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Charcot-Marie-Tooth Disease and Other Genetic Polyneuropathies

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ABSTRACT

Purpose of Review: Genetic polyneuropathies are rare and clinically heterogeneous. This article provides an overview of the clinical features, neurologic and electrodiagnostic findings, and management strategies for Charcot-Marie-Tooth disease and other genetic polyneuropathies as well as an algorithm for genetic testing.
Recent Findings: In the past 10 years, many of the mutations causing genetic polyneuropathies have been identified. International collaborations have led to the development of consortiums that are undertaking careful genotype-phenotype correlations to facilitate the development of targeted therapies and validation of outcome measures for future clinical trials. Clinical trials are currently under way for some genetic polyneuropathies.
Summary: Readers are provided a framework to recognize common presentations of various genetic polyneuropathies and a rationale for current diagnostic testing and management strategies in genetic polyneuropathies.

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INTRODUCTION

Chronic polyneuropathies have a broad differential, ranging from the relatively common causes, such as diabetes mellitus, to rare genetic polyneuropathies. While at times strong evidence exists for an underlying genetic polyneuropathy (eg, clinical presentation in youth, positive family history, slowly progressive course), genetic polyneuropathies can occur from de novo mutations, are clinically heterogeneous, and can mimic other disorders. Given the long list of possible etiologies and the limited treatment options, defining the specific diagnostic workup and extent of genetic testing can be challenging.[1,2] This article presents a perspective on clinical evaluation, testing, and management of genetic polyneuropathies, focusing on the primary hereditary motor sensory neuropathies, known collectively as Charcot-Marie-Tooth disease (CMT); the hereditary sensory and autonomic neuropathies; and the polyneuropathies associated with genetic disorders that have systemic neurologic manifestations.

PRIMARY HEREDITARY MOTOR SENSORY NEUROPATHIES

The primary hereditary motor sensory neuropathies are known collectively as Charcot-Marie-Tooth disease (CMT) after the three investigators who described a familial slowly progressive peroneal muscular atrophy in 1886.[3,4] Around the same time, Dejerine and Sottas described a hypertrophic interstitial neuritis associated with a severe infantile form of CMT.[5]

Classification of Charcot-Marie-Tooth Disease

Early classification schemes divided CMT into three types: CMT1, a predominantly demyelinating polyneuropathy based on uniformly slow conduction velocities of 38 meters per second or less in the upper extremities; CMT2, a predominantly axonal polyneuropathy with relatively normal velocities but prominently reduced sensory nerve or compound muscle action potential (CMAP) amplitudes, indicating axonal loss; and CMT3, speculated to include recessive disorders with a severe phenotype.[6–9]

The spectrum of neuropathic disorders in the CMT category has broadened, but several aspects of the original classification scheme have been retained. CMT remains broadly classified into CMT1 (demyelinating) and CMT2 (axonal). Dejerine-Sottas disease is now preferred over CMT3 to describe the group of severely affected infants with CMT regardless of inheritance pattern or genetic mutation. CMT4 refers to autosomal recessive CMT. With the discovery of the causal genetic mutations, letters have been added to indicate the gene. For example, duplication of the peripheral myelin protein 22 gene (PMP22) causes CMT1A, and mutations in the mitofusin 2 gene (MFN2) cause CMT2A.

The current CMT classification system is shown in **Table 7-1**.[10] This system does not fully accommodate the full genotypic and phenotypic variability of CMT. For example, CMT1X does not fit into this scheme as it has intermediately slowed conduction velocities and X-linked inheritance, so it is grouped separately. Some dominantly inherited forms of CMT have intermediate-range slowing of conduction velocities in the arms and are grouped separately as a dominant-intermediate form. As

the number of known mutations in genes has grown, a new system that emphasizes genetic classification is now under consideration.[11]

Genetics of Charcot-Marie-Tooth Disease

Over 90% of patients with CMT harbor a mutation in the PMP22, MFN2, myelin protein zero (MPZ), or gap junction protein beta 1 (GJB1) gene.[12] For the remaining 10%, inheritance patterns and associated comorbidities can help define the genetic etiology (**Table 7-1**).[10] Most cases of CMT are inherited in an autosomal dominant manner. An autosomal dominant mutation can also occur de novo in a patient. Children of a parent with an autosomal dominant neuropathy have a 50% chance of inheriting the disease, although variable expression often results in a milder or more severe disease than the parent. If the autosomal dominant mutation occurred de novo, children of the affected parent will also have a 50% chance of having the disorder. Some cases of CMT are X-linked dominant; only one mutant gene copy is needed for the disease to be present. An affected mother with CMT1X has a 50% chance of passing it on to her sons or to her daughters. An affected father with CMT1X will never transmit the mutation to his sons, but has a 100% chance of transmitting it to his daughters. Finally, some CMT cases are inherited in an autosomal recessive manner; persons with one normal copy and one mutant copy are carriers and are unaffected. The children of two carriers have a 25% chance of inheriting both copies and having the disease. All children of an affected parent with autosomal recessive disease will have one copy of the mutant gene; assuming the other parent is not also a carrier, none of the children will have the disease.

Approximately 80% to 90% of cases of autosomal dominant CMT1 are

CMT1A, which is due to a 1.4-Mb duplication of the *PMP22* gene on chromosome 17p11.2, expressed in Schwann cells that produce myelin sheaths for peripheral nerves. One percent to nine percent are due to a *PMP22* deletion, which causes hereditary neuropathy with liability to pressure palsies (HNPP), presenting with recurrent pressure palsies. Of the autosomal dominant CMT1 cases, 10% are due to CMT1B, caused by mutations in the *MPZ* gene, which results in deleterious overexpression of the major myelin structural protein.[12–14]

CMT1X is caused by a mutation on the X chromosome in the *GJB1* gene, also known as the connexin 32 gene.

