Peripheral neuropathy in mitochondrial disorders

Why is peripheral neuropathy common but mild in many mitochondrial disorders, and why is it, in some cases, the predominant or only manifestation? Although this question remains largely unanswered, recent advances in cellular and molecular biology have begun to clarify the importance of mitochondrial functioning and distribution in the peripheral nerve. Mutations in proteins involved in mitochondrial dynamics (ie, fusion and fission) frequently result in a Charcot-Marie-Tooth phenotype. Peripheral neuropathies with different phenotypic presentations occur in mitochondrial diseases associated with abnormalities in mitochondrial DNA replication and maintenance, or associated with defects in mitochondrial respiratory chain complex V. Our knowledge of mitochondrial disorders is rapidly growing as new nuclear genes are identified and new phenotypes described. Early diagnosis of mitochondrial disorders, essential to provide appropriate genetic counselling, has become crucial in a few treatable conditions. Recognising and diagnosing an underlying mitochondrial defect in patients presenting with peripheral neuropathy is therefore of paramount importance.

Introduction

Peripheral nerves are highly dependent on energy metabolism, since they have long axons that are wrapped by myelin lamellae provided by Schwann cells. Thus, it is not surprising that a third of patients with mitochondrial disorders develop peripheral neuropathy.1–3 Although often mild or subclinical, peripheral neuropathy can be severe and might be the main or only feature of a mitochondrial disorder. Identification and characterisation of peripheral neuropathy can be fundamental in diagnosing mitochondrial disorders. Peripheral neuropathy often occurs in mitochondrial disorders associated with defects in mitochondrial DNA (mtDNA) maintenance and replication or defects in respiratory chain complex V. The distribution of mitochondria along peripheral axons is regulated by a continuous process of mitochondrial fusion and fission (this is termed mitochondrial dynamics and is fundamental for regulating number, shape, and transport of these organelles), and abnormalities in mitochondrial dynamics are increasingly understood to be a cause of peripheral nerve dysfunction. Additionally, nuclear genes associated with mitochondrial disorders are continuously being identified, and new phenotypes are expanding the list of atypical presentations of known mitochondrial disorders.

This Review addresses peripheral neuropathy in mitochondrial disorders, particularly when it is the key or only feature. Peripheral neuropathy as a unique or predominant manifestation of a mitochondrial disorder is rare, and is restricted to disorders of mitochondrial dynamics associated with MFN2 and GDAP1 mutations;1–4 a few mitochondrial disorders related to defects in mtDNA replication and maintenance, caused by mutations in nuclear genes such as POLG1, C100RF2, TYMP, and MPV17; or respiratory chain complex V defects associated with MTATP6 mutations leading to decreased ATP synthesis.2,5,6,8 Whereas disorders of mitochondrial dynamics usually present with a Charcot-Marie-Tooth neuropathy (CMT), disorders of mtDNA replication and maintenance and respiratory chain complex V abnormalities are associated with a range of neuropathic phenotypes (panel). Peripheral neuropathy can occur in mitochondrial disorders other than those due to disorders of mitochondrial dynamics or mtDNA replication and maintenance, but it is usually mild or subclinical.

Chronic sensorimotor axonal polyneuropathy is the pattern most often seen in cases of peripheral neuropathy associated with mitochondrial disorders.1,3,8,9,13–17 Deemyelinating neuropathy is less common,13,8,9,15,16 but is often associated with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE; related to TYMP mutations)16 and occasionally with Leber hereditary optic neuropathy,18 Leigh syndrome,19 myoclonic epilepsy and ragged-red fibres (MERRF) syndrome,20 and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome.21 Sensory ataxic neuropathy is another syndrome associated with mitochondrial disorders, particularly ataxia neuropathy spectrum related to POLG1 mutations, and neuropathy, ataxia, and retinitis pigmentosa (NARP) syndrome associated with MTATP6 mutations.1–3,8,11

In most mitochondrial disorders, peripheral neuropathy occurs in the setting of multisystem neurological impairment as a minor manifestation that is useful for diagnosis but with little effect on patient disability. A small proportion of patients develop moderate-to-severe peripheral neuropathy in the context of multisystem diseases such as MELAS and MERRF syndromes, Leigh syndrome, and Kearns-Sayre syndrome.1–3,8 In these cases, peripheral neuropathy might be the first manifestation, subsequently complicated by involvement of other neurological systems and extraneurological organs.

It is important for neurologists to know when a mitochondrial disorder might be the underlying cause of peripheral neuropathy—ie, they should know the clinical presentations, diagnostic clues, examinations to be performed, differential diagnoses, and disorders amenable to treatment. This Review aims to provide an update on peripheral neuropathy in mitochondrial disorders with a practical diagnostic approach.
Mitochondrial CMT

CMT is a heterogeneous group of hereditary neuropathies characterised by distal limb muscle wasting and weakness, with sensory loss, reduced or absent deep tendon reflexes, and foot deformities. Subdivision into demyelinating (CMT if autosomal dominant and CMT4 if autosomal recessive) and axonal forms (CMT2, which is typically dominant but can be recessive) is based on nerve conduction velocities (demyelinating if ≤38 m/s in upper limb motor nerves vs axonal if >38 m/s). Intermediate forms between CMT1 and CMT2 include X-linked CMT (CMTX1), and dominant and recessive intermediate CMT types. Pure motor forms are labelled as distal hereditary motor neuropathies. Rare subtypes include hereditary motor and sensory neuropathy type V, which indicates CMT plus corticospinal tract involvement (CMT5), and type VI, which is CMT with optic atrophy (CMT6). More than 50 genes (eg, MFN2 and GDAP1) have been associated with CMT or distal hereditary motor neuropathies and contribute to their further subclassification.2,22,23

CMT might be the presenting phenotype of disorders of mitochondrial dynamics and other mitochondrial dysfunctions, including respiratory chain complex V deficit. The main forms of mitochondrial CMT are listed in table 1. Pure autosomal dominant CMT2 of varying severity, sometimes complicated by pyramidal involvement or optic atrophy, is associated with mutations in MFN2, whereas GDAP1 mutations usually result in autosomal recessive CMT with normal or decreased nerve conduction velocities.

MFN2 and GDAP1 are involved in the fusion and fission of mitochondria (mitochondrial dynamics), processes that are fundamental in regulating mitochondrial shape, size, number, and transport along the cell (figure 1).24 Fusion is governed by dynamin-like GTPases located in the outer membrane (MFN1 and MFN2) and inner membrane (OPA1).25 MFN1 and MFN2 form homotypic and heterotypic oligomers, tethering mitochondria during fusion. OPA1 is important for inner membrane fusion and cristae shaping. GDAP1, located in the outer membrane, has a role in mitochondrial fission.24 At least three proteins involved in mitochondrial dynamics are associated with peripheral neuropathy—ie, mutations affecting MFN2 and GDAP1 can cause CMT,26,27,28 and OPA1 mutation carriers can develop neuropathy.28,29 So far, no phenotype has been associated with MFN1 mutations.

