Address correspondence to
Dr Mario A. Saporta,
Rua Republica do Peru 362/602,
Rio de Janeiro, 22021-040, Brazil,
mariosaporta@gmail.com.

Relationship Disclosure:
Dr Saporta reports no disclosure.

Unlabeled Use of Products/Investigational Use Disclosure:
Dr Saporta reports no disclosure.

Charcot-Marie-Tooth Disease and Other Inherited Neuropathies

Mario A. Saporta, MD, PhD

ABSTRACT

Purpose of Review: Inherited peripheral neuropathies are among the most common genetic neuromuscular disorders worldwide. However, their diagnosis can be challenging due to genotypic and phenotypic variability. Charcot-Marie-Tooth disease (CMT), the most common form, is associated with mutations or copy-number variations in over 70 genes, representing proteins with fundamental roles in the development and function of Schwann cells and peripheral axons. Other genetic peripheral neuropathies are associated with multisystem manifestations, including familial amyloid neuropathy and neuropathies associated with metabolic or other genetic syndromes. This article reviews the most recent discoveries in the field and how they are changing the way neurologists diagnose this specific group of peripheral neuropathies.

Recent Findings: In the past few years, several large cohort studies on the molecular diagnosis of CMT have been published, providing guidelines for genetic testing in clinical practice. In the same period, next-generation sequencing technology has accelerated the discovery of new CMT genes, expanding our knowledge on genotype-phenotype correlations.

Summary: Recent advances in sequencing technology and genotype-phenotype correlation studies are changing the way neurologists diagnose inherited neuropathies. New therapeutic strategies for familial amyloid neuropathy are paving the way for innovative treatments for genetic neuropathies.

Continuum (Minneap Minn) 2014;20(5):1208–1225.

CHARCOT-MARIE-TOOTH DISEASE AND RELATED DISORDERS

The eponym Charcot-Marie-Tooth disease (CMT) is used to define a group of genetic neuropathies in which the peripheral neuropathy is either the sole or major component of the clinical syndrome. This group is represented by diseases associated with point mutations or copy-number variations in genes coding for proteins with strategic functions in Schwann cell or peripheral axon development and physiology, including myelin proteins, transcription factors, cytoskeletal components, and mitochondrial proteins. Currently, over 70 distinct genes have been associated with at least one of the CMT phenotypes, which include motor and sensory neuropathies (hereditary motor and sensory neuropathies; commonly abbreviated as HMSN), predominantly autonomic and sensory neuropathies (hereditary sensory and autonomic neuropathies; commonly abbreviated as HSAN), and pure motor neuropathies (distal hereditary motor neuropathies; commonly abbreviated as dHMN). Interestingly, recent genotype-phenotype correlation studies have demonstrated

significant overlap between specific genes and phenotypes. Therefore, mutations in the same gene can manifest as distinct phenotypes, and the same phenotype can be caused by mutation in different genes. This added complexity challenges the general neurologist, as well as neuromuscular and CMT specialists, to remain up-to-date with this ever-changing field.

Epidemiology

CMT and related disorders are the most common inherited neuromuscular conditions worldwide. Population prevalence is estimated to be between 1 in 2500[1] and 1 in 1214,[2] depending on ethnic background and ascertainment method. In Western countries with mixed ethnicities, autosomal dominant and X-linked dominant forms predominate. However, in countries with a homogenous or isolated population or where consanguineous marriages are part of the social norm, autosomal recessive forms can be seen more frequently and may even be the most common type of CMT diagnosed.

Recently, several epidemiologic studies describing the prevalence of specific forms of CMT in specialized clinics[3,4] and in the general population[2] have been published (**Table 2-1**[2–5]). Two of these studies were carried out in large Western countries (the United States and United Kingdom), reporting very similar findings. Demyelinating CMT type 1 (CMT1) represents approximately half of the cases presenting to the clinic. More than 90% of CMT cases in which a molecular diagnosis has been reached are associated with changes in four genes: *PMP22*, *GJB1*, *MFN2*, and *MPZ*. All other CMT genes were responsible for less than 1% to 2% of cases individually. However, in approximately one-third of all studied cases a molecular diagnosis could not be reached, demonstrating that multiple CMT causative genes remain to be identified. Of note, a report from Norway found very similar frequencies for CMT1 (37.6%) and CMT type 2 (CMT2) (35.9%) phenotypes and a lower success rate for molecular diagnosis (approximately 30%).[2] Whether these differences are because of specific features of the population studied or because of distinct ascertainment methods (general population versus patients from specialized clinics) remains to be determined.

Clinical Presentation and Diagnostic Strategies

Any length-dependent neuropathy can potentially have a genetic etiology, and it is very important to keep this in mind while making the differential diagnosis of patients with peripheral neuropathies. Inherited neuropathies are a common final diagnosis of neuropathies previously considered idiopathic, and it is not uncommon for patients in whom treatment for an inflammatory neuropathy fails to be eventually diagnosed with a genetic condition. When a clear family history cannot be identified, diagnosing an inherited neuropathy can be challenging. Some features from history and physical examination that can be helpful in raising the suspicion of a genetic neuropathy include symptom onset during infancy, long and slowly progressing symptoms, foot deformities (*pes cavus* and hammertoes), and lack of positive sensory symptoms despite clear sensory involvement.

The inherited neuropathies are classified according to inheritance and neurophysiologic pattern. Two major groups were historically defined by median nerve conduction velocities[6]: demyelinating CMT1, in which median conduction velocity is less than 38 m/s, and axonal CMT2, with median conduction velocity greater than 38 m/s. More recently, intermediate conduction velocities, ranging from 35 m/s to 45 m/s, have been

KEY POINTS

- Currently, over 70 distinct genes have been associated with at least one of the Charcot-Marie-Tooth disease phenotypes, which include motor and sensory neuropathies, predominantly autonomic and sensory neuropathies, and pure motor neuropathies.
- In Western countries with mixed ethnicities, autosomal dominant and X-linked dominant forms of Charcot-Marie-Tooth disease predominate. However, in countries with homogenous or isolated population or where consanguineous marriages are part of the social norm, autosomal recessive forms can be seen more frequently and may even be the most common type of Charcot-Marie-Tooth disease diagnosed.
- More than 90% of Charcot-Marie-Tooth disease cases in which a molecular diagnosis has been reached are associated with changes in four genes: *PMP22*, *GJB1*, *MFN2*, and *MPZ*.

TABLE 2-1 Epidemiologic Studies of Charcot-Marie-Tooth Disease

Author	Country	Institution	Year	Number of CMT Patients	Phenotype Distribution	Genotype Distribution
England et al[5]	Compilation of international studies	American Academy of Neurology	2009	2400 (from 10 studies)	Not specified	*PMP22* duplication: 43% *GJB1*: 12% HNPP: 11% *MPZ*: 5% *PMP22* mutation: 2.5% All other forms: <1% each
Saporta et al[3]	US	Wayne State University	2011	787	CMT1: 55.2% CMT2: 12.2% CMT4: 0.9%	67% received molecular diagnosis *PMP22* duplication: 55% *GJB1*: 15.2% HNPP: 9.1% *MPZ*: 8.5% *MFN2*: 4.0% All other forms: <1% each
Murphy et al[4]	UK	University College London	2012	425 (specialized clinic)	CMT1: 56.5% CMT2: 27.1% ICMT: 15.6%	62.6% received a molecular diagnosis *PMP22* duplication: 63.2% *GJB1*: 17.3% *MPZ*: 4.9% *MFN2*: 4.5% *PMP22* mutation: 2.3% All other forms: <2% each
Murphy et al[4]	UK	University College London	2012	1182 (diagnostic laboratory)	CMT1: 37.7% CMT2: 28.3% ICMT: 0.4% Unknown: 32%	37.7% received a molecular diagnosis *PMP22* duplication: 55.4% *GJB1*: 22.6% *MPZ*: 4.0% *MFN2*: 10.7% *PMP22* mutation: 1.1% All other forms: <1% each
Braanthen[2]	Norway	Akershus University Hospital	2012	245	CMT1: 37.6% CMT2: 35.9% ICMT: 2.9% Unknown: 23.6%	28.6% received a molecular diagnosis *PMP22* duplication: 19.6% *GJB1*: 4.8% *MPZ*: 1.1% *MFN2*: 3.2% All other forms: <1% each