TABLE 7-1	Classification Scheme of Charcot-Marie-Tooth Disease[a]					
Type	**Pathology/Phenotype**	**Inheritance**	**Percentage of Charcot-Marie-Tooth Cases**		**Subtype**	**Gene/Chromosome**
CMT1	Myelin abnormalities; distal weakness, atrophy, and sensory loss; onset: ~5 to 20 years; motor nerve conduction velocity <38 meters per second	Autosomal dominant	50–80		CMT1A	*PMP22*
					CMT1B	*MPZ*
					CMT1C	*LITAF*
					CMT1D	*EGR2*
					CMT1E	*PMP22*
					CMT1F/2E	*NEFL*
CMT2	Axonal degeneration; distal weakness and atrophy, variable sensory involvement; complicated and severe cases described; motor nerve conduction velocity >38 meters per second; onset: variable	Autosomal dominant	10–15		CMT2A	*MFN2*
					CMT2B	*RAB7A*
					CMT2C	*TRPV4*
					CMT2D	*GARS*
					CMT2E/1F	*NEFL*
					CMT2F	*HSPB1*
					CMT2G	*12q12-q13*
					CMT2H/2K	*GDAP1*
					CMT2I/2J	*MPZ*
					CMT2L	*HSPB8*
					CMT2M	*SYNM*
					CMT2N	*AARS*
					CMT2O	*DYNC1H1*
					CMT2P	*LRSAM1*
					CMT2S	*IGHMBP2*
					CMT2T	*DNAJB2*
					CMT2U	*MARS*
Intermediate form	Myelinopathy and axonal; Motor nerve conduction velocity >25 meters per second and <38 meters per second	Autosomal dominant	Less than 4		DI-CMTA	Unknown
					DI-CMTB	*DNM2*
					DI-CMTC	*YARS*
					DI-CMTD	*MPZ*
					DI-CMTF	*GNB4*

Type	Pathology/Phenotype	Inheritance	Percentage of Charcot-Marie-Tooth Cases	Subtype	Gene/Chromosome
CMT4	Demyelinating; recessive; variable presentations/phenotypes	Autosomal recessive	Rare	CMT4A	*GDAP1*
				CMT4B1	*MTMR2*
				CMT4B2	*SBF2*
				CMT4B3	*SBF1*
				CMT4C	*SH3TC2*
				CMT4D	*NDRG1*
				CMT4E	*EGR2*
				CMT4F	*PRX*
				CMT4G	*HK1*
				CMT4H	*FGD4*
				CMT4J	FIG4
				CMT2B1	*LMNA*
				CMT2B2	*MED25*
CMTX	Axonal degeneration with myelin abnormalities	X-linked	10–15	CMTX1	*GJB1*
				CMTX2	*Xp22.2*
				CMTX3	Unknown
				CMTX4	*AIFM1*
				CMTX5	*PRPS1*
				CMTX6	*PDK3*

CMT = Charcot-Marie-Tooth disease; DI = dominant intermediate.

[a] Modified with permission from McCorquodale D, et al, J Multidiscip Healthc.[10] © 2016 The Authors.
dovepress.com/management-of-charcotndashmariendashtooth-disease-improving-long-term–peer-reviewed-fulltext-article-JMDH.

The gene is expressed in myelinating Schwann cells and the mutation is thought to cause a loss of function.[15,16] CMT2A accounts for 20% to 30% of all causes of CMT2 due to mutations in the *MFN2* gene.[17,18]

Clinical Presentation

CMT is the most common genetic neuromuscular disorder, with a prevalence between 1 in 1213 to 1 in 2500.[19,20] Historically, patients have one of three clinical patterns. The typical phenotype is characterized by normal motor milestones but slowly progressive symmetric distal leg weakness with sensory loss, usually beginning in the first to third decade and progressing to footdrop and hand weakness (**Case 7-1**). On examination, besides the distal weakness and sensory loss, reflexes are often globally suppressed or absent. At most, these patients require ankle-foot orthoses for ambulation.[8,9,21] A second presentation is characterized by an earlier onset of symptoms with delayed walking (after age 15 months or more), toe walking, or clumsiness in childhood. Patients with this phenotype progress to above-the-knee bracing, walkers, or wheelchairs for ambulation.[22–25] A third presentation is characterized by adult onset (around 40 years) with variable subsequent progression. The same CMT gene mutation can present in any

KEY POINT

■ Pes cavus and hammer toes, while an important physical feature of Charcot-Marie-Tooth disease, are not specific to the disease and may occur in isolation or in conjunction with other disorders of the central nervous system.

Case 7-1

A 16-year-old boy with no family history of neuropathy was brought to the clinic by his parents for evaluation of clumsy gait, tripping, and falling. The patient denied any problems but had pes cavus and bilateral footdrop and walked with a steppage gait; he had mild hand intrinsic muscle atrophy and was areflexic. His nerve conduction studies showed a conduction velocity of 22 meters per second along the ulnar and median motor nerves without conduction block or temporal dispersion. Because of his youth and the lack of family history, his pediatrician had tried monthly IV immunoglobulin (IVIg) for 6 months in the hope that this was chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), without benefit. Genetic testing confirmed a diagnosis of Charcot-Marie-Tooth disease type 1A (*PMP22* duplication).

Comment. De novo mutations, as in this case, are not uncommon in Charcot-Marie-Tooth disease. In young patients, when the differential diagnosis includes a potentially treatable disorder, genetic testing becomes more valuable and is less costly and safer than a treatment trial of IVIg.

of these three ways, demonstrating the marked phenotypic variability of a single genotype.