MFN2-related CMT and more complex phenotypes

MFN2 is a 19-exon gene on chromosome 1p36.22 that encodes a 757-aminoacid protein containing a GTPase domain, two transmembrane domains, and two coiled-coil regions that mediate binding with other mitofusin molecules.26 MFN2 tethers mitochondria to the endoplasmic reticulum and might have a role in calcium release and influx to mitochondria.30 MFN2 is also involved in increasing permeability of the outer membrane, oxidative phosphorylation and gradient coupling, and mitochondrial transport along neurons through the microtubule system.26,27 This is a crucial process that allows proper distribution of mitochondria in the cell, including concentration in particular regions of peripheral neurons (eg, Ranvier’s nodes and synaptic terminations).27 Although MFN2 is ubiquitously expressed, mutations in this protein have been associated only with neurological dysfunction, particularly CMT. Low levels of MFN1 in neurons, which are not sufficient to compensate the MFN2 defect, are postulated to contribute to the organ specificity of the disease.30,31

Clinical characteristics and presentation

MFN2 mutations are usually associated with autosomal dominant axonal CMT2 (CMT2A), and MFN2 is the most frequently mutated gene in CMT2 (in up to about 20% of
Most patients with CMT2A have disabling neuropathy with early onset (during childhood or adolescence), a progressive course, and motor predominance, sometimes leading to loss of ambulation and severe proximal weakness. Other cases show less severe phenotype and later onset. De-novo mutations occur with a high frequency in CMT2A. Almost 100 sequence variants are known, mainly in the lower limbs. Very rarely, nerve conduction velocities are preserved or slightly slowed, with varying reduction in amplitudes of compound muscle and sensory action potentials, mainly in the lower limbs. Very rarely, nerve conduction velocity is slowed out of proportion with the reduction in compound muscle action potential amplitude determined by axonal loss, suggesting secondary myelin abnormalities. Nerve biopsies usually show predominant chronic axonal degeneration sometimes with the presence of small onion bulbs (figure 2). Some reports described mitochondrial abnormalities with distal accumulation of abnormally shaped mitochondria with cristae alterations.

More complex phenotypes that are sometimes seen with CMT2A include the presence of hand tremor and hearing loss, which are non-specific features also observed in other CMT types. About 10–20% of patients with MFN2-related neuropathy develop optic atrophy, showing that MFN2 mutations are a molecular basis for hereditary motor and sensory neuropathy type VI (CMT6). Patients might develop subacute visual loss with subsequent good or incomplete recovery—resembling Leber hereditary optic neuropathy—or insidious and gradually worsening visual impairment. Mutations in different domains have been associated with hereditary motor and sensory neuropathy type VI, although members of the same CMT2A family might or might not develop optic neuropathy type VI (CMT6). Discrete T2 hyperintense signals have been reported in brain MRIs of patients with CMT2A, although unspecific, the occurrence of this finding in several young patients suggests an association with the disease. A few families have been reported with early-onset axonal neuropathy and homozygous or compound heterozygous MFN2 mutations (some mutations were intragenic deletions), which manifest as recessive or semidominant traits with no or few signs in heterozygous carriers. The phenotype ranged from a severely disabling neuropathy with optic neuropathy, cranial nerve, and respiratory involvement, to typical CMT2.

Table 1: Main forms of mitochondrial CMT

<table>
<thead>
<tr>
<th>Gene</th>
<th>Inheritance</th>
<th>Nerve conduction velocity</th>
<th>Neuropathology</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT2A</td>
<td>MFN2</td>
<td>Autosomal dominant</td>
<td>Normal to slightly reduced</td>
<td>Axonal changes</td>
</tr>
<tr>
<td>CMT2A</td>
<td>MFN2</td>
<td>Autosomal recessive or semidominant</td>
<td>Normal to slightly reduced</td>
<td>Axonal changes</td>
</tr>
<tr>
<td>CMT5 (HMSN type V) with pyramidal involvement</td>
<td>MFN2</td>
<td>Autosomal dominant</td>
<td>Preserved</td>
<td>Axonal changes</td>
</tr>
<tr>
<td>CMT5 (HMSN type VI) with optic atrophy</td>
<td>MFN2</td>
<td>Autosomal dominant</td>
<td>Preserved</td>
<td>Axonal changes</td>
</tr>
<tr>
<td>Autosomal dominant CMT2K</td>
<td>GDAP1</td>
<td>Autosomal dominant</td>
<td>Normal to slightly reduced</td>
<td>Axonal changes</td>
</tr>
<tr>
<td>CMT4A</td>
<td>GDAP1</td>
<td>Autosomal recessive</td>
<td>Slowed nerve conduction velocity, severely reduced</td>
<td>Mainly axonal changes, with or without secondary myelin abnormalities</td>
</tr>
<tr>
<td>Recessive intermediate CMTA</td>
<td>GDAP1</td>
<td>Autosomal recessive</td>
<td>Intermediate</td>
<td>Mainly axonal changes, with or without secondary myelin abnormalities</td>
</tr>
<tr>
<td>Autosomal recessive CMT2K</td>
<td>GDAP1</td>
<td>Autosomal recessive</td>
<td>Preserved</td>
<td>Mainly axonal changes, with or without secondary myelin abnormalities</td>
</tr>
<tr>
<td>CMT2 and dHMN</td>
<td>MTATP6</td>
<td>Matrilineal</td>
<td>Normal to slightly reduced</td>
<td>Onion bulbs in one biopsy</td>
</tr>
<tr>
<td>CMT2Q</td>
<td>DHX10</td>
<td>Autosomal dominant</td>
<td>Normal to slightly reduced</td>
<td>Not determined</td>
</tr>
<tr>
<td>CMT4X (Cowchock syndrome)</td>
<td>AIM1</td>
<td>X-linked</td>
<td>Preserved</td>
<td>Not determined</td>
</tr>
<tr>
<td>CMTX6</td>
<td>PDK3</td>
<td>X-linked</td>
<td>Varying, slightly slowed</td>
<td>Not determined</td>
</tr>
</tbody>
</table>

CMT=Charcot-Marie-Tooth neuropathy. HMSN=hereditary motor and sensory neuropathy. CMAP=compound muscle action potential. dHMN=distal hereditary motor neuropathy. *Other genes are also associated with CMT5.
Review