CMT = Charcot-Marie-Tooth disease; HNPP = hereditary neuropathy with liability to pressure palsy; CMT1 = Charcot-Marie-Tooth disease type 1; CMT2 = Charcot-Marie-Tooth disease type 2; CMT4 = Charcot-Marie-Tooth disease type 4; ICMT = Intermediate Charcot-Marie-Tooth disease.

associated with a specific set of genes (*GJB1*, *DNM2, YARS, MPZ, IFN2, GNB4*). These three groups of neurophysiologic patterns are then combined with the mode of inheritance to define the major CMT types. Autosomal dominant demyelinating CMT is designated CMT type 1 (CMT1), autosomal dominant axonal

CMT is CMT type 2 (CMT2), X-linked CMT is CMTX, and autosomal recessive CMT is CMT type 4 (CMT4) (most of which have a demyelinating pattern on nerve conduction studies). Early-onset forms, historically termed Dejerine-Sottas disease, are sometimes termed CMT type 3 (CMT3). Since the discovery of genes associated with CMT, subtypes of inherited neuropathies have been defined by the addition of a letter after the number of a specific type of CMT. CMT1A, for example, designates the subtype of CMT1 caused by duplication of a segment of chromosome 17 containing the *PMP22* gene.

When evaluating a patient with possible CMT, identifying characteristic phenotypes or associated symptoms can help guide genetic testing. The following phenotypes can be used for this purpose:

Classic CMT Phenotype, Autosomal Dominant Inheritance, and Slow Nerve Conduction Velocities

The classic CMT phenotype includes normal initial development followed by gradual distal weakness and sensory loss appearing within the first 2 decades of life, reduced deep tendon reflexes, and skeletal deformities in the feet. Affected children are often slow runners and have difficulty with activities that require balance (eg, skating or walking across a log). Ankle-foot orthoses are frequently required by the third decade. Fine movements of the hands for activities such as turning a key or using buttons and zippers may be impaired, but the hands are rarely as affected as the feet. Most patients remain ambulatory throughout life and have a normal lifespan.

This clinical pattern is strongly associated with CMT1A, the most common form of CMT, representing 55% to 60% of all CMT cases with a positive molecular diagnostic test. CMT1A is caused by a 1.4 Mb duplication of chromosome 17p11.2 that includes the *PMP22* gene. Overexpression of *PMP22* is the mechanism responsible for the neuropathy, as determined by animal model studies. Nerve conduction studies often disclose absent sensory responses, motor conduction studies with homogeneously reduced conduction velocities (around 25 m/s), and significantly reduced amplitudes due to secondary axonal loss.

In cases presenting with a classic phenotype, but which are negative for the *PMP22* duplication, special attention should be given to the family history. If no male-to-male transmission can be identified in the family, CMTX is the most probable diagnosis. CMT1X, the most common form of CMTX, is caused by mutations in *GJ1B*, which encodes the gap junction protein connexin 32 and is responsible for 15% to 20% of CMT cases with a defined molecular diagnosis. As in other X-linked diseases, male patients with CMT1X present with a more severe phenotype, and women are usually only mildly affected; however, severely affected female patients with CMT1X have been identified as a consequence of skewed X-inactivation of the nonmutated allele. A split hand syndrome (abductor pollicis brevis more wasted and weaker than the first dorsal interosseus) can often be observed in patients with CMT1X. Asymmetrical slowing of nerve conduction velocities, which is characteristic of hereditary neuropathy with liability to pressure palsy (HNPP) and acquired inflammatory neuropathies, may be found in patients with missense mutations in *GJB1* (as well as in *PMP22, MPZ,* and *EGR2)*, leading to misdiagnosis as an inflammatory neuropathy and unnecessary immunosuppressive treatment. CMT1X is also a common cause of intermediate nerve conduction velocities.

Patients with a classic CMT1 phenotype and male-to-male transmission in the family who tested negative for the

KEY POINTS

- Any length-dependent neuropathy can potentially have a genetic etiology, and it is very important to keep this in mind while making the differential diagnosis of patients with peripheral neuropathies.
- Features that can be helpful in raising the suspicion of a genetic neuropathy include symptom onset during infancy, long and slowly progressing symptoms, foot deformities and lack of positive sensory symptoms despite clear sensory involvement.
- Identifying characteristic phenotypes or associated symptoms can help guide genetic testing.
- The classic Charcot-Marie-Tooth disease phenotype includes normal initial development followed by gradual distal weakness and sensory loss appearing within the first 2 decades of life, reduced deep tendon reflexes, and skeletal deformities in the feet.
- The classic Charcot-Marie-Tooth disease phenotype is strongly associated with Charcot-Marie-Tooth disease type 1A, representing 55% to 60% of all Charcot-Marie-Tooth disease cases with a positive molecular test.

KEY POINTS

- In cases presenting with a classic Charcot-Marie-Tooth disease phenotype, but which are negative for the *PMP22* duplication, special attention should be given to the family history. If no male-to-male transmission can be identified in the family, X-linked Charcot-Marie-Tooth is the most probable diagnosis.
- Patients with a classic Charcot-Marie-Tooth disease type 1 phenotype and male-to-male transmission in the family who test negative for the *PMP22* duplication should then be tested for Charcot-Marie-Tooth disease type 1B, which is the third most common cause of Charcot-Marie-Tooth disease type 1.
- Dejerine-Sottas disease is currently used primarily to denote severe early-onset clinical phenotypes regardless of the inheritance pattern. These cases are usually associated with *PMP22* duplication or point mutations, *MPZ* mutations, and, in rare cases, other Charcot-Marie-Tooth disease type 1 genes or recessive forms.

PMP22 duplication should then be tested for CMT1B. CMT1B is associated with mutation in the *MPZ* gene and is the third most common cause of CMT1. Patients with CMT1B tend to cluster in two distinct phenotypes: those with a severe, early-onset, demyelinating neuropathy with conduction velocities less than 10 m/s and those with a late-onset axonal neuropathy with normal or near-normal conduction velocities.

Other less common causes of a CMT1 phenotype include mutations in *SIMPLE* (CMT1C), *EGR2* (CMT1D), *PMP22* (CMT1E), and *NEFL* (CMT1F), which should be considered in patients who have tested negative for the most common genes associated with CMT1 (**Table 2-2** and **Figure 2-1A**).

Early-Onset CMT With Very Slow Nerve Conduction Velocities (Less Than 15 m/s)

A minority of CMT1 patients have a more severe phenotype with delayed motor milestones and onset in infancy. Particularly severe cases are classified as congenital hypomyelination if myelination appears to be disrupted during intrauterine development. Many patients have *de novo* autosomal dominant disorders, and the term Dejerine-Sottas disease is currently used primarily to denote severe early-onset clinical phenotypes regardless of the inheritance pattern. These cases are usually associated with *PMP22* duplication or point mutations, *MPZ* mutations, and, in rare cases, other CMT1 genes or recessive forms. Therefore, sequencing of the *PMP22* and *MPZ* genes is recommended if *PMP22* duplication is negative (**Figure 2-1B** and **Case 2-1**).

