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Neurophysiological profile of peripheral neuropathy associated with childhood mitochondrial disease

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ABSTRACT

Introduction: Peripheral nerve involvement is common in mitochondrial disease but often unrecognised due to the prominent central nervous system features. Identification of the underlying neuropathy may assist syndrome classification, targeted genetic testing and rehabilitative interventions.
Methods: Clinical data and the results of nerve conduction studies were obtained retrospectively from the records of four tertiary children's hospital metabolic disease, neuromuscular or neurophysiology services. Nerve conductions studies were also performed prospectively on children attending a tertiary metabolic disease service. Results were classified and analysed according to the underlying genetic cause.
Results: Nerve conduction studies from 27 children with mitochondrial disease were included in the study (mitochondrial DNA (mtDNA) – 7, *POLG* – 7, *SURF1* – 10, PDHc deficiency – 3). Four children with mtDNA mutations had a normal study while three had mild abnormalities in the form of an axonal sensorimotor neuropathy when not acutely unwell. One child with MELAS had a severe acute axonal motor neuropathy during an acute stroke-like episode that resolved over 12 months. Five children with *POLG* mutations and disease onset beyond infancy had a sensory ataxic neuropathy with an onset in the second decade of life, while the two infants with *POLG* mutations had a demyelinating neuropathy. Seven of the 10 children with *SURF1* mutations had a demyelinating neuropathy. All three children with PDHc deficiency had an axonal sensorimotor neuropathy. Unlike CMT, the neuropathy associated with mitochondrial disease was not length-dependent.
Conclusions: This is the largest study to date of peripheral neuropathy in genetically- classified childhood mitochondrial disease. Characterising the underlying neuropathy may assist with the diagnosis of the mitochondrial syndrome and should be an integral part of the assessment of children with suspected mitochondrial disease.

1. Introduction

Childhood mitochondrial diseases have a heterogeneous phenotype with many different systems being affected including the peripheral nervous system. Around 30% of children with a mitochondrial disease have an associated peripheral neuropathy (Colomer et al., 2000), but the neuropathy is often unrecognised due to the overwhelming central

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nervous system manifestations. Mutations in nuclear genes responsible for mitochondrial dynamics and axonal transport, including *MFN2* and *GDAP1*, are recognised causes of Charcot-Marie-Tooth disease (CMT) (Niemann et al., 2005; Züchner et al., 2004). Recently, mutations in *MT-ATP6* and *SURF1*, genes known to cause Leigh syndrome and other multisystemic mitochondrial diseases, have also been shown to cause phenotypes characterised predominantly by a peripheral neuropathy (Echaniz-Laguna et al., 2013; Pitceathly et al., 2012). Identifying the presence of a peripheral neuropathy and defining its characteristics may help with classifying the mitochondrial syndrome and targeted genetic testing (Menezes and Ouvrier, 2012). The associated peripheral neuropathy may be symptomatic and disabling and specific treatment and rehabilitative intervention may be needed.

2. Methods

Children with mitochondrial disease and identified mutations who had previously undergone nerve conduction studies were identified from the mitochondrial diseases database at the Murdoch Childrens Research Institute, Melbourne, Australia, the records of the Genetic Metabolic Disorders Clinic at The Children's Hospital at Westmead, Sydney, Australia, the Sydney Children's Hospital Randwick Nerve and Muscle Clinic and the Neurophysiology Department at Great Ormond Street Children's Hospital, London, UK. Nerve conduction studies were also performed prospectively according to a defined protocol (see Supplementary Methods) on children from the Genetic Metabolic Disorders Clinic at The Children's Hospital at Westmead who had identified mitochondrial mutations and consented to inclusion in the study. Children with pyruvate dehydrogenase complex (PDHc) deficiency were included if there was biochemical confirmation of the PDHc deficiency, even if a genetic mutation had not been identified. The data from both retrospective and prospective groups were combined and classified according to the underlying genetic cause. The results were compared with age-matched normative values (Cai and Zhang, 1997). Because of a lack of published paediatric electrodiagnostic criteria for demyelination in inherited neuropathies, the EFNS/PNS electrodiagnostic criteria for demyelination in chronic inflammatory demyelinating neuropathy were used (Hughes et al., 2006). These criteria require a 30% reduction of motor conduction velocity below the lower limit of normal in at least one nerve. Both retrospective and prospective studies were approved by the Sydney Children's Hospital Network Ethics Committee (10/56), and the retrospective study at Great Ormond Street Hospital by the National Research Ethics Committee London Bloomsbury, UK.

