

Inherited Neuropathies

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Opinion statement

Inherited peripheral neuropathies are among the most common hereditary diseases of the nervous system. Charcot-Marie-Tooth (CMT) disease, also known from previous classifications as hereditary motor and sensory neuropathy (HMSN), is certainly the most common inherited neuropathy. In the past several years, various treatments for CMT have been proposed, although specific therapies are not yet available. In clinical practice, rehabilitative strategies remain the most helpful therapeutic approach to these patients. There is still a lack of consensus on the best way to rehabilitate patients affected by CMT. Based on our personal experience and on a review of the literature, we first recommend the prescription of ankle-foot orthoses (AFO) for patients affected by CMT; the choice of which patient, which AFO, and when to apply it depends on the individual condition of each patient and on the experience of the physician/therapist. Second, adaptive equipment (eg, button hook, long-handled shoehorn, elastic shoe laces) is available to compensate for hand deformities, sensory loss, and weakness. Third, moderate to intense strength training and aerobic exercise are well tolerated by patients affected by CMT; further studies are needed to establish whether these approaches are effective in improving their motor function and strength. There is not enough evidence to recommend muscle stretching exercises or proprioceptive kinesiotherapy, although in our experience both approaches may be helpful in selected CMT patients to prevent tendon retractions, muscle tightening, and loss of strength, and to improve balance. There is growing knowledge of the underlying genetic defects and molecular pathophysiology in CMT. To date, only a few clinical trials in CMT patients have been performed. A neurotrophic factor, neurotrophin 3, was used in a small sample of CMT1A patients with promising results, but it has not been tested in a larger cohort and there is currently no reason to suggest this therapy for CMT1A neuropathy. Based on positive results in an animal model of CMT1A,

three trials with ascorbic acid (AA) were completed in a large number of patients with this neuropathy, with results that were negative overall. Therefore, it is not possible to recommend the use of AA in CMT1A patients at this time, but the results of a larger Italian-UK study and an American trial with higher doses of AA are still awaited. It is important to remember that a superimposed inflammatory/disimmune process may complicate the course of the neuropathy; in this case, severe worsening (especially motor) in a matter of weeks or months is a “red flag” that should suggest immunosuppressive or immunomodulatory treatment such as steroids, intravenous immunoglobulin, or plasma exchange. In fact, steroid-sensitive cases of HMSN were described many years ago, well before the genetic diagnosis was available. Symptomatic treatment to reduce neuropathic and nociceptive pain, both of which have been reported in patients affected by CMT, should be prescribed according to recently published guidelines for the therapy of pain. No evidence suggests any specific surgical intervention or change in diet or lifestyle for patients affected by various types of CMT.

Introduction

Inherited peripheral neuropathies affect approximately one in 2,500 people and are among the most common hereditary diseases of the nervous system. Recently, inherited neuropathies have been classified into two groups: 1) those in which the neuropathy is the sole or primary part of the disorder, and 2) those in which the neuropathy is part of a more generalized neurologic or multisystem disorder [1].

Within the first group, Charcot-Marie-Tooth disease (CMT), also known from previous classifications as hereditary motor and sensory neuropathy (HMSN) [2], is certainly the most common form. Recently, several treatment strategies for CMT have been proposed, although specific therapies are not yet available [3•]. This review concentrates on the therapeutic options presently available for CMT. However, we wish to underscore that there also have been major advances in the treatment of the inherited neuropathies included in group 2: examples include liver transplantation for familial amyloid neuropathy [4], enzyme replacement for storage disorders such as Fabry disease [5], and transplantation of bone marrow and hematopoietic cells for leukodystrophies with peripheral neuropathy [6].

On the basis of neurophysiologic properties and neuropathology, CMT has been divided into primary demyelinating and primary axonal types. The primary demyelinating neuropathies include CMT1, Dejerine-Sottas disease (DSD), congenital hypomyelinating neuropathy (CHN), and hereditary neuropathy with

liability to pressure palsies (HNPP). The primary axonal neuropathies have been classified as CMT2. Most cases of CMT, of both the demyelinating and axonal types, show autosomal dominant inheritance, although X-linked dominant (CMTX) and autosomal recessive forms (CMT4) have been also described. Apparent sporadic cases exist, as dominantly inherited disorders may begin as “de novo” mutations in a given patient.

Depending upon the specific genetic causes, several subtypes of CMT have been identified (Table 1). Knowing the genetic mechanism underlying each type of CMT may, theoretically, lead to disease-specific therapies. For example, CMT1A, the most common subtype of CMT1, is due to a duplication of the peripheral myelin protein 22 (*PMP22*) gene, resulting in an increased quantity of the protein and peripheral nerve demyelination, with secondary axonal loss [7]. Conversely, a deletion of the *PMP22* gene leads to hereditary neuropathy with liability to pressure palsies (HNPP), which is characterized by decreased expression of *PMP22* and, clinically, by focal episodes of weakness, sensory loss, or both [8]. Therefore, molecular strategies to regulate levels of *PMP22* mRNA and protein are currently under investigation to find specific therapies for CMT1A and perhaps HNPP. Characterization of point mutations in subtypes of CMT (Table 1) will be important to target common molecular mechanisms such as protein misfolding and endoplasmic reticulum retention, altered Schwann cell-axonal interactions, and mitochondrial dysfunction [3•].