Autosomal Dominant, Early-Onset or Classic CMT Phenotype and Normal (or Near-Normal) Conduction Velocities

This pattern defines CMT2. CMT2 accounts for approximately 25% to 30% of all CMT cases. However, this prevalence may be an underestimation, as only a minority of CMT2 patients have a molecular diagnosis (approximately 25%).[4] It is possible that

TABLE 2-2 Autosomal Dominant and X-linked Demyelinating Charcot-Marie-Tooth Disease

Type	Gene
Charcot-Marie-Tooth disease type 1A (CMT1A)	*PMP22* (17p) dup *PMP22* point mutation
CMT1B	*MPZ*
CMT1C	*LITAF*
CMT1D	*EGR2*
CMT1F	*NEFL*
CMT1 plus	*FBLN5*
Hereditary neuropathy with liability to pressure palsy (HNPP)	17p del. (*PMP22*) *PMP22* point mutation
X-linked CMT type 1 (CMTX1)	*GJB1*
CMTX4 (Cowchock syndrome)	*AIFM1*
CMTX5	*PRPS1*
CMTX6	*PDK3*

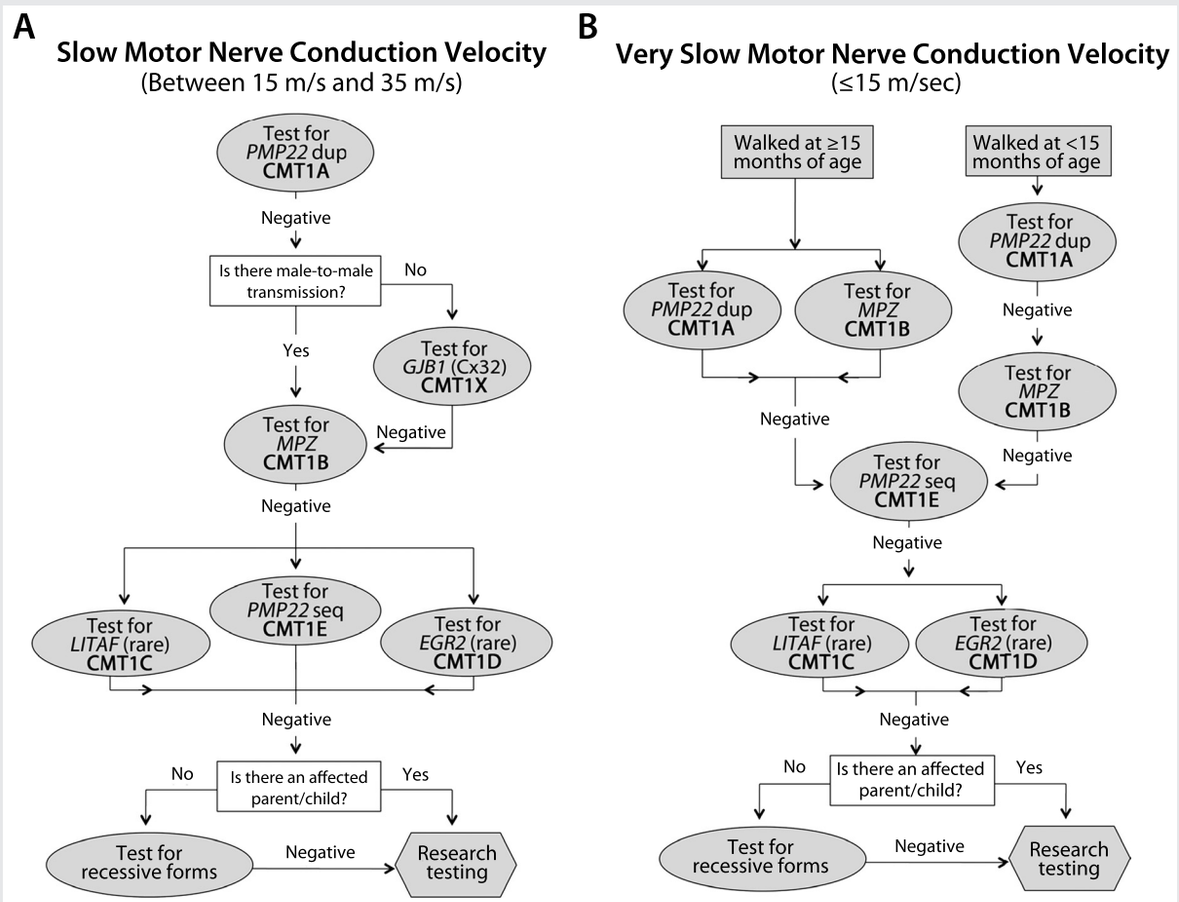

FIGURE 2-1 Algorithm for the genetic diagnosis of patients with Charcot-Marie-Tooth disease and slow (*A*) or very slow (*B*) upper extremity motor nerve conduction velocities.

PMP22 = peripheral myelin protein 22; dup = duplication; CMT = Charcot-Marie-Tooth disease; *GJB1* = gap junction protein beta 1 32kDa; Cx32 = connexin 32; *MPZ* = myelin protein zero; *LITAF* = lipopolysaccharide-induced TNF factor; seq = sequencing; *EGR2* = early growth response 2.

Modified with permission from Saporta AS, et al, Ann Neurol.[3] © 2011 American Neurological Association. *onlinelibrary.wiley.com/doi/10.1002/ana.22166/abstract*.

a significant number of idiopathic axonal neuropathies, including those with late onset, have a yet-unidentified genetic etiology.

CMT2A is caused by mutations in the *MFN2* gene and accounts for approximately 20% of axonal CMT (5% overall) cases. People with CMT2A typically have a severe phenotype, with onset in infancy or early childhood, and usually need a wheelchair for ambulation by 20 years of age. The minority of patients may present with a mild or moderate clinical phenotype. *MFN2* contains a large number of polymorphisms, so care must be taken to ensure that mutations are disease causing. Most disease-causing mutations are in the guanosine triphosphatase domain, coiled-coil domains, or other evolutionary conserved regions of the protein.

Most other axonal CMT types are of rare occurrence and difficult to diagnose (**Table 2-3**). Relying on associated symptoms to narrow the list of genes to be tested is a common strategy in specialized centers (**Table 2-4** and **Figure 2-2A**). Unfortunately, as

KEY POINTS

- Charcot-Marie-Tooth disease type 2 (CMT2) accounts for approximately 25% to 30% of all Charcot-Marie-Tooth disease cases. However, this prevalence may be an underestimation, as only a minority of CMT2 patients have a molecular diagnosis (approximately 25%).
- Most other axonal Charcot-Marie-Tooth disease types are of rare occurrence and difficult to diagnose. Relying on associated symptoms to narrow the list of genes to be tested is a common strategy in specialized centers.
- The nomenclature ''intermediate Charcot-Marie-Tooth disease'' should be used to define families with individuals presenting with median motor nerve conduction velocities in the demyelinating range while other affected members demonstrate velocities in the axonal range.
- Mutations in *GJB1*, *MPZ*, *DNM2, YARS, IFN2,* and *GNB4* have all been associated with intermediate Charcot-Marie-Tooth disease and therefore should be tested in such cases.