Figure 1: Overview of mechanisms underlying the main mitochondrial peripheral neuropathies

(A) MFN2 is located in the outer mitochondrial membrane and interacts with Miro and Milton proteins, which belong to the molecular complex that links mitochondria to kinesin (KHC) motors. (B) MFN2 participates in bringing the outer membranes of two mitochondria into close proximity. Thus, MFN2 mutations can lead to defects in mitochondrial motility along the cytoskeletal microtubular tracks, and to dysfunction in fusion of the outer mitochondrial membranes of opposing mitochondria. Similarly, mutations in OPA1, which is located in the inner mitochondrial membrane, lead to dysfunction in the fusion process of the inner mitochondrial membrane. (C) Loss-of-function mutations in GDAP1, located in the outer mitochondrial membrane, can lead to dysfunction in the mitochondrial fission process, since GDAP1 might be a positive effector of assembly of the fission mediator DRP1. Dysfunction is shown by red oblique bars. (D) Dysfunctions in the respiratory chain can be due to the following: direct mutations in mitochondrial protein-coding genes (red segment of circular mtDNA) ND1, ND4, and ND6, which encode for subunits of complex I (NADH dehydrogenase), and MTATP6, which encodes for a subunit of complex V (ATP-synthase); mutations in mitochondrial tRNA-coding genes (light blue segment) MTTL1 and MTTK, which lead to dysfunction in transcription of mitochondrial protein-coding genes; or direct mutations in the nuclear gene SURF1 (in green), which encodes an ancillary protein involved in complex IV (cytochrome c oxidase) assembly. Dysfunction in the corresponding respiratory chain complexes are shown by red, light blue, and green asterisks, respectively. Encircled numbers show the number of subunits encoded by mtDNA. (E) Dysfunctions of the respiratory chain can also occur as a result of changes in mtDNA synthesis (red oblique bar), which lead to mtDNA depletion or multiple mtDNA deletions. mtDNA synthesis might be disturbed by the following: mutations in nuclear genes encoding components of the mitochondrial replisome—ie, polymerase gamma POLG and the helicase C10ORF2 genes; loss-of-function mutations (red oblique bar) in genes involved in the synthesis of nucleotides—ie, RRMI and TYMP—which lead to nucleotide depletion (red lines show inhibition); or mutations in MPV17, a nuclear gene encoding an inner mitochondrial membrane protein of unknown function. Finally, mitochondrial peripheral neuropathies might result from changes in intermediary metabolism that eventually lead to decreased ATP synthesis. Mutations in SLC25A19 inhibit the passage of TPP from the cytosol to the mitochondrial matrix, thus leading to lactate accumulation and an increase in αKGD (an intermediate of the Krebs cycle), since TPP is an essential cofactor of PDH and αKGD (green lines show stimulation); similarly, a gain-of-function mutation (green tick mark) in PDK3 might lock PDH in an inactive state, limiting glucose oxidation and favoring a switch toward anaerobic lactate production. nDNA=nuclear DNA, mtDNA=mitochondrial DNA, NDDP=nucleoside diphosphates, dNDP=deoxynucleoside diphosphates, dCTD=deoxycytidine, dCMP=deoxyadenosine monophosphate, dCTP=deoxycytosine triphosphate. α-KG=α-ketoglutarate. α-KGD=α-ketoglutarate dehydrogenase. SCA=succinyl-CoA. TPP=thiamine pyrophosphate. PDH=pyruvate dehydrogenase.

The spectrum of MFN2-related phenotypes is rapidly broadening, and complex clinical pictures have been reported. Macrocephaly and mild diffuse signal abnormalities in cerebral white matter occurred in two patients with CMT2A. Del Bo and colleagues reported a family with CMT2A with cognitive and visual impairment and, in one case, spastic paraparesis. Boaretto and colleagues studied a family carrying a heterozygous intronic MFN2 mutation, where late-onset, rapidly progressive CMT2 was complicated by subacute, lethal, Wernicke-like encephalopathy in four individuals; MRI and autopsy showed symmetric vascular–necrotic lesions in the upper brainstem and periaqueductal gray matter.

Recently, a large family harbouring a novel Asp210Val substitution in the GTPase domain of MFN2 showed a very complex phenotype, with the following features present to a varying extent in affected individuals: optic atrophy, predominantly sensory axonal neuropathy, hearing loss, pyramidal involvement, cognitive impairment, proximal myopathy, cerebellar syndrome, cataracts, supratentorial white matter changes, and muscle
mitochondrial abnormalities (including ragged red fibres and multiple mtDNA deletions). A de-novo Asp210Tyr substitution was also reported in a girl affected by a severe multisystem disorder with psychomotor retardation, microcephaly, chorea, neuropathy, optic atrophy, hearing loss, and mtDNA depletion.

Diagnosis of CMT related to MFN2 mutations

MFN2-related neuropathy should be suspected in all cases of axonal CMT, particularly if autosomal dominant, whatever the age of onset. Sporadic axonal CMT of early onset and severe course is a typical presentation related to the frequency of de-novo mutations. The co-occurrence of optic atrophy (CMT6) strongly points to MFN2 as a causative gene, and the presence of pyramidal involvement (CMT5) is another feature that warrants MFN2 mutation screening. The frequency with which mutated MFN2 causes very complex phenotypes is still unknown.

Pathological mechanisms

How MFN2 mutations result in CMT2 or more complex phenotypes is unclear. In cellular studies, some MFN2 mutations affect mitochondrial fusion, whereas others do not. Abnormal mitochondrial transport leading to distal axonal degeneration probably explains peripheral neuropathy and pyramidal involvement in CMT2A and CMT5, with the longest axons preferentially affected. The occurrence of optic atrophy in patients with CMT6 links MFN2 dysfunction to OPA1, since mutations in this gene sometimes complicated by a multisystem neurological disorder with multiple mtDNA deletions or even depletion. Dominant optic atrophy is probably due to impaired mitochondrial transport and not to abnormal mitochondrial transport. MFN2-related optic atrophy and more complex phenotypes could be the result of changes in MFN2 functions other than mitochondrial transport—eg, mitochondrial fusion or oxidative phosphorylation coupling, as seen with OPA1 mutations. Such dysfunction might lead to altered maintenance, instability, and secondary abnormalities of mtDNA, the ultimate pathophysiological basis for complex phenotypes.

GDAP1-related CMT

GDAP1 is encoded by a six-exon gene on chromosome 8q21.11 and contains two glutathione S-transferase domains, one transmembrane domain, one hydrophobic domain, and an alpha4-alpha5 loop important for protein interaction. GDAP1 is involved in mitochondrial fission, although the mechanism is unknown. It is debated whether it is exclusively localised in axons or is also expressed in myelinating Schwann cells.