Foot deformities, such as pes cavus and hammer toes, are common in CMT and are often the reason providers first consider the diagnosis. Foot deformities may progress to contracture with marked osseous changes (**Figure 7-1**).[26] However, these deformities are not always associated with neuropathies and may occur in isolation or in conjunction with central nervous system or developmental disorders.[27,28]

CMT in children and adults is associated with psychological stress, reduced health-related quality of life, and other comorbidities.[29–31] Although historically characterized as painless, a significant proportion of children and adults with CMT report pain that may be neurogenic, musculoskeletal, or both.[32–34] Males with CMT1X may rarely present with strokelike symptoms, including dysarthria, ataxia, weakness, and transient white matter hyperintensities on MRI (**Figure 7-2** and **Case 7-2**).[35] Hearing loss, hip dysplasia, and sleep apnea are also reported findings with CMT.[36,37]

Electrophysiology

Electrodiagnostic studies, especially nerve conduction studies, are important tools to establish the presence of polyneuropathy, extent of damage, and demyelinating versus axonal physiology. Demyelinating forms of CMT are diagnosed based on uniformly slowed conduction velocities of 38 meters per second or less in the upper extremities, without evidence of conduction block or temporal dispersion (the latter two are features associated with acquired demyelinating neuropathies). Diagnosis of axonal forms is based on relatively normal velocities but prominently reduced sensory nerve action potential (SNAP) amplitudes, reduced CMAP amplitudes, or both.[6–9]

An Approach to Diagnosis and Genetic Testing

Obtaining a detailed family pedigree, ideally of three generations or more, is one of the most important steps in establishing a possible diagnosis in CMT. Patients should specifically be asked about early deaths in the extended family, consanguinity, and

FIGURE 7-1 Classification of Charcot-Marie-Tooth disease foot deformity. *A*, First stage: flexible cavus foot, reducible. *B*, Second stage: equinus and pronation of first ray (the column of bones and joints forming the medial border of the forefoot), possible reducible clawing of great toe. *C*, Third stage: equinus of whole forefoot, varus of the heel, irreducible clawing of great toe, no osseous structural abnormalities. *D*, Fourth stage: structural osseous changes, irreducible clawing of toes, possible tarsal movements. *E–G*, Fifth stage: firmly fixed deformity, pronounced osseous changes, irreducible clawing of toes with subluxation or luxation of metatarsophalangeal joints.

Reprinted with permission from Faldini C, et al, J Bone Joint Surg Am.[26] © 2015 The Journal of Bone and Joint Surgery, Incorporated. *journals.lww.com/jbjsjournal/Abstract/2015/03180/ Surgical_Treatment_of_Cavus_Foot_in.13.aspx.*

family members with walking problems without a clear diagnosis. The likelihood of genetic neuropathy is high in the patient with symmetric distal weakness and sensory loss starting in youth, pes cavus foot deformity with hammer toes, slowed conduction velocities on nerve conduction studies, and a strong family history. The diagnosis is not obvious when the family history is unknown or the mutation is de novo, the neuropathy is axonal, or symptom onset is later in life. Concluding that a patient may have a genetic polyneuropathy without a specific rationale is often not in the patient's best interest. More specific diagnosis provides the patient with the most accurate inheritance and risk information, which is important in making reproductive decisions. Different mutations progress at different rates and are associated with different comorbidities that physicians should look for in individuals who are at risk.

Motor nerve conduction velocities in the upper extremities can be used in diagnostic algorithms (**Figure 7-3**, **Figure 7-4**, **Figure 7-5**, and **Figure 7-6**).[12] The conduction velocity convention
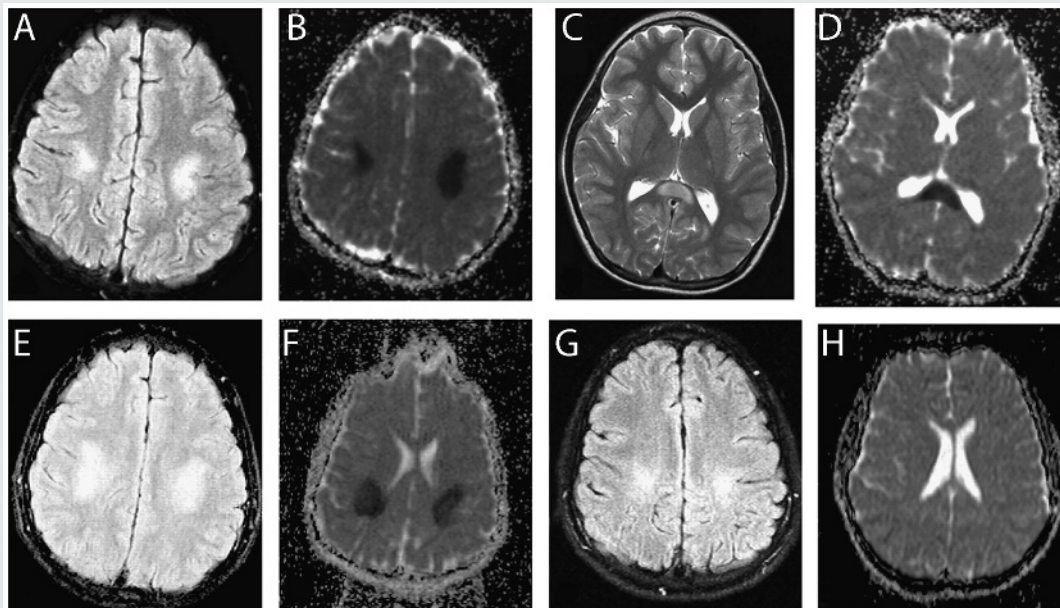
FIGURE 7-2 Imaging from a boy who presented at age 12 with three episodes of transient right face, arm, and leg motor and sensory symptoms over a 3-day period, lasting 4 to 10 hours. MRI on the third day showed abnormal increased T2 signal and reduced diffusion in the posterior portion of the centrum semiovale bilaterally (*A*, *B*), as well as in the splenium of the corpus callosum (*C*, *D*). He was noted to have hyporeflexia at the ankles and minimal weakness in ankle dorsiflexion; a family history of Charcot-Marie-Tooth disease (CMT) and subsequent genetic testing confirmed X-linked CMT. At age 15, he developed 2 days of mild right arm weakness and worsening handwriting, followed by 8 hours of severe hemiparesis of the left face and arm, dysarthria, and dysphagia, which lasted about 8 hours, with complete resolution. MRI performed 2 days later again showed symmetric abnormally increased T2 signal and diffusion reduction in the posterior frontal and parietal white matter bilaterally (*E*, *F*). Repeat brain MRI 11 weeks later showed a return to normal diffusion and improvement in the abnormal T2 signal, with some mild areas of persistently increased T2 signal in the white matter (*G*, *H*).

