SVOA Neurology

ISSN: 2753-9180

ScienceVolks Open Access

Review

Charcot-Marie-Tooth Disease – Clinician's Perspective Overview

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***Received:** August 25, 2022 **Published:** September 19, 2022*

Abstract

Charcot–Marie–Tooth (CMT) disease is the most common degenerative disorder of the peripheral nervous system (PNS) and among the most common inherited neurological disorders. Currently incurable, CMT represents a group of inherited neuropathies, with diverse underlying genetic mechanisms, from point mutations to copy number variation and allelic heterogeneity, age-dependent penetrance, and variable expressivity. Typical phenotype is presented by chronic sensory-motor neuropathy, causing significant and slowly progressive disability with normal life expectancy. Rare infants develop severe congenital disabilities whereas some patients have few if any disease-related health issues. Over the past three decades over fifty genes carrying causative CMT mutations have been identified and a wide range of therapeutics have been proposed following two approaches: disease-specific (targeted to each CMT form unique mechanism) and common approach (targeted to pathways shared by several or all CMT types), including gene silencing, gene replacement therapies, and small molecule treatments. Although CMT is still incurable, potentially curative treatments are investigated currently like in the ongoing PXT3003 trial.

***Keywords:** Charcot Marie Tooth disease, peripheral nervous system, neuropathy, nerve conduction studies, inheritance, clinical presentation*

Introduction

CMT disease encompasses a heterogeneous group of inherited disorders presenting with chronic, progressive motor and sensory neuropathy, also known as HMSNs (hereditary motor and sensory neuropathies).

These genetically distinct disorders reflect a genetic spectrum that spans more than eighty so far known genes still with a similar clinical presentation with a broad spectrum of variable motor, sensory, autonomic, and other organs involvement, making classification and diagnosis establishing complex and challenging.

Historical milestones

The condition was first described more than 130 years ago by Professor Jean Martin Charcot and his student Pierre Marie *("Progressive Muscular Atrophy)* who were presuming that the primarily affected region in their five described patients is the spinal cord [1]. Three months later Tooth localized pathology to the peripheral nerves *("Peroneal Type of Progressive Muscular Atrophy")* [2]. Dejerine and Sottas, while observing hypertrophic interstitial neuritis leading to onion bulb peripheral nerves formations, described more severe infancy-onset cases in two siblings [3] and Roussy and Levy described cases associated with static tremor as a characteristic feature [4].

Before Charcot, Marie, and Tooth's reports, patients with similar conditions had been described by Virchow, Eichhorst, Friedreich, Osler, and others. [5,6,7,8]

Pathophysiology and Classification

In the late 1960s, neurophysiologic testing allowed the classification of CMT into 2 groups based on nerve conduction studies and family history determined mode of inheritance [9]:

1) CMT1 with slow nerve conduction velocities (NCV) <35 m/s and histologic features of a hypertrophic demyelinating neuropathy (hereditary motor and sensory neuropathy type 1 (HMSN1). It is typically presented by slowly progressive distal weakness, muscle atrophy, and sensory loss associated with foot deformity (pes cavus) and bilateral foot drop and becoming symptomatic between patients' years 5-25 and less than 5% wheelchair dependent with normal life span.

2) CMT2 with relatively normal NCV >45m/s and axonal and neuronal degeneration (HMSN2) resulting in low action potential (AP amplitudes); also, with distal muscle weakness and atrophy but less disabling and sensory loss.

Subtypes with NCV within the intermediate range are called DI-CMT, defined as NCV 35-45 m/s and relatively typical clinical findings.

The classification has been expanded and modified as 80+ new causative genes were identified.

The majority of patients have an autosomal dominant (AD) pattern of inheritance, although both X-linked dominant and autosomal recessive (AR) demyelinating (CMT4 or AR-CMT1) and axonal (AR-CMT2) forms exist. Sporadic cases also occur as a new mutation in a patient with no familiar history of CMT.

