ORIGINAL ARTICLE

Peripheral neuropathy is a common manifestation of mitochondrial diseases: a single-centre experience

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Background and purpose: Peripheral neuropathy in mitochondrial diseases (MDs) may vary from a subclinical finding in a multisystem syndrome to a severe, even isolated, manifestation in some patients.

Methods: To investigate the involvement of the peripheral nervous system in MDs extensive electrophysiological studies were performed in 109 patients with morphological, biochemical and genetic diagnosis of MD [12 A3243G progressive external ophthalmoplegia (PEO)/mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), 16 myoclonic epilepsy with ragged-red fibres (MERRF), four mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), 67 PEO with single or multiple deletions of mitochondrial DNA, 10 others].

Results: A neuropathy was found in 49 patients (45%). The incidence was very high in MNGIE (100%), MELAS (92%) and MERRF (69%), whilst 28% of PEO patients had evidence of peripheral involvement. The most frequent abnormality was a sensory axonal neuropathy found in 32/49 patients (65%). A sensory-motor axonal neuropathy was instead detected in 16% of the patients and sensory-motor axonal demyelinating neuropathy in 16%. Finally one Leigh patient had a motor axonal neuropathy. It is interesting to note that the great majority had preserved tendon reflexes and no sensory disturbances.

Conclusions: In conclusion, peripheral involvement in MD is frequent even if often mild or asymptomatic. The correct identification and characterization of peripheral neuropathy through electrophysiological studies represents another tile in the challenge of MD diagnosis.

Introduction

Numerous studies have demonstrated the importance of mitochondria for nerve function, bolstered by the fact that patients with alteration of mitochondrial dynamics may present a Charcot–Marie–Tooth phenotype [1]. Thus, the involvement of peripheral nerves in mitochondrial disorders is relatively common but, with few exceptions, represents a minor manifestation in the context of a multisystem impairment. For this reason the exact prevalence of polyneuropathy is not well defined.

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The occurrence and characteristics of peripheral nerve involvement vary considerably amongst various syndromes and genetic background. It is a major or a common feature of a variety of nuclear DNA defects (e.g. TYMP-, MPV17- and POLG-related disorders) but also of specific point mutations of mitochondrial DNA (e.g. m.8993T G->C and m.3243A->G) [2–6].

Chronic axonal polyneuropathy is the pattern most often seen in mitochondrial disorders [7–10]. Demyelinating neuropathy is less common [7–10], is typically associated with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE; related to TYMP mutations) [5] and occasionally observed in other conditions [1]. Sensory ataxic neuropathy is often part of POLG1-related disorders [11], and neuropathy, ataxia

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and retinitis pigmentosa is a well characterized syndrome associated with MTATP6 mutations [8].

In most mitochondrial disorders peripheral neuropathy has no clinical relevance, whilst in a small proportion of patients it may represent the first or the key symptom and may be severe or rapidly evolving in the context of a multisystem syndrome such as mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) and myoclonic epilepsy with ragged-red fibres (MERRF), Leigh syndrome or POLG1-related disorders [7,8,11].

In this work nerve conduction studies (NCSs) from a large cohort of patients with mitochondrial diseases (MDs) were investigated in order to characterize peripheral nerve involvement in different subsets of MD.

Patients and methods

In all, 109 MD patients investigated in our Neurology Department in a 25-year interval (1989–2014) were studied. Patients with defined primary mitochondrial disorders on the basis of clinical phenotype [MELAS, MERRF, MNGIE, progressive external ophthalmoplegia (PEO) or other MDs] and morphological, biochemical (presence of respiratory chain defects) and genetic criteria were included. MD patients with a predisposing neuropathic condition such as diabetes, alcoholism, chronic kidney disease, chronic viral infection or autoimmune disorders were not excluded. On clinical examination the presence of signs or symptoms suggestive of neuropathy was also evaluated.

Our study was approved by our Ethics Committee from the Catholic University of the Sacred Heart in Rome (CE1136511). All patients agreed to perform a neurophysiological examination, which is part of the routine diagnostic work-up in MDs and does not require a specific written consent.