Table 1. Subtypes of Charcot-Marie-Tooth disease: mechanisms and therapeutic approaches

Type	Gene/locus	Mechanism/therapeutic target	Drug/therapeutic strategy
Autosomal dominant demyelinating (CMT1)			
CMT1A	PMP22	Duplication/Gene dosage Intracellular processing Axon loss/neuroprotection	AA ^a , onapristone, gene therapy Curcumin, intermittent fasting EPO, CNTF, NT-3 ^a
CMT1B	MPZ	PM/intracellular processing	Curcumin
CMT1C	LITAF	PM	?
CMT1D	EGR2	PM	?
CMT1E	PMP22	PM/intracellular processing	Curcumin, intermittent fasting
CMT1F	NEFL	PM	?
HNPP	PMP22	Deletion/Gene dosage	?
X-linked CMT1 (CMT1X)			
CMT1X	GJB1	PM	Gene therapy
Autosomal recessive demyelinating (CMT4)			
CMT4A	GDAP	PM	?
CMT4B1	MTMR2	PM	?
CMT4B2	MTMR13	PM	?
CMT4C	KIAA1985	PM	?
CMT4D (HMSNL)	NDRG1	PM	?
CMT4E	EGR2	PM	?
CMT4F	PRX	PM	?
CMT4H	FGD4	PM	?
CMT4J	FIG4	PM	?
CCFDN	CTDP1	PM	?
HMSN Russe	10q22-q23	PM	?
ARCMT1	PMP22	PM	?
ARCMT1 (DSN-CH)	MPZ	PM	?
Autosomal dominant axonal (CMT2)			
CMT2A1	KIF1B	PM	?
CMT2A2	MFN2	PM	?
CMT2B	RAB7A	PM	?
CMT2B1	LMNA	PM	?
CMT2B2	MED25	PM	?
CMT2C	TRPV4	PM	?
CMT2D	GARS	PM	?
CMT2E	NEFL	PM	Gene therapy
CMT2F	HSPB1	PM	?
CMT2G	12q12-q13	PM	?
CMT2I/J	MPZ	PM	?
CMT2H/K	GDAP1	PM	?
CMT2L	HSPB8	PM	?
Autosomal recessive axonal CMT (ARCMT2)			
ARCMT2A	LMNA	PM	?
ARCMT2B	19q13.1-13.3	PM	?
ARCMT2	GDAP1	PM	?
Dominant intermediate CMT (DI-CMT)			
DI-CMTA	10q24.1-25.1	PM	?
DI-CMTB	DNM2	PM	?
DI-CMTC	YARS	PM	?

^aHuman trials available

?, no data from literature on putative therapeutic strategies either in experimental models or in human patients; AA, ascorbic acid; CMT, Charcot-Marie-Tooth; *CTDP1*, CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) phosphatase, subunit 1; *DNM2*, dynamin 2; *EGR2*, early growth response gene 2; EPO, erythropoietin; *FGD4*, *FGD1*-related F-actin binding protein; *FIG4*, phosphatidylinositol 3,5 biphosphate; *GARS*, glycyl-tRNA synthetase; *GDAP*, ganglioside-induced differentiation-associated protein 1; *GJB1*, gap junction protein, beta 1; HNPP, hereditary neuropathy with liability to pressure palsies; *HSPB1*, heat shock 27-kDa protein 1; *KIAA1985* (*SH3TC2*), SH3 domain and tetratricopeptide repeats 2; *KIF1B*, kinesin family member 1B; *LITAF*, lipopolysaccharide-induced TNF factor; *LMNA*, laminin A; *MED25*, mediator of RNA polymerase II transcription subunit 25; *MPZ*, myelin protein zero; *MTMR2*, myotubularin-related protein 2; *MTMR13*, myotubularin-related protein 13; *NDRG1*, N-myc downstream-regulated element 1; *NEFL*, neurofilament light polypeptide; PM, point mutation; *PMP22*, peripheral myelin protein 22; *PRX*, periaxin; *RAB7*, Ras-related protein Rab-7a; *TRPV4*, transient receptor potential cation channel subfamily V member 4; *YARS*, tyrosyl-tRNA synthetase, cytoplasmic

Physical therapy and exercise, orthotics, orthopedic surgery, dietary supplements, and pain management have been used to treat CMT patients, although evidence of efficacy is still lacking [9]. Recently, an unaffected pregnancy was successfully carried out after preimplantation genetic diagnosis [10, Class IV].