As more genes causing CMT were identified and as the overlap of neuropathy phenotypes and modes of inheritance became apparent, in 2018, Magy et al proposed a gene-based classification of inherited neuropathies.[10]

Demographics

Internationally, CMT is among the most common heritable neurologic disorders with an estimated prevalence of 10 cases per 100,000 worldwide [11], in people of all races and ethnic groups.[12]

In the United States CMT is the most common inherited neurologic disorder, approximately 1 person per 2500 population [11], less common among black people (might be due to the lower frequency of the specific mutations or protection through unknown disease-modifying genes).

Overall, CMT1A accounts for about 60% of all AD neuropathies, CMT2 for about 22%, CMTX (X-linked) for about 16%, and CMT1B for approximately 1.6%.[13] The other forms are rarer, except in populations with high consanguinity, where AR phenotypes (CMT4) are significantly more common.

CMT may have a more severe phenotype in men, possibly because of environmental (nerve trauma) or X-linked neuroprotective factors, but, with great phenotypic variability between and within families. Also, CMTX, while more severe in men, is commonly associated with obvious, even severe, disease in women, most likely because of unequal inactivation of the X chromosome.

Clinical Presentation

CMT phenotype is typical despite genetic heterogeneity [14] and cardinal features of CMT are related to length-dependent sensory-motor neuropathy (SMN).

Although classical neuropathy, in CMT, central nervous system (CNS) features and/or non-neurologic manifestations, have also been described.

Age of onset varies and depends on CMT form, type of inheritance, familiar phenotype, and environmental factors. Diagnosis is usually not made until late adolescence or early or late adulthood, except for DSS and other severe phenotypes, mostly because most symptoms starting in childhood are discrete and obvious only to families with previous knowledge of the condition existing. Frequently, asymptomatic individuals are detected during one diagnosed relative family screening. In childhood, careful observers may notice delay in motor milestones, clumsiness, unusual gait, frequent ankle injuries, and specific toe walking.[15] Adolescents may present with thin lower legs, steppage gait, or foot deformities.

In typical CMT, symptoms are chronic and slowly progressive, with weakness beginning in the distal lower extremities muscles before it affects the upper ones. The first complaint is most often walking difficulty with tripping, ankle sprains, and falls. As weakness progress, foot drop occurs with steppage gait and classical foot deformity ("pes cavus") reflecting deep hypotrophy of intrinsic foot muscles with frequent (painful) calluses, ulcers secondary skin infections become obvious.

Hand weakness is manifested as poor finger control, handwriting, difficulty using zippers and buttons, and clumsiness in manipulating small objects. [16].

Patients usually do not complain of numbness as not perceiving sensation lacking but pain and muscle cramps may be common and relieved by wearing ankle-foot orthoses.[17] Scoliosis is common and leads to back pain.

Autonomic symptoms usually are absent, with seldom reported impotence.

Symptoms may be episodic with focal asymmetry in patients with hereditary neuropathy with liability to pressure palsy (HNPP) or with proximal muscles weakness (in patients with inherited brachial plexus neuropathy (IBPN) or hereditary neuralgic amyotrophy (HNA).

Thickened, very firm superficial cervical and upper extremities nerves are noticeable in more than 25% of patients with CMT1 or DSS.

Life expectancy is normal in most patients with a variable degree of disability according to the CMT subtype, between and within families, even between identical twins affected. HNPP patients have a good prognosis with about 10% incomplete recovery from episodes of nerve palsy rate. Rarely, patients with CMT may have laryngeal dysfunction, aspiration and voice problems, and, seldom, respiratory failure. Patients with DSS are often disabled in early childhood. CHN can lead to early death.

The classification has been expanded and modified as 80+ new causative genes were identified.

Table 1: CMT Subtype; Gene/Product/Locus; Inheritance; Phenotype.