Motor NCSs of median, ulnar, peroneal and tibial nerves were performed using standard techniques, as described previously [12,13]. All studies were performed in a warm room and skin temperature was >32°C; if needed, an infrared lamp was used to warm the studied segment. Distal motor latency was measured at the onset of compound muscle action potential and the low- and high-frequency filters were set at 20 Hz and 10 kHz. F wave was recorded according to the standard technique [12]. A minimum of 20 stimuli were passed to obtain the F waves from lower limbs and a minimum of 10 from upper limbs. Supramaximal stimulation of motor nerves with a frequency of 0.5 Hz was given. No facilitation manoeuvres were used. The minimum amplitude for an interpretable F wave was considered to be 40 μV.

Sensory NCSs of sural, radial, median and ulnar nerves were performed using standard techniques [12,14]. For the sural nerve antidromic stimulation was used, whilst the orthodromic method was performed for sensory NCSs of the upper limbs. Sensory nerve action potential amplitude and nerve conduction velocity were measured as previously described [15].

Neuropathy was defined as (a) sensory axonal with a reduction of sensory nerve action potential amplitude at least in the sural nerve bilaterally or in more sensory nerves, (b) motor axonal with a reduction of the compound muscle action potential amplitude at least in the tibial nerve bilaterally or in more motor nerves and (c) sensory-motor axonal in the presence of axonal involvement of both motor and sensory nerves. Finally, demyelinating neuropathy was diagnosed according electrophysiological criteria for definite chronic inflammatory demyelinating neuropathy (motor distal latency prolongation; reduction of motor conduction velocity; prolongation or absence of F-wave latency) [16]. Normal cut-off values of our laboratory are provided in Table 1.

Results

Patients

In all, 109 MD patients underwent NCSs in our department during the period examined (1989–2014). Age at onset varied from 3 to 70 years (mean 32.50, median 31, SD ±19.40). Age at examination varied from 8 to 80 years (mean 48.4, median 48, SD ±16.8). The ratio of men to women was 0.70:1 (45/64). Diabetes was reported in 15 cases; other conditions predisposing to a neuropathy occurred in six patients (two hepatitis C virus; one hepatitis B virus; one with rheumatoid arthritis; one with chronic renal failure; one with previous assumption of chemotherapies). Symptoms suggestive of neuropathy (i.e. distal dysesthesias or paraesthesias) were reported in nine cases (8%). Signs of neuropathy (abolished or reduced tendon reflexes) were observed in 47 patients (43%). Seven patients (6.4%) had optic atrophy: one MELAS; one MERRF; one PEO; one MNGIE; two other MDs. Other clinical findings classically showed a multisystem involvement and differed amongst MD subsets (Figs 1–4).

Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes was observed in 12 cases (11%). Age at onset varied from 5 to 40 years (mean 22.50, median 17, SD ±14.48). Age at examination varied from 16 to 52 years (mean 35.92, median 35.50, SD ±12.20). The ratio of men to women was 0.5:1 (4/8). Diabetes was reported in six cases; other conditions

Table 1 Nerve conduction study mean values in different mitochondrial disease (MD) subgroups and in healthy subjects

