Diagnosis, natural history, and management of Charcot–Marie–Tooth disease

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Charcot–Marie–Tooth disease is the most common inherited neuromuscular disorder. There have been substantial advances in elucidating the molecular bases of this genetically heterogeneous neuropathy and, in most cases, molecular diagnosis is now possible. The diagnostic approach requires careful assessment of clinical presentation and mode of inheritance, nerve-conduction studies, and DNA testing, and current research is focused on assessing natural history and finding effective treatments. Disease course is variable because of genotypic and phenotypic heterogeneity. At present, there is no drug therapy for Charcot–Marie–Tooth disease, and rehabilitation therapy and surgical procedures for skeletal deformities are the only available treatments, although best practice has not been defined. Animal models are proving useful for the identification of therapeutic targets and approaches. Progesterone antagonists, neurotrophic factors, ascorbic acid, and curcumin have shown promising results in experimental models, and ascorbic acid is being studied in large randomised controlled trials.

Introduction

More than 120 years have elapsed since the first description of Charcot–Marie–Tooth disease (CMT), which is named after the three scientists who first reported it. Since the identification of this disease, many pioneering neurologists have contributed to its classification and clinical definition.[1] The substantial amount of knowledge of the pathophysiology of CMT gained over the past few years has dramatically changed the clinical approach to the disease and is opening up a new era in which possible treatments can be devised and tested.

CMT is the most common hereditary neuromuscular disorder, with a prevalence estimated at up to 40 individuals in every 100 000, equating to 200 000 cases in the European Union.[2] As for many other diseases, patients with CMT often have questions about diagnosis, prognosis, and treatment. For most patients with CMT, questions regarding diagnosis can be answered, as about 70% of patients can now receive a precise molecular genetic diagnosis. At least 25 genes have so far been identified to be associated with CMT, and the diagnostic process has become complicated and must follow a logical sequence of investigations. Unfortunately, there are still few answers to the questions about prognosis and treatment. In this Review, we focus on the diagnosis, natural history, and management of CMT, and discuss directions for future research.

For more on **genes associated with CMT** see http://www.molgen.ua.ac.be/CMTMutations/Mutations/Default.cfm

Clinical presentation

CMT is a genetically heterogeneous disorder with a common clinical phenotype (figures 1 and 2, tables 1 and 2).[1,3–10,11] As motor and sensory peripheral nerves are affected, this disease is also known as hereditary motor and sensory neuropathy (HMSN). When, in more rare instances, only motor nerves are involved, the term distal hereditary motor neuro(no)pathy (dHMN) is used.

CMT is caused by mutations in genes that encode proteins with different locations, including compact and non-compact myelin, Schwann cells, and axons, and that are involved in very different functions, ranging from compaction and maintenance of myelin to cytoskeleton formation, axonal transport, and mitochondrial metabolism (table 3).[5,7,12] Whatever the metabolic or structural defect that primarily affects the myelin or the axon, the final common pathway is represented by an axonal degenerative process that, in most cases, mainly involves the largest and longest fibres.[3,12,13]

The secondary axonal degenerative process explains the typical CMT phenotype, with distal predominance of limb-muscle wasting, weakness, and sensory loss, as well as the disto-proximal progression over time.[1,3–6] Motor symptoms start from the feet, which develop high arches, hammer toes, and intrinsic muscle weakness and wasting; subsequently, the disease gradually affects the leg and then the lower third of the thigh, producing the typical distal atrophy of the lower limbs. At this stage, the hands are also affected and then the forearms. Sensory loss follows the same pathway, affecting mostly feet and hands, commonly with decreased sensation of vibration, touch, and pain; sometimes proprioceptive sensory loss can cause sensory ataxia. Deep-tendon reflexes are reduced or absent following the same distal to proximal gradient. Skeletal deformities, which commonly involve the feet, might also include scoliosis.

The disease onset usually occurs in the first two decades of life and subsequently shows a slow progression over decades. Symptoms and signs indicative of CMT include: pes cavus (or pes planus, often later progressing to cavus deformity); hammer toes; difficulty in running; twisting of the ankle and tripping; difficulty in walking; foot drop; steppage gait; wasting, weakness, and sensory loss of distal segments of lower and then upper limbs; difficulties in hand manipulation; and reduced or absent deep-tendon reflexes.[1,3–7] Other common symptoms and signs are hand tremors, muscle cramps (particularly of the foot and leg), cold feet, foot callosities, and acrocyanosis. Positive sensory symptoms such as paraesthesias are

rare, but pain is common, particularly in the feet, lower limbs, and lumbar spine. Onset can sometimes occur so early that it causes hypotonia (floppy baby syndrome), delayed motor development, and toe walking, whereas in other cases, the onset can occur late in life.

The presence of other affected family members is often a clue to diagnosis. All mendelian inheritance modes are described for CMT: this disease is more commonly transmitted as an autosomal-dominant trait; X-linked transmission is not uncommon; and autosomal-recessive inheritance is generally uncommon, except in countries that have a high rate of consanguineous marriages.[1,5]

Classification

On the basis of nerve-conduction studies and nerve pathology, CMT is subdivided into two main groups: 1) a demyelinating form (CMT1 if autosomal dominant, CMT4 if autosomal recessive), characterised by slowed nerve-conduction velocities (<38 m/s in upper-limb motor nerves) and prominent myelin abnormalities (ie, onion-bulb formations) at nerve biopsy; and 2) an axonal form (CMT2), with preserved or only mildly slowed nerve-conduction velocities (>38 m/s) and pathological evidence of chronic axonal degeneration and regeneration.[1,3–7] This distinction is clinically useful, because mode of inheritance and nerve-conduction studies rapidly enable proper diagnosis. However, knowledge of exceptions to this clear division is increasing and intermediate forms between CMT1 and CMT2 are recognised: the main one is X-linked CMT (CMTX1); moreover, rare dominant-intermediate (DI) CMT types have been recognised and some patients with mutations in genes associated with CMT1 or CMT2 can present with mixed features.[3,5] A third smaller group is represented by the pure motor forms (dHMN), characterised by sparing of sensory nerves on clinical, electrophysiological, and pathological examinations. The CMT phenotype is sometimes complicated by pyramidal involvement in HMSN type V (CMT5) and optic atrophy in HMSN VI (CMT6).[3,5] CMT3 (HMSN III) is the term sometimes used to indicate Déjèrine-Sottas neuropathy, which was once used to describe severe early-onset hereditary neuropathy with motor delay, very low nerve-conduction velocities, increased concentrations of proteins in the cerebrospinal fluid, nerve hypertrophy, and severe dysmyelination at nerve biopsy; today, Déjèrine-Sottas neuropathy is considered the most severe form of demyelinating CMT.[1,3,4]

Further subdivision of these CMT types is based mainly on causative genes and assigned loci (table 2).[3–7] In most cases, CMT1 is associated with a 1·4-Mb duplication on chromosome 17p11·2–p12—a region that includes the *peripheral myelin protein 22* (*PMP22*) gene.[14,15] CMT1A is the most common CMT type, accounting for 40–50% of all cases, and is caused by overexpression of PMP22, which has a gene-dosage effect. Much less commonly, CMT1 is caused by *PMP22* point mutations (CMT1A; 1% of CMT1 cases) or by point mutations in *myelin protein zero* (*MPZ*; CMT1B; 3–5% of cases).[7,16–19]