Clinical characteristics and presentation

GDAP1 mutations are usually associated with severe, early-onset, autosomal recessive CMT. Axonal (autosomal recessive CMT2K), demyelinating (CMT4A), and intermediate recessive (RI-CMT) forms have been described, leading to uncertainty about whether the primary defect is in the myelin or axon. Neuroptathy is characterised by a severe course, with onset in infancy and rapid progression to loss of distal movements, proximal weakness, and wheelchair dependence typically by age 20–30 years. Hoarseness of voice due to vocal cord palsy occurs in a high proportion of cases, and diaphragm involvement can also be observed.

Nerve conduction velocity is often preserved; however, when reduced (sometimes substantially), it is accompanied by marked decrease in compound muscle action potential amplitude, suggesting concomitant severe axonal loss. Nerve biopsy shows constant and predominant chronic axonal degeneration, with preferential loss of large myelinated fibres; demyelination features depend on the extent of axonal damage, in keeping with a primary axonal neuropathy, with secondary myelin changes ensuing with disease progression (figure 3). More than 40 mutations associated with GDAP1-related CMT have been described, with either compound heterozygosity or homozygosity. Most of these are nonsense mutations involving the glutathione S-transferase domains or the alpha4-alpha5 loop, but several frameshift, nonsense, and splicing mutations have also been reported. Recessive truncating mutations might
be associated with more severe disease, suggesting that the C-terminal portion is necessary for protein targeting to mitochondria, and related mutations lead to a complete loss of function. Missense mutations might produce a protein that is still targeted to the outer membrane but has reduced or altered function, resulting in less severe consequences.\(^5\) Ten different heterozygous *GDAP1* mutations have been reported to cause autosomal dominant CMT2K, a form of CMT with later onset and less severe phenotype than recessive forms related to *GDAP1*, slowly progressive course, and only rarely leading to severe impairment; these patients show preserved or slightly slowed nerve conduction velocity, without evidence of relevant myelin derangement.\(^5\)–\(^13\)

### Diagnosis of *GDAP1*-related CMT

Mutations in *GDAP1* frequently cause recessive CMT and should be screened for in all patients with early-onset and severe CMT, irrespective of nerve conduction velocities, and particularly if electrophysiology or nerve biopsy show prominent loss of axons. Vocal cord palsy is another feature suggesting *GDAP1*-related neuropathy. The frequency of *GDAP1* mutations in autosomal dominant CMT2 is undetermined, but might be high in regions with founder mutations (ie, Spain).\(^5\)–\(^13\) Differential diagnoses include acquired and inherited causes of severe neuropathy with onset in infancy and childhood (table 2).

### Pathological mechanisms

A few *GDAP1* mutations cause neuropathy in heterozygotes, whereas many others are associated with disease only when both alleles are mutated. Niemann and colleagues\(^6\) showed that recessive mutations behave as loss-of-function mutations and are associated with decreased mitochondrial fission, whereas dominant mutations can cause a gain of abnormal function resulting in impaired fusion (as with *MFN2* mutations), increased production of reactive oxygen species, and enhanced apoptosis. In both cases, changes in mitochondrial dynamics might lead to altered transport of mitochondria and the distal axonal degeneration typical of CMT, albeit with different degrees of severity. Decreased activity of respiratory chain complex I was reported in muscle and fibroblasts from patients with dominant *GDAP1*-associated CMT.\(^6\) Two families with CMT had combined mutations in *MFN2* and *GDAP1*.\(^6\)\(^,\)\(^5\)\(^5\) These individuals had severe neuropathy and substantial mitochondrial functional abnormalities (ie, reduced respiratory chain complex I activity and energy uncoupling in fibroblasts, and enlarged mitochondria with distorted cristae seen on nerve biopsy), because of the combined effect of the mutations on different parts of the same pathway in mitochondrial dynamics.

### MTATP6-related CMT

Maternally-inherited mutations in the mitochondrial ATP-synthase subunit 6, encoded by *MTATP6*, usually present with NARP syndrome or Leigh syndrome; rarely, isolated peripheral neuropathy was reported in association with 9185T→C or 8993T→C mutations.\(^5\)\(^6\)–\(^6\)\(^0\) Screening for the 8993T→C mutation in 96 clinically diagnosed (genetically undiagnosed) cases of CMT did not show any cases with the mutation;\(^6\)\(^1\) however, Pitcaithly and colleagues\(^6\)\(^2\) recently found the 9185T→C mutation in 1·1% of 270 patients with genetically undiagnosed CMT2.

Three families and one sporadic patient presented with a phenotype that included pure motor or predominantly motor neuropathy (CMT2 and distal hereditary motor neuropathy); associated features were learning disabilities, pyramidal involvement, sensorineural hearing loss, retinitis pigmentosa, proximal neurogenic weakness, and illness with symptoms similar to those of Leigh syndrome. In another family, CMT2 was associated with the 9176T→C mutation.\(^6\)\(^3\) Therefore, differential diagnosis of CMT2 now includes *MTATP6* mutations, particularly when there are mild associated features and transmission is compatible with matrilineal inheritance.

### Other CMT types

Recently, a large Chinese family with autosomal dominant CMT2 was shown to carry a nonsense mutation in *DHTKD1*, which is involved in mitochondrial energy production;\(^6\)\(^4\) additionally, CMTX4\(^6\)\(^5\) and CMTX6\(^6\)\(^6\) have been associated with mutations in two genes involved in mitochondrial metabolism (table 1).
Peripheral neuropathy with visual impairment

Visual loss due to optic atrophy or pigmentary retinopathy in combination with polyneuropathy is a phenotype highly suggestive of mitochondrial dysfunction, as in dominant optic atrophy plus syndrome (OPA1 mutations). Leber hereditary optic neuropathy (ND1, ND4, ND6), CMT6 (MFN2), and NARP syndrome (MTATP6). In CMT6, peripheral neuropathy precedes optic involvement and both might be prominent. In dominant optic atrophy plus syndrome, visual loss is almost always a predominant feature and peripheral neuropathy is a possible subsequent finding, often of minor importance. Leber hereditary optic neuropathy is only rarely complicated by peripheral neuropathy. Neuropathy and retinopathy are both typical of NARP syndrome and can be severely disabling.