Disorder	Phenotype	Gene/Product/Locus
CMT1: Dominant; Demyelinating *accounts for more than two-thirds of all cases of CMT* *onset - first 2 decades of life: weakness and wasting predominantly in the distal legs, deep tendon reflexes absent in demyelinating or present in axonal forms* *foot deformity (e.g., pes cavus, hammertoes, and high-arched feet) with hands affection follow* *in adulthood, the distal mild sensory loss is common (proprioception loss, decreased pain, and temperature sensation in typical stocking and glove distribution, reports of cold feet, hair loss, or leg edema). Patients may deny sensory symptoms despite the marked loss of sensation on examination.* *paresthesias are typically less severe in marked contrast to acquired neuropathies.* *autosomal recessive (AR) inheritance with late onset in earlier generations must be considered when family history is absent*		
CMT 1A	"Classical", most common form, <60% of all CMT1 patients symptoms develop in the first two decades of life and progress very slowly most patients remain ambulatory lifespan expected hand weakness appears not more than ten years after legs affection one of the highest de novo mutation rates	PMP22 duplication Peripheral myelin protein 22 17p11.2
CMT 1B	Somewhat typical phenotype, often with more severe presentation (pronounced calf wasting) wide range of severity, from DSS* to milder later-in-life onset forms	P_0 Myelin protein zero 1q22
CMT 1C	Distal weakness, atrophy, and sensory loss with slow NCV scores	SIMPLE, LITAF Simple 16p13.1-p12.3
CMT 1D	Most cases are severe while a few have milder phenotypes presenting later in life	EGR2 Early growth response protein 2 10q21.1–q22.1
CMT1E		PMP22, Peripheral myelin protein22, 17p11.2
CMT 1F	A very small percentage of cases	NEFL, Neurofilament triplet L protein, 8p21
CMTX1	Second most common CMT form, 10-16% of all cases onset typically in adolescence or childhood normal lifespan may have asymmetrical atrophy features (especially of intrinsic hand muscles), paresthesias, and sensory loss males are affected more severely (first decade of life) with NCV resembles CMT1 males cannot pass the defect to sons but will pass it to all daughters females may be mildly affected, symptoms free with only subtle signs or, rarely, with the more severe presentation, because of predominant inactivation of the normal X chromosome with NCV resembles CMT2 females have a 50% chance of passing the mutation to either sons or daughters	GJB1 (gap junction beta 1 protein) connected to connexin-32, Xq13
CMTX2		Unknown/Xp22.2
CMTX3		Unknown/Xq26
HNPP		PMP-22/17p11

Dejerine-Sottas* (HMSN 3)		PMP-22, 8q23, EGR2 17p11,8q23,10q21
DI-CMT	Rare, "dominant intermediate" CMT form both myelin and axon equally damaged presentation similar to CMT1 and 2 variants	
CMT2: Dominant; Axonal About one-third of all dominant CMT cases wider age range for onset between ages 10 and 20 years and more variation in the degree of disability. presentation similar CMT1 with deep tendon reflexes slightly more likely to be maintained, greater atrophy and distal leg weakness with relatively less hand weakness characteristic features such as enlarged nerves and near-pathognomonic neurophysiologic findings absent		
CMT 2A	Commonly presented in the first decade of life wide spectrum of severity from mild to (more often) wheelchairs restricted ambulation distal weakness, hyporeflexia, wasting, mild pan-modal sensory loss, can include optic atrophy	MFN2 Mitofusin 2 1p36
CMT 2B	Possibly pure sensory neuropathy and not CMT neurophysiologic findings early in life, clinical onset much later severe ulceration problems	RAB7 Ras-related protein Rab-7 3q21
CMT2B1		*LMNA*/Lamin A/C/1q21.2
CMT 2B2		Unknown/19q13.3
CMT 2C	Very rare form usually starts in the first decade of life mild sensory loss limbs, diaphragm, intercostal muscles, and vocal cords paresis that can lead to early death	TRPV4 12q23-q24
CMT 2D	Purely motor or sensorimotor neuropathy occurs between 16-30 years may have a worse hand than leg weakness and slow progression with tendon reflexes absent in the upper and decreased in lower extremities	GARS Glycyl-tRNA synthetase 7p14
CMT 2E	Onset in the second and third decades of life, slow progression worse leg weakness with pes cavus in all patients older than 20 years sometimes associated with hyperkeratosis	NF-68 neurofilament light gene 8p21
CMT 2F	Onset between ages 15-25 years, slow symmetric progression, disability after 15-20 years, life span not restricted worse distal weakness and legs muscles atrophy wasting of arms with clawing occurs several years later. depressed or absent deep tendon reflexes observed at an early stage. mild-to-moderate sensory impairments in stocks and gloves fashion in all patients.	HSPB1 (HSP 27) Heat-shock protein B1 7q11
CMT 2G		Unknown/12q12
SMT 2H		GDAP1/8q21.3
CMT 2L		HSPB8/12q24
CMT 2 P_0		P_0/1q22