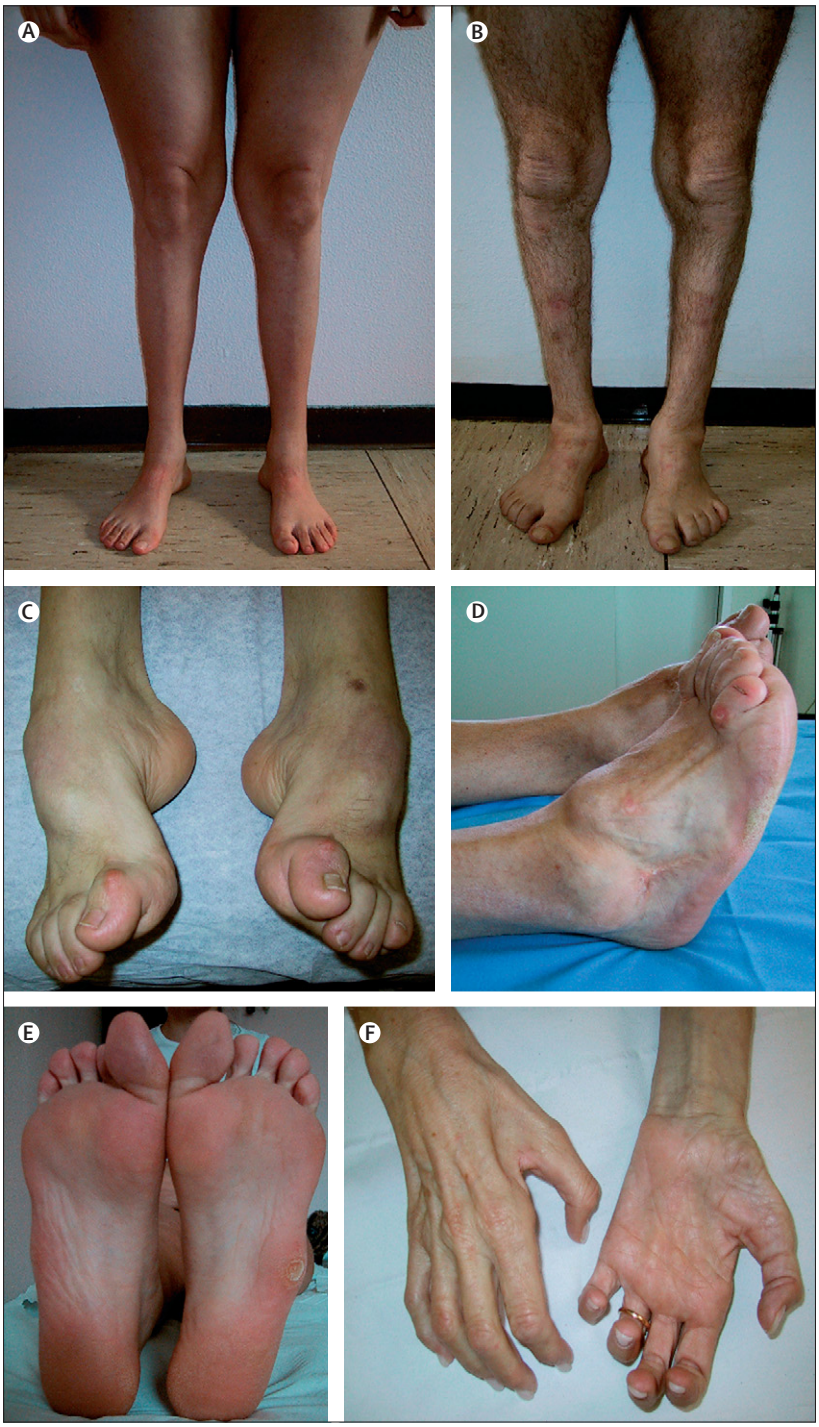

Figure 1: **Patients with Charcot–Marie–Tooth disease**
(A–B) Muscle wasting of the legs and the lower third of the thigh. (C–E) Foot deformities of different severities, with high arches, hammer toes, and callosities. (F) Severe atrophy of intrinsic hand muscles (main en griffe, claw hand).

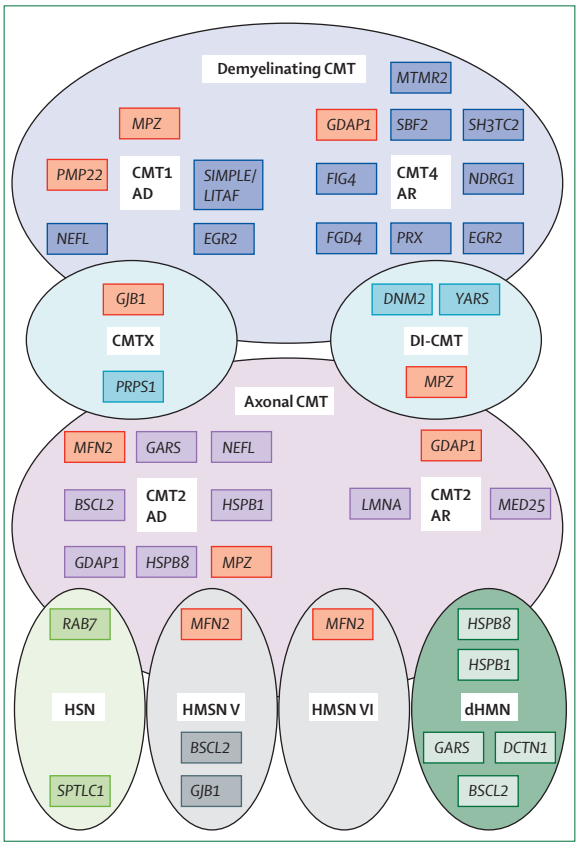

Figure 2: **Different forms of Charcot–Marie–Tooth disease and associated genes**

There are areas of overlap between different types of CMT. Red shading indicates the most commonly involved genes. Adapted from Pareyson,[11] with permission from Lippincott Williams & Wilkins. AD=autosomal dominant. AR=autosomal recessive. *BSCL2*=Berardinelli-Seip congenital lipodystrophy type 2. CMT=Charcot–Marie–Tooth disease. CMTX=X-linked CMT. *DCTN1*=dynactin. dHMN=distal hereditary motor neuropathy. DI=dominant intermediate. *DNM2*=dynamin 2. *EGR2*=early-growth-response 2. *FGD4*=FGD1-related F-actin binding protein. *FIG4*=FIG4 homologue of *Saccharomyces cerevisiae*. *GARS*=glycil-tRNA synthetase. *GDAP1*=ganglioside-induced differentiation-associated protein 1. *GJB1*=gap junction B1. HMSN=hereditary motor and sensory neuropathy. HSN=hereditary sensory neuropathy. *HSPB1*=heat shock 27-kDa protein 1. *HSPB8*=heat shock 22-kDa protein 8. *LMNA*=lamin A/C nuclear envelope protein. *MED25*=mediator of RNA polymerase II transcription, subunit 25. *MFN2*=mitofusin 2. *MPZ*=myelin protein zero. *MTMR2*=myotubularin-related protein 2. *NDRG1*=N-myc downstream-regulated gene 1. *NEFL*=neurofilament light chain. *PMP22*=peripheral myelin protein 22. *PRPS1*=phosphoribosylpyrophosphate synthetase 1. *PRX*=periaxin. *RAB7*=small GTPase late endosomal protein RAB7. *SBF2*=set-binding factor 2. *SH3TC2*=SH3 domain and tetratricopeptide repeat domain 2. *SIMPLE/LITAF*=small integral membrane protein of lysosome/late endosome; lipopolysaccharide-induced tumour necrosis factor. *SPTLC1*=serine palmitoyltransferase long chain subunit 1. *YARS*=tyrosyl-tRNA synthetase.

CMTX1 is the second most common type of CMT (about 10% of all patients) and is associated with mutations in the *gap-junction B1* (*GJB1*) gene, which encodes connexin-32.

CMT2 has a highly heterogeneous genotype and there is no prevalent gene involved; the gene most often mutated is *mitofusin 2* (*MFN2;* up to 20% of CMT2 cases), followed by *MPZ* (5%), and then by *neurofilament light chain* (*NEFL*).[5,7,11,17–20] Autosomal-recessive forms are more severe than the dominant forms, have early onset, and can be either axonal (AR-CMT2) or demyelinating (CMT4). In both cases, the gene that encodes ganglioside-induced differentiation-associated protein-1 (*GDAP1*) is the most frequently mutated gene in AR-CMT2 and CMT4.[21,22] dHMNs are also very heterogeneous and are classified in accordance with inheritance mode and mutated gene.