Treatment

Pharmacologic treatment

- To date, there are no pharmacologic approaches specific for CMT. However, disease-modifying treatments based on molecular pathomechanisms are now emerging. The availability of in vitro and in vivo models for some types of CMT is also extremely important to test experimental therapies, which may then be transferred to human trials. In this section, we summarize the pathogenetic mechanisms that may be considered as optimal therapeutic targets and report on the therapies that have been tried in human or experimental CMT.

Gene dosage

- The severity of CMT1A and HNPP neuropathy is associated with the number of extra or missing *PMP22* genes, indicating that an altered *PMP22* gene dosage is the principal cause of these hereditary neuropathies [11, 12]. Indeed, direct evidence that abnormal *PMP22* gene dosage alone is sufficient to cause CMT1A or HNPP was provided by animal and in vitro models with *PMP22* transgenes or *PMP22* null mutations, respectively [13, 14]. *PMP22* point mutations are also known to cause hereditary neuropathies, but they are responsible for even more severe phenotypes, which were previously classified as Dejerine-Sottas disease [15] and are now called CMT1E (Table 1).
- In order to develop pharmacologic treatments for CMT1A, therapeutic strategies have aimed to reduce *PMP22* expression levels in animal models and human patients. Neurosteroids, like progesterone, increase expression of both *PMP22* mRNA and protein levels and myelin protein zero (MPZ) [16]. Administration of onapristone, a selective antagonist of the progesterone receptor, reduced overexpression of *PMP22* mRNA in a rat model of CMT1A and improved the clinical, neurophysiologic, and neuropathologic phenotype of the animals [17]. Interestingly, treating these rats with progesterone significantly worsened their CMT phenotype. To date, there are no clinical trials with onapristone in human CMT1A because of the obvious toxicity of progesterone blockers in humans.
- At approximately the same time, another research group treated a mouse model of CMT1A with ascorbic acid (AA) and lowered levels of *PMP22* [18]. Treated animals had less severe neuropathy than untreated controls, as shown by clinical and histologic findings. Some clinical parameters even improved during treatment, suggesting partial reversion of the phenotype. The mechanism underlying downregulation of

PMP22 by AA is still not completely known; it is possible that it acts by influencing cAMP levels in Schwann cells (SC) [19].

- This observation led to the initiation of randomized controlled trials (RCTs) to test AA efficacy for the human disease. Three such trials have been completed. A proof-of-concept Dutch trial showed no effect in 11 patients treated with 2 g/d of AA [20]. In Australia, 81 children were treated with 30 mg/kg per day of AA, again with negative results [21••, Class I]. Finally, a French three-arm trial was performed on 179 CMT1A patients using 1 g/d or 3 g/d of AA or placebo, without any significant benefit [22••, Class I]. In these trials, besides the obvious failure of AA to treat CMT1A, negative results may also be due to factors such as the choice of primary outcome measures or the trial duration. Motor conduction velocity (MCV) of the median nerve, used in the first two trials, is known to be unrelated to clinical severity and progression. The CMT Neuropathy Score (CMTNS), used in the third trial, is a composite scale of symptoms, signs, and motor and sensory amplitudes of one nerve in the upper limb. The CMTNS is sensitive to worsening in CMT1A, but this scale has not yet been used in clinical trials [23, Class I]. Interestingly, post hoc analyses of trials 1 and 3 showed that five Australian AA-treated children, in the first trial, had a large increase of MCV in the median nerve, and in the third trial, the clinical component of the CMTNS improved significantly more in the group receiving 3 g/d of AA than in the other groups. However, findings obtained from post hoc analyses should be interpreted with caution [24, 25]. A multicenter RCT to assess the efficacy and tolerability of 2 years of treatment with AA in CMT1A patients in Italy and in the United Kingdom was recently completed, but results are still pending (D. Pareyson, personal communication).
- Another interesting therapeutic option in CMT1A is to boost PMP22 clearance by activating the autophagy machinery of the cell. This has been shown to be effective in animal models of CMT1A [26••, Class I]. To date, there are no data regarding this approach in human CMT1A.
- Despite the importance of the gene dosage mechanism, we must underscore that PMP22 mRNA and protein levels are extremely variable among CMT1A patients, as well as in animal models [13, 27]. This variability suggests that correction of PMP22 dysregulation must be carefully planned in humans, and results from animal models must be interpreted with caution before planning clinical trials.

Intracellular processing of mutated proteins

- Though gene dosage can account for about half of the cases of CMT, point mutations in at least 25 genes may be detected in the remaining patients. Most *PMP22* [28, 29] and different myelin protein zero (P0) mutants [30, 31] are retained intracellularly and ap-

pear to belong to a growing class of mutations termed “endoplasmic reticulum (ER) retention mutations,” which are recognized by ER-resident folding proteins or molecular chaperones [32].