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Case 7-2

The 9-year-old son of a woman with mild Charcot-Marie-Tooth disease presented to the emergency department with 3 hours of sudden-onset slurred speech and left-sided clumsiness. Examination showed mild ataxia of the left arm and leg, slightly high-arched feet, and weakness of bilateral ankle dorsiflexion. MRI of the brain showed acute white matter changes in the posterior fossa. The patient's symptoms slowly improved over the next 24 hours as he was kept in observation and completely resolved over the next 10 days.

   Comment. This is a typical case of Charcot-Marie-Tooth disease type 1X with transient strokelike symptoms. The gap junction protein connexin 32 is not only expressed in Schwann cells but also in the central nervous system oligodendrocytes. Symptom resolution may take weeks, and, while rare, repeated attacks may occur.

used in this classification system defines normal as greater than 45 meters per second, intermediate as 35 meters per second to 45 meters per second, slow as 15 meters per second to 35 meters per second, and very slow as less than 15 meters per second.

Diagnostic algorithms work most effectively when used with patients suspected to be at risk for CMT. The percent of positive gene tests for CMT was 18% in one large study of a diverse population of patients with neuropathy,[38] compared with 60% in a
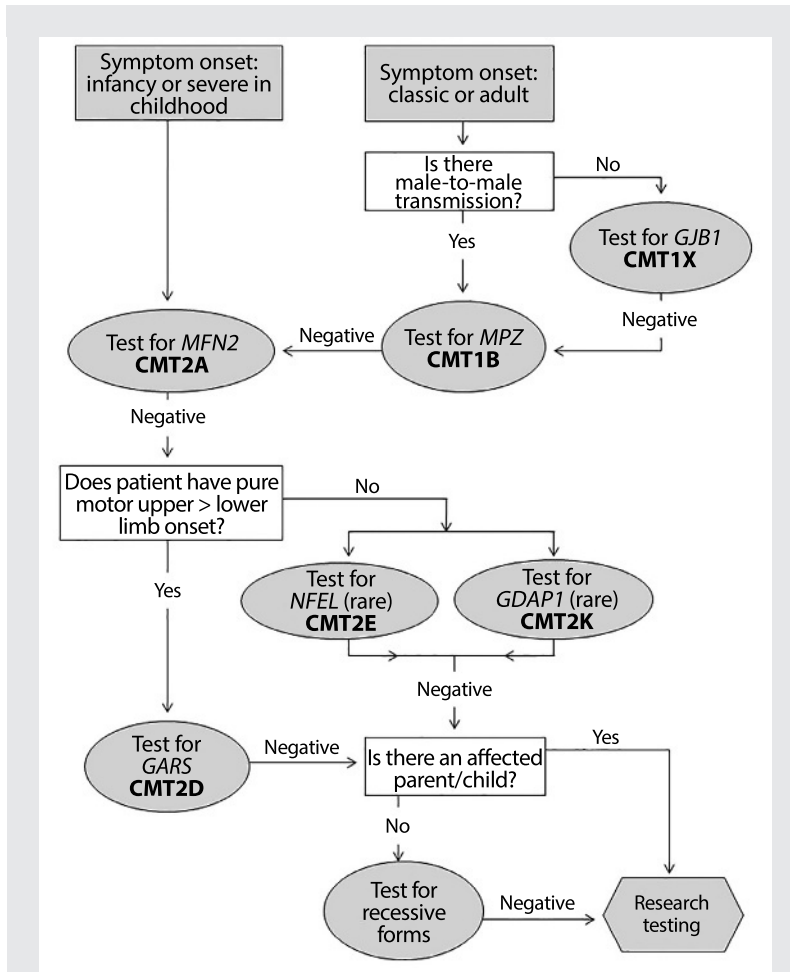

FIGURE 7-3 Axonal Charcot-Marie-Tooth disease with normal motor nerve conduction velocity. Algorithm for genetically diagnosing Charcot-Marie-Tooth disease in patients with normal motor nerve conduction velocities and evidence of axonal loss. In most cases, motor nerve conduction velocities in upper extremities are greater than 45 meters per second. However, in severe cases, these potentials may be absent. In those cases, it is important to test proximal nerves to ensure that the patient does not have a severe demyelinating neuropathy that can mimic axonal Charcot-Marie-Tooth disease. This algorithm is designed to be a general guide and is not intended to encompass every potential clinical scenario or all possible genetic etiologies.

CMT = Charcot-Marie-Tooth disease.