Nerve	All MDs group (109 patients)	MELAS (12 patients)	MERRF (16 patients)	MNGIE (four patients)	PEO (67 patients)	Other MDs (10 patients)	Controls (627 subjects)
Median							
DML (ms)	3.0 ± 0.7	3.2 ± 0.5	3.1 ± 0.9	4.3 ± 0.6	2.9 ± 0.6	3.3 ± 0.8	3.0 ± 0.4
MCV (m/s)	53 ± 7.1	52 ± 2.5	48 ± 5.4	47 ± 2.7	54 ± 8.0	51 ± 3.6	58 ± 9.3
CMAP (mV)	7.4 ± 3.5	4.9 ± 3.4	8.7 ± 5.3	6.4 ± 1.6	7.6 ± 3.1	7.2 ± 3.3	9.9 ± 3.8
F wave (ms)	29.5 ± 0.7	26.5 ± 1.9	30.4 ± 4.2	37.1 ± 2.4	30.0 ± 2.8	29.2 ± 2.1	26.9 ± 2.3
Tibial							
DML (ms)	3.6 ± 0.8	4.1 ± 1.0	3.6 ± 0.7	4.4 ± 0.6	3.5 ± 0.7	3.5 ± 0.9	3.5 ± 0.5
CMAP (mV)	8.8 ± 5.3	7.3 ± 6.6	11.4 ± 6.1	5.7 ± 3.0	8.9 ± 4.8	8.8 ± 5.2	12.6 ± 4.3
F wave (ms)	51.5 ± 7.0	51.0 ± 7.9	49.6 ± 5.9	72.1 ± 4.2	51.0 ± 6.0	52.3 ± 8.1	49.0 ± 4.3
Radial							
SCV (m/s)	53 ± 7.1	52 ± 6.5	48 ± 5.4	46 ± 5.6	54 ± 8.0	59 ± 6.7	55 ± 5.1
SNAP (μV)	9.4 ± 6.4	12.6 ± 7.9	6.0 ± 1.4	5.5 ± 0.7	9.6 ± 6.8	7.6 ± 4.8	19.8 ± 7.4
Sural							
SCV (m/sec)	53 ± 9.3	49 ± 4.2	50 ± 13.6	34 ± 7.5	55 ± 7.7	56 ± 6.9	53 ± 5.4
SNAP (μV)	16.3 ± 12.5	8.5 ± 7.6	18.9 ± 8.8	7.3 ± 1.7	16.8 ± 12.4	20.6 ± 14.2	21.0 ± 9.8

MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibres; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; PEO, progressive external ophthalmoplegia; DML, distal motor latency; MCV, motor conduction velocity; CMAP, compound muscle action potential; F wave, mean F-wave latency; SCV, sensory conduction velocity; SNAP, sensory nerve action potential.

Normal values in our laboratory were the following: median nerve, CMAP ≥4 mV, DML ≤4 ms, MCV ≥45 m/s; tibial nerve, CMAP ≥5 mV, DML ≤4.5; radial nerve, SNAP ≥5 μV; SCV ≥45 m/s; sural nerve [15]. F-wave cut-off was corrected for the height: median nerve, 150 cm ≤25 ms, 160 cm ≤27 ms, 170 cm ≤29 ms, 180 cm ≤30 ms, 190 cm ≤ 31 ms; tibial nerve, 150 cm ≤44 ms, 160 cm ≤48 ms, 170 cm ≤53 ms, 180 cm ≤58 ms, 190 cm ≤60 ms. Mean age of controls was 52 ± 18 (range 8–94 years).

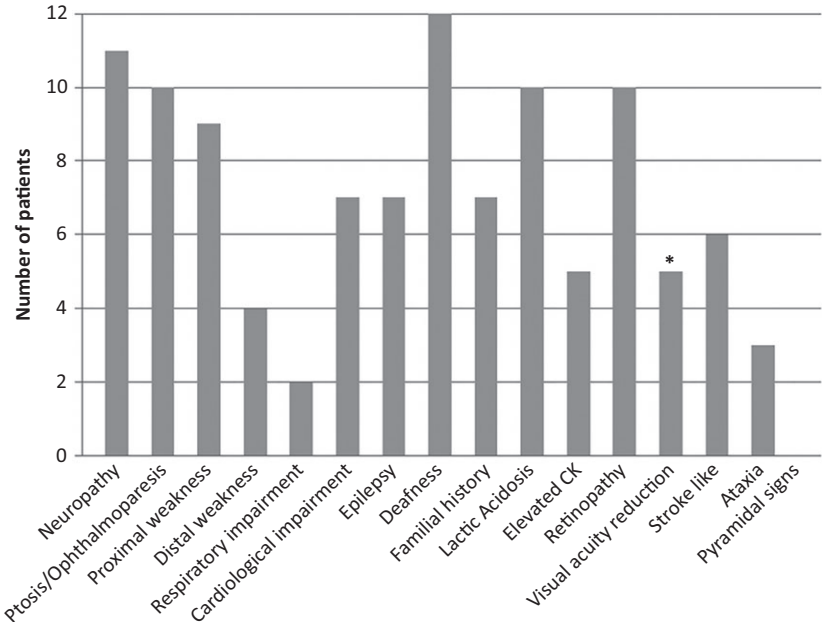

Figure 1 Multisystem manifestations in MELAS syndrome. Number of patients are on the *Y* axis and clinical features are shown on the *X* axis. *One patient with optic atrophy.

predisposing to a neuropathy occurred in one patient (hepatitis B virus). Symptoms suggestive of neuropathy were reported in two cases (17%). Signs of neuropathy were observed in seven patients (58%). Other clinical findings are summarized in Fig. 1.