PMP22, *MPZ*, *GJB1*, *MFN2*, and *GDAP1* are therefore the most important genes for diagnostic purposes, but there is a long list of genes that, although rarely mutated, have been associated with the different forms of CMT and dHMN. Some of these genes have been reported in single families (tables 1 and 2).[5]

Diagnostic approach

The diagnostic approach to the definition of the CMT subtype proceeds in accordance with the following steps: definition of the clinical phenotype, identification of inheritance pattern, electrophysiological examination, molecular analyses, and, for selected cases, nerve biopsy.[1,3,4,6,7,19]

Clinical phenotype

The so-called typical phenotype, as described earlier, can be associated with most CMT types, although is more frequently found in CMT1A associated with the *PMP22* duplication.[23] Many clinical findings can be useful in guiding molecular investigations (table 2), including age of onset, disease severity, presence of uncommon associated features such as involvement of cranial nerves, vocal cord palsy, pupillary abnormalities, glaucoma, optic atrophy, pyramidal involvement, predominant upper-limb involvement, and prominent sensory abnormalities.[1,3–6,19]

Mode of inheritance

Autosomal-dominant inheritance is the most common pattern, seen in CMT1 and most CMT2 and dHMN cases. It is important to bear in mind that CMTX1, transmitted as an X-linked dominant trait, is characterised by no male-to-male transmission and causes more severe disease in hemizygous men than heterozygous women. Autosomal-recessive transmission is indicative of CMT4 (demyelinating), AR-CMT2 (axonal), and AR-dHMN (pure motor) forms of CMT. Sporadic cases are not uncommon and are a diagnostic challenge. De novo mutations occur, particularly for the CMT1A duplication and *MFN2* mutations associated with CMT2A, but also for other CMT types.[7,19,20,24] Family history can be falsely unremarkable, because of the extent of variable expression and oligosymptomatic patients who elude diagnosis. Therefore, clinical and, in many cases, electrophysiological examination of first-degree relatives is warranted to ascertain the inheritance pattern.

Electrophysiological examination

Nerve-conduction studies should be done to assess the presence, degree, and pattern of nerve-conduction slowing. Diffuse and homogeneous nerve-conduction velocity slowing (<38 m/s in upper-limb motor nerves) indicates demyelinating CMT (CMT1 and CMT4), whereas normal or only mildly slowed nerve-conduction velocities (>38 m/s in median or ulnar motor nerves) with reduced

	Inheritance	Phenotype	Mutated genes
CMT1	AD	Usually typical clinical phenotype Uniform and diffuse motor and sensory NCV slowing (<38 m/s in upper-limb motor nerves) Nerve biopsy: onion bulbs or other myelin abnormalities; secondary axonal degeneration	*PMP22* duplication *MPZ* *PMP22* point mutations *EGR2* *SIMPLE/LITAF* *NEFL*
CMT2	AD or AR	Usually typical phenotype Normal or slightly reduced NCV (>38 m/s in upper-limb motor nerves) and decreased amplitudes Nerve biopsy: chronic axonal neuropathy usually without any specific diagnostic features	*MFN2* *MPZ* *NEFL* *HSPB1 (HSP27)* *HSPB8 (HSP22)* *RAB7* *GARS* *GDAP1* (AD/AR) *LMNA* (AD/AR) *MED25* (AR)
CMTX	X-linked	CMTX1: men more affected than women; motor NCV commonly intermediate in men (30–45 m/s) and in the lower range of CMT2 in women; NCV slowing can be non-uniform and asymmetrical; nerve biopsy: axonal loss and some demyelination, few onion bulbs; occasional CNS involvement Other CMTX types: only males affected	*GJB1/Cx32* *PRPS1*
Intermediate CMT	AD	Mild to moderate severity NCVs intermediate between CMT1 and CMT2 (25–45 m/s) Pathological features of both CMT1 and CMT2	*MPZ* *DNM2* *YARS* *(NEFL)*
CMT3 (HMSN III; DSN-CHN)	AD or AR	Early onset; more severe than CMT1 Very slow NCVs Nerve biopsy: dysmyelination, onion bulbs CHN: congenital onset, extreme severity, hypomyelination	*PMP22* *MPZ* *EGR2* *PRX*
CMT4	AR	Earlier onset and more severe course than CMT1 Vocal cord paresis, sensorineural deafness, and facial and diaphragmatic weakness can occur Slowed NCV (<38 m/s)	*GDAP1* *MTMR2* *SBF2/MTMR13* *KIAA1985/SH3TC2* *NDRG1* *EGR2* *PRX* *FGD4* *FIG4*
dHMN	AD or AR X-linked	Pure motor involvement on clinical, electrophysiological, and morphological basis Preserved or mildly slowed NCVs; >38 m/s in upper-limb motor nerves; normal sensory action potential Sural nerve biopsy normal or near-normal	*HSBP1* *HSBP8* *GARS* *BSCL2* *DCTN1* *(IGHMBP2)*
CMT5 with pyramidal features (HMSN V)	AD	Pyramidal involvement ranges from increased deep-tendon reflexes with Babinski sign to spastic paraplegia Electrophysiology: usually axonal loss; reduced sensory action potential amplitudes	*MFN2* *BSCL2* *GJB1*
CMT6 with optic atrophy (HMSN VI)	AD	Early onset Severe visual loss with optic atrophy NCVs preserved or mildly slowed	*MFN2*

AD=autosomal dominant. AR=autosomal recessive. *BSCL2*=Berardinelli-Seip congenital lipodystrophy type 2. CHN=congenital hypomyelinating neuropathy. CMT=Charcot–Marie–Tooth disease. CMTX=X-linked CMT. *DCTN1*=dynactin. dHMN=distal hereditary motor neuronopathy. *DNM2*=dynamin 2. *EGR2*=early-growth-response 2. DSN=Déjèrine-Sottas neuropathy. *FGD4*=FGD1-related F-actin binding protein. *FIG4*=FIG4 homologue of *Saccharomyces cerevisiae*. *GARS*=glycil-tRNA synthetase. *GDAP1*=ganglioside-induced differentiation-associated protein 1. *GJB1/Cx32*=gap junction B1/connexin 32. HMSN=hereditary motor and sensory neuropathy. *HSPB1/HSP27*=heat shock 27-kDa protein 1. *HSPB8/HSP22*=heat shock 22-kDa protein 8. *IGHMBP2*=immunoglobulin mu binding protein 2. *KIAA1985/SH3TC2*=SH3 domain and tetratricopeptide repeat domain 2. *LMNA*=lamin A/C nuclear envelope protein. *MED25*=mediator of RNA polymerase II transcription, subunit 25. *MFN2*=mitofusin 2. *MPZ*=myelin protein zero. *MTMR2*=myotubularin-related protein 2. NCV=nerve-conduction velocity. *NDRG1*=N-myc downstream-regulated gene 1. *NEFL*=neurofilament light chain. *PMP22*=peripheral myelin protein 22. *PRPS1*=phosphoribosylpyrophosphate synthetase 1. *PRX*=periaxin. *RAB7*=small GTPase late endosomal protein RAB7. *SBF2/MTMR13*=set-binding factor 2/myotubularin-related protein 13. *SIMPLE/LITAF*=small integral membrane protein of lysosome/late endosome; lipopolysaccharide-induced tumour necrosis factor-alpha factor. *YARS*=tyrosyl-tRNA synthetase.

Table 1: **CMT subtypes and their associated phenotypes and mutated genes**

compound muscle and sensory action potential amplitudes is typical of CMT2. The main diagnostic problems occur in patients with intermediate nerve-conduction velocities (25–45 m/s in upper limbs): such velocities should alert clinicians to the possibility of CMTX1 in men, or DI-CMT (a much less common form) in both men and women. CMTX1 presents in a particular way: conduction slowing is greater in men than women, with a wide range of nerve-conduction velocities (between 18 and 60 m/s); in men, these velocities are commonly intermediate between those for CMT1 and CMT2, whereas they are in the lower range of the velocities for CMT2 in women.[3,25,26] Moreover, nerve-conduction abnormalities in CMTX1 can be asymmetric and non-homogeneous along nerve trunks, and there can be excessive temporal dispersion and even conduction blocks. Rarely, conduction block can occur in CMT1B with mutations in *MPZ*.[27] If nerve-conduction velocities are normal or near-normal and sensory action potentials are preserved, the most likely diagnosis is a dHMN form of CMT.