AR-CMT2:Recessive; Axonal		
AR-CMT2A	Lamin A/C	1q21
AR-CMT2B		19q13
CMT4	Rare, various phenotypical presentations more severe than AD inherited disorders often with systemic symptoms, such as cataracts and deafness CMT4A and CMTB are demyelinating and CMT 4C is axonal neuropathy	
CMT 4A	Clinical onset at age 2 Delayed developmental milestones of sitting or walking Many patients wheelchair dependent by the end of the first decade of life Hoarse voice and vocal cord paresis reported	GDAP1 Ganglioside-induced differentiation protein 1 8q13-21
CMT4B	Presents with focally folded myelin sheaths in nerve biopsies patients become symptomatic early in life (average onset at 34 months) both proximal and distal weakness present	
CMT 4B1		MTMR2/11q23
CMT 4B2		SBF2/MTMR13/11q15

*More than one type of CMT may be referred to as Dejerine-Sottas syndrome (DSS, HMSN3), coined before the genetic causes of CMT were identified to describe severely disabled patients who developed CMT in infancy, by 3 years of age, delayed motor milestones and severe motor, sensory and skeletal defects. DSS was thought to be AR inherited, but AD mutations of PMP22, MPZ, EGR2, PRX, and GDAP have been discovered currently.

**Term congenital hypomyelination (CH) is originally used to describe peripheral nerves so abnormal that suggesting a developmental failure of the PNS myelination. Patients with CH were hypotonic within the first year of life, had developmental delays in walking, and had swallowing or respiratory difficulties. Some patients with CH were considered "floppy" infants. It is difficult to distinguish between DSS and CH since both have severe pathological changes on sural nerve biopsies and both have very slow NCV.

Diagnostic Considerations

When considering an inherited neuropathy, the goal is to prove or refute this diagnosis and possibly discover coexisting treatable conditions such as nerve entrapment and acquired neuropathy.

Uniform conduction slowing distinguishes most type CMT1 cases from acquired disorders such as chronic inflammatory demyelinating polyneuropathies (CIDP), in which conduction slowing typically varies along the same nerve and between nerves. The Guillain-Barré syndrome (GBS) also has asymmetric slowing and more rapid onset. Dispersion and conduction block are rarely described in CMT and are more compatible with acquired neuropathies.

If the patient has neuropathy and positive family history, CMT becomes likely and slow NCV distinguishes CMT1 from CMT2.

Workup

The workup must address acquired causes of neuropathies such as endocrine, infectious, immunologic, medication, vitamin and nutritional abnormalities, deficiencies, and nerve compression.

Clinical examination and electrodiagnostic study findings often cannot definitively establish a precise diagnosis because of the clinical syndromes overlap and the significant variability between family members.

Establishing inheritance patterns, if available, can narrow the differential diagnosis and eliminate the need for genotyping but the limitations must be recognized because:

a) Testing is possible only for mutations in known genes sufficiently common to make commercialization feasible

b) Tests do not exclude mutations with 100% certainty and

c) de novo mutations are particularly common with *PMP22,* but they can occur with any gene.

Screening tests should include rapid plasma reagin, vitamin B-12, folate, antinuclear antibodies, erythrocyte sedimentation rate, thyroid-stimulating hormone, serum and urine protein electrophoresis and urine protein electrophoresis.

Imaging Studies

In CMT 1A, high-resolution ultrasonography (US) of the median nerve and other peripheral nerves may serve as an adjunct to NCS [18].

MRI can demonstrate enlarged spinal roots and limb nerves.

MRI of LE muscles can help in the differentiation between CMT1A (significant involvement of peroneal nerve innervated muscles) and CMT2A (fatty infiltration involving superficial posterior compartment muscles) and can be used to follow the progression of the disease in patients with CMT [19].