Myoclonic epilepsy with ragged-red fibres was diagnosed in 16 cases (15%). Age at onset varied from 3 to 46 years (mean 26.19, median 26.50, SD ±14.57). Age at examination varied from 31 to 62 years (mean 38.69, median 39.50, SD ±14.10). The ratio of men to women was 0.45:1 (5/11). Diabetes was not reported; other conditions predisposing to a neuropathy were not present. Symptoms suggestive of neuropathy were reported in one case (6%). Signs of neuropathy were observed in nine patients (56%). Other clinical findings are summarized in Fig. 2.

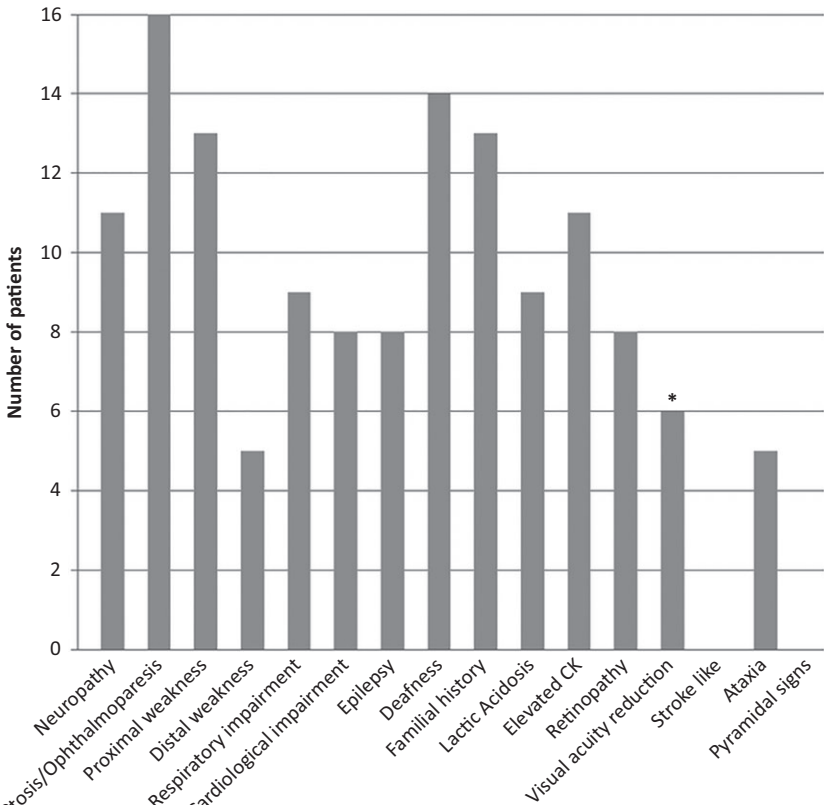

Figure 2 Multisystem manifestations in MERRF syndrome. Number of patients are on the Y axis and clinical features are shown on the X axis. *One patient with optic atrophy.