Molecular tests

The previous steps should enable proper diagnosis of the CMT type and determination of the subsequent genetic tests needed, the order of which parallels the relative frequency of mutations for each gene in that CMT subtype.[4,7,19] There are now so many genes associated with CMT (tables 2 and 3, figure 2) that a single laboratory

	OMIM number	Locus	Associated gene	Frequency and specific clinical phenotype
CMT1 (dominant, demyelinating)				
CMT1A	118220	17p11·2–p12	*PMP22* duplication or point mutations	60–90% of CMT1; typical phenotype; variable severity, usually mild to moderate; more severe in cases of point mutations than duplication
CMT1B	118200	1q22	*MPZ*	≤5% of CMT1; onset commonly in the first decade; variable degree of progression with severe disability in some patients at 20–40 years of age
CMT1C	601098	16p13·3–p12	*SIMPLE/LITAF*	<1% of CMT; typical CMT1 (one patient diagnosed with CMT2)
CMT1D	607678	10q21·1–q22·1	*EGR2*	<1% of CMT; severe phenotype; cranial nerve involvement
CMT1F	607734	8p21	*NEFL*	Rare; early onset; tremor and cerebellar ataxia in some patients
CMTX (X-linked dominant)				
CMTX1	302800	Xq13·1	*GJB1/Cx32*	7–12% of all CMT; moderate to severe in men, usually mild in women; subclinical CNS involvement (mild clinical signs, abnormalities of central components of multimodal-evoked potentials; cerebral white-matter abnormalities on MRI); rarely, there is severe transient CNS dysfunction
CMTX (X-linked recessive)				
CMTX2	302801	Xp22·2	Unknown	Rare; infantile onset; mental retardation
CMTX3	302802	Xq26·3–q27·1	Unknown	Three families reported: early onset; pain and paresthesias; spastic paraparesis in one family; women unaffected
CMTX4	310490	Xq24–q26·1	Unknown	Severe neuropathy, mental retardation, and deafness (Cowchock syndrome)
CMTX5	311070	Xq22·3	*PRPS1*	Two families reported: early onset; mild to moderate neuropathy; optic atrophy and deafness
CMT (dominant intermediate)				
DI-CMTA	606483	10q24·1–q25·1	Unknown	One Italian family reported: moderate severity; slow progression
DI-CMTB	606482	19p12–p13·2	*DNM2*	Rare; neutropenia can occur
DI-CMTC	608323	1p34–p35	*YARS*	Rare; moderate severity; slow progression
DI-CMTD	607791	1q22	*MPZ*	Variable severity
CMT2 (dominant, axonal)				
CMT2A	609260	1p36·2	*MFN2*	Up to 20% of CMT2; can be severe; optic atrophy, hearing loss, pyramidal involvement, and cerebral white-matter abnormalities can be observed
CMT2B	600882	3q21	*RAB7*	Rare; prominent sensory loss, hyperkeratosis and severe foot ulcerations
CMT2C	606071	12q23–q24	Unknown	Rare; early onset; involvement of vocal cords, diaphragm, and intercostal, and proximal muscles
CMT2D	601472	7p15	*GARS*	Upper-limb predominance
CMT2E	607684	8p21	*NEFL*	<2% of CMT; variable severity; occasionally intermittent ataxia
CMT2F	606595	7q	*HSPB1* (*HSP27*)	Three families reported: slowly progressive course
CMT2G	608591	12q12–13·3	Unknown	One large family reported: slowly progressive walking difficulties
CMT2I/J	607677/607736	1q22	*MPZ*	5% of AD-CMT2; late onset; can be severe; pupillary abnormalities, hearing loss, pain, and dysphagia are possible
CMT2L	608673	12q24	*HSPB8* (*HSP22*)	One Chinese family described
CMT2K	607831	8q13–q21·1	*GDAP1*	Rare; phenotype milder than in the recessive forms; slowly progressive course
Other	..	1q21·2	*LMNA*	Associated with myopathy and cardiomyopathy[8]
CMT2 (recessive, axonal)				
CMT2B1	605588	1q21·2	*LMNA*	Rapid course, progressing to proximal involvement
CMT2B2	605589	19q13·3	*MED25*	One large family described: typical CMT2 phenotype[9]
CMT2H/K	607731/607831	8q13–q21·1	*GDAP1*	Very early onset (<2 years); severe course; frequent vocal cord paresis

(Continues on next page)

	OMIM number	Locus	Associated gene	Frequency and specific clinical phenotype
(Continued from previous page)				
CMT4 (recessive, demyelinating)				
CMT4A	214400	8q13–q21·1	*GDAP1*	Very early onset (<2 years); severe course; frequent vocal cord paresis
CMT4B1	601382	11q22	*MTMR2*	Early onset and severe course; diffuse myelin outfolfdings at nerve biopsy; cranial nerve involvement
CMT4B2	604563	11p15	*SBF2*/*MTMR13*	Similar to CMT4B1; diffuse myelin outfolfdings at nerve biopsy; early-onset glaucoma
CMT4C	601596	5q32	*KIAA1985* (*SH3TC2*)	Early onset; frequent relevant scoliosis
CMT4D	601455	8q24·3	*NDRG1*	HMNS-L; people with Gypsy ancestry; severe course; hearing loss; possible CNS involvement
CMT4E	605253	10q21·1–10q21·2	*EGR2*	One family with severe phenotype (CHN)
CMT4F	145900	19q13·1–q13·2	*PRX*	Early onset; variable course (DSN/CMT)
CMT4G	605285	10q23·2	Unknown	HMNS-R; people with Gypsy ancestry; severe distal muscle weakness
CMT4H	609311	12p11·21–q13·11	*FGD4*	Very early onset (<2 years); slow progression; scoliosis; myelin outfolding at nerve biopsy
CMT4J	611228	6q21	*FIG4*	Asymmetric, distal and proximal weakness; severe motor neuronopathy and demyelinating sensorimotor neuropathy
dHMN (dominant)				
dHMN I	182960	7q34–q36	Unknown	Early onset (2–20 years); pronounced weakness and wasting
dHMN II	158590 608634	12q24·3 7q11·21	*HSPB8* (*HSP22*) *HSPB1* (*HSP27*)	Later onset (childhood to adulthood)
dHMN V (HMN5A)	600794	7p15	*GARS*	Onset in adolescence; upper-limb predominance (as in CMT2D)
dHMN V (HMN5B)	600794	11q13	*BSCL2*	Upper-limb predominance; phenotype variable, can include spastic paraplegia with distal upper-limb atrophy (Silver syndrome, *SPG17* [OMIM number 270685]), pure spastic paraplegia, and CMT2
dHMN VII A	158580	2q14	Unknown	Onset in first or second decade of life; unilateral or bilateral vocal cord paralysis; atrophy can start from the hands
dHMN VII B	607641	2p13	*DCTN1*	Early adulthood onset; bilateral vocal cord palsy causing respiratory difficulty; progressive facial and limb wasting and weakness
dHMN (recessive)				
dHMN III	607088	11q13·3	Unknown	Onset from infancy to young adulthood; slow progression, possible late diaphragmatic involvement
dHMN IV	607088	11q13	Unknown	More severe than dHMN III
dHMN VI (SMARD1)	604320	11q13·2–q13·4	*IGHMBP2*	Onset: congenital to ≤2 months; intrauterine growth retardation, low birth weight and failure to thrive; hypotonia; diaphragmatic paralysis, severe respiratory distress; death or respiratory failure at <3 months
dHMN-Jerash	605726	9p21·1–p12	Unknown	Childhood onset; pyramidal features
Other	..	7q11·21	*HSPB1* (*HSP27*)	One family:[10] typical dHMN
Recurrent focal neuropathies (autosomal dominant)				
HNPP	162500	17p11·2–12	*PMP22* deletion or nonsense mutations	Frequent; transient painless recurrent focal mononeuropathies and brachial plexopathies caused by compression or without apparent precipitating cause; can have CMT-like phenotype; conduction slowing or blocks at entrapment sites in nerve-conduction studies, and generalised neuropathy; nerve biopsy: tomacula
HNA	162100	17q25	*SEPT9*	Episodes of pain followed by weakness and atrophy, usually involving the brachial plexuses