Dominant optic atrophy plus syndrome and OPA1

OPA1 is a 690-aminoacid protein encoded by a 30-exon gene on chromosome 3q29, and is involved in mitochondrial fusion, cristae organisation, oxidative phosphorylation, and maintenance of mitochondrial membrane potential. Heterozygous mutations lead to early-onset and progressive dominant optic atrophy.1 About 20% of patients develop subsequent hearing loss and further neurological abnormalities, such as progressive external ophthalmoplegia, peripheral neuropathy, proximal myopathy, and cerebellar ataxia (dominant optic atrophy plus syndrome); this multisystem disorder is associated with missense mutations in the GTPase domain.2-25 Muscle biopsy often shows multiple mtDNA deletions and sometimes depletion, ragged red fibres, and COX-deficient fibres. Neuropathy is usually mild, sensorimotor or mostly sensory, and axonal, manifesting as reduced-to-absent deep tendon reflexes, sensory loss, varying ataxia (sensory and cerebellar), and distal muscle wasting and weakness. Pes cavus can be seen. Nerve conduction studies show preserved nerve conduction velocity but reduced compound muscle action potential amplitudes.10,17,58,59

Absence of deep tendon reflexes, distal wasting and weakness, distal sensory loss, and sensory ataxia.57-59 Electrophysiology shows chronic axonal degeneration and reduced sensory action potential amplitudes.30,37,38,39 MTATP6 mutations can manifest as a pure neuropathy. Mild-to-moderate neuropathy was the only manifestation in four individuals from three unrelated families harbouring 8993T→C or 8993T→C mutations;56,59,60 one individual had a previous diagnosis of CMT with ataxia.60 Another family carrying the 8993T→C mutation showed adult-onset, slowly progressive ataxia and polyneuropathy.67 Diagnosis is difficult when the clinical picture is incomplete. Furthermore, plasma lactic acid concentrations are not increased and muscle biopsy usually does not show mitochondrial histochemical abnormalities, since MTATP6 is involved in the final step of ATP production in energy coupling.

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Leber hereditary optic neuropathy and Kearns-Sayre syndrome

Leber hereditary optic neuropathy is associated with mutations in the mitochondrial genes ND1, ND4, and ND6, which encode respiratory chain complex I subunits, and is only very rarely complicated by severe neuropathy that can be demyelinating.30 Peripheral neuropathy can occur in Kearns-Sayre syndrome, which is due to single mtDNA macrodeletions and is characterised by pigmentary retinopathy.30

Table 2: Differential diagnoses of the main mitochondrial disorders presenting with peripheral neuropathy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Differential diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT2</td>
<td>MFN2</td>
</tr>
<tr>
<td>CMT5</td>
<td>MFN2</td>
</tr>
<tr>
<td>CMT6</td>
<td>MFN2</td>
</tr>
<tr>
<td>Recessive CMT</td>
<td>GDAP1</td>
</tr>
<tr>
<td>Dominant CMT</td>
<td>GDAP1</td>
</tr>
<tr>
<td>DOA plus</td>
<td>OPA1</td>
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</tbody>
</table>

Table 2: Differential diagnoses of the main mitochondrial disorders presenting with peripheral neuropathy
<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Pathophysiology</th>
<th>Neuropathy</th>
<th>Type</th>
<th>Nerve conduction velocities</th>
<th>Severity range</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFN2</td>
<td>Autosomal dominant much more frequent than recessive</td>
<td>CMT2A, HMSN type V, HMSN type VI</td>
<td>Mitochondrial dynamics</td>
<td>Sensory-motor axonal</td>
<td>Normal or slightly decreased</td>
<td>Mild to severe</td>
<td>Usually the only feature</td>
</tr>
<tr>
<td>GDAP2</td>
<td>Autosomal recessive more frequent than dominant</td>
<td>CMT4A, CMT2K, recessive intermediate CMT</td>
<td>Mitochondrial dynamics</td>
<td>Sensory-motor axonal (with or without secondary demyelinating changes)</td>
<td>Normal or decreased</td>
<td>Autosomal recessive is severe; autosomal dominant is mild to moderate</td>
<td>Usually the only feature</td>
</tr>
<tr>
<td>OPA1</td>
<td>Autosomal dominant</td>
<td>DOA plus</td>
<td>Mitochondrial dynamics</td>
<td>Sensory-motor axonal</td>
<td>Normal or slightly decreased</td>
<td>Subclinical to mild</td>
<td>Occurs with other features</td>
</tr>
<tr>
<td>MTATP6</td>
<td>Mitochondrial</td>
<td>NARP and MILS, CMT2-like and dHMN-like</td>
<td>Oxidative phosphorylation coupling, ATP synthesis</td>
<td>Predominantly sensory axonal; predominantly motor in CMT2-like</td>
<td>Normal or slightly decreased</td>
<td>Moderate to severe</td>
<td>Can be the sole or presenting feature</td>
</tr>
<tr>
<td>POLG1</td>
<td>Autosomal recessive more frequent than dominant</td>
<td>Alpers-Huttenlocher syndrome, SANDO, IRMAS, MNGIE-like</td>
<td>mtDNA replication and maintenance</td>
<td>Sensory axonal; hypomyelinating when early onset</td>
<td>Normal or slightly decreased</td>
<td>Moderate to severe</td>
<td>Can be the sole or presenting feature</td>
</tr>
<tr>
<td>C10ORF2</td>
<td>Autosomal dominant or recessive</td>
<td>SANDO, IOSCA, progressive external ophthalmoplegia</td>
<td>mtDNA replication and maintenance</td>
<td>Usually sensory axonal</td>
<td>Normal or slightly decreased</td>
<td>Mild or subclinical, rarely severe</td>
<td>Prominent</td>
</tr>
<tr>
<td>TYMP</td>
<td>Autosomal recessive</td>
<td>MNGIE</td>
<td>mtDNA replication and maintenance</td>
<td>Sensory-motor demyelinating</td>
<td>Decreased</td>
<td>Subclinical to severe</td>
<td>Can be the presenting feature</td>
</tr>
<tr>
<td>RR2M2</td>
<td>Autosomal recessive</td>
<td>MNGIE-like</td>
<td>mtDNA replication and maintenance</td>
<td>Sensory-motor demyelinating</td>
<td>Decreased</td>
<td>Only one case reported</td>
<td>Occurs with other features</td>
</tr>
<tr>
<td>MPV17</td>
<td>Autosomal recessive</td>
<td>Navajo neurohepatopathy</td>
<td>mtDNA maintenance</td>
<td>Sensory-motor axonal or demyelinating</td>
<td>Normal or slightly decreased</td>
<td>Severe</td>
<td>Substantial feature</td>
</tr>
<tr>
<td>MTTL1 3243A→G (and other mitochondrial mutations)</td>
<td>Mitochondrial</td>
<td>MELAS</td>
<td>Respiratory chain disorder</td>
<td>Sensory-motor predominantly axonal</td>
<td>Normal or decreased</td>
<td>Varies, usually mild</td>
<td>Frequently occurs with other findings, rarely severe</td>
</tr>
<tr>
<td>MTTK 8344A→G (and other mitochondrial mutations)</td>
<td>Mitochondrial</td>
<td>MERRF</td>
<td>Respiratory chain disorder</td>
<td>Sensory-motor usually mixed</td>
<td>Varies, often decreased</td>
<td>Varies, usually mild, only rarely severe</td>
<td>Frequent but mild and with other findings</td>
</tr>
<tr>
<td>mtDNA ND1, ND4, ND6</td>
<td>Mitochondrial</td>
<td>LHON</td>
<td>Respiratory chain disorder</td>
<td>Sensory-motor and predominantly demyelinating</td>
<td>Slightly decreased</td>
<td>Varies, rarely severe</td>
<td>Infrequent</td>
</tr>
<tr>
<td>mtDNA large deletion</td>
<td>Mitochondrial</td>
<td>Kearns-Sayre syndrome</td>
<td>Respiratory chain disorder</td>
<td>Sensory-motor axonal</td>
<td>Normal</td>
<td>Varies, usually mild</td>
<td>Infrequent</td>
</tr>
<tr>
<td>SURF1, PDHA1</td>
<td>Autosomal recessive</td>
<td>Leigh syndrome</td>
<td>Respiratory chain disorder</td>
<td>Sensory-motor demyelinating</td>
<td>Decreased</td>
<td>Varies, rarely severe</td>
<td>Infrequent</td>
</tr>
<tr>
<td>SLC25A19</td>
<td>Autosomal recessive</td>
<td>Bilateral striatal necrosis</td>
<td>mtDNA replication and maintenance</td>
<td>Motor or sensory-motor axonal</td>
<td>Normal</td>
<td>Moderate to severe</td>
<td>One report</td>
</tr>
</tbody>
</table>