Case 2-1

A 25-year-old man with no family history of neuropathy had been weak since infancy. He was able to stand independently by 3 years of age but was never able to run normally and always had an abnormal gait. At the time of his clinic visit he was only able to walk if wearing ankle-foot orthoses. He also had pronounced weakness with fine movements of his fingers and was unable to button his clothes, cut his own food, or perform activities such as turning a key in his front door. His neurologic function had been relatively stable since his teenage years. Nerve conduction studies showed markedly slowed conduction velocities (less than 10 m/s) in his upper extremities; nerve conduction responses in his legs were unobtainable at routine recording sites. Compound muscle amplitude potentials were significantly reduced in the arms and absent in the legs. Sensory nerve action potentials were absent in the arms and legs. Genetic testing revealed an Arg98Cys mutation in *MPZ* leading to a diagnosis of severe Charcot-Marie-Tooth (CMT) type 1B.

Comment. In North America, if one has a genetically diagnosable form of CMT, it is likely that the causal mutation is in one of four genes (*PMP22*, *MPZ*, *GJB1*, or *MFN2*), unless the family history strongly suggests an autosomal recessive inheritance pattern (multiple affected siblings with no parents affected). CMT1A, the most common form of CMT, typically has nerve conduction velocities around 20 m/s in the arms and a classic CMT phenotype with normal early milestones and gradual weakness developing in the first two decades of life. Delayed early milestones and nerve conduction velocities less than 10 m/s are suggestive of an early-onset form of CMT1B. *GJB1* mutations causing CMT1X typically have intermediately slowed nerve conduction velocities (35 m/s to 45 m/s) with an X-linked inheritance. *MFN2* mutations cause the most frequent form of CMT2.

previously mentioned, the success rate of molecular diagnosis for CMT2 is much lower than that of CMT1.

Classic CMT Phenotype With Conduction Velocities in the Intermediate Range (35 m/s to 45 m/s)

The nomenclature ''intermediate CMT'' should be used to define families with individuals presenting with median motor nerve conduction velocities in the demyelinating range while other affected members demonstrate velocities in the axonal range. This pattern suggests a combined pathology in Schwann cells and peripheral axons. Therefore, a single conduction velocity does not define this pattern, as both CMT1 and CMT2 cases can have conduction velocities in the 35 m/s to 45 m/s range.

It is important to acknowledge this specific pattern of CMT because of its association with specific genes. Mutations in *GJB1*, *MPZ*, *DNM2, YARS, IFN2*, and *GNB4* have all been associated with intermediate CMT and therefore should be tested in such cases (**Figure 2-2B** and **Table 2-5**).

Episodic or Asymmetric Inherited Neuropathies

Some specific inherited neuropathies are associated with episodic or asymmetrical phenotypes. HNPP is caused by the reciprocal deletion of the 1.4 Mb segment of chromosome 17p11.2 containing the *PMP22* gene. Approximately 15% of individuals with HNPP have this phenotype due to a frameshift, splice site, or point mutation of the *PMP22* gene. HNPP is the third most common type of CMT, affecting

about 9.1% of genetically diagnosed patients, with a *de novo* rate of about 20%. HNPP is characterized by transient and recurrent motor and sensory mononeuropathies, typically occurring at entrapment sites, such as the carpal tunnel, ulnar groove, and fibular head. These palsies may last hours, days, weeks, or occasionally longer. In some cases, HNPP can progress to long-term peripheral neuropathy phenotypically indistinguishable from CMT1. Electrophysiologic features of HNPP include marked slowing of the ulnar and sural sensory nerve conduction velocities, with or without reduced sensory nerve action potential amplitudes and relatively preserved motor nerve conduction velocities, prolonged distal motor latencies, particularly in the median and fibular nerves, and conduction block and focal slowing at entrapment sites, particularly during a palsy episode.

Hereditary brachial plexus neuropathy is an autosomal dominant disorder associated thus far with missense mutations and copy-number variations in the *SEPT9* gene. Patients present with attacks of brachial plexopathy or even isolated upper extremity mononeuropathies often associated with severe pain and early muscle atrophy. Treatment of attacks with high-dose IV steroids can help control pain, but usually does not change the natural history of neurologic deficits.

It is important to note that CMT1X (*GJB1*) can present as an asymmetric neuropathy, both clinically and electrophysiologically, which can be mistaken for an acquired immune-mediated neuropathy. However, compared with the two previously described conditions (HNPP and hereditary brachial plexus neuropathy), CMT1X will rarely present as episodic neuropathies, although acute CNS dysfunction, in the form of transient strokelike episodes with MRI changes, has been reported in some male patients.

TABLE 2-3 Axonal Charcot-Marie-Tooth Disease

Type	Gene
Autosomal dominant Charcot-Marie-Tooth disease type 2 (CMT2)	
CMT2A	*MFN2*
CMT2B or hereditary sensory and autonomic neuropathy type 1B	*RAB7A*
CMT2C	*TRPV4*
CMT2D	*GARS*
CMT2E	*NEFL*
CMT2F	*HSPB1*
CMT2I	*MPZ*
CMT2J	*MPZ*
CMT2K	*GDAP1*
CMT2L	*HSPB8*
CMT2M	*DNM2*
CMT2N	*AARS*
CMT2P	*LRSAM1*
CMT2Q	*DHTKD1*
Hereditary motor and sensory neuropathy with proximal dominance	*TFG*
CMT2	*MARS*
CMT2	*HARS*
Hereditary spastic paraplegia type 10	*KIF5A*
CMT2	*MT-ATP6*
Autosomal recessive CMT2	
CMT2B1	*LMNA*
CMT2B2	*MED25*
Neuromyotonia and axonal neuropathy	*HINT1*
Autosomal recessive CMT2R	*TRIM2*

Recessive CMT

Recessive forms of CMT are rare, especially in Western countries where consanguinity is uncommon. Specific phenotypes and associated symptoms

TABLE 2-4 Associated Symptoms of Charcot-Marie-Tooth (CMT) Disease and Other Inherited Neuropathies

Associated Symptom	CMT or Other Inherited Neuropathy Type	Gene
Macular degeneration	Charcot-Marie-Tooth disease type 1 (CMT1)	*FBLN5*
Optic atrophy	CMT2A	*MFN2*
	X-linked Charcot-Marie-Tooth disease type 5 (CMTX5)	*PRPS1*
Glaucoma	CMT4B2	*SBF2/MTMR13*
Cataracts	Dominant intermediate CMT type B/CMT type 2M	*DNM2*
	Congenital cataracts, facial dysmorphism, and neuropathy (CCFDN)	*CTDP1*
Facial and bulbar weakness	CMT4B1	*MTMR2*
	CMT4C	*SH3TC2*
	Hereditary motor neuropathy type 7B (HMN7B)	*DCTN1*
Hearing loss	CMT2J	*MPZ*
	CMT4D	*NDRG1*
	Hereditary sensory neuropathy type 1E (HSNIE)	*DNMT1*
	Peripheral neuropathy, myopathy, hoarseness, and hearing loss (PNMHH)	*MYH14*
	CMTX4	*AIFM1*
	CMTX5	*PRPS1*
Vocal cord paralysis	CMT2C	*TRPV4*
	CMT4A	*GDAP1*
	HMN7A	*SLC5A7*
	Peripheral neuropathy, myopathy, hoarseness, and hearing loss (PNMHH)	*MYH14*
Diaphragm paralysis	CMT4A	*GDAP1*
Pyramidal signs	HMN5A	*BSCL2*
	CMT2A	*MFN2*
	Spastic paraplegia type 10	*KIF5A*
	CMT2	*MT-ATP6*
	Juvenile ALS type 4	*SETX*
	Spinal muscular atrophy lower extremity-predominant, 1, autosomal dominant (SMALED)	*BICD2, DYNC1H1*
	HMN5B	*REEP1*
	Hereditary sensory neuropathy with spastic paraplegia	*CCT5*
Predominant hand wasting	HMN5A	*BSCL2*
	CMT2D/HMN5A	*GARS*
	HMN5B	*REEP1*
Mutilating sensory neuropathy	CMT2B/Hereditary sensory and autonomic neuropathy type IB (HSANIB)	*RAB7A*
	HSANIA	*SPTLC1*
	HSANIC	*SPTLC2*
	HSANID	*ATL1*
	HSANIIA	*WNK1*
	HSANIIB	*FAM134B*
	HSANIIC	*KIF1A*
	Hereditary sensory neuropathy with spastic paraplegia	*CCT5*