AD=autosomal dominant. *BSCL2*=Berardinelli-Seip congenital lipodystrophy type 2. CHN=congenital hypomyelinating neuropathy. CMT=Charcot–Marie–Tooth disease. *DCTN1*=dynactin. dHMN=distal hereditary motor neuronopathy. DI=dominant intermediate. *DNM2*=dynamin 2. DSN=Déjèrine-Sottas neuropathy. EGR2=early-growth-response 2. *FGD4*=FGD1-related F-actin binding protein. *FIG4*=FIG4 homologue of *Saccharomyces cerevisiae*. *GARS*=glycil-tRNA synthetase. *GDAP1*=ganglioside-induced differentiation-associated protein 1. *GJB1*/*Cx32*=gap junction B1/connexin 32. HMNS-L=hereditary motor and sensory neuropathy–Lom type. HMNS-R=hereditary motor and sensory neuropathy–Russe type. HNA=hereditary neuralgic amyotrophy. HNPP=hereditary neuropathy with liability to pressure palsies. *HSPB1*/*HSP27*=heat shock 27-kDa protein 1. *HSPB8*/*HSP22*=heat shock 22-kDa protein 8. *IGHMBP2*=immunoglobulin mu binding protein 2. *KIAA1985*/*SH3TC2*=SH3 domain and tetratricopeptide repeat domain 2. *LMNA*=lamin A/C nuclear envelope protein. *MED25*=mediator of RNA polymerase II transcription, subunit 25. *MFN2*=mitofusin 2. *MPZ*=myelin protein zero. *MTMR2*=myotubularin-related protein 2. *NDRG1*=N-myc downstream-regulated gene 1. *NEFL*=neurofilament light chain. *PMP22*=peripheral myelin protein 22. *PRPS1*=phosphoribosylpyrophosphate synthetase 1. *PRX*=periaxin. *RAB7*=small GTPase late endosomal protein RAB7. *SBF2*/*MTMR13*=set-binding factor 2/myotubularin-related protein 13. *SEPT9*=septin 9. *SIMPLE*/*LITAF*=small integral membrane protein of lysosome/late endosome; lipopolysaccharide-induced tumour necrosis factor-alpha factor. *SMARD1*=spinal muscular atrophy with respiratory distress 1. *YARS*=tyrosyl-tRNA synthetase.

***Table 2*: CMT subtypes and their associated genes, frequency, and specific features**

cannot afford to undertake all the investigations. Therefore, requests for DNA testing need to take this limitation into account. In autosomal-dominant or sporadic CMT with electrophysiological evidence of demyelination (CMT1), the CMT1A duplication should first be investigated. If absent, a diagnosis of CMTX1 needs to be considered, and (if there is no male-to-male transmission) presence of mutations in *GJB1* determined; if CMTX1 is ruled out, searches must be carried out for point mutations in *MPZ* and *PMP22*, and, if possible, also in the genes that encode small integral membrane protein of lysosome/late endosome (*SIMPLE*; also known as lipopolysaccharide-induced tumour necrosis factor [*LITAF*]), early growth response 2 (*EGR2*), and neurofilament light chain (*NEFL*), in this order. If CMT2 is diagnosed, molecular tests should be directed towards *MFN2* and *MPZ*. CMTX1 must always be borne in mind, particularly for women, and, if ruled out, other genes

	Phenotype	Location and function of gene product
PMP22	CMT1A, DSN, (CHN, HNPP)	Compact myelin protein; myelination, cell growth, differentiation
MPZ/P0	CMT1B, CMT2I/J, DI-CMTD, DSN, CHN	Compact myelin protein; adhesion role
SIMPLE/LITAF	CMT1C	Schwann-cell cytoplasm; stimulator of monocytes and macrophages; causes secretion of tumor necrosis factor-α and other inflammatory mediators; might play a part in protein-degradation pathways
EGR2	CMT1D, CMT4E, DSN, CHN	Schwann cells; transcription factor; activates transcription of several myelin-associated genes; plays a part in peripheral nervous system myelin development and maintenance
NEFL	CMT1F, CMT2E	Cytoskeleton; neurofilament organisation; axonal transport
GJB1/Cx32	CMTX1	Schwann cells, oligodendrocytes; gap-junction-forming protein in non-compact myelin
PRPS1	CMTX5	Ubiquitously expressed in human tissues, including cochlea; mediates biochemical step in purine metabolism and nucleotide biosynthesis; mutation causes reduced enzyme activity
DNM2	DI-CMTB	Family of large GTPases; part of cellular fusion–fission of cellular membrane apparatus
YARS	DI-CMTC	Ubiquitous expression, including brain and spinal cord; concentrated in granular structures in growth cones, branch points and distal neuritis; aminoacil tRNA synthetase, catalyses aminoacylation of $tRNA^{tyr}$ with tyrosine
MFN2	CMT2A, CMT5, CMT6	Mitochondrial outer membrane and endoplasmic reticulum; fusion of mitochondria and endoplasmic reticulum–mitochondria interactions
RAB7	CMT2B	Late endosomes; family of RAS-related GTP-binding proteins; regulator of vesicular transport and membrane trafficking; might have a role in linking vesicles and target membranes to the cytoskeleton
GARS	CMT2D, dHMN V	Ubiquitous expression; aminoacyl tRNA synthetases; protein synthesis
HSPB1 (HSP27)	CMT2F, dHMN	Member of the small heat shock protein family; regulation and maintenance of cytoskeleton; interacts with intermediate filament proteins
HSPB8 (HSP22)	CMT2L, dHMN II	High expression in motor and sensory neurons of spinal cord; member of the small heat shock protein family; interacts with heat shock binding protein 1 ; mutated protein promotes formation of intracellular aggregates
GDAP1	CMT2H/K, AR-CMT2, CMT4A,	Expressed in neurons (brain and spinal cord) and Schwann cells; localised in mitochondria; function might be associated with the maintenance of the mitochondrial network
LMNA	CMT2B1	Intermediate filament; structural protein of the nuclear lamina network; gene transcription
MED25	CMT2B2	Subunit of the human activator-recruited cofactor, a family of large transcriptional coactivator complexes related to the yeast mediator; exact physiological function in transcriptional regulation remains obscure
MTMR2	CMT4B1	High levels in neurons, myelinating and non-myelinating Schwann cells; belongs to the myotubularin family; dephosphorylates phosphatidylinositol 3-phosphate and phosphatidylinositol 3,5-bisphosphate
SBF2/MTMR13	CMT4B2	Belongs to the myotubularin family; phosphatase, involved in phosphoinositides metabolism; possibly associated with control of myelination
KIAA1985 (SH3TC2)	CMT4C	Neural tissues, including peripheral nerve; possible role in assembly of protein complexes
NDRG1	CMT4D	Ubiquitous expression, high levels in Schwann cells; possible functions are growth arrest and cell differentiation, and signalling protein shuttling between cytoplasm and nucleus
PRX	CMT4F, DSN	Membrane protein of Schwann cells; interaction between plasma membrane, proteins, and cytoskeleton; maintenance of peripheral nerve myelin

(Continues on next page)

associated with CMT2 should be tested, starting with *NEFL*.

When sensory symptoms are predominant with acral ulcers, genes that encode RAS-associated GTP-binding protein (*RAB7*) and serine palmitoyltransferase long chain subunit 1 (*SPTLC1*) are possibly involved. Patients with intermediate nerve-conduction velocities should be investigated for *GJB1* (CMTX1), and subsequently for genes that might present with intermediate CMT, such as *MPZ*, *NEFL*, dynamin 2 (*DNM2*), and tyrosyl-tRNA synthetase (*YARS*).