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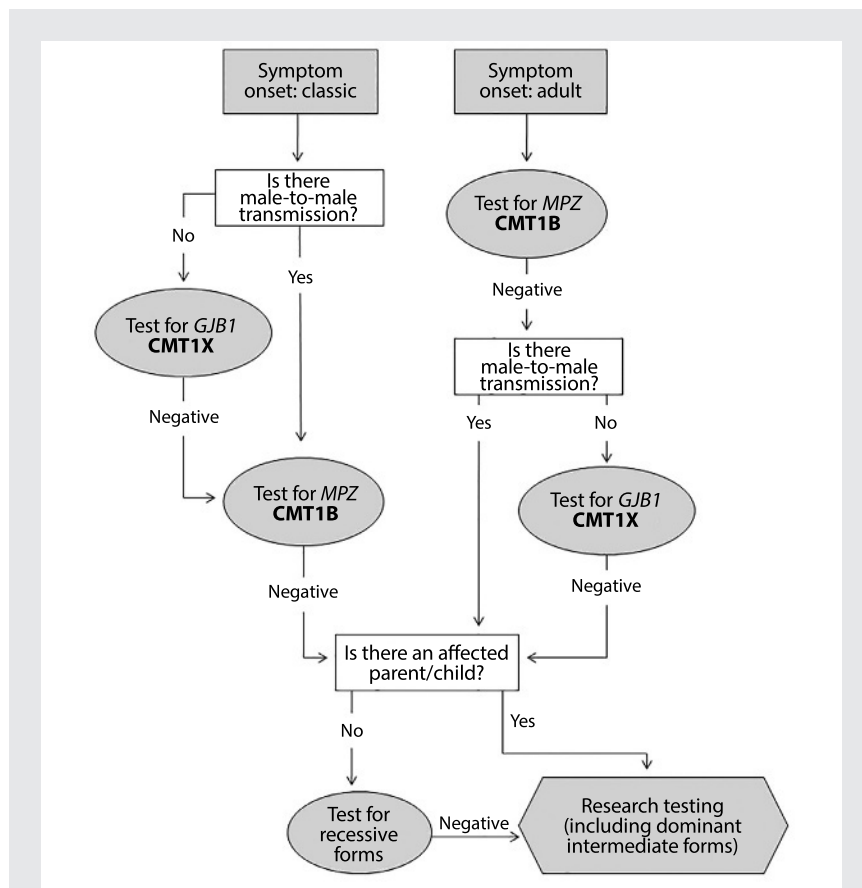
FIGURE 7-4 Charcot-Marie-Tooth disease with intermediate motor nerve conduction velocity. Algorithm for genetically diagnosing Charcot-Marie-Tooth disease in patients with intermediate upper extremity motor nerve conduction velocities. This algorithm is designed to be a general guide and is not intended to encompass every potential clinical scenario or all possible genetic etiologies.
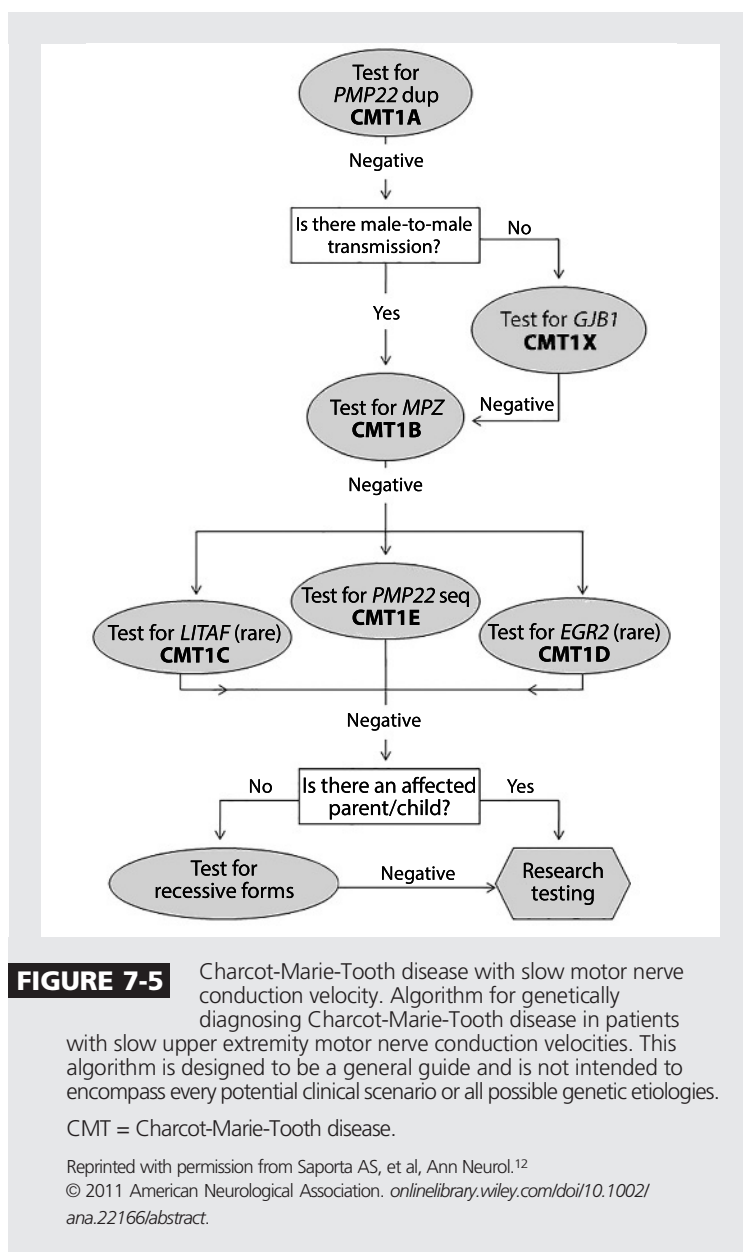
CMT = Charcot-Marie-Tooth disease.