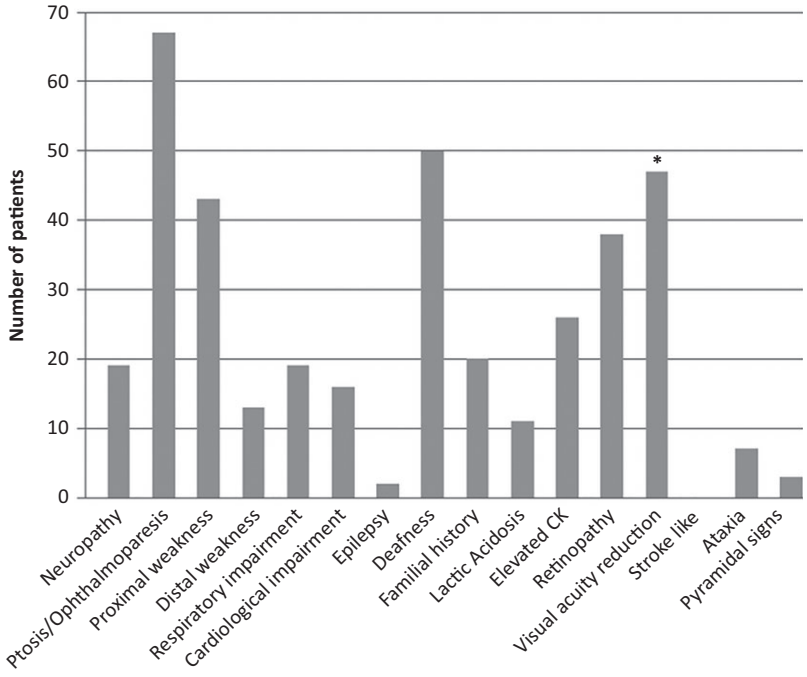

Figure 3 Multisystem manifestations in PEO syndrome. Number of patients are on the *Y* axis and clinical features are shown on the *X* axis. *One patient with optic atrophy.

Four patients were affected by MNGIE. Age at onset varied from 7 to 18 years (mean 10.33, median 7, SD ±6.66). Age at examination varied from 22 to 41 years (mean 35.50, median 39, SD ±9.26). The ratio of men to women was 3:1 (3/1). Diabetes was not reported; other conditions predisposing to a

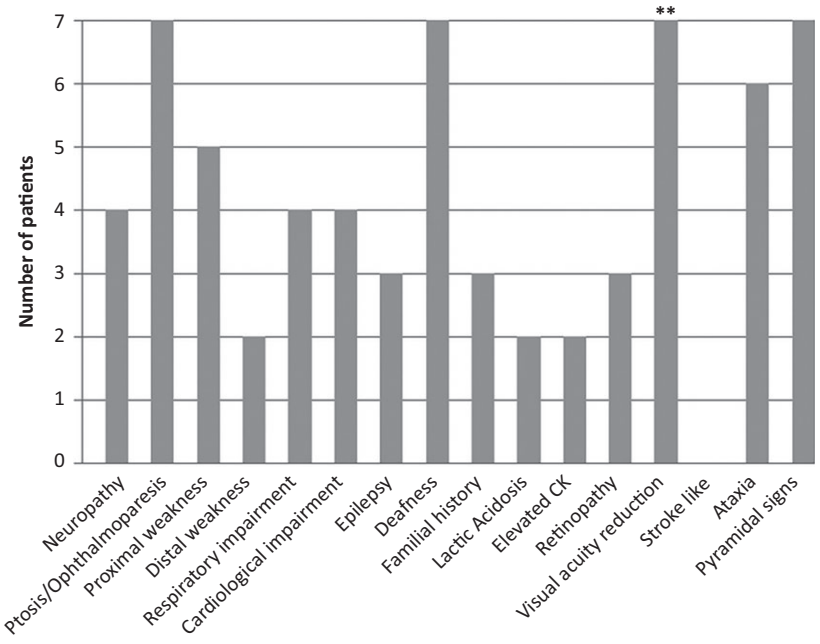

Figure 4 Multisystem manifestations in other mitochondrial diseases. Number of patients are on the *Y* axis and clinical features are shown on the *X* axis. **Two patients with optic atrophy.

neuropathy were not present. Symptoms suggestive of neuropathy were not reported. Signs of neuropathy were observed in all patients. Other clinical findings were typical for MNGIE syndrome and were present in all patients (PEO and ptosis, progressive gastrointestinal dismotility and abdominal pain, postprandial emesis, cachexia, symmetrical and distal weakness especially in lower extremities and diffuse leucoencephalopathy in cranial magnetic resonance imaging). One patient also showed optic atrophy.

Progressive external ophthalmoplegia was observed in 67 cases (61%). Age at onset varied from 6 to 70 years (mean 36.65, median 38, SD ±19.66). Age at examination varied from 19 to 80 years (mean 54.88, median 57, SD ±14.90). The ratio of men to women was 0.63:1 (26/41). Diabetes was reported in eight cases; other conditions predisposing to a neuropathy occurred in five patients (two hepatitis C virus; one with rheumatoid arthritis; one with chronic renal failure; one with previous assumption of chemotherapies). Symptoms suggestive of neuropathy were reported in six cases (9%). Signs of neuropathy were observed in 27 patients (40%). Other clinical findings are summarized in Fig. 3.