In autosomal-recessive cases, *GDAP1* should be the first gene to be investigated, both in patients with axonal and demyelinating forms; subsequent tests need to be carefully weighted depending on ethnic background (mutations in the gene that encodes N-myc downstream-regulated 1, *NDRG1,* are present only in people with Gypsy ancestry), nerve biopsy findings, and overall clinical presentation. Genes associated with dHMN that can be tested are those that encode Bernardinelli-Seip congenital lipodystrophy 2 (*BSCL2*), glycyl tRNA synthetase (*GARS*), small heat shock 22 kDA protein (*HSPB1*), and small heat shock 27 kDA protein (*HSPB8*); all these genes might also be involved in development of CMT2, and *BSCL2* and *GARS* usually cause predominant upper-limb involvement in both CMT2 and dHMN. The presence of pyramidal involvement (HMSN V/CMT5) should prompt investigation for *GJB1*, *MFN2*, and *BSCL2* mutations. Optic atrophy in HMSN VI (CMT6) is highly suggestive of *MFN2* mutations.[3–7]

Neuropathology

Since molecular tests have been available, nerve biopsy has become unnecessary in most cases, although this test can be useful in selected cases (ie, sporadic cases for differential diagnosis or in familial cases when the main genetic investigations are negative and nerve biopsy might give relevant information). For example, peculiar myelin abnormalities can orient diagnosis: myelin uncompaction and small tomacula can be found in association with *MPZ* mutations, and abundant myelin outfoldings are typical of CMT4 associated with mutations in myotubularin-related protein 2 and 13 (*MTMR2* and *MTMR13* [also known as set-binding factor 2; *SBF2*]), and frabin (FGD1-related F-actin binding protein; *FGD*4) genes. All three genes (and FIG4 homologue [*FIG4*, associated with another type of CMT4) are involved in the metabolism of phosphoinositides.[28] Giant axons have been reported in cases of *NEFL* mutations. Basal lamina onion bulbs, formed by Schwann cell basal membrane with no or little cytoplasm, are thought to be highly typical of CMT4C associated with mutations in *SH3TC2* (SH3 domain and tetratricopeptide repeat domain 2).[22,29]

Differential diagnosis

The first differential diagnosis to be made is between the different CMT types.[4,11,30] There is substantial overlap

(figure 2) between CMT1, CMT2, and the intermediate forms, and between CMT2 and dHMN. Four genes can cause both CMT2 and dHMN, leading to a predominant motor neuronopathy and no (dHMN) or mild (CMT2) sensory neuronopathy. Moreover, CMT2 can overlap with some of the hereditary sensory neuropathies:[5,11] CMT2B is characterised by severe sensory loss with acral ulcers and amputations similar to hereditary sensory neuropathy 1, which, in turn, might not be a pure sensory neuropathy but can cause distal motor involvement with pes cavus. CMT also needs to be differentiated from other hereditary neuropathies, from acquired neuropathies, distal myopathies, motor neuron diseases, hereditary ataxias, mitochondrial disorders, hereditary spastic paraplegias, and leucodystrophies (table 4).[7,19,30]

Natural history and prognosis

In typical cases, symptom onset occurs in the first or second decade of life and the disease subsequently has a slowly progressive course. However, age of onset, disease course, rate of progression, and overall severity vary depending on the CMT form, causative gene, and type of mutation. Moreover, substantial phenotypic variability occurs even within the same CMT type.

CMT1A

CMT1A caused by duplication of *PMP22* is the best characterised form of CMT, with several patient series reported[13,31–39] and followed up.[31,40–45] CMT1A usually shows the typical phenotype that is relatively benign compared with other subtypes and almost all patients remain ambulatory throughout their life. However, this form of the disease is characterised by a widely varying disease severity. Some patients have delayed motor milestones and severe skeletal deformities (including scoliosis), and develop considerable proximal weakness, require walking aids, or can, in rare cases, become chairbound.[23,33–36,46] By contrast, other patients with CMT1A have a normal or near-normal life, are almost or completely asymptomatic, or are unaware of being affected. Such substantial disease variability can also occur within the same family; monozygotic twins with different levels of disease severity have been reported.[47] Research is now focused on genetic and environmental modifier factors that can affect disease severity. The pathogenic mechanism in CMT1A is attributed to an excess gene copy number of *PMP22*, leading to protein overexpression,[23] and factors that modify the expression levels of PMP22 might potentially be effective for treatment.

Symptoms usually appear during childhood or adolescence; the first signs are pes cavus or planus, lower-limb areflexia, and wasting and weakness of intrinsic foot muscles and, later, of peroneal and anterior tibialis muscles.[39,43] In many cases, subtle hand involvement is present from the early stages;[48] afterwards, impairment and disability slowly progress.[31,41,43–45] Whether the progression rate is constant or associated with age is not clear. Dyck and co-workers[31] reported possible slower progression during adolescence, whereas Shy and co-workers[45] provided data that suggested slightly faster progression in older patients. Electrophysiological abnormalities are detectable from infancy compared with controls, starting with prolongation of distal motor latencies in the first months of life, and later followed by clear abnormalities in nerve-conduction velocities. These velocities are slower than normal from the age of 2 years, but do not substantially change after childhood and do not correlate with disease severity.[31,40–42,49,50] Abnormalities in amplitudes of compound muscle action potential occur early and slowly progress thereafter.[13,43,49,51] Clinical impairment and disability correlate with secondary axonal loss, as shown by decreased amplitude of compound muscle action potential and changes in estimation of motor unit numbers.[13,36,51]

Other CMT types

Knowledge of the natural history and prognosis of other CMT types is less well established.[52] Point mutations in *PMP22* are usually associated with severe CMT1 or Déjèrine-Sottas neuropathy.[23] Mutations in *MPZ* give rise to two very different phenotypes. Most mutations produce early-onset and commonly severe dysmyelinating or demyelinating CMT1B (or CMT3/Déjèrine-Sottas neuropathy); other mutations are associated with axonal CMT2, which has late onset but often has a severe disease course, with some patients becoming chairbound.[12,53]

	Phenotype	Location and function of gene product
(Continued from previous page)		
FGD4	CMT4H	Cytoplasm; binds along sides of actin fibres; family of Rho GDP/GTP nucleotide exchange factors; alters Schwann cell shape: induces formation of filopodia and lamellipodia; possible disease mechanism: impaired Rho GTPase signalling
FIG4	CMT4J	Vacuolar membrane localisation; phosphatase, involved in phosphoinositides content and vesicular trafficking
BSCL2	dHMN V, Silver syndrome, CMT2	Seipin, membrane protein of the endoplasmic reticulum, widely expressed in the CNS; involved in RNA transport and glycosylation
DCTN1	dHMN VIIB	Mediates transport along microtubules in peripheral nerves; role in prevention of neurodegeneration
IGHMBP2	dHMN VI (SMARD1)	Widespread tissue distribution; RNA processing

AR=autosomal recessive. *BSCL2*=Berardinelli-Seip congenital lipodystrophy type 2. CHN=congenital hypomyelinating neuropathy. CMT=Charcot–Marie–Tooth disease. *DCTN1*=dynactin. dHMN=distal hereditary motor neuronopathy. DI=dominant intermediate. *DNM2*=dynamin 2. DSN=Déjèrine-Sottas neuropathy. *EGR2*=early-growth-response 2. *FGD4*=FGD1-related F-actin binding protein. *FIG4*=FIG4 homologue of *Saccharomyces cerevisiae*. *GARS*=glycil-tRNA synthetase. *GDAP1*=ganglioside-induced differentiation-associated protein 1. *GJB1/Cx32*=gap junction B1/connexin 32. *HNPP*=hereditary neuropathy with liability to pressure palsies. *HSPB1/HSP27*=heat shock 27-kDa protein 1. *HSPB8/HSP22*=heat shock 22-kDa protein 8. *IGHMBP2*=immunoglobulin mu binding protein 2. *KIAA1985/SH3TC2*=SH3 domain and tetratricopeptide repeat domain 2. *LMNA*=lamin A/C nuclear envelope protein. *MED25*=mediator of RNA polymerase II transcription, subunit 25. *MFN2*=mitofusin 2. *MPZ*=myelin protein zero. *MTMR2*=myotubularin-related protein 2. *NDRG1*=N-myc downstream-regulated gene 1. *NEFL*=neurofilament light chain. *PMP22*=peripheral myelin protein 22. *PRPS1*=phosphoribosylpyrophosphate synthetase 1. *PRX*=periaxin. *RAB7*=small GTPase late endosomal protein RAB7. *SBF2/MTMR13*=set-binding factor 2/myotubularin-related protein 13. *SIMPLE/LITAF*=small integral membrane protein of lysosome/late endosome; lipopolysaccharide-induced tumour necrosis factor-alpha factor. SMARD1=spinal muscular atrophy with respiratory distress 1. *YARS*=tyrosyl-tRNA synthetase.