Neuropathologic Studies

Interpreting histologic studies from the era before modern genetic classification is difficult. With the advent of genetic testing, muscle and nerve biopsy are now rarely performed for diagnostic purposes.

Electrodiagnostic studies

Electromyography (EMG) and nerve conduction studies should be performed first if CMT disease is suggested. [20].

While significant variation in NCV exists between and within families, this parameter does not predict severity, except for the very low (i.e., < 5 m/s) velocities observed in Dejerine-Sottas syndrome (DSS) and congenital hypomyelination neuropathy (CHN).

The distinction between demyelinating and non-demyelinating CMT is not always clear. Median motor NCV is below 38 m/s in CMT1 and above in CMT2.

Conduction values are symmetric in CMT1, and few differences exist between proximal and distal segments. Nerves are often refractory to stimulation or require higher amplitude and prolonged stimulation. CMT1 is typically associated with diffuse and uniform conduction slowing. As stable and secure, conduction blocks or dispersion are rare. Sensory NCV in all CMT1forms is reduced or unrecordable. Sensory loss correlates with median sensory NCV and CMAP amplitudes. F-wave responses are prolonged and EMG shows evidence of denervation. Brainstem auditory evoked potentials (EP) can demonstrate the delay in wave 1.

In CMTX1 due to CX32 mutations, NCS findings are more variable, and axonal features are more common. Asymmetry may be prominent, and conduction block and dispersion have been observed. The nerve conduction velocity range is 25-43 m/s in men and 31-50 m/s in women. Because of the CNS expression of CX32, subclinical CNS involvement has been documented in some patients who have abnormal visual, motor, and brainstem auditory EP. MRI abnormalities have been reported as well.

Nerve conduction studies in CMT2 typically reveal mild slowing, with median nerve velocities above 38 m/s, reduced compound motor action potential (CMAP) amplitudes to less than 4 mV, and reduced sural nerve sensory action potential (SNAP) amplitudes to less than 10 mV or sural nerve sensory responses absent. Phrenic CMAP also shows reduced amplitudes. EMG reveals signs of chronic denervation.

In children, NCS findings are normal at birth, except for children with CHN and DSS. As the PNS matures, abnormal NCV develops being then stable for life. Changes are fully manifest at age 2-4 years, even in asymptomatic patients.

In HNPP, background polyneuropathy independent of superimposed entrapment neuropathy, which becomes more prevalent with age, is typically present. The variability within families may be considerable. In patients with PMP22 deletion, a multifocal polyneuropathy with diffusely increased distal motor latencies (DML) is typical, with more normal motor conduction velocities, and diffuse reduction of sensory nerve action potentials, and multiple instances of focal slowing at anatomic entrapment sites. These features, including focal slowing, were also observed in several patients with a clinical CMT rather than an HNPP phenotype; this indicates that NCS findings suggest PMP22 deletion, even when the clinical features do not suggest this. Neurophysiologic findings were similar in oligosymptomatic and asymptomatic patients and became characteristic as early as the second decade of life.

EMG findings are normal in proximal muscles but may show distal changes with increased motor unit potentials (MUP) duration and amplitude. Active denervation (increased insertional activity and fibrillation potentials) is not prominent in unaffected muscles.

In HNA, evidence for generalized neuropathy is absent.