Continued on next page

TABLE 2-4 **Associated Symptoms of Charcot-Marie-Tooth (CMT) Disease and Other Inherited Neuropathies** *(Continued)*

Associated Symptom	CMT or Other Inherited Neuropathy Type	Gene
Neuromyotonia	Autosomal recessive CMT2/Neuromyotonia and axonal neuropathy	*HINT1*
Scoliosis	CMT4C	*SH3TC2*
	CMT4H	*FGD4*
Renal failure (focal segmental glomerulosclerosis)	Dominant Intermediate CMT type E	IFN2
Focally folded myelin in nerve biopsy	CMT4B1	*MTMR2*
	CMT4B2	*SBF2/MTMR13*
	CMT4B3	*SBF1*
	CMT4F	*PRX*

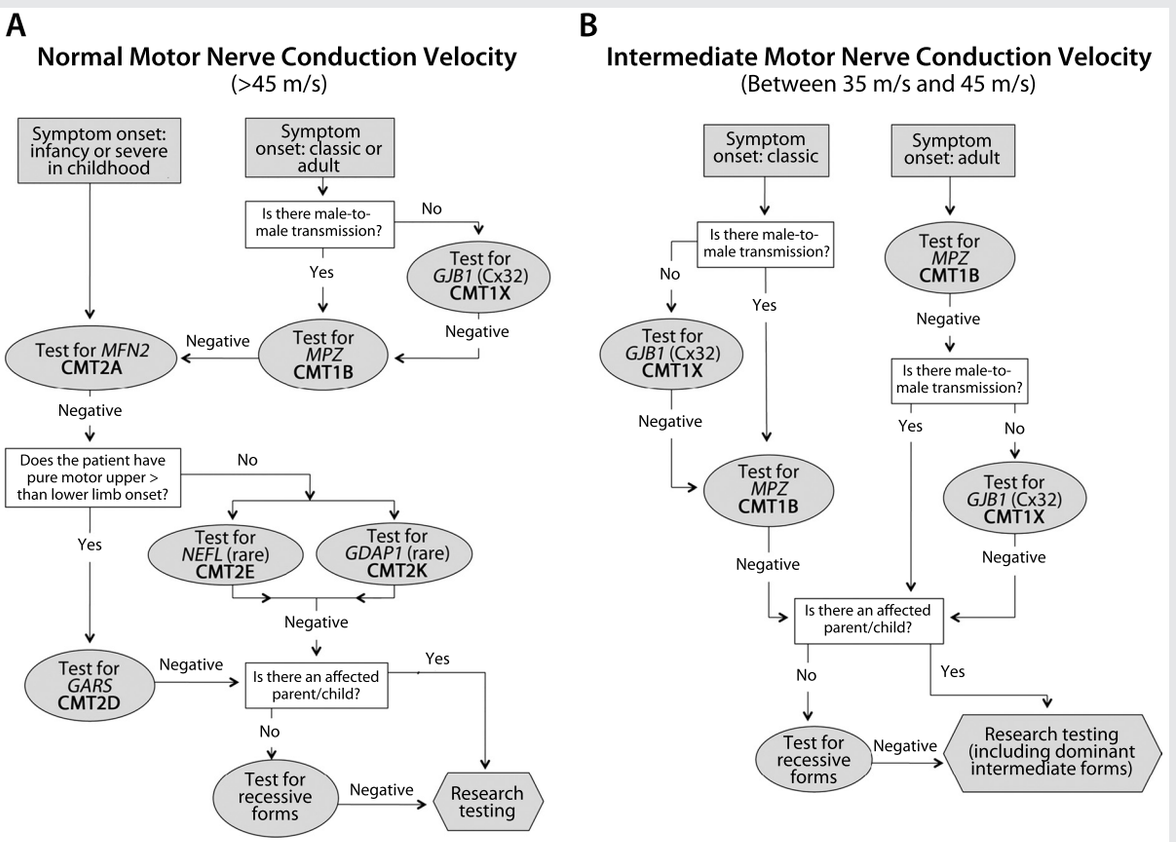

FIGURE 2-2 Algorithm for the genetic diagnosis of patients with Charcot-Marie-Tooth disease and normal (*A*) or intermediate (*B*) upper extremity motor nerve conduction velocities.

GJB1 = gap junction protein beta 1 32kDa; Cx32 = connexin 32; CMT = Charcot-Marie-Tooth disease; *MFN2* = mitofusin 2; *MPZ* = myelin protein zero; *NEFL* = neurofilament light polypeptide; *GDAP1* = ganglioside-induced differentiation-associated protein 1; *GARS* = glycyl-tRNA synthetase.

Modified with permission from Saporta AS, et al, Ann Neurol.[3] © 2011 American Neurological Association. *onlinelibrary.wiley.com/doi/10.1002/ana.22166/abstract.*

KEY POINTS

- Recessive forms of Charcot-Marie-Tooth disease are suspected in families with multiple affected siblings and asymptomatic parents or in patients with no family history but specific phenotypes.
- Distal hereditary motor neuropathies are a distinct phenotype of inherited neuropathies, characterized by a length-dependent, slowly progressive, exclusively motor neuropathy.
- Hereditary sensory and autonomic neuropathies designate phenotypes in which sensory or autonomic symptoms predominate, although a minor motor component can still be observed.

TABLE 2-5 Intermediate Charcot-Marie-Tooth (CMT) Disease

Type	Gene
Dominant intermediate CMT type B	*DNM2*
Dominant intermediate CMT type C	*YARS*
Dominant intermediate CMT type D	*MPZ*
Dominant intermediate CMT type E	*IFN2*
Dominant intermediate CMT type F	*GNB4*
Recessive intermediate CMT type A	*GDAP1*
Recessive intermediate CMT type B	*KARS*
Recessive intermediate CMT	*PLEKHG5*

are usually used to guide molecular testing, similar to what has been described for CMT2 (**Table 2-4** and **Table 2-6**). Recessive forms of CMT are suspected in families with multiple affected siblings and asymptomatic parents or in patients with no family history but specific phenotypes.

Predominantly Motor Neuropathy

Distal hereditary motor neuropathies are a distinct phenotype of inherited neuropathies, characterized by a length-dependent, slowly progressive, exclusively motor neuropathy. Some of the distal hereditary motor neuropathies are actually allelic to the more typical sensorimotor inherited neuropathies (**Table 2-7**).