- A typical example of an ER retained mutation is the most common cause of cystic fibrosis, the $\Delta F508$ mutation, which results in a mutant protein that is misprocessed in the ER and targeted for degradation, instead of transferring to the plasma membrane, where it forms a chloride channel. Among ER retention diseases, however, inherited neuropathies caused by *PMP22* and myelin protein zero (*MPZ*) gene mutations are unique because they are dominant gain-of-function diseases.
- Curcumin, the principal curcuminoid of the popular Indian curry spice turmeric, promotes the translocation of misfolded proteins from the ER to the plasma membrane, thereby likely reducing cytotoxicity of the mutant proteins [33]. Khajavi and colleagues [34, 35] demonstrated in vitro that curcumin partially released selected P0 mutants, as well as the *PMP22* mutants from the ER, and decreased cellular apoptosis. Moreover, newborn Trembler-J mice which carry a point mutation in the *PMP22* gene, treated with oral administration of curcumin (daily for 90 days) showed a significant dose-dependent improvement of motor performance, and pathologic studies confirmed increased axonal size and myelin thickness. No relevant side effects were observed in treated animals [34].
- Curcumin bioavailability after oral administration [36] was generally considered to be poor, but this was not the case in Trembler-J mice, whose curcumin blood concentration showed a peak within 2 h and a diffuse tissue distribution, including the central and peripheral nervous system [34]. Curcumin may, therefore, be a promising approach for treating selected types of CMT diseases, especially *MPZ* and *PMP22* mutations causing altered intracellular trafficking and ER retention.
- A different experimental setting evaluated a protocol of 5 months of intermittent fasting in Trembler-J mice [37••, Class I]. Animals treated with dietary restriction showed a significant improvement of motor behavior, forelimb grip strength, and increase of peripheral myelin protein expression, while weight gain was unaffected. Intermittent fasting may provide a nonpharmacologic approach to improve the cellular synthesis of chaperone molecules and protein degradation through the autophagy-lysosomal system [38]. It is difficult to predict whether this approach can be translated into clinical practice, but the idea of counterbalancing protein misfolding by increasing cellular detoxification properties deserves consideration.

Mitochondrial function

- Several disorders affecting the nervous system, the muscles, or both are caused by mutations (acquired or inherited) in mitochondrial

DNA or in nuclear genes that code for mitochondrial components; these may be collectively called mitochondrial diseases. Mitochondrial abnormalities have been found in several neurodegenerative disorders [39, 40], in multiple sclerosis [41], and in an increasing number of axonal inherited neuropathies [42, 43]. Interestingly, it has been shown that rounding of mitochondria and reduction in axonal diameter occurred before disruption of the neurofilament network in a model of CMT2E, indicating that mitochondrial dysfunction contributes to the pathogenesis of this disease [43]. Indeed, recent discoveries have highlighted that neurons are reliant particularly on the dynamic properties of mitochondria [44]. Remarkably, in several disease models, the manipulation of mitochondrial fusion or fission can partially rescue disease phenotypes [45, 46].

- At least two types of CMT—CMT2A and CMT4A—are due to mutations in genes coding for mitochondrial proteins. CMT2A is an autosomal dominant (AD), axonal, sensory-motor polyneuropathy caused by mutations in the gene coding for the mitofusin2 (MFN2) protein [47]. MFN2 is an outer mitochondrial membrane protein, which belongs (with MFN1 and Opa1) to the dynamin family of GTPases. Both the mitofusins and Opa1 are essential for mitochondrial fusion [48]. The overall morphology and activity of the mitochondrial population depends largely on the correct balance between organelle fusion and fission. Perturbation of mitochondrial fusion, as happens in CMT2A, results in defects in mitochondrial membrane potential and respiration, poor cell growth, and increased susceptibility to cell death [48]. Furthermore, loss of MFN2 alone affects mitochondria movements and transport along the axon, suggesting that this may be the cause of the length-dependent axonal degeneration observed in CMT2A [49]. Interestingly, exogenous expression of MFN1 is able to compensate for loss of MFN2 in dorsal root ganglion (DRG) neurons, suggesting a possible therapeutic strategy for CMT2A, such as using drugs that would augment MFN1 expression [50]. Nevertheless, the mechanism by which *MFN2* mutations cause neuropathy likely involves a toxic gain of function rather than a haploinsufficiency or a loss of function [50]. Mouse models of CMT2A have been developed and may be the ideal experimental setting to test therapeutic strategies for this type of CMT [51].
- CMT4A is a severe, autosomal recessive, sensory-motor polyneuropathy due to mutations in the ganglioside-induced differentiation-associated protein 1 (*GDAP1*) gene. CMT4A may show either a predominant axonal or demyelinating phenotype. CMT families carrying dominant *GDAP1* mutations have been also described. *GDAP1* is expressed in the outer mitochondrial membrane and regulates mitochondrial fission [52]. Recessively inherited *GDAP1* mutants reduce mitochondrial fission activity, whereas dominant ones interfere with the fusion process [53].
- An impairment of mitochondrial function has been also observed in an experimental model of CMT2E, which is due to mutation in the

NEFL gene encoding for the light neurofilament subunit (NFL) [54••].