Disorder	Gene/Product/Locus	Locus
CMT1: Dominant; Demyelinating		
CMT 1A	PMP22/Peripheral myelin protein 22	17p11.2
CMT 1B	P_0 /Myelin protein zero	1q22
CMT 1C	SIMPLE,LITAF/simple	16p13.1-p12.3
CMT 1D	EGR2/ Early growth response protein 2	10q21.1–q22.1
CMT1E	PMP22/Peripheral myelin protein 22	17p11.2
CMT 1F	NEFL/ Neurofilament triplet L protein	8p21
CMTX1	GJB1 (Connexin-32)	Xq13
CMTX2	Unknown	Xp22.2
CMTX3	Unknown	Xq26
HNPP	PMP-22	17p11
Dejerine-Sottas (HMSN 3)	PMP-22 8q23 EGR2	17p11 8q23 10q21
DI-CMT (Intermediate NCV)	DNM2 10q24 1p34 P_0 CMT-X	19p12 10q24 1p34 1q22 Xq13
CMT2: Dominant; Axonal		
CMT 2A	MFN2/ Mitofusin 2	1p36
CMT 2B	RAB7/Ras-related protein Rab-7	3q21
CMT2B1	*LMNA*/ Lamin A/C	1q21.2
CMT 2B2	Unknown	19q13.3
CMT 2C	TRPV4	12q23-q24
CMT 2D	GARS Glycyl-tRNA synthetase	7p14
CMT 2E	NF-68	8p21
CMT 2F	HSPB1 (HSP 27) Heat-shock protein B1	7q11
CMT 2G	Unknown	12q12
SMT 2H	GDAP1	8q21.3
CMT 2L	HSPB8	12q24
CMT 2 P_0	P_0	1q22
AR-CMT2: Recessive; Axonal		
AR-CMT2A	Lamin A/C	1q21
AR-CMT2B		19q13
CMT 4A	GDAP1 Ganglioside-induced differentiation protein 1	8q13-21
CMT 4B1	MTMR2	11q23
CMT 4B2	SBF2/MTMR13	11q15
CMT 4C	SH3/TPR	5q23
CMT 4D (Lom)	NDRG1	8q24
CMT 4E	EGR2	10q21
CMT 4F	Periaxin	19q13
CMT 4G	HK1	10q23.2
CMT 4H	FIG4	6q21
Dejerine-Sottas (HMSN 3)	P_0 CMT 4F	Autosomal
Congenital hypomyelination neuropathy	P_0 EGR2 PMP-22	Autosomal
CCFDN	CTDP1	18q23
Giant axonal neuropathy	Cytoskeletal protein gigatons	Unknown

Prognosis

Because CMT1A occurs relatively frequently as a new mutation, it will remain a prevalent condition, even if affected patients have no children.

Secondary prevention focuses on awareness and avoidance of intercurrent medical problems or interventions that can lead to systemic or focal neuropathies, such as diabetes mellitus, hypothyroidism, vitamin deficiencies, neurotoxic drugs, carpal tunnel syndrome, and prolonged immobilization of limbs during surgery.

In most inherited neuropathies, the life span is not altered. Most patients need some kind of ankle support at some time in their life. Disability is highly variable and difficult to predict.

In general, weakness due to CMT rarely spreads to the proximal leg or arm muscles. If progression accelerates, other, acquired or inherited conditions should be considered.

Patients with DSS are more likely to lose their ability to ambulate independently and patients with HNPP have an excellent quality of life.

Patients with CMT are encouraged to lead a full lifestyle, avoiding exhaustion and, in HNPP patients, avoiding activities that can injure nerves. Increased risk of depression and maladjustment is present in all patients' age groups.

Orthotics and ankle-foot orthoses (AFO) enable patients to continue performing enjoyable activities while preventing falls and Achilles tendon shortening while extending near-normal ambulation.

Depending on the degree of foot deformities, patients may benefit from Achilles tendon lengthening, tendon transfers, hammertoe correction, and release of the plantar fascia. Treatment of secondary joint problems at more proximal sites and in the evaluation and treatment of scoliosis is considered when needed.

Conclusion

CMT encompasses a wide variety of hereditary neuropathies, spanning a large number of gene mutations and cellular abnormalities. Multiple neurophysiological deficits are identified in persons with CMT, including disruption of axonal transport, abnormalities in protein transport or genes responsible for RNA processing, misfolding and retention in the endoplasmic reticulum. The development of effective disease modifying treatments for CMT is challenging because significant number of genes linked with significant clinical heterogeneity. Research is needed to develop rehabilitative strategies to limit disease burden and improve psychosocial and physical performance. Clinical management should be multidisciplinary. Goals should include maximizing functional independence and quality of life while minimizing disability and secondary morbidity.

Conflict of Interest

The authors declare no conflict of interest.

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Citation: Gavrilovic A, Komatina N. "Charcot-Marie-Tooth Disease – Clinician's Perspective Overview". *SVOA Neurology* 2022, 3:5, 199-207.