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confirmed CMT population,[39] emphasizing the need to select the right patient for the right test.

Next-generation gene sequencing can search for mutations in panels of genes, including cost-effective core panels that look for mutations in *PMP22*, *MPZ*, *GJB1*, and *MFN2*, comprising the etiology of 90% of mutations in CMT patients.[12] Bulk gene surveys also increase the probability of identifying variants that may or may not be pathologic. Using a reference sequence database, such as the National Heart, Lung, and Blood Institute Exome Sequencing Project Exome Variant Server (*evs.gs.washington.edu/EVS/*), can help distinguish common polymorphisms from pathologic variants. Genetic counseling also serves an important role before testing to determine the appropriateness of the test and the most cost-effective testing strategy. After testing, genetic counseling can aid in the interpretation of results and direct future testing if needed.

FIGURE 7-5
Charcot-Marie-Tooth disease with slow motor nerve conduction velocity. Algorithm for genetically diagnosing Charcot-Marie-Tooth disease in patients with slow upper extremity motor nerve conduction velocities. This algorithm is designed to be a general guide and is not intended to encompass every potential clinical scenario or all possible genetic etiologies.

CMT = Charcot-Marie-Tooth disease.

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Management

Currently no disease-modifying treatment exists for CMT. Several large multicenter trials showed no effect of varying doses of ascorbic acid to treat CMT1A[40–42] but laid the groundwork for an international collaboration studying the natural history of CMT[39] and validating new outcome measures for future clinical trials.[43–45] Currently, an international trial is under way evaluating the safety and efficacy of PXT3003, a combination of naltrexone, baclofen, and sorbitol, in 300 patients with CMT1A (NCT02579759).[46]

Current patient management can be optimized with a multidisciplinary approach to care. An annual evaluation by a neurologist, physiatrist, or both can assess the patient's function and continuing needs. Additional ancillary services are important to retain functional independence. Physical therapy plays a major role in gait retraining,
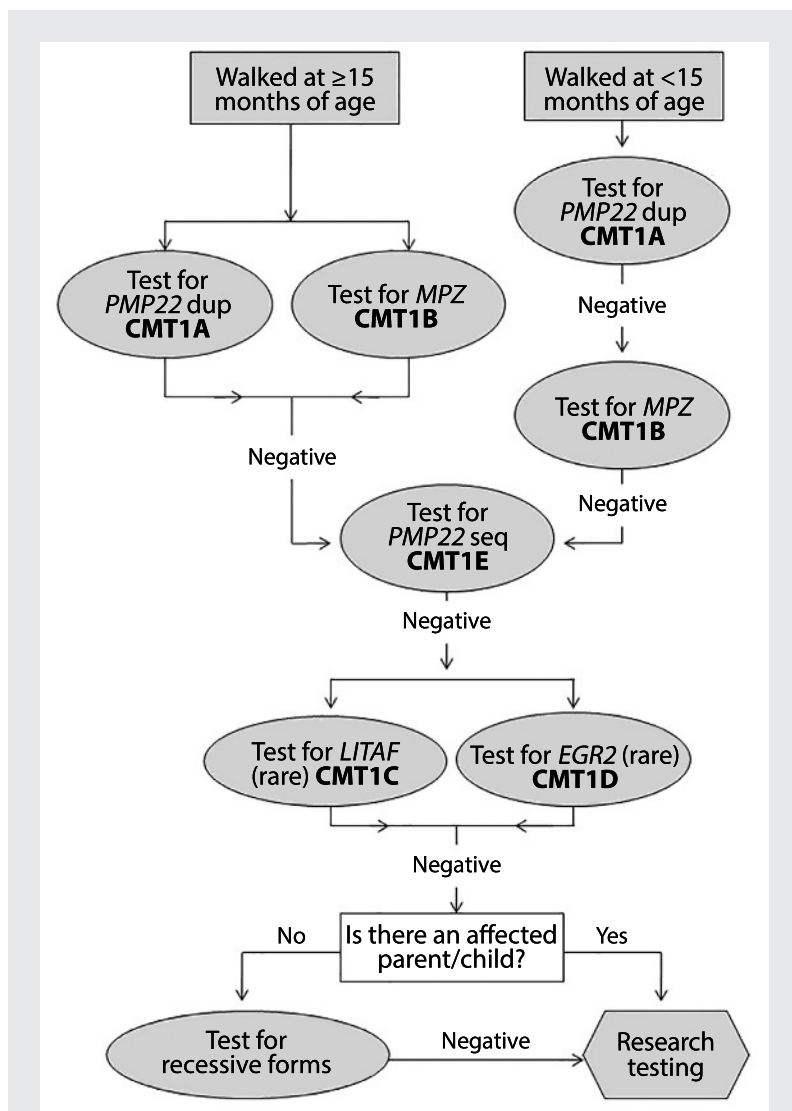
FIGURE 7-6 Charcot-Marie-Tooth disease with very slow motor nerve conduction velocity. This algorithm is designed to be a general guide and is not intended to encompass every potential clinical scenario or all possible genetic etiologies.

CMT = Charcot-Marie-Tooth disease.