Table 3: **Mutated genes, associated phenotypes, and mutated protein locations and functions in CMT neuropathies**

Mutations in *MFN2* cause CMT2A, which, depending on mutation type, can start early in life and have a rapid progression or can have a late onset and mild course; some mutation carriers are even asymptomatic.[20,54,55] CMTX1 usually manifests in the first or second decade of life in men, with an inevitably progressive course and considerable impairment later in life. Women who are heterozygous carriers for CMTX1 can be completely asymptomatic or show mild clinical and electrophysiological evidence of CMT; however, rare cases of severe CMT have been reported and attributed to skewed X-chromosome inactivation.[3,56,57] Autosomal-recessive forms of CMT (axonal AR-CMT2 and demyelinating CMT4) are usually more severe than the dominant forms, with early onset and a more severe course.[3,21,22] Patients with mutations in *GDAP1* have loss of foot and hand movements, develop proximal weakness, and commonly become chairbound by the second or third decade of life.[58] Different levels of disease severity in patients carrying the same mutation, other than CMT1A duplication, in CMT-related genes have also been reported (eg, in *PMP22*, *MPZ*, *MFN2*, and *EGR2*).[53,59–61]

Comorbidity also has a role in severity of CMT. Concomitant diabetes, vincristine treatment, and superimposition of chronic or acute inflammatory demyelinating polyradiculoneuropathy can result in a more severe disease course or sudden worsening.[30,62–64] Rare instances of co-occurrence of mutations in two different CMT-related genes in the same patient have led to more severe disease.[65]

Natural history studies are important in the design of clinical trials, and efforts are now devoted to developing suitable, reproducible, and change-sensitive outcome measures for CMT.[66–71]

	Differential diagnoses	Useful examinations and criteria
Dysimmune and other acquired neuropathies		
Dysmyelinating or demyelinating CMT (CMT1, CMTX, CMT4, DSN, intermediate forms)	Chronic inflammatory demyelinating polyradiculoneuropathy Anti-MAG neuropathy Paraproteinemic neuropathy	Clinical distribution and course NCS Examination of the cerebrospinal fluid Anti-ganglioside antibodies Anti-MAG antibodies Search for monoclonal gammopathy
dHMN (HNPP)	Motor neuropathy with multifocal conduction blocks	Clinical course, response to therapy EMG, NCS Anti-GM1 antibodies
CMT2	Toxic, metabolic, and nutritional neuropathies	Clinical data Haematological assessment
Other hereditary neuropathies		
Demyelinating CMT and CMT2	HNPP	NCS (entrapments) DNA test (*PMP22* deletion or nonsense mutations) Nerve biopsy
CMT2	Hereditary amyloidosis	Course, sensory and autonomic involvement DNA test: transthyretin gene (*TTR*) Biopsy (amyloid deposition in different tissues)
CMT2, CMT5	Giant axonal neuropathy	Curly hair, CNS involvement DNA test: gigaxonin gene (*GAN*) Nerve biopsy
CMT1, CMT4	Refsum's disease	Phytanic acid levels DNA tests: phytanoyl-CoA hydroxylase (PHYH), peroxisome biogenesis factor 7 (PEX7)
Other neuromuscular disorders		
dHMN	Distal myopathies	Creatine kinase concentrations, EMG, muscle biopsy, DNA tests
dHMN	Lower motor neuron disorders (spinal muscle atrophy and so on)	EMG
Other genetic disorders with CNS involvement		
CMT5	Spastic paraplegias	Clinical picture DNA tests
Demyelinating CMT, CMT2, CMT5	Krabbe's leucodystrophy, metachromatic leucodystrophy	Brain MRI, enzyme assays
CMT2, CMT5	Hereditary ataxias	Brain and cervical cord MRI DNA tests Haematological assessment
Demyelinating CMT, CMT2, CMT5, CMT6	Mitochondrial encephalomyopathies (*MNGIE*, *POLG1* mutations)	Other clinical features Lactate and pyruvate levels Muscle biopsy DNA tests
CMT2, dHMN	Spinal dysraphism	Lumbar spine MRI

CMT=Charcot–Marie–Tooth disease. dHMN=distal hereditary motor neuronopathy. DSN=Déjèrine-Sottas neuropathy. EMG=electromyography. HNPP=hereditary neuropathy with liability to pressure palsies. NCS=nerve-conduction study. *MNGIE*=mitochondrial neurogastrointestinal encephalopathy syndrome. *POLG1*=polymerase gamma subunit 1.

Table 4: **Differential diagnoses of CMT**

Treatment

There is still no effective drug therapy for CMT.[72,73] Supportive treatment is limited to rehabilitative therapy and surgical treatment of skeletal deformities and soft-tissue abnormalities. The therapeutic management requires a multidisciplinary approach, with a close collaboration between the neurologist and other professional figures.[6] Research is focused on developing new treatment strategies, some of which are being tested in animals, with some clinical trials being carried out.[72,74,75]

Rehabilitation, orthotics, and supportive treatment

Different rehabilitative approaches have been used for treating CMT. However, only a few randomised clinical trials have been properly done. There is evidence that mild to moderate exercise is effective and safe for patients with CMT and leads to a significant improvement in walking ability and lower-limb strength.[72,76–78] Patients with CMT show reduced peak oxygen consumption and decreased functional aerobic capacity, and some studies suggest that aerobic exercise might improve functional ability and aerobic capacity.[78–80] Whether weakness from excessive use occurs in CMT is a controversial matter and, until this issue is resolved, high-resistance training should be avoided.[81–83] Although passive stretching is advised to prevent and counteract tendon retractions, the real effect of this treatment has not been definitely ascertained in CMT.[84] Intervention aimed at improving posture and balance is also considered to be useful.[85]

Shoe modifications, plantars, orthoses, and assistive devices can be of help. Plantars are commonly used to

correct foot position and thus avoid pressure and contact sores and calluses. Ankle–foot orthoses are commonly prescribed to overcome foot drop and facilitate walking, although they are often uncomfortable and therefore poorly tolerated.[86] Custom-fitted ankle–foot orthoses are more comfortable, enable better compliance, and might relieve painful pes cavus.[87,88] Bracing orthotics are also useful when upper-limb involvement is severe.[6,88]

Respiratory failure, caused by diaphragm weakness or vocal-cord palsy in adduction, is rare in CMT, but has been reported in CMT1A, CMT2C, and other types of CMT.[5,34,89] Proper treatment includes assisted ventilation and laser arytenoidectomy.

Surgical treatment

Many different approaches have been used to treat skeletal deformities, particularly of the feet.[90,91] The progression of foot deformities in CMT is not well documented: most patients develop flexible cavovarus deformities during childhood and adolescence, which gradually progress to a fixed deformity.[91]

Proposed treatments include soft-tissue surgery, osteotomies, and joint fusions, either alone or in combination.[90,91] Soft-tissue surgery includes plantar fasciotomy (to reduce cavus deformity), various types of tendon transfers (peroneus longus to peroneus brevis, tibialis anterior to lateral cuneiform, posterior tibial to the anterior compartment, and so on), and tendon releases. Various types of osteotomies can be used when equinocavovarus deformities are becoming fixed or are severe, and can be done on the calcaneal, metatarsal (particulary the first), tarso-metatarsal, and tarsal bones.[91] Triple arthrodesis, consisting of surgical fusion of the talocalcaneal, talonavicular, and calcaneocuboid joints, have long been used to treat the most severe foot deformities; however, long-term results, investigated in only a few studies, have indicated a high occurrence of ostheoarthrosis of the other foot joints.[90,91] With regard to foot surgery, there is still no clear indication about who should receive it and when and how this should be done: prospective studies and better retrospective analysis of long-term results are needed.

Tendon transfers in upper limbs can also be of help in recovering thumb opposition or wrist extension. Substantial scoliosis is present in 15–25% of patients with CMT and, in the most severe cases, requires surgical treatment.[92,93]

Symptomatic drug therapy

Pain is an emerging feature of CMT, and seems to be mainly of the osteo-arthropathic type associated with skeletal deformities and posture abnormalities, but also partly related to muscle fatigue, and sometimes of true neuropathic type.[94,95] Further investigations to determine the frequency and characteristics of pain in CMT are underway. Treatment includes physical therapy and plantars to correct posture, foot surgery when deemed necessary, and drugs for non-neuropathic and neuropathic pain.[74,75,87,88]

Patients with CMT also present with fatigue,[96,97] which is probably associated with different factors, including reduced muscle strength and possibly impaired cardiopulmonary performance. Whether obstructive sleep apnoea syndrome, which might be common in patients with CMT, also has a role in generating fatigue, and whether correcting it would be beneficial, is not known.[89,98,99] The analeptic drug modafinil was tested to treat fatigue in four patients with CMT1A: some benefit was shown, but there were also substantial side-effects.[100] The risk–benefit ratio seems unfavourable and the centrally acting mechanism is non-specific.