Table 3: Genetic causes and characteristics of mitochondrial neuropathies in mitochondrial disorders with peripheral nerve involvement

**Sensory ataxic neuropathies**

Sensory ataxia as an isolated manifestation or, more commonly, in the setting of a more widespread neurological disorder is another possible presentation of a mitochondrial disorder caused by respiratory chain complex V deficit, as in NARP syndrome, or by defects in mtDNA replication and maintenance, as with mutations in POLG1 and C10ORF2.

**POLG1 and C10ORF2 mutations**

Mutations in the nuclear gene POLG1, which encodes the catalytic subunit of mitochondrial gamma-polymerase involved in mtDNA replication, lead to complex phenotypes that often include peripheral neuropathy, particularly when onset occurs in adolescents or adults. Ataxia neuropathy spectrum encompasses a range of phenotypes associated with...
*POLG1* mutations, including cerebellar and sensory ataxia. Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO), by definition characterised by peripheral neuropathy, is usually inherited as an autosomal recessive trait with juvenile-to-adult onset. The neuropathy is mainly sensory, with ataxia, loss of proprioception and vibration sense, touch and pinprick sensory changes (to a lesser extent), and a varying degree of distal muscle wasting and weakness; pes cavus is sometimes reported. Nerve conduction studies show decreased or absent sensory action potentials and sometimes reported. Nerve conduction studies show decreased or absent sensory action potentials and sometimes reported. Nerve conduction studies show decreased or absent sensory action potentials and sometimes reported. Nerve conduction studies show decreased or absent sensory action potentials and sometimes reported.

**MNGIE and TYMP mutations**

MNGIE is a rare autosomal recessive disease associated with mutations in *TYMP*, which encodes thymidine phosphorylase, a cytosolic transferase that catalyses the breakdown of thymidine into thymine and deoxyribose-1-phosphate and is involved in mitochondrial nucleotide pool homeostasis. MNGIE combines mtDNA depletion syndrome (MTDPS1) with accumulation of multiple deletions and point mutations. Clinical diagnosis is based on the presence of severe gastrointestinal dysmotility (with pseudo-obstructions), cachexia, ptosis and ophthalmoparesis, demyelinating peripheral neuropathy, and diffuse (though generally asymptomatic) leukencephalopathy. Age at onset ranges between 0.5–52 years, although the disease often starts during childhood or adolescence. Progression varies, sometimes with rapid course and often proving lethal between ages 20 and 40 years; however, some patients live into their sixties. Diagnosis is based on demonstrating substantial decrease in thymidine phosphorylase activity in leucocytes or platelets, increase in thymidine and deoxyuridine urinary excretion and plasma concentrations, and definitively by *TYMP* mutations.

Muscle biopsy shows ragged red fibres and COX-deficient fibres, and multiple mtDNA deletions or depletion in the most severe cases; however, in some cases, no mitochondrial abnormalities are found.

Neuropathy can also occur as the result of mutations in another gene involved in mtDNA replication—ie, *C10ORF2*, which encodes twinkle helicase. Affected individuals present with dominant or recessive phenotypes that can include progressive external ophthalmoplegia, myopathy, dysarthria, dysphagia, parkinsonism, hearing loss, seizures, dementia, diabetes, and liver damage. Neuropathy is often mild or subclinical. In a few patients it was prominent, with predominant motor involvement in one family, and sensory ataxic presentation in other instances, including a family with SANDO associated with a heterozygous mutation. Multiple mtDNA deletions, ragged red fibres, and COX-deficient fibres are often present and might help to guide diagnosis.

Sensory ataxic neuropathy caused by degeneration of dorsal root ganglia is a key feature of infantile onset spinocerebellar ataxia with sensory neuropathy (IOSCA), a rare autosomal recessive spinocerebellar ataxia of the Finnish population that is associated with *C10ORF2* mutations. IOSCA is an mtDNA depletion syndrome (hepatocerebral form of MTDPS7), with mtDNA depletion affecting the brain and liver.

**Peripheral neuropathy and gastrointestinal manifestations**

Peripheral neuropathy has been associated with disrupted gastrointestinal motility in MNGIE and with liver disease in Navajo neurohepatopathy; both disorders also show brain white matter abnormalities on MRI.

Peripheral neuropathy was the onset manifestation in 12% of patients with MNGIE in a large series, and eight of 102 patients were initially misdiagnosed as having chronic inflammatory demyelinating polyradiculoneuropathy or CMT. Other investigators have also reported a presentation similar to chronic inflammatory demyelinating polyradiculoneuropathy in patients with MNGIE. Conduction blocks and symptom fluctuations occur and, together with frequent CSF protein increase, contribute to misdiagnosis. In another five cases, the clinical presentation mimicked CMT, with initial (predominantly) sensorimotor demyelinating neuropathy with pes cavus.