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maintaining core muscle strength, energy conservation, and use of serial casting and night splinting to improve range of motion.[47–50] Occupational therapy can improve hand range of motion and provide tools to improve activities of daily living, such as buttoning clothing, opening bottles, and using eating utensils.[51] An orthotist may provide ankle-foot orthoses to improve gait and energy conservation, prevent falls, and reduce long-term damage to knee and hip joints.[52,53] Orthopedic interventions, such as tendon lengthening and tendon transfer, can help maintain long-term

function,[26,54] and guidelines are currently being developed to direct proper timing of interventions to optimize outcomes. Pain management for genetic neuropathies follows the same principles as for other chronic neuropathies, including encouragement of movement and activity, maintenance of a healthy body mass index, and avoidance of narcotics for long-term pain control.[55]

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES

The primary hereditary sensory and autonomic neuropathies (HSANs) predominantly affect myelinated and unmyelinated sensory nerves but also have motor nerve involvement.

Classification of Hereditary Sensory and Autonomic Neuropathies

The disorders are broadly classified into five types: HSAN I with autosomal dominant inheritance (the most common form, but genetically heterogeneous), HSAN II (autosomal recessive inheritance, early onset), HSAN III (familial dysautonomia, also known as Riley-Day syndrome, with autosomal recessive inheritance), and HSAN IV and HSAN V (congenital insensitivity to pain with anhidrosis; autosomal recessive inheritance). HSAN IV is also associated with developmental delay.[56]

Genetics of Hereditary Sensory and Autonomic Neuropathies

HSAN I is clinically heterogeneous, resulting from mutations in the serine palmitoyltransferase long chain base subunit 1 (SPTLC1), serine palmitoyltransferase long chain base subunit 2 (SPTLC2), atlastin GTPase 1 (ATL1), DNA methyltransferase 1 (DNMT1), and atlastin GTPase 3 (ATL3) genes. The SPTCL1 gene encodes for serine palmitoyltransferase, which synthesizes sphingolipids. Mutations in SPTCL1 result in neurotoxic sphingolipid metabolite accumulation.[57] HSAN II is caused by mutations in the WNK lysine deficient protein kinase 1 gene (WNK1). HSAN III is caused by mutations in the inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein gene (IKBKAP) and is limited to children of Ashkenazi Jewish descent. HSAN IV and HSAN V are caused by mutations in neurotrophic receptor tyrosine kinase 1 gene (NTRK1) and the nerve growth factor gene (NGF).[56]

Clinical Presentation

The typical presentation of patients with HSAN I includes sensory loss and neuropathic pain, sometimes with foot ulceration. While mean age of presentation is in the mid-twenties, patients have presented in their teens and in the late seventies to eighties. Autonomic and motor involvement can be variable. Some patients also have sensorineural deafness and dementia. Pes cavus and absent reflexes can be seen on examination.[58] HSAN II, involving both large and small nerve fibers, presents with loss of pain, temperature, pressure, and touch sensation. It is associated with self-mutilation of fingers and toes and can come to initial medical attention because of recurrent infections.[59] HSAN III presents with sympathetic autonomic dysfunction, including orthostatic hypotension, excessive salivation, gastrointestinal dysmotility, bladder dysfunction, decreased or absent tearing, absent fungiform tongue papillae, pupillary dilatation, hypohidrosis, and episodic hyperhidrosis. Episodes of dysautonomic crises can be triggered by physical and emotional stress.[60] Patients with HSAN IV present in infancy with mild to moderate developmental

delay; profound insensitivity to pain; and self-mutilation of digits, face, and mouth regions. HSAN IV differs from HSAN III by preservation of tearing and tongue papillae. Almost 20% of patients with HSAN die from hyperpyrexia before the age of 3.[61] HSAN V presents as a milder phenotype of HSAN IV; developmental delay, if present, is mild.[62]

Electrophysiology

Nerve conduction studies in HSAN are highly variable, reflecting the genetic heterogeneity. HSAN I mostly presents with an axonal sensory more than motor neuropathy; however, motor nerve conduction slowing into the demyelinating range can be seen.[63] HSAN II mainly shows an axonal neuropathy with absent sensory responses. HSAN III, similar to HSAN I, is associated with sensory more than motor involvement.[64] HSAN IV and HSAN V, which predominantly affect small myelinated and unmyelinated nerve fibers, typically show normal nerve conduction studies.

Diagnosis and Management

Prominent sensory and autonomic manifestations should raise concern for the diagnosis of HSAN. The diagnosis of HSAN I secondary to *SPTLC1* mutations should be considered in patients with a motor and sensory neuropathy, even in the presence of demyelinating features, particularly if the patient has marked sensory involvement and a family history (**Case 7-3**). Intrauterine diagnosis of HSAN III can now be made with about 98% percent accuracy using linked genetic markers in affected families,[65] and prenatal screening for this disease has contributed to its marked decline in the United States.[66]

Experimental studies have attempted to reduce the level of toxic sphingolipid metabolites to ameliorate HSAN I. Dietary supplementation with oral L-serine in *SPTLC1*-mutant mice reduced the sphingolipid metabolites and improved motor and sensory performance. Fourteen patients with HSAN I who received L-serine supplementation for 10 weeks also showed reduced sphingolipid metabolites.[67] However, despite these promising studies, no specific treatment exists for HSAN. Chronic sores and infections can lead to osteomyelitis and eventual amputation.[68] Management requires protection of the extremities, shoes that fit properly, orthotics for footdrop, treatment of callus formation, proper dressing of wounds to promote healing, and avoidance of trauma to the hands and feet.[69] Similarly, supportive care and symptomatic

Case 7-3

A 12-year-old girl had been repeatedly seen in urgent care over several months for symptoms of pain in the feet. Examination showed no visible foot deformities, limited strength examination because of pain, and allodynia to all sensory modalities at the feet with reduced perception to pin and vibration in the distal legs. Nerve conduction studies showed a demyelinating motor-sensory polyneuropathy. Genetic testing for *PMP22* deletion, duplication, and sequencing were negative. The girl's father had a long-term history of disabling pain in the feet. Testing for the *SPTLC1* mutation was positive.