Predominantly Sensory Neuropathy

Hereditary sensory and autonomic neuropathies designate phenotypes in which sensory or autonomic symptoms predominate, although a minor motor component can still be observed. Patients may develop distinct presentations according to the gene mutated, including distal lower limb sensory loss and neuropathic pain,

TABLE 2-6 Autosomal Recessive Charcot-Marie-Tooth (CMT) Disease

Type	Gene
CMT4A	*GDAP1*
CMT4B1	*MTMR2*
CMT4B2	*SBF2/MTMR13*
CMT4B3	*SBF1*
CMT4C	*SH3TC2*
CMT4D	*NDRG1*
CMT4E	*EGR2*
CMT4F	*PRX*
CMT4G	*HK1*
CMT4H	*FGD4*
CMT4J	*FIG4*
Congenital cataracts, facial dysmorphism, and neuropathy (CCFDN)	*CTDP1*

TABLE 2-7 Hereditary Motor Neuropathies

Type	Gene
Hereditary motor neuropathy type 2A (HMN2A)	*HSPB8*
HMN2B	*HSPB1*
HMN2C	*HSPB3*
HMN with pyramidal features	*SETX*
Distal spinal muscular atrophy type 5	*DNAJB2* (*HSJ1*)
HMN5A	*BSCL2*
HMN5A	*GARS*
HMN5B	*REEP1*
HMN6	*IGHMBP2*
HMN7A	*SLC5A7*
HMN7B	*DCTN1*
Spinal muscular atrophy, distal, X-linked 3 (SMAX3)	*ATP7A*
Spinal muscular atrophy, lower extremity–predominant, 1, autosomal dominant (SMALED)	*BICD2, DYNC1H1*
Peripheral neuropathy, myopathy, hoarseness, and hearing loss (PNMHH)	*MYH14*
Scapuloperoneal spinal muscular atrophy	*TRPV4*
HMN[a]	*AARS*

[a] The HMN genotype does not currently have a specific phenotypic designation.

congenital insensitivity to pain, or pure autonomic dysfunction. The most prevalent types of hereditary sensory and autonomic neuropathies are autosomal recessive, with congenital or early-onset presentations. However, autosomal dominant forms are also seen, with later onset of symptoms, which are closer to what is seen in the more typical hereditary sensory and motor neuropathies (Table 2-8).

Next-Generation Sequencing in the Evaluation of Patients With Inherited Peripheral Neuropathies

Recently, whole genome and whole exome sequencing have been used to determine the genetic abnormality in families with unknown CMT.[7–9] This new technology allows for parallel sequencing of multiple genes, significantly reducing time and cost of molecular testing. Several CMT research groups are now using next-generation sequencing as their method of choice for molecular diagnosis of CMT patients.[10] This approach is particularly useful for patients with axonal or recessive forms in whom sequential testing by Sanger sequencing (the standard current method of direct sequencing, one gene at a time) can be extremely expensive and low yield. As the technology develops and prices drop, next-generation sequencing will probably become the standard method for molecular diagnosis of patients with CMT, as it will soon be less expensive than sequencing multiple single genes using direct sequencing techniques. The wealth of information provided by these techniques will require careful and standardized approaches to define pathogenicity of the genetic abnormalities identified, both *in silico* (using computer simulation) and *in vivo*.

KEY POINTS

- The most prevalent types of hereditary sensory and autonomic neuropathies are autosomal recessive, with congenital or early onset presentations. However, autosomal dominant forms are also seen, with later onset of symptoms.
- As the technology develops and prices drop, next-generation sequencing will probably become the standard method for molecular diagnosis of patients with Charcot-Marie-Tooth disease, as it will soon be less expensive than sequencing multiple single genes using direct sequencing techniques.

KEY POINTS

- Patients with inherited neuropathies are best managed by a multidisciplinary team of professionals, including genetic counselors, physical and occupational therapists, nurses, neurologists, orthopedic surgeons, and physiatrists.
- The decision to have genetic testing or not should always rest with the patient. Reasons for pursuing a molecular diagnosis include family planning, etiologic elucidation of the neuropathy, eligibility to enroll in type-specific clinical trials, and application for some government benefits. Issues associated with testing, on the other hand, include psychological distress, social and work discrimination, and high financial cost of the test.

TABLE 2-8 Hereditary Sensory Neuropathies

Type	Gene	Inheritance
Hereditary sensory and autonomic neuropathy type IA (HSANIA)	*SPTLC1*	Autosomal dominant
HSANIC	*SPTLC2*	Autosomal dominant
Charcot-Marie-Tooth disease type 2B (CMT2B)	*RAB7A*	Autosomal dominant
Hereditary sensory neuropathy type 1D (HSNID)	*ATL1*	Autosomal dominant
HSNIE	*DNMT1*	Autosomal dominant
HSANIIA	*WNK1*	Autosomal recessive
HSANIIB or HSANIB	*FAM134B*	Autosomal recessive
HSNIIC	*KIF1A*	Autosomal recessive
HSANIII, familial dysautonomia (Riley-Day syndrome)	*IKBKAP*	Autosomal recessive
Insensitivity to pain, paroxysmal extreme pain disorder, primary erythermalgia, small fiber neuropathy	*SCN9A*	Autosomal recessive
Congenital insensitivity to pain (CIPA) or HSANIV	*NTRK1*	Autosomal recessive
HSANV	*NGF*	Autosomal recessive
HSAN and dementia	*PRNP*	Autosomal dominant
HSN with spastic paraplegia	*CCT5*	Autosomal recessive

Management of Patients With Inherited Peripheral Neuropathies

Patients with inherited neuropathies are best managed by a multidisciplinary team of professionals, including genetic counselors, physical and occupational therapists, nurses, neurologists, orthopedic surgeons, and physiatrists, reflecting the many dimensions of care required by these patients.

Genetic counseling. Genetic counseling should be offered to any patient suspected of having a genetic neuropathy. If a clear inheritance pattern can be determined by family history, the risk for present and future progeny can be estimated. During counseling, patients should also be informed about genetic testing and its implications, as risk estimation is better performed after a final molecular diagnosis is reached. However, the decision to be tested or not should always rest with the patient. Reasons for pursuing a molecular diagnosis include family planning, etiologic elucidation of the neuropathy, eligibility to enroll in type-specific clinical trials, and application for some government benefits. Issues associated with testing, on the other hand, include psychological distress, social and work discrimination, and high financial cost of the test.

Management of neuropathy risk factors. Patients with inherited neuropathies are particularly susceptible to conditions that induce or exacerbate peripheral neuropathies. Recent studies have demonstrated that patients with CMT1A and diabetes mellitus present with a more severe neuropathy in comparison with the general CMT1A population.[11,12] This is particularly true for motor impairment and reduction in compound muscle action potential

amplitudes, but not for conduction velocities. Therefore, patients with inherited neuropathies should be periodically screened for diseases that may exacerbate their impairment, including diabetes mellitus, hypothyroidism, vitamin deficiencies, and monoclonal gammopathies, and correction of any abnormality should be done promptly. Also, patients with rapidly progressing symptoms after a period of relative stability should be investigated for a superimposed acquired inflammatory neuropathy.

Medications known to induce neuropathy should be avoided whenever possible. These include certain chemotherapy agents (vincristine, cisplatin, oxaliplatin, bortezomib, thalidomide, eribulin mesylate, paclitaxel), antibiotics (metronidazole, nitrofurantoin), antiretroviral drugs (didanosine, stavudine, zalcitabine), gold salts, leflunomide, amiodarone, colchicine, dapsone, and disulfiram.

Rehabilitation. Rehabilitation is an essential component of the management of patients with CMT. It should be as comprehensive as possible and include evaluation and interventions for distal as well as proximal weakness, ambulation, balance, manual dexterity, fatigue, and physical conditioning. Planning of the rehabilitation strategy should focus not only on the specific symptoms affecting quality of life and activities of daily living, but also on the prevention of complications, especially falls and joint deformity. Unfortunately, no large controlled clinic trials have been done to guide intervention, which is usually based on individual experience or small case series. Nonetheless, assistive devices, including inserts and ankle-foot orthoses, and occupational therapy focused on developing tools and strategies to cope with activities of daily living, should be used to improve functionality and quality of life of patients with CMT.