The symptoms of MNGIE are an example of a mitochondrial syndrome caused by an mtDNA replication dysfunction that results from an imbalance in the mitochondrial nucleotide pool. Indeed, there is an overload of thymidine and deoxythymidine triphosphate...
caused by loss-of-function mutations in \textit{TYMP}. However, mtDNA replication dysfunction is probably due to both thymidine and deoxythymidine triphosphate overload and secondary depletion of deoxycytidine triphosphate. It has been proposed that thymidine and deoxythymidine triphosphate overload might inhibit mitochondrial thymidine kinase 2 thus leading to limited mitochondrial deoxycytidine triphosphate availability—thymidine kinase 2 is a deoxyribonucleoside kinase that catalyses phosphorylation of intramitochondrial pyrimidine nucleosides, including deoxycytidine, to monophosphate nucleotides (figure 1).

\textbf{MNGIE-like disorders}

MNGIE-like phenotypes have occurred in association with recessive \textit{POLG} or \textit{RRM2B} mutations; leukoencephalopathy was either absent (\textit{POLG}) or patchy (\textit{RRM2B}), unlike the diffuse white matter changes of \textit{TYP}-related MNGIE. Neuropathy was demyelinating in a patient carrying \textit{RRM2B} mutations, whereas patients with \textit{POLG1} mutations had mainly sensorimotor axonal or sensory ataxic axonal neuropathy.

\textbf{Navajo neurohepatopathy and MPV17}

Peripheral neuropathy is a main feature of Navajo neurohepatopathy, a rare mtDNA depletion syndrome (MTDPS6) associated with a homozygous recessive mutation (Arg50Trp) in \textit{MPV17}.\textsuperscript{14,49} The disease begins in infancy or childhood, and is characterised by liver disease, corneal ulcers, leukoencephalopathy, and recurrent metabolic acidosis. Affected patients develop severe sensorimotor neuropathy with progressive muscle wasting and weakness, loss of deep tendon reflexes, marked sensory deficit leading to acromutilations, and corneal anaesthesia. Nerve conduction velocities are slowed. Nerve biopsy shows myelinated fibre depletion and degenerative changes in unmyelinated fibres.\textsuperscript{19} This unusual neuropathic phenotype seems to be limited to the Navajo population of the southwestern USA.\textsuperscript{14,49} A 21-year-old Pakistani man and a 65-year-old man of European origin carrying other \textit{MPV17} recessive mutations developed axonal sensorimotor neuropathy in the context of a multisystem disorder, with multiple mtDNA deletions seen in muscle biopsy.\textsuperscript{19,49}

\textbf{Peripheral neuropathy in other mitochondrial disorders}

Peripheral neuropathy occurs in many other syndromic and non-syndromic mitochondrial disorders; however, it only rarely manifests as a predominant feature. Peripheral nerve involvement is common but often subclinical in MELAS syndrome, where it is frequently axonal and predominantly sensory.\textsuperscript{1,4,8,9} A Guillain-Barré-syndrome-like neuropathy was reported in one patient with MELAS syndrome.\textsuperscript{11} Although common, neuropathy is rarely relevant in MERRF syndrome, particularly in patients with multiple lipomas, and is usually demyelinating and sensorimotor.\textsuperscript{12} Occasionally prominent neuropathy has been reported in Leber hereditary optic neuropathy,\textsuperscript{23} Kearns-Sayre syndrome,\textsuperscript{9} and Leigh syndrome,\textsuperscript{9} and in primary coenzyme Q10 deficiency due to \textit{ADCK3} mutations, which is usually characterised by cerebellar ataxia sometimes associated with mental retardation, seizures, and peripheral neuropathy.\textsuperscript{23}

Moderate-to-severe progressive motor or sensorimotor axonal neuropathy with foot deformities was reported in four siblings affected by bilateral striatal necrosis with recurrent episodes of flaccid paralysis and encephalopathy. CSF lactate concentration was elevated but respiratory chain complex activity was normal. Homozygosity mapping led to the identification of a homoyzogous mutation in \textit{SLC25A19}, encoding the mitochondrial thiamine pyrophosphate transporter.\textsuperscript{19}

\textbf{Diagnosis of peripheral neuropathies associated with respiratory chain dysfunction}

Peripheral neuropathy in individuals with disrupted mitochondrial dynamics typically presents as CMT, and \textit{MTATP6} mutations should be considered in patients with CMT2 or distal hereditary motor neuropathy, particularly when there are mild associated features and inheritance might be matrilineal. Not all patients presenting with pes cavus and sensorimotor neuropathy have CMT, thus MNGIE (when peripheral neuropathy is demyelinating) or \textit{POLG1}-related disorders (when peripheral neuropathy is axonal) should be considered. Similarly, MNGIE should not be misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy. Sensory ataxia is a possible presentation in mitochondrial disorders and might suggest \textit{POLG1}-related neuropathy or NARP syndrome. The differential diagnosis includes Friedreich’s ataxia and vitamin E deficiency (table 2).

In patients presenting with peripheral neuropathy, a mitochondrial disorder should be suspected when there are other features, which are sometimes subtle, suggesting mitochondrial dysfunction—eg, ptosis, ophthalmoplegia, gastrointestinal dismotility, cerebellar ataxia, decreased visual acuity, pigmentary retinopathy, hearing loss, and white matter changes on MRI. Lactic acid assay and muscle biopsy to detect ragged red fibres, COX-deficient fibres, respiratory chain complex deficiency, and mtDNA depletion and deletions can aid diagnosis. Histochemical and biochemical evidence of a mitochondrial disorder are sometimes absent; therefore, physicians must rely on clinical suspicion and look for mutations in common mtDNA hotspots, such as \textit{MTATP6}, or in nuclear genes, such as \textit{POLG1} and \textit{OPA1} (table 4).

\textbf{Treatment}

Effective therapy for mitochondrial diseases is very limited, as noted in a recent Cochrane review.\textsuperscript{24} Current treatment for mitochondrial diseases is largely supportive and mainly includes vitamins and cofactors supplements—ie, antioxidants (coenzyme Q10,
idebenone, vitamin C, vitamin E), respiratory chain cofactors (thiamine, riboflavin, coenzyme Q10), and compounds that correct secondary biochemical deficiencies (carnitine, creatine) or improve lactic acidosis (dichloroacetate).195