Comment. The diagnosis of HSAN I secondary to *SPTLC1* mutations should be considered in patients with a motor and sensory neuropathy, even in the presence of demyelinating features, particularly if the patient has marked sensory involvement and a family history.

therapies are the mainstay of HSAN III management.

POLYNEUROPATHIES ASSOCIATED WITH GENETIC DISORDERS THAT HAVE SYSTEMIC NEUROLOGIC MANIFESTATIONS

Many systemic disorders caused by genetic mutations have a coexisting neuropathy. Often the neuropathy is overshadowed by the systemic manifestations of the disease. An overview of selected disorders having CMT-like features and specific treatment options are described in the following sections.

Spinocerebellar Ataxias

Spinocerebellar ataxias are a heterogeneous group of genetic disorders associated with cerebellar and brainstem dysfunction. Some spinocerebellar ataxia subtypes have an associated axonal peripheral neuropathy, with reduced muscle stretch reflexes and vibration sense. The presence of pyramidal and cerebellar signs points in the direction of spinocerebellar ataxia.[70]

Hereditary Spastic Paraplegia

Hereditary spastic paraplegia is a heterogeneous group of genetic disorders characterized by very slowly progressive symmetric lower extremity spasticity and weakness.[71] They are classified as "uncomplicated" if other neurologic signs are not present and "complicated" if they are accompanied by ataxia, seizures, memory problems, or axonal peripheral neuropathy. Bilateral lower extremity spasticity and hyperreflexia with extensor plantar responses on examination raises concern for hereditary spastic paraplegia.

Tangier Disease

Mutations in ATP binding cassette subfamily A member 1 (*ABCA1*), which regulates intracellular cholesterol trans-port, causes Tangier disease. Cholesterol esters deposit in the tonsils (orange tonsils), gastrointestinal tract, bone marrow, and Schwann cells. Children present with neuropathy characterized by fluctuating numbness and sensory loss with distal muscle weakness. Initiation of a low-fat diet may improve the neuropathy symptoms.[72]

Abetalipoproteinemia

Mutations in the microsomal triglyceride transfer protein cause this disease, resulting in failure to absorb and transport vitamin E, which causes a sensorimotor neuropathy as well as signs of myelopathy, vision impairment with retinitis pigmentosa, and fat malabsorption with steatorrhea. Typical clinical features, along with laboratory findings of acanthocytosis, very low triglyceride and total cholesterol levels, and absent β-lipoproteins, aid in the diagnosis. Treatment with vitamin E (150 mg/kg/d) and other fat-soluble vitamins can prevent and partially reverse the neurologic manifestations.[73]

Refsum Disease

Refsum disease, which is due to deficient activity of the peroxisomal enzyme phytanoyl-coenzyme A hydroxylase caused by mutations in the pytanoyl-CoA 2-hydroxylase (*PHYH*) gene, results in accumulation of phytanic acid, a branched-chain fatty acid typically present in dairy products and the meat of ungulates. Patients present in late teens to young adulthood with peripheral polyneuropathy, cerebellar ataxia, retinitis pigmentosa, and albuminocytologic dissociation. Strict reduction in dietary phytanic acid, or plasma exchange, can improve clinical manifestations.[74]

Lysosomal Storage Diseases

This is a group of heterogeneous neurodegenerative disorders characterized by accumulation of unmetabolized

macromolecules within lysosomes. Fabry disease, Krabbe disease, and metachromatic leukodystrophy are three of these disorders that exhibit peripheral neuropathy.

Fabry disease. Fabry disease is an X-linked glycolipid storage disease caused by mutations in the α-galactosidase A gene, resulting in systemic accumulation of glycosphingolipids in lysosomes of blood vessels, nerves, and organs and leading to progressive renal failure, cardiac disease, strokes, skin lesions, and a painful small fiber neuropathy. Enzyme replacement therapy (agalsidase) can improve all outcomes in Fabry disease, with greater benefits seen with earlier initiation of treatment.[75]

Krabbe disease. Krabbe disease is an autosomal recessive disorder caused by deficiency of the enzyme galacto-cerebrosidase, which causes toxic accumulation of galactosylsphingosine in the white matter of the central nervous system and peripheral nerves. While the majority of patients show infantile onset of symptoms (irritability, spasticity, and developmental delay, progressing to death by age 2), 10% to 15% have a later onset with slower progression, presenting with spastic paraparesis. The peripheral neuropathy associated with Krabbe disease is a uniformly demyelinating polyneuropathy.[76]

Metachromatic leukodystrophy. Metachromatic leukodystrophy is an autosomal recessive lysosomal storage disease caused by mutations in the arylsulfatase A gene (*ARSA*), resulting in accumulation of sulfatides in cells that produce myelin in the central and peripheral nervous systems. The most common presentation is in late infancy, with patients losing speech, becoming weak, developing gait disturbances, and gradually becoming hypertonic to the point of rigidity until they succumb in childhood. Of individuals with metachromatic leukodystrophy, 10% to 15%

have an adult onset of symptoms and present either with psychiatric manifestations or spastic paraparesis. The peripheral neuropathy associated with metachromatic leukodystrophy is a uniform or nonuniform demyelinating polyneuropathy.[77]

CONCLUSION

The genetic polyneuropathies are a heterogeneous group of rare disorders with the common feature of disrupted peripheral nerve function. The discovery of the underlying genetic mutations responsible for CMT and other genetic neuropathies has helped identify the molecules needed for normal peripheral nerve function, leading to efforts to expand diagnostic and treatment options for these disorders.

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