Surgical interventions. Orthopedic procedures are common in patients with CMT, despite the lack of controlled clinical trials to attest their efficiency. Foot surgery is sometimes offered to correct inverted feet, *pes cavus*, and hammertoes; alleviate pain over pressure points; and prevent plantar ulcers. Tendon lengthening and transfers may improve walking and function. However, orthopedic surgery is often unnecessary and does not improve weakness and sensory loss. More aggressive procedures, such as triple arthrodesis, should be avoided, due to their high incidence of complications.

Disease-modifying treatments. Currently, no specific treatments exist for CMT. Multiple strategies are under investigation in preclinical studies based on known disease mechanisms. The first to reach the randomized clinical trial stage was the use of ascorbic acid to reduce *PMP22* expression in peripheral nerves. The rationale for this strategy was based on rodent studies demonstrating beneficial effects in clinical phenotype.[13] Unfortunately, several clinical trials testing distinct doses of vitamin C failed to demonstrate any therapeutic effect in patients with CMT1A.[14–16] Besides drug ineffectiveness, a few possible reasons for this include the slowly progressive nature of CMT1A, the low sensitivity of current outcome measures, biological differences between species, and the timing of intervention. It is possible that, for most inherited neuropathies, therapeutic intervention has to be done early in the development of the peripheral nervous system to be able to reverse symptoms or induce meaningful therapeutic effects.

Endoplasmic reticulum accumulation of misfolded proteins and unfolded protein response activation are possible common mechanisms in CMT associated with point mutations in myelin-related

KEY POINTS

- Patients with inherited neuropathies should be periodically screened for diseases that may exacerbate their impairment, including diabetes mellitus, hypothyroidism, vitamin deficiencies, and monoclonal gammopathies, and correction of any abnormality should be done promptly.
- Assistive devices, including inserts and ankle-foot orthoses, and occupational therapy focused on developing tools and strategies to cope with activities of daily living, should be used to improve functionality and quality of life of patients with Charcot-Marie-Tooth disease.

KEY POINT

- Transthyretin familial amyloid polyneuropathy usually presents as a small fiber neuropathy around the third or fourth decade of life, which progresses to a large fiber sensorimotor severe neuropathy. Autonomic dysfunction is common, affecting the cardiovascular, gastrointestinal, and genitourinary systems. The disease progresses relentlessly, with patients usually dying within 10 years of diagnosis.

genes, including *PMP22* and *MPZ*. Therefore, compounds that either relieve endoplasmic reticulum stress or reduce unfolded protein response activation are promising therapeutic strategies to treat patients with mutations that cause misfolded proteins to accumulate in the endoplasmic reticulum of Schwann cells.

Treatment strategies for axonal forms of CMT have not been as easily identified as for demyelinating forms. Recently, histone deacetylase 6 (HDAC6) inhibitors have been shown to correct axonal transport defects in a mouse model of CMT2F associated with point mutations in the *HSPB1* gene, rescuing the axonal loss and clinical phenotype of these mice.[17] It remains to be shown whether this same strategy could be useful in other forms of axonal CMT, but correcting axonal transport defects may be a common treatment option for most of these CMT types.

Complex Inherited Neuropathies

Peripheral neuropathies can be part of a more complex genetic syndrome. In some conditions, the syndrome is relatively restricted to the central and peripheral nervous system, as is the case of specific forms of hereditary spastic paraplegia or spinocerebellar ataxia with neuropathy. In other instances, more generalized multisystem disorders can affect the peripheral nervous system, as well as other organs, including the heart, kidneys, skin, and eyes (**Table 2-9**). The presence of symptoms and signs outside the peripheral nervous system distinguishes this group of neuropathies from most forms of CMT.

FAMILIAL AMYLOID POLYNEUROPATHY

Familial amyloid polyneuropathies are a group of severe, autosomal dominant multisystem disorders associated with deposition of amyloid fibrils in the peripheral nerves. Three precursor proteins are associated with familial amyloid polyneuropathy: transthyretin, apolipoprotein A-1, and gelsolin. Transthyretin is by far the most common cause of familial amyloid polyneuropathy. Portugal, Japan, and Sweden have large numbers of families with transthyretin familial amyloid polyneuropathy, but cases can be found in other countries where large communities of expatriates from these countries are seen (such as in Brazil) or in isolated families elsewhere. Transthyretin familial amyloid polyneuropathy usually presents as a small fiber neuropathy around the third or fourth decade of life, which progresses to a large fiber sensorimotor severe neuropathy. Autonomic dysfunction is common, affecting the cardiovascular, gastrointestinal, and genitourinary systems (**Case 2-2**). The disease progresses relentlessly, with patients usually dying within 10 years of diagnosis. Diagnosis is confirmed by the identification of amyloid deposits in sural nerve or abdominal fat biopsies, and the final molecular diagnosis is reached by direct sequencing of the causative gene (most frequently, the transthyretin gene).

Liver transplantation is the current treatment of choice for familial amyloid polyneuropathy as it removes the main source of mutant transthyretin and seems to halt disease progression and increase survival, especially when performed early. Recently, innovative treatment strategies aiming to reduce amyloidogenesis or even block the expression of transthyretin have been developed, with some of them already in the clinical trial phase. Tafamidis, a transthyretin stabilizer, is a pharmacologic chaperone of transthyretin that prevents tetramer dissociation into monomers, which is the rate-limiting step in amyloid fibril formation. Tafamidis was shown to reduce disease progression, preventing neurologic, quality-of-life, and body mass index

TABLE 2-9 Complex Inherited Neuropathies

Group	Disease	Inheritance	Gene or Locus
Hereditary spastic paraplegia (SPG) with peripheral neuropathy	SPG3A, 9, 10, and 17	Autosomal dominant (AD)	*ATL1*, 10q23, *KIF5A*, *BSCL2*
	SPG7, 11, 15, 20, and 39	Autosomal recessive (AR)	*SPG7*, *SPG11*, *ZFYVE26*, *SPG20, NTE*
	SPG2 and 16	X-linked	*PLP1*, Xq11
Spinocerebellar ataxia (SCA) with peripheral neuropathy	SCA1, 2, 3, 4, 7, 8, 12, 14, 27, 18, and 25	AD	*ATXN1*, *ATXN2*, *ATXN3*, 16q22, ATXN7, *ATXN8OS*, *PPP2R2B*, *PRKCG*, *FGF14*, 7q31, 2p15-p21
	Friedreich ataxia, vitamin E deficiency, infantile onset SCA, SCA autosomal recessive 10, SCA autosomal recessive 14, Marinesco-Sjögren syndrome, autosomal recessive spastic ataxia of Charlevoix-Saguenay, ataxia with oculomotor apraxia 1	AR	*FXN*, *TTPA, C10orf2*, *ANO10*, *SPTBN2*, *SIL1*, *SACS*, *APTX*
Familial amyloid neuropathy		AD	*TTR*, *APOA1*, *GSN*
Leukodystrophy	Metachromatic	AR	*ARSA*
	Krabbe disease	AR	*GALC*
	Adrenoleukodystrophy	X-linked recessive	*ABCD1*
Peroxisomal disorders	Refsum disease	AR	*PHYH*, *PEX7*
	Fabry disease	XR	*GLA*
Lipoprotein deficiency	Tangier disease	XR	*ABCA1*
	Cerebrotendinous xanthomatosis	AR	*CYP27A1*
	Abetalipoproteinemia	AR	*MTTP*
Porphyria	Acute intermittent	AD	*HMBS*
Defective DNA repair and maintenance	Xeroderma pigmentosa	AR	*XPC*
	Ataxia telangiectasia	AR	*ATM*
Mitochondrial	Myopathy and external ophthalmoplegia, neuropathy, gastrointestinal, encephalopathy (MNGIE)	AR	*TYMP*
	Sensory axonal neuropathy, dysarthria, ophthalmoparesis (SANDO)	AR	*POLG*
	Neuropathy, ataxia and retinitis pigmentosa (NARP)	Inherited by maternal mitochondrial DNA mutation	*MT-ATP6*
Other	Giant axonal neuropathy	AR	*GAN*
	Neurofibromatosis type 1	AD	*NF1*
	Neurofibromatosis type 2	AD	*NF2*

DNA = deoxyribonucleic acid.