- Taken together, these data underscore the importance of mitochondria fusion/fission and transport in maintaining axonal health and trophism in the peripheral nervous system. Acting on mitochondrial function may then be a future area of research for developing therapeutic strategies in some forms of CMT. For example, increasing expression of heat shock proteins (HSP) in a model of CMT2E not only maintained the neurofilament network but also prevented mitochondrial abnormalities [54••, Class I].

Schwann cell–axon interactions

- Schwann cells (SC) cover most of the surface of all axons in the peripheral nervous system. A constant and dynamic communication between the SC and the axon occurs to mutually regulate their development, function, and maintenance [55, 56••]. A disruption of SC-axon interaction due to primary damage of SC, as it happens in demyelinating neuropathies, leads to changes in the phosphorylation status and packing density of the neurofilament, which ultimately results in axonal damage and degeneration [57]. Accordingly, clinical and neurophysiologic studies suggest that the degree of disability in CMT1 depends more on the rate of axonal degeneration than on the extent of demyelination [58]. Impairment of molecular signals from the SC to the axon [56••] and thinning or loss of the myelin sheath may be involved in this process. Both these mechanisms theoretically may be targeted by appropriate strategies.
- Among the molecules released by the SC to support axon survival, neurotrophic factors such as neurotrophin 3 (NT-3) or the ciliary neurotrophic factor (CNTF) may play a role in the therapy of CMT. NT-3 promoted axonal regeneration in a human CMT1A xenograft in nude mice [59, Class IV]. The same paper reported promising results of a pilot study in which eight patients with CMT1A received intradermal NT-3 for 6 months. NT-3 was also well tolerated. Unfortunately, these results have not been confirmed in larger studies. A deficit of CNTF has been found in sciatic nerves of a CMT1A rat model [60]. Interestingly, administration of CNTF to an in vitro model of CMT1A prevents dephosphorylation of the neurofilament [60, Class IV]. To date, the side effects of CNTF prevent its use in human disease, even if analogues of this molecule are under investigation for the cure of obesity [61]. The use of trophic factors in human studies may be also limited by the methods of delivery and the low bioavailability of these drugs at the tissue level. Thus, further studies are needed to clarify the real role of neurotrophic factors as therapeutic agents in human hereditary neuropathies.
- Erythropoietin (EPO) is another molecule released by SC that is able to reduce axonal degeneration in various experimental conditions

[56, 62]. EPO has been used as a neuroprotective agent in experimental diabetic neuropathy [63]. Moreover, intermittent expression of EPO in DRG, achieved through a regulatable vector, protects against the progression of neuropathy in diabetic animals [64, Class IV]. Interestingly, derivatives of EPO that lack hematopoietic activity but retain neuroprotective effects were recently developed to overcome a potential limitation to the use of this molecule in human trials [65]. Therefore, EPO may be considered a promising molecule to treat axonal degeneration in patients with CMT.

- Finally, we described an impairment of intracellular calcium homeostasis in CMT1A SC [66], which could lead to secondary axonal damage. Restoring intracellular calcium in SC, by genetic or pharmacologic approaches, is able to reverse SC dysfunction in vitro [66].
- It is well known that loss or thinning of the myelin sheath impairs the conduction velocity along myelinated axons. However, whether chronic demyelination may directly lead to axonal degeneration is still a matter of debate. In multiple sclerosis, an acquired demyelinating disease of the central nervous system, a link between loss of myelin, dysfunction of mitochondria in the axon, and axonal degeneration has been proposed in both the acute inflammatory and chronic progressive stages [67]. To date, there is no evidence that similar events occur in demyelinating CMT, even if preliminary results from our laboratory seem to suggest so (Visigalli, personal communication). Interestingly, a role of the myelin as a source of energy for the axon was recently proposed [68]. These authors found functional F_0F_1 -ATP synthase and respiratory chain complexes in isolated myelin vesicles, which are able to conduct aerobic metabolism to support the axonal energy demand [69]. Similarly, various mitochondrial proteins were previously found by other scientists in extracts from central myelin [70, 71]. Loss of myelin could, therefore, lead to axonal degeneration by directly affecting the oxygen absorption and aerobic metabolism of the axons [69].
- In this setting, preventing demyelination or promoting remyelination is another therapeutic strategy to treat CMT and reduce secondary axonal damage. Glial myelination is influenced by axonal contact [72], diameter [73], or electrical activity [74]. Therefore, there must be signals from the axon to the SC that regulate myelin thickness. Several pathways involved in this process have been described [56]. Some of them may be putative targets to promote remyelination in the peripheral nervous system. The neuregulin family of proteins and their receptors, belonging to the erbB family of tyrosine kinase receptors (erbB-2 to erbB-3 in SC), are important to regulate SC development and myelin thickness [75]. Neuregulin 1 type III is expressed on the membrane of peripheral axons and plays a crucial role in determining the fate of SC in forming myelin and controlling the thickness of myelin [76]. Manipulation of this pathway theoret-

ically may be used to increase myelin thickness, particularly since neuregulin 1 type III is cleaved by a secretase (BACE 1) in a soluble N-terminal fragment, which becomes a signaling molecule itself [77]. Besides using soluble molecules that promote myelination as therapeutic agents, secretases also are potential therapeutic targets because they are accessible and multiple secretase inhibitors are already available [56••]. The fact that single secretases target multiple molecules raises the question of the low specificity of drugs modulating the action of these enzymes and limits their therapeutic use.

