (nDNA) especially in nuclear-mitochondrial inter-genomic communication disorders (Van Goethem et al., 2003). In addition peripheral neuropathy occurs as a unique or sole manifestation in disorders of mitochondrial dynamics associated with mutations in Mitofusin-2 (*MFN2*) and Ganglioside-induced Differentiation Associated Protein-1 (*GDAP1*) (Pareyson et al., 2013).

The recognition of mitochondrial disorder as the underlying etiology of peripheral neuropathy is important in clinical practice for targeted metabolic and genetic testing. Phenotype genotype correlations in mitochondrial neuropathies are still evolving and need to be defined further. This study reports the profile of peripheral neuropathy in a cohort of patients with genetically characterized mitochondrial disorder.

2. Patients and methods

The Institute Ethics Committee of National Institute of Mental Health and Neurosciences, Bangalore, India, approved the study protocol. The recruitment and selection of the patients were done as per the methods described previously (Bindu et al., 2015). Over a period of eight years (2006–2013) a total of 605 patients were recruited as part of a study on neurological disorders associated with mtDNA mutations. All patients underwent a complete clinical and laboratory evaluation and follow-up by a single clinical team (ABT, PSB, SS, MN). Patients were recruited into the study when a comprehensive evaluation, with serum lactate, muscle histopathology, respiratory chain complex assays, brain magnetic resonance imaging, nerve conduction studies, electroencephalography and evoked potential studies, tailored to the clinical phenotype suggested a probable diagnosis of mitochondrial disorder. The evaluation also included estimation of fasting blood sugar, thyroid function tests, and serum vitamin B12 levels as a part of diagnostic work up of peripheral neuropathy.

Standard definitions were used for the phenotypic characterization of the classical mitochondrial syndromes. Complete mitochondrial genome sequencing was done in all the patients. Genetic evaluation also included sequencing of the nuclear genes: Polymerase gamma 1 and 2 (*POLG 1* and *2*) (n = 304) and Surfeit Locus Protein 1 (*SURF1*) (n = 91). Mitochondrial gene sequencing revealed 128 variations in 135 patients, which included known pathogenic mutations (n = 20), benign polymorphisms/possible disease associated mutations (n = 37) and novel variations (n = 70). Mitochondrial rearrangements were looked for in eight patients and one showed single large deletion. *POLG* screening revealed mutations in 24 patients (*POLG1* = 12, *POLG2* = 12), while mutations in *SURF1* were noted in seven. All 52 patients with a genetic diagnosis underwent nerve conduction studies and those patients who had electrophysiological evidence of neuropathy (n = 18) were included in final analysis. Their phenotypic features, nerve conduction abnormalities and genetic diagnoses were reviewed.

2.1. Nerve conduction studies

Nerve conduction studies were performed using standard techniques. Median, ulnar, common peroneal and sural nerve recordings were done. Difference in recorded values greater than two standard deviation from the mean values standardized at our laboratory was considered abnormal (Supplementary Table 1).The normative values have been collected using the methods described previously (Gupta et al., 1994; Taly et al., 1991). For children included in the study, we used the reference values given by Parano et al. and Gamstorp et al. (Parano et al., 1993; Gamstorp, 1963). Based on the nature of electrophysiological abnormalities, patients were categorized to (i) axonal or demyelinating neuropathy; and (ii) sensory, motor or sensorimotor neuropathy. Demyelination in children was defined using the criteria for Chronic Inflammatory Demyelinating Polyneuropathy by Nevo et al. (Nevo & Topaloglu, 2002).

3. Results

There were 18 patients (age range: 18 months–50 years, M:F- 1.2:1) in the study. The phenotypes, genotypes and the type of neuropathy of these patients are summarized in Table 1. Consanguinity was noted in 10 (50%) and a positive family history in 5 (25%). Phenotypes included Leighs and Leigh like syndrome (n = 5), Myoclonic Epilepsy with Ragged Red Fibers syndrome (MERRF, n = 4), Mitochondrial Encephalopathy Lactic Acidosis Stroke like syndrome (MELAS, n = 3), and one patient each of ataxia neuropathy, Mitochondrial Spinocerebellar Ataxia Epilepsy (MSCAE), Neuropathy Ataxia Retinitis Pigmentosa syndrome (NARP), chronic progressive ophthalmoplegia (CPEO), Lebers Hereditary Optic Neuropathy (LHON) plus syndrome, and sensory ataxic neuropathy, dysarthria, ophthalmoparesis (SANDO) syndrome. Signs of peripheral neuropathy such as wasting of the distal muscles of the lower limb, weakness and hyporeflexia were noted in 14 (77.8%) patients. Positive sensory symptoms were present in two and autonomic symptoms in one. One patient with MERRF syndrome (Patient 3) had diabetes. Diagnostic evaluation for other causes of peripheral neuropathy was negative in the rest of the patients.

3.1. Genetic findings

Genetic findings included: mtDNA point mutations, n = 11; *SURF1* mutations, n = 4; and *POLG1* mutations, n = 3.

3.2. Histopathological findings

One patient underwent nerve biopsy (Patient 1), which showed significant loss of large fibers in Kulchitsky Pal stain. Other findings included Schwann cell proliferation and regenerating clusters.

3.3. Nerve conduction abnormalities

Details of nerve conduction studies of the entire cohort are given in Supplementary Table 1. Axonal neuropathy was noted in 12 (66.6%) patients. This could be further classified as sensory axonal (n = 4, 22.2%), motor axonal (n = 4, 22.2%) and sensorimotor axonal (n = 4, 22.2%) neuropathy. Sensorimotor demyelinating neuropathy was noted in six patients (30%). Majority had axonal neuropathy which was length dependent and involved the sensory more than motor nerves. In majority of the patients, neuropathy was mild and was detected based on the presence of signs of neuropathy and confirmed by electrophysiological