Ten patients (9%) had other mitochondrial encephalomyopathies, including Leigh syndromes. Age at onset varied from 5 to 61 years (mean 33.60, median 35.50, SD ±25.69). Age at examination varied from 8 to 70 years (mean 40.80, median 38, SD ±19.65). The ratio of men to women was 1.5:1 (6/4). Diabetes was reported in one case; other conditions predisposing to a neuropathy were absent. Symptoms suggestive of neuropathy were reported in one case (10%). Signs of neuropathy were not observed. Other clinical findings are summarized in Fig. 4.

Nerve conduction study results

Nerve conduction studies revealed the presence of a polyneuropathy in 49/109 cases (45%): 11/12 (92%) with MELAS, 11/16 (69%) with MERRF, 4/4 (100%) with MNGIE, 19/67 (28%) with PEO, 4/10 (40%) with other MDs.

In patients with PEO a further sub-classification according to genetic cause (single deletion versus multiple deletions) was also performed. Genetic results were available for 56 cases (39 with single deletion versus 17 with multiple deletions). Of these cases 18 showed a polyneuropathy (four with single deletion versus 14 with multiple deletions).

Considering the entire population the most frequent abnormality was a sensory axonal neuropathy found in 32/49 (66%) cases: 7/11 (64%) with MELAS, 9/11 (82%) with MERRF, 13/19 (68%) with PEO, 3/4 (75%) with other MDs. A sensory-motor axonal neuropathy was instead observed in 8/49 (16%) cases: 4/11 (36%) with MELAS, 2/11 (18%) with MERRF, 2/19 (11%) with PEO. Conversely, a sensory-motor axonal and demyelinating neuropathy was detected in 8/49 (16%) cases: 4/4 (100%) with MNGIE, 4/19 (21%) with PEO. Finally 1/4 (25%) cases with other MDs, namely Leigh encephalopathy, had a motor axonal neuropathy.

Mean values of NCS results in different groups are summarized in Table 1.

Follow-up NCSs were available for 21 cases (two with MELAS; three with MERRF; 11 with PEO; five with other MDs). Mean follow-up was 68.7 months (range 8–188; SD 52.8). In four cases (two with MERRF, one with PEO and one with other MD) the development of a sensory axonal neuropathy was observed.

Mean values of NCS results in different groups at baseline and at follow-up are summarized in Table 2. Demographic and clinical data of the four patients developing a sensory axonal neuropathy at follow-up are summarized in Table S1.

Discussion

Although the involvement of peripheral nerves in MDs is a well-known concept [1], few studies have systematically evaluated patients with primary mitochondrial disorders according to strict electrophysiological criteria. Our work shows that peripheral neuropathy is a common feature in different subsets of MD, being present in 49/109 patients (45%), with a particularly high incidence in MNGIE (100%), MELAS (92%) and MERRF (69%).

In the literature, the occurrence of neuropathy in MELAS patients varies widely from 10.5% [17] to 22% [18] to 77% [4]. Interestingly, all work, including our study, proved the absence of correlation between neuropathy and diabetes.

In patients harbouring the A8344G mutation polyneuropathy is frequently described in single case records, whilst very few studies have been reported on larger groups of patients. Neuropathy was found in 6.8% of patients in a large retrospective study [19] and in 47% of patients in our previous single-centre study on MERRF [20].

In PEO the presence of a neuropathy varies according to the genetic background. Horga *et al.* suggested that 'peripheral neuropathy predicts nuclear gene defect', being present in 52% of MD patients with Mendelian transmission against 2% with a single deletion of mitochondrial DNA [21]. In our series, slightly higher percentages were found, however, that clearly confirmed the trend. Indeed 14/17 (82%) PEO cases with multiple deletions showed a polyneuropathy compared with only 4/39 (10%) with a single deletion ($P < 0.0001$). In our study peripheral neuropathy could even be the presenting or the dominating manifestation in nuclear DNA defects but was instead often subclinical in PEO with a single deletion. So, despite a strong association between nuclear mutations and polyneuropathy, the presence of neurophysiological abnormalities in patients with PEO does not exclude a single deletion, especially if they are consistent with sensory axonal neuropathy.