- Another putative pharmacologic target is the axoglial apparatus at nodes of Ranvier, paranodal, juxtapanodal, and internodal regions. Each one of these segments expresses specific proteins and ion channels [78]. Mutations in genes coding for nodal and paranodal proteins underlie some types of CMT (Table 1), and autoantibodies against the ganglioside GM1, which is expressed at the node, cause disimmune neuropathies like the Guillain-Barré syndrome. These findings underscore the functional importance of these regions in the peripheral nervous system. Therefore, therapeutic strategies aimed at limiting the attack on the axoglial apparatus or promoting its reformation could preserve the role of this region in myelination and impulse transmission.

Role of the immune system and superimposed inflammation

- Activation of the immune system plays a role in the initial stages of demyelination in animal models of CMT [79]. The CMT1B mouse model was the first to reveal a role for CD8⁺ T cells and F4/80⁺ macrophages in the progression of pathology [80]. Similar findings were later made in models of CMTX but not CMT1A [80, 81]. As far as therapy is concerned, inactivation of T lymphocytes and macrophages in models for CMT1B and CMTX results in substantially milder pathologic alterations [81]. In fact, crossbreeding these mouse models with RAG-1^{-/-} and TCR α -deficient mice induces histologic and functional amelioration [81]. The fact that a similar role of T lymphocytes and B lymphocytes was not observed in animal models of CMT1A suggests that further studies must be performed in this field, but there is some evidence that demyelination also may be mediated by macrophages in CMT1A [82]. Interestingly, several years ago it was reported that, in sural nerve biopsies of patients with HMSN type 1 (now called CMT1), SC express HLA-DR antigens [83]; cases of CMT1 sensitive to steroid therapy are sometimes observed [2, Class IV]. Taken together, these data suggest that in the future, some form of immunosuppressive therapy may be used in patients with CMT1.
- In our opinion, the suspicion that a superimposed inflammatory, immune-mediated process could be present should be raised when a chronically evolving disease such as CMT changes its course and shows a subacute worsening over weeks or months. In such cases, a

trial with steroids at adequate dosage (1 mg/kg per day) or other immunomodulating approaches should be planned, such as one course of intravenous immunoglobulin (0.4 g/d for 5 days) or four to six plasma exchanges.

Physical therapy and assistive devices

Rehabilitation

- Rehabilitation represents a symptomatic treatment and may play an important role in preventing complications and improving the quality of life of patients with CMT. However, the efficacy of rehabilitation, the most appropriate physiotherapy protocol, and the optimal frequency of treatment are still unclear. In fact, although different rehabilitative approaches have been used for CMT, most studies are either anecdotal or give conflicting results.
- Recently, two Cochrane reviews focused on the treatment of CMT and on the rehabilitative approaches to peripheral neuropathies; they concluded that very few studies on the rehabilitation of patients with CMT met acceptable scientific criteria [84, 85]. In particular, only one randomized study recruited a relatively high number of CMT patients ($n=29$) who underwent home-based strength training and were then evaluated using outcome measures such as isokinetic knee extension and flexion; maximal voluntary contraction; endurance at 80% MVC; ability to descend and climb stairs and stand up from a chair or from lying supine; and time to walk 6 m at a comfortable pace or 50 m quickly [86, Class II]. This trial showed a significant reduction in the time taken for a 6-meter walk at 24 weeks after starting the exercise, with a weighted mean difference of 0.7 (95% CI, 0.23–1.17). No other significant improvements in time-scored functional activities were observed [86]. Other studies used low-intensity to moderate-intensity strength training programs in patients with neuromuscular disease, including CMT, with varying results [87, 88, Class III]. Both studies observed limited improvement in upper-body and lower-body strength, but Kilmer and coauthors [88] observed a high number of injuries in their patients and concluded that increases in training frequency, volume, and especially intensity may put patients with neuromuscular disease at increased risk of training-induced injury.
- Recently, an open-label, 24-week cycling program using a cycloergometer in limited number of patients (4 with CMT1A and 4 with CMT2) proved to be effective in improving exercise tolerance and functional ability in the absence of significant changes in fatigue resistance [89, Class III]. Previously, another study tested the effects of a 12-week, home-based resistance exercise program on strength, body composition, and activities of daily living (ADLs) in 9 men and 11 women with CMT1A ($n=18$) and CMT2 ($n=2$) [90]. Strength and ADLs improved equally in men and women, and there were no differences between CMT1A and CMT2 [90]. Therefore, it is possible

that similar rehabilitative approaches may be useful in patients affected by CMT, but further studies are needed to test the safety and efficacy of such rehabilitation. More importantly, questions about improvement of balance, effects of aerobic exercise, and correlations between impairment, disability, and quality of life after physiotherapy have not yet been addressed.