KEY POINT

- Metabolic disorders are another cause of multisystem diseases that also affect the peripheral nervous system. This group includes some leukodystrophies (metachromatic, Krabbe, adrenoleukodystrophy), peroxisomal diseases (Fabry, Refsum), lipoprotein deficiencies (Tangier, cerebrotendinous xanthomatosis), porphyrias, and mitochondrial diseases.

Case 2-2

A 28-year-old man first developed symptoms at the age of 21, when he noted loss of temperature and pain perception in his feet. His condition gradually progressed, and by the age of 25, he had sensory impairment up to his waist and midforearms, steppage gait, urinary retention, sexual impotence and constipation, with frequent episodes of diarrhea and vomiting. Neurophysiologic studies disclosed an axonal neuropathy with mild demyelinating features. Tilt table test showed severe autonomic dysfunction with orthostatic hypotension and no compensatory sympathetic activation. Sural nerve biopsy confirmed a chronic axonal neuropathy due to amyloid deposition, and molecular testing of a blood sample demonstrated a Val30Met mutation in the transthyretin gene, confirming the diagnosis of transthyretin familial amyloid polyneuropathy. He had a liver transplantation while he was still ambulatory and independent in all activities of daily living. Unfortunately, his condition progressed, with worsening of the gastrointestinal symptoms, weight loss, and increasing difficulty walking.

Comment. This is a typical case of Val30Met transthyretin familial amyloid polyneuropathy. Patients present around the third or fourth decade of life with a small fiber neuropathy, which rapidly evolves to affect large sensorimotor fibers. Autonomic symptoms are frequent and debilitating, eventually leading to cachexia and life-threatening cardiovascular complications. These patients usually benefit from liver transplantation; however, surgical success and prognosis are directly dependent on an early intervention.

deterioration, when compared with placebo, in a phase 2/3 randomized, double-blind trial,[18] and this effect was still observed after 30 months of treatment initiation.[19]

Strategies to pharmacologically reduce transthyretin gene expression are currently under investigation. These include RNA interference using antitransthyretin small interfering RNA, which has been the subject of a phase 1 trial,[20] demonstrating reductions of approximately 80% in both mutant and wild-type transthyretin levels.

OTHER COMPLEX INHERITED NEUROPATHIES

Metabolic disorders are another cause of multisystem diseases that also affect the peripheral nervous system. This group includes some leukodystrophies (metachromatic, Krabbe, adrenoleukodystrophy), peroxisomal diseases (Fabry, Refsum), lipoprotein deficiencies (Tangier, cerebrotendinous xanthomatosis), porphyrias, and mitochondrial diseases (**Table 2-9**). A comprehensive review of these conditions is beyond the scope of this article; however, it is important to include this group of diseases in the differential diagnosis of patients with inherited neuropathies and signs of dysfunction beyond the peripheral nervous system

CONCLUSION

Inherited peripheral neuropathies are phenotypically and genotypically heterogeneous. Mode of inheritance, nerve conduction velocities, and age of onset of symptoms should be used to narrow down the diagnosis. Of the approximately two-thirds of cases in which a molecular diagnosis will be reached, mutations in four genes (*PMP22*, *GJB1*, *MPZ*, and *MFN2*) will account for more than 90% of patients. The remaining 10% of cases are individually rare and will depend on associated features and careful family history to be diagnosed. Next-generation sequencing as well

as increasing biological understanding of the inherited peripheral neuropathies will improve our ability to diagnose them and accelerate the identification of potential drug targets in CMT.

ACKNOWLEDGMENTS

The author would like to thank Anita Saporta, MD, and Michael Shy, MD, for reviewing this article.

REFERENCES

1. Skre H. Genetic and clinical aspects of Charcot-Marie-Tooth's disease. Clin Genet 1974;6(2):98–118.
2. Braathen GJ. Genetic epidemiology of Charcot-Marie-Tooth disease. Acta Neurol Scand Suppl 2012;(193):iv–22.
3. Saporta AS, Sottile SL, Miller LJ, et al. Charcot-Marie-Tooth disease subtypes and genetic testing strategies. Ann Neurol 2011;69(1):22–33.
4. Murphy SM, Laura M, Fawcett K, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. J Neurol Neurosurg Psychiatry 2012;83(7):706–710.
5. England JD, Gronseth GS, Franklin G, et al. Practice parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology 2009;72(2):185–192.
6. Harding AE, Thomas PK. The clinical features of hereditary motor and sensory neuropathy types I and II. Brain 1980;103(2):259–280.
7. Lupski JR, Reid JG, Gonzaga-Jauregui C, et al. Whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy. N Engl J Med 2010;362(13):1181–1191.
8. Montenegro G, Powell E, Huang J, et al. Exome sequencing allows for rapid gene identification in a Charcot-Marie-Tooth family. Ann Neurol 2011;69(3):464–470.
9. Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. N Engl J Med 2013;369(16):1502–1511.
10. Rossor AM, Polke JM, Houlden H, Reilly MM. Clinical implications of genetic advances in Charcot-Marie-Tooth disease. Nat Rev Neurol 2013;9(10):562–571.
11. Ursino G, Alberti MA, Grandis M, et al. Influence of comorbidities on the phenotype of patients affected by Charcot-Marie-Tooth neuropathy type 1A. Neuromuscul Disord 2013;23(11):902–906.
12. Sheth S, Francies K, Siskind CE, et al. Diabetes mellitus exacerbates motor and sensory impairment in CMT1A. J Peripher Nerv Syst 2008;13(4):299–304.
13. Passage E, Norreel JC, Noack-Fraissignes P, et al. Ascorbic acid treatment corrects the phenotype of a mouse model of Charcot-Marie-Tooth disease. Nat Med 2004;10(4):396–401.
14. Burns J, Ouvrier RA, Yiu EM, et al. Ascorbic acid for Charcot-Marie-Tooth disease type 1A in children: a randomised, double-blind, placebo-controlled, safety and efficacy trial. Lancet Neurol 2009;8(6):537–544.
15. Pareyson D, Reilly MM, Schenone A, et al. Ascorbic acid in Charcot-Marie-Tooth disease type 1A (CMT-TRIAAL and CMT-TRAUK): a double-blind randomised trial. Lancet Neurol 2011;10(4):320–328.
16. Lewis RA, McDermott MP, Herrmann DN, et al. High-dosage ascorbic acid treatment in Charcot-Marie-Tooth disease type 1A: results of a randomized, double-masked, controlled trial. JAMA Neurol 2013;70(8):981–987.
17. d'Ydewalle C, Krishnan J, Chiheb DM, et al. HDAC6 inhibitors reverse axonal loss in a mouse model of mutant HSPB1-induced Charcot-Marie-Tooth disease. Nat Med 2011;17(8):968–974.
18. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology 2012;79(8):785–792.
19. Coelho T, Maia LF, da Silva AM, et al. Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. J Neurol 2013;260(11):2802–2814.
20. Coelho T, Adams D, Silva A, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. N Engl J Med 2013;369(9):819–829.