Regarding neurophysiological aspects, the most common finding was a sensory axonal neuropathy independently from the MD subset with the exception of MNGIE that classically showed also demyelinating features. Conversely a motor involvement was less frequent, observed in only 16% of cases. Interestingly, predisposing factors seem not to influence the occurrence of polyneuropathy. In particular, diabetes was not significantly associated with a polyneuropathy, being observed in six cases with MELAS (five with neuropathy and one without) and in eight with PEO (one with neuropathy and seven without). This result is interesting considering the high prevalence of polyneuropathy in patients affected by both types 1 and 2 diabetes and could be related to the complex metabolic asset in patients affected by MDs [22].

To our knowledge, there are no studies on electrophysiological follow-up of neuropathy in MD patients. However, from a clinical point of view, analysis of the Italian registry reported a higher occurrence of polyneuropathy at follow-up in MELAS (3.2%−10.3%), PEO with a single deletion (1.3%−4.4%) and MERRF (6.8%−14.7%) patients [23]. In the subgroup of our population who underwent serial NCSs the development of a neuropathy in four patients (4/21, 19%) including two MERRF patients was observed. Instead, mean values of different NCS parameters were not significantly modified at follow-up evaluation in the other patients.

Table 2 Follow-up nerve conduction study mean values

Nerve	Baseline (21 patients)	Follow-up (21 patients)
Median		
DML (ms)	2.8 ± 0.5	2.9 ± 0.4
MCV (m/s)	57 ± 4.0	51 ± 7.3
CMAP (mV)	7.5 ± 4.3	9.5 ± 5.4
F wave (ms)	30.2 ± 1.7	28.3 ± 0.7
Tibial		
DML (ms)	4.0 ± 0.9	3.9 ± 0.6
CMAP (mV)	7.8 ± 5.3	6.6 ± 4.8
F wave (ms)	52.9 ± 5.8	54.2 ± 5.4
Radial		
SCV (m/s)	57 ± 4.0	59 ± 9.2
SNAP (μV)	8.2 ± 5.3	8.5 ± 7.2
Sural		
SCV (m/s)	53 ± 6.8	50 ± 6.5
SNAP (μV)	18.9 ± 13.4	12.5 ± 9.9

DML, distal motor latency; MCV, motor conduction velocity; CMAP, compound muscle action potential; F wave, mean F-wave latency; SCV, sensory conduction velocity; SNAP, sensory nerve action potential.

Neuropathy was generally asymptomatic. In fact only 8% of our patients reported sensory symptoms. Clinically, tendon reflexes were reduced or abolished in about half of patients (47/109, 43%), but 11 from these group, all affected by PEO, showed normal NCSs.

In contrast to the high frequency of peripheral nerve involvement, optic neuropathy was not common in this cohort of patients. In fact, although a reduction of visual acuity was present in 60% of the patients, optic atrophy was observed in only seven (one MELAS; one MERRF; one PEO; one MNGIE; two other MDs). Six of these patients also had a sensory neuropathy, which means that only 12% of 49 MD with peripheral neuropathy patients had optic neuropathy. This intriguing observation suggests that optic and peripheral nerves, although both very susceptible to energy failure, are damaged following different pathogenic mechanisms and are preferentially compromised in different subsets of mitochondrial disorders, perhaps due to the specific anatomical differences. In support of this hypothesis is the fact that most patients with Leber hereditary optic neuropathy do not have clinical or electrophysiological evidence of peripheral neuropathy [24].

Our study demonstrated that the peripheral nervous system is frequently involved in mitochondrial primary disorders when this population is systematically examined following strict clinical and electrophysiological criteria. Thus, the higher incidence of peripheral neuropathy in this series compared to previous reports may be ascribed in part to a different definition of peripheral neuropathy (clinical versus neurophysiological criteria) and to the fact that the majority of previous studies are based on retrospective database searches.

In conclusion, nerve involvement in MDs is frequent even if often mild or asymptomatic. The correct identification and characterization of peripheral neuropathy through electrophysiological studies represents another tile in the challenge of MD diagnosis.

Disclosure

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Demographic and clinical findings of patients developing sensory axonal neuropathy at follow-up nerve conduction studies.

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