- A further issue concerns the observation that patients with chronic neuromuscular disorders may undergo overwork weakness due to overloading of the weakened muscles [91, Class IV]. Obviously, overwork may further weaken patients with CMT, but this conclusion has never been confirmed by controlled studies and has been recently denied [92, 93, Class IV].
- A physical therapy program for patients with CMT should also involve muscle stretching to prevent muscle tightening and loss of strength. Stretching exercises affect both muscle and the surrounding connective tissues. Regular stretching can prevent or reduce joint deformities that may result from uneven pulling of muscle on bones. Serial night casting for 4 weeks induced a small increase in ankle dorsiflexion range in children and young adults with CMT, but this effect was not maintained with stretching at 8 weeks [94, Class III]. Although passive stretching is advised to prevent and counteract tendon retractions, the real effect of this treatment has not been definitely ascertained in CMT [95]. A recent case report even suggested that a conserved range of motion at the ankle could be detrimental to stance and gait when triceps surae muscles are weakened [96, Class IV].
- Patients with CMT show reduced peak oxygen consumption and decreased functional aerobic capacity, and some studies suggest that aerobic exercise improve functional ability and aerobic capacity [97, Class IV]. Aerobic walking has been used in neuromuscular disorders and was effective in ameliorating peak power output and peak oxygen intake, walking ability, and metabolic changes. Aerobic exercising may be helpful in the rehabilitation of patients with CMT.
- A randomized, multicenter, clinical trial testing the efficacy and safety of a composite program consisting of walking on a treadmill, stretching, and proprioceptive exercises (TreSPE) in 92 patients with CMT1A is under way in Italy, and results will be available in about 2 years.

Normalizing gait

- Ankle-foot orthoses (AFOs) may be useful in treating patients with CMT. There are several different AFOs, whose choice depends on the patient's individual condition. AFOs compensate for weakness and correct foot drop. They can offer a control of the foot, can help control unwanted inward rotation of the foot, and facilitate a more normal gait pattern. Optimizing the AFO prescription for a patient with CMT can enhance physiological performance and perceived

exertion at submaximal activity levels [98, Class IV].

- Postural kinesitherapy may be helpful in reducing the need to control joints from three joints (hip, knee, and ankle) to one joint (hip), and proprioceptive kinesitherapy may help to improve coordination [99, Class IV].
- As botulinum toxin type A (BoNT-A) can modify foot deformity in other conditions of muscle imbalance, the effectiveness of BoNT-A on pes cavus progression has been tested in pediatric CMT1A. The intramuscular BoNT-A injections proved safe and were well tolerated, but they did not affect the progression of pes cavus in these patients [100, Class IV].

Preventing falls

- Gait and balance problems are important risk factors for falls in CMT as well as in other peripheral neuropathies. Falls may be prevented by wearing proper shoes with orthoses and by paying attention to the floor, avoiding uneven ground, being wary of rugs and carpets, avoiding dark places, using a handrail when going up and down the stairs, avoiding haste, and staying slim. When falls are frequent, a walking stick, one or two crutches, or a walking frame is required; it is advisable to use a wheelchair outside of the house (Vinci P, personal communication).

Addressing problems with manual dexterity

- People with CMT may experience weakness in their arms and hands, causing difficulty in gripping and finger movement. Normal daily activities such as dressing, bathing, holding cutlery, or writing can become difficult. Tripod pinch strength and thumb opposition are major determinants of manual dexterity in CMT and should therefore be the focus of intervention strategies that aim to preserve or enhance manual dexterity in CMT [101].
- In the early stages of the disease, it is very important to prescribe special tools or modifications of tools normally used, in order to avoid overwork weakness and improve performance. Later, hand or forearm splinting may be necessary because of wasting of the hand muscles.
- Another treatment option may include a conservative exercise program to help maintain and strengthen the hand and forearm. Exercises may include the use of putty and rubber bands of different strengths.
- Adaptive equipment may be prescribed to compensate for the hand deformities, sensory loss, and weakness. Examples include a button hook, a long-handled shoehorn, and elastic shoelaces.