Specific drug therapy

None of the drugs tested over the past 25 years have proven effective, including oral creatine monohydrate.[72] Strategies for developing new treatments include studying pathogenic mechanisms and treatment effects in animals. There are several spontaneous and transgenic animal models, including rats and mice that overexpress murine *Pmp22* or human *PMP22* or that harbour *Pmp22* point mutations (ie, Trembler [*Tr*] and Trembler^{J} [*Tr*^{J}] mice carrying the Gly150Asp and Lys16Pro mutations, respectively), different *Mpz* mutations, and *Gjb1* knock outs.[12,56,101,102]

Progesterone and its derivatives can increase in vitro expression of *Mpz* and *Pmp22*. Sereda and co-workers[103] gave progesterone to transgenic CMT1A rats overexpressing *PMP22* and showed its detrimental effect on clinical and neuropathological findings. The progesterone antagonist onapristone proved effective, resulting in clinical and neuropathological improvement, and exerted a protective effect on axonal loss.[104] Unfortunately, onapristone is too toxic to be given to human beings, but new studies are continuing to test another progesterone antagonist (Sereda M, Max-Planck-Institute of Experimental Medicine).

Neurotrophin 3 (NT3), a neurotrophic factor that promotes axonal growth, was tested on animals and in a small clinical pilot study.[105] This neurotrophic factor favoured axonal regeneration in a xenograft model that involved axons of nude mice being ensheathed by human CMT1A Schwann cells, and enhanced regeneration after sciatic nerve crush in *Tr*^{J} mice. In a double-blind, placebo-controlled, pilot trial in which eight patients with CMT1A received intradermal NT3 for 6 months, this neurotrophic factor seemed to improve sensory loss and increase the number of small-diameter solitary myelinated fibres (thought to be an index of axonal regeneration) in sural nerves. No further studies have been done yet.

Ascorbic acid is known to favour myelination in vitro, and, very rarely, peripheral neuropathy has been reported in scurvy. Passage and co-workers[106] have shown that, compared with untreated mice, treatment of CMT1A mice with chronic high-dose ascorbic acid increased their

lifespan and improved their clinical performance. Moreover, sciatic nerves of treated animals had more myelinated fibres and thicker myelin than untreated mice. Although the mechanism of the effect of ascorbic acid is not completely understood, the authors provided evidence for the role of ascorbic acid in reducing mRNA levels of PMP22 through a cAMP-mediated pathway.[106,107] Whether the CMT1A mouse is a proper model for the human disease is debatable, but, because ascorbic acid is easily available and mostly without side-effects, these factors have prompted initiation of clinical trials that are now underway in several countries. The trials with the highest number of patients, involving hundreds of patients, are being undertaken in France, the USA, and (jointly) Italy and the UK.[72,108] Although different dosages of ascorbic acid and trial designs are used, a European NeuroMuscular Centre workshop was useful in agreeing on a protocol with common core features so that a meta-analysis can effectively combine data from different trials.[109] Chronic treatment with high-dose ascorbic acid (5 g per day for 2 years; 12 patients) seems to be poorly tolerated, with 50% of patients developing intolerable gastrointestinal side-effects and a 42% withdrawal rate,[110] even though, in our experience,[108] 1·5 g per day for 2 years was well tolerated, with only 32 (11·8%) of 271 patients withdrawing (9 [<4%] for gastrointestinal disturbances) now that the trial is finishing. In a randomised controlled trial with ascorbic acid in 81 children with CMT1A, no significant difference for any of the study outcome measures was observed between children who received the drug and those who received placebo after 1 year.[111] Whether this result is related to lack of efficacy of ascorbic acid or to the study being underpowered or of a short duration is not known. Ongoing studies with larger sample sizes and longer duration might hopefully give an answer.

Curcumin, a molecule derived from the curry spice turmeric, stimulates the translocation of misfolded proteins from the endoplasmic reticulum to the plasma membrane, thereby reducing cytotoxicity of the mutant proteins. This property might be particularly helpful for selected CMT1A and CMT1B forms, in which various *MPZ* and *PMP22* mutations cause intracellular accumulation of mutant proteins, primarily within the endoplasmic reticulum. In transfected HeLa cells, curcumin released selected forms of mutated MPZ, as well as the *Tr and Tr*^{J} Pmp22 mutant proteins, from the endoplasmic reticulum into the cytoplasm, and reduced apoptosis.[112,113] Studies of *Tr*^{J} mice chronically treated with oral curcumin confirmed reduced apoptosis, revealed increased axonal size and myelin thickness, and a dose-dependent improvement in motor performance, with no side-effects seen. Curcumin has been used in clinical trials for treating different types of cancer and degenerative diseases.[114] Although thought to be poorly absorbed through the gastrointestinal route, discrete bioavailability and detectable diffuse tissue distribution (including in the sciatic nerve) of curcumin has been shown after oral administration.[113] Curcumin might, therefore, be a promising approach in treating selected types of CMT, particularly with *MPZ* and *PMP22* mutations causing altered intracellular trafficking and endoplasmic reticulum retention.

The immune system is known to have a role in the pathophysiology of CMT, as shown in animal studies and, in some reports, in inflammatory neuropathies superimposed on CMT.[30,102,115] Some of these patients responded to steroids or intravenous immunoglobulin treatment. However, in most cases of CMT, immunomodulatory treatment is unlikely to be beneficial.

Patients with CMT should avoid taking drugs that cause peripheral nerve toxicity, particularly chemotherapeutic drugs such as vinka alkaloids, cisplatin, oxaliplatin, and taxol derivatives.[116] Acute neuropathy resembling Guillain-Barré syndrome has been precipitated by vinka alkaloids in patients with unrecognised CMT.[116]

Genetic counselling

Proper information and genetic counselling is important for patients with CMT and their families.[7,74] Prenatal and, in many countries, preimplantation genetic diagnosis can be offered, taking ethical concerns and the national regulations and laws into account.[74]

Conclusions

We are entering a new phase in the study of CMT, in which research is unravelling pathophysiological mechanisms and new treatments are being developed. One important unsolved basic research question concerns the interactions between Schwann cells and axons. Understanding why and how axonal degeneration occurs and develops will be important in curing CMT and other peripheral neuropathies: for example, the abnormal unfolded protein response, which is activated in response to altered intracellular trafficking of mutant proteins, might be a relevant therapeutic target.[12] Clinical research is focused on natural history studies and on developing suitable outcome measures to undertake clinical trials in adults and children.[66–69,71] The selection of outcome measures is important for future trials in CMT, as well as the identification of biological markers. Skin biopsy, an easy and minimally invasive method to investigate sensory nerves that are myelinated in the dermis, could be a valuable tool in the identification of these biomarkers.[117,118] Use of MRI can show early denervation in clinically unaffected muscles and might be a useful paraclinical outcome measure.[119,120]

As the best approaches to rehabilitative therapy and foot surgery still have to be defined, prospective studies will be important. Pending the results of the trials with ascorbic acid, other drugs (ie, curcumin) and novel treatment approaches could be investigated. Theoretically, post-transcriptional gene modulation could reduce overexpression of PMP22 in CMT1A and expression of other mutated proteins associated with gain-of-function toxicity: small double-stranded RNAs, small interfering

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "Charcot–Marie–Tooth", "HMSN", and "Déjèrine-Sottas" from January 1, 1989, until March 31, 2009. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed.

RNAs, ribozymes, and antisense oligonucleotides can downregulate mRNAs in a sequence-specific way.[74,75] Compounds that enable translational read-through of stop codons might overcome the nonsense mRNA-mediated decay that occurs in mutations that cause premature protein termination. One such compound is being tested for Duchenne muscular dystrophy.[121] Advances in such novel approaches might lead to development of specific drug therapies for CMT in the coming years.

Contributors

DP designed and wrote the Review, searched published works, and designed the tables and figures. CM helped to write the Review, search published works, collaborate in the design of the figures and tables, and prepare the tables.

Conflicts of interest

We have no conflicts of interest.

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