3. Results

Nerve conduction data were available from 27 children from 25 families with a genetically classified mitochondrial disease or biochemically-defined PDHc deficiency. The data were collected over a six-year period (2010–2015). Retrospective nerve conduction studies were available for 20 children and prospective nerve conduction studies were performed on seven children. All nerve conduction studies in the retrospective series were performed because of the clinical suspicion of a neuropathy, except in individual 3, who was investigated because of the known association of a neuropathy with retinitis pigmentosa. One child in the prospective study also had data included from another nerve conduction study performed four years previously. Seven children had mitochondrial genome mutations and 20 had nuclear DNA mutations (*POLG* – 7, *SURF1* – 10, PDHc deficiency – 3). All genetic diagnoses were established after Sanger sequencing of individual nuclear or mitochondrial genes or after testing of a panel of common mitochondrial genome mutations. None of the diagnoses were established by next generation sequencing technologies. All identified mutations have been previously reported as pathogenic except the c.897G>A (p.Met299Ile) variant in *POLG* (individual 9 in Table 2). The neurophysiological results were categorised by the causative gene (Tables 1–4).

3.1. Mitochondrial DNA mutations

Neurophysiologic findings in seven children (from six families) with mutations in the mitochondrial genome were evaluated (Table 1). Three had Leigh/NARP (neurogenic muscle weakness, ataxia, and retinitis pigmentosa) syndrome due to the m.8993T>C mutation in *MT-ATP6*, one had MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) due to the m.3243A>G mutation in *MT-TL1* and two individuals had single large mtDNA deletions. This group of children had normal studies or mild abnormalities, usually in the form of an axonal sensorimotor neuropathy.

Of the children with ***MT-ATP6* mutations**, two (individuals 1 and 3) had presented in the second year of life with developmental delay.

Table 1
Neurophysiological profile of children with mitochondrial genome mutations (n = 7).

Pt./sex	Syndrome	Mutation	Age at presentation	Signs suggestive of neuropathy	Age at NCS, retrospective/prospective	Upper limb motor [CMAP(mV)/CV(m/s)]	Lower limb motor [CMAP(mV)/CV(m/s)]	Upper limb sensory [μV]	Lower limb sensory [μV]
1/M	Leigh	*MT-ATP6* m.8993T>C	2 y	hypotonia, ataxia, generalised weakness (acute with illness)	5 y/R	(M) 14.2/54	(P) **1.7**/46 (T) **1.4**/**38**	(M) 25	(S) 38
2/F	Leigh	*MT-ATP6* m.8993T>C	12 y	–	12 y/P	(M) 4.9/52	(P) 3.5/43	(M) 16	(S) **NR**
3/F	NARP	*MT-ATP6* m.8993T>C	16 y	–	16 y/R	(M) NA/46	(P) NA/46	(M) 15	(S) 10
4/M	MELAS	*MT-TL1* m.3243A>G	9 y	–	11 y/P	(M) 9/54 (U) 9.6/60	(P) 5.3/46 (T) 17.3/49	(M) 26 (U) 20	(S) 5
5/M	MELAS	*MT-TL1* m.3243A>G	10 y	ataxia, areflexia (during acute episode)	12 y/P	(M) **2.7**/56 (U) **NR**/**NR**	(P) **NR**/**NR** (T) **NR**/**NR**	(M) 23 (U) 15	(S) **NR**
					13 y/P	(M) 10.3/59 (U) 9.5/59	(P) **2.0**/47 (T) **8.7**/51	(M) 26 (U) 12	(S) **NR**
6/M	Pearson	Single mtDNA deletion	7 m	–	4 y/P	(M) 7.6/45 (U) 6.7/62	(T) 9.9/48	(M) 35	(S) 9
7/M	Kearns-Sayre	Single mtDNA deletion	11 y	–	15 y/P	(M) 14.8/68 (U) 13.9/65	(P) 5.1/58 (T) 23.2/58	(M) 10 (U) 11	(S) 16

Abnormal results (<2SD) in bold. Reference values from Cai et al.(Cai and Zhang, 1997). Hz – homozygous, w – weeks, m– months, y – years, R – retrospective, P – prospective, CMAP – compound muscle action potential, CV – conduction velocity, SNAP – sensory nerve action potential, M – median, U – ulnar, P – peroneal, T – tibial, S – sural, Sp – superficial peroneal, Mp – medial plantar, NR – not recordable, NA – not available, sup – superficial, empty box indicates this nerve was not studied.

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