Surgery

- Patients with CMT may require orthopedic surgery to correct severe pes cavus deformities, scoliosis, and hand joint deformities. There are

few reports in the orthopedic literature concerning the surgical management of foot deformities in CMT. Treatment is determined by the age of the patient and the cause and severity of the deformity. Different surgical approaches have been described to treat patients who have cavovarus foot deformities secondary to CMT. A combination of procedures involving bone and soft tissue is typically necessary for optimal outcome [102, 103, Class IV]. Bony procedures include fusion of the ankle, hindfoot, midfoot, or the great toe interphalangeal joint, all of which are performed in concert with deformity correction. Joint-sparing osteotomies, most commonly of the calcaneus and metatarsals or medial midfoot, have the same goals. Soft tissue operations include plantar fascia release, plantar-medial stripping procedures, and transfers of multiple tendons.

- Patients in advanced stages of hand impairment can take advantage of surgical interventions aimed at improving or recovering the pinch between the tips of the thumb and forefinger. Surgery has been shown to be effective in improving function in patients with CMT. Static block techniques or tenodesis to prevent hyperextension of the metacarpophalangeal joints were performed in patients with severe clawing to improve function without the need for external splints [102–104, Class IV].

Diet and lifestyle

- Before the identification of the first gene mutations causing CMT neuropathies, few therapeutic approaches were developed with the aim of modifying the biology of CMT. Intramuscular injection of a mixture of gangliosides extracted from the bovine brain (Cronassial; Fidia Pharmaceutical Corporation, Padova, Italy) was not effective in 30 patients affected by CMT, in a RCT [105, Class II]. Similarly, the administration of linoleic and γ -linoleic essential fatty acid in a small RCT did not improve neuromuscular function in 20 CMT patients [106, Class IV]. Interestingly, in this study the patients treated with placebo containing Vitamin E did show some improvement in neurologic disability measures [106].
- A single small study of low-dose coenzyme Q10 reported some benefit in three patients affected by CMT [107, Class IV].

Emerging therapies and future developments

Gene therapies

- Gene therapy refers to treating disease by transferring, altering, or removing genes or gene products within affected cells or tissues [108]. There are three types of gene therapy strategies: 1) replacement of deficient gene products by introducing genetic material or proteins (such as enzymes in lysosomal storage diseases); 2) compensatory and salvage action of drugs that function as protein chaperones interfering with protein misfolding; and 3) manipulation of gene expression by nonsense suppression and by control of pre-mRNA splicing [108]. Generally speaking, gene therapy has significant potential obstacles such as deliv-

ery, achievement of sustained expression, avoidance of a deleterious immunologic or tissue-based response, and the possibility of inducing secondary diseases after integration of vectors and disruption of genes at the DNA insertion site [108].

- Like any other mendelian disorder, hereditary neuropathies may theoretically benefit from gene therapy. Both the use of drugs or gene strategies interfering with misfolding of proteins and the manipulation of gene expression could be used in patients affected by different types of CMT. In recent years, a new class of molecular therapies targeting RNA has arisen, including the use of small interfering RNA (siRNA) to degrade mRNA transcripts, microRNA (miRNA) to suppress protein translation, and antisense oligonucleotides to manipulate splicing [108, 109]. To our knowledge, similar strategies have not been applied so far to CMT disease. Potential therapeutic applications of siRNA include silencing of mutant alleles, which lead to a toxic gain of function, or of alternatively spliced mRNA to regulate expression of protein isoforms [110]. The miRNAs are small, endogenous RNA-duplex transcripts of about 22 nucleotides that play a pivotal role in the regulation of mRNA in eukaryotic cells [110]. After being processed from pre-miRNAs to mature miRNAs by a complex containing Dicer, a type-III ribonuclease, mi-RNA are loaded into the RNA-induced silencing complex (RISC) to mediate translational modulation or mRNA degradation [111, 112]. Therefore, the use of appropriate miRNA could be of help in controlling expression of myelin-related proteins like PMP22 or MPZ. Interestingly, it was recently demonstrated that selective inhibition of Dicers in SC results in severe impairment of myelination both in vitro and in vivo [113••–115••]. Identifying the nature and characteristics of miRNAs that regulate the myelination process in SC will be fundamental to deeply understanding the biology of SC and of SC-axon interaction, and to developing future therapies for hypomyelinating inherited neuropathies [115••].

Symptomatic treatment: relief of pain and fatigue

- In the past, pain was considered to be rare in patients affected by CMT [116], but recent studies suggest that pain is emerging as a relatively common feature of CMT neuropathy [117]. Both nociceptive and neuropathic pain may be seen in patients with CMT. Pharmacologic treatment of neuropathic pain must be based on the practical guidelines recently produced by a task force of the European Federation of Neurological Societies [118, Class I].
- Fatigue also may be observed in patients with CMT. Recently, the analeptic drug modafinil was used in four patients with CMT1A and significant fatigue, prescribed at a dosage of 200 mg each morning [119, Class IV]. All the patients tolerated modafinil well and reported significant benefit from the therapy [119]. Unfortunately, the study is anecdotal and outcome measures to quantify fatigue were not used.

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No potential conflicts of interest relevant to this article were reported.

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