Specific treatment is available for only a few diseases. Supplementation can successfully treat primary coenzyme Q10 deficiency and often improve secondary deficiencies.96 Platelet infusion transiently restores circulating thymidine phosphorylase and reduces plasma thymidine and deoxyuridine concentrations in patients with MNGIE.96 Allogeneic haemopoietic stem-cell transplantation can potentially halt MNGIE progression, although morbidity and mortality rates are high if general conditions are compromised, thus timely diagnosis is necessary.97 Enzyme replacement therapy (encapsulated in red cell ghosts) might be suitable for patients whose general condition precludes allogeneic haemopoietic stem cell transplantation.98 Early and prolonged treatment with idebenone in patients with Leber hereditary optic neuropathy improved the frequency of visual recovery and possibly changed the natural history,99 a small pilot trial of idebenone for dominant optic atrophy reported some improvement in visual function.100 Gene therapies (gene insertion or shifting, and nuclear transfer) are being tested in cellular and animal models of hereditary optic neuropathies and other mitochondrial disorders.101,102 An open-label trial with EPI-743 (a third-generation quinone molecule) recently showed possible halting of disease progression in Leigh syndrome and Leber hereditary optic neuropathy.103 L-Arginine seems to be a promising treatment for stroke-like episodes in MELAS syndrome.104 Some studies have reported increased muscle strength with aerobic exercise and resistance training in adults with peripheral neuropathy, although such treatments attenuated the decline in ankle dorsiflexion strength.105 There are no data on possible treatments for mitochondrial diseases in which neuropathy represents a major manifestation, such as NARP syndrome, SANDO, and dominant optic atrophy; however, it is common practice to offer treatment with coenzyme Q10, often combined with thiamine, riboflavin, and vitamin C, mostly to children with a proven diagnosis of a mitochondrial disorder.

Conclusion and future directions

We reviewed mitochondrial disorders where peripheral neuropathy is a key feature. Peripheral neuropathy as a unique or predominant finding is frequent in disorders affecting mitochondrial dynamics, where abnormal mitochondrial transport along axons seems to be the main pathological mechanism and neuropathy presents as CMT. Novel MFN2-related phenotypes are emerging and resemble the complex clinical scenarios of dominant optic atrophy plus syndrome and other mitochondrial disorders. Indeed, peripheral neuropathy might be the only or main presenting feature of some disorders of mtDNA replication and maintenance, and of specific disorders of the respiratory chain, including ATP-synthase defects. The number of genes and phenotypes associated with mitochondrial disorders is rapidly expanding. The availability of novel genetic techniques, including whole

<table>
<thead>
<tr>
<th>Associated genes and diagnoses</th>
<th>Axonal CMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MFN2 and CMT2A; GDAP1 and autosomal dominant or autosomal recessive CMT2K; MTATP6 and CMT2 or NARP; POLG1 and SANDO</td>
</tr>
<tr>
<td>Demyelinating CMT and neuropathy</td>
<td>GDAP1 and autosomal recessive CMT4A, or recessive intermediate CMT, TYMP (and RRMs28) and MNGIE, MPV17 and Navajo neurohepatopathy, MERRF</td>
</tr>
<tr>
<td>Neuropathy plus visual loss</td>
<td>MFN2 and CMT6, DPA1 and DOA plus; ND1, ND4, ND6 and LHON</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>MTATP6 and NARP; Kearns-Sayre syndrome</td>
</tr>
<tr>
<td>Neuropathy plus pyramidal involvement</td>
<td>MFN2 and CMT5</td>
</tr>
<tr>
<td>Pure motor neuropathy with or without other neurological features</td>
<td>MTATP6</td>
</tr>
<tr>
<td>Sensory ataxic neuropathy</td>
<td>POLG1, C10orf2 and SANDO, ataxia neuropathy spectrum; C10orf2 and IOSCA, MTATP6 and NARP</td>
</tr>
<tr>
<td>Predominantly sensory neuropathy with atrophy</td>
<td>MPV17 and Navajo neurohepatopathy</td>
</tr>
<tr>
<td>Axonal neuropathy with CNS involvement</td>
<td>MELAS, MERRF, Kearns-Sayre syndrome, Leigh syndrome, MILS</td>
</tr>
<tr>
<td>Neuropathy with gastrointestinal manifestations</td>
<td>TYMP (RRM28, POLG1) and MNGIE, MPV17 and Navajo neurohepatopathy and related disorders</td>
</tr>
</tbody>
</table>

Table 4: Associated genes and diagnoses according to neuropathic presentation

CMT=Charcot-Marie-Tooth neuropathy, dHMN=distal hereditary motor neuropathy, NARP=neuropathy, ataxia, and retinitis pigmentosa. SANDO=sensory ataxia, neuropathy, dysarthria, and ophthalmoplegia. MNGIE=mitochondrial neurogastrointestinal encephalopathy. MERRF=mysterious encephalopathy with ragged-red fibres. DOA plus-autosomal dominant optic atrophy plus syndrome. LHON=Leber hereditary optic neuropathy. IOSCA=infantile-onset spinocerebellar ataxia. MELAS=mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes. MILS=maternally inherited Leigh syndrome.
Search strategy and selection criteria

References for this Review were identified by searches of PubMed from Jan 1, 1989, until May 31, 2013, with the terms “peripheral neuropathy and mitochondria/mitochondrial disease”, “Charcot-Marie-Tooth”, “DNA”, “HMSN-V”, “HMSN VI”, “I0SCA”, “Leber optic atrophy”, “Leigh syndrome”, “LHON”, “MILS”, “NARP”, “SANDO”, “C10ORF2”, “GDAP1”, “MFN2”, “MPV17”, “OPA1”, “PEO1”, “POLG1”, “SURF1”, “TYMP”, “Twinkle”, “mitochondrial disease and therapy”. Articles were also identified through searches of the authors’ own files. Only reports published in English or French were reviewed. Selection criteria were newness, ease of access, importance, originality, quality, relevance to the scope of this Review, and opportunities for further references.

Exome sequencing, will allow detection of other diseases characterised by mitochondrial dysfunction and prominent or exclusive peripheral neuropathy. Growing knowledge of the pathological mechanisms is leading to development of treatment options for some mitochondrial disorders. Thus, the list of treatable disorders will increase, as will the need for early diagnosis. Finally, preimplantation genetic testing raises hopes that prevention of human mtDNA disease transmission is feasible; however, successful translation to clinical practice requires further research to test safety and efficacy, and remains controversial for ethical concerns.

Contributors

DP designed and wrote the Review, did the literature search, and designed the tables. GP helped to write the Review and do the literature search, and collaborated on designing and preparing the tables. IM wrote part of the Review, helped to do the literature search, and collaborated on designing figures and tables. ES helped to write the Review and collaborated on designing and preparing figures and tables. MZ gave intellectual contribution and reviewed the manuscript.

Conflicts of interest

DP received research funding from ACMT-Rete and Pfizer Italia, and travel expenses from Kedrion SpA and Pfizer Italia. GP received travel expenses from Pfizer Italia. ES received travel expenses from Actelion Pharmaceuticals. All other authors reported no conflicts of interest.

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