BMJ Best Practice

Charcot-Marie-Tooth disease

Straight to the point of care

Last updated: May 09, 2024

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Summary

Charcot-Marie-Tooth (CMT) disease comprises a group of hereditary peripheral neuropathies with different genetic abnormalities.

Absence of a family history does not rule out the condition.

Key features include clumsiness as a child, weak ankles, symmetrical nerve conduction changes, and a steppage gait (lifting legs up excessively to clear the toes).

Pes cavus (high foot arches with hammer toes) and distal atrophy of the hands and legs are characteristic.

Genetic testing should be carefully considered.

Appropriate rehabilitative and orthotic treatments can keep patients highly functional.

Definition

CMT disease, also known as hereditary motor and sensory neuropathy (HMSN), encompasses the majority of hereditary peripheral neuropathies. Both motor and sensory nerves are typically affected, with symmetrical changes noted on nerve conduction studies. Nerve conductions can be either demyelinating (velocity <38 m/second in ulnar nerve), or axonal (reduced amplitudes with >38 m/second velocity), or have features of both. CMT is a genetically heterogeneous condition, with over 90 genes and loci known to cause the condition when mutated.

Epidemiology

Charcot-Marie-Tooth (CMT) disease is the most common inherited neurological disorder, affecting at least 1 in every 2500 people, and as many as 1 in 1200 in some countries.[1] [2] The condition affects people of all ages, sexes, and ethnicities, and prevalence is constant throughout the world.

The most common subtype of CMT is CMT1A due to a duplication of PMP22 on chromosome 17, which accounts for 50% of all cases, and for 70% of all demyelinating cases (CMT type 1), leading to a prevalence of 1 in every 5000 people.[3] The second most common subtype is CMT1X due to mutations of GJB1 (connexin 32), which accounts for approximately 10% of all cases, and for 20% of patients with demyelinating conductions in whom the CMT1A duplication has already been excluded.

The most common subtype of axonal CMT (CMT type 2) is CMT2A due to mutations in mitofusin, and, of those with CMT2, 20% to 25% will have CMT2A.[4]

Recessive mutations (CMT type 4) account for 5% to 10% of all cases, but may account for up to 50% of patients who have consanguineous parents.[5]

Hereditary neuropathy with liability to pressure palsies (HNPP) due to a deletion of PMP22 has a prevalence of at least 16 per 100,000, although its subtle features suggest that it is underdiagnosed.[6] One study found HNPP accounted for about 6% of all CMT cases.[7]

Aetiology

Charcot-Marie-Tooth (CMT) is a genetic condition, and there are no known risk factors for the condition, other than a family history. Depending on the inheritance pattern of the CMT subtype, the risk of passing the condition on to the next generation differs. In autosomal dominant forms (CMT1 [defined as both demyelinating conductions and dominant inheritance], CMT2 [axonal conductions and dominant inheritance], or dominant-intermediate [intermediate conduction velocities and dominant inheritance]), one parent with the genetic disorder is sufficient to pass on the condition, and each child has a 50% chance of inheriting the disorder. In autosomal recessive forms (CMT4 [any conduction velocity, with recessive inheritance]), both parents carry the genetic mutation, but do not usually have clinical manifestations of the disease, as they have one working copy of the gene. In such cases, each child has a 25% chance of getting the disorder, a 50% chance of being a carrier, and a 25% chance of inheriting two working copies of the gene and being an unaffected non-carrier. Females with an X-linked form of CMT have a 50% chance of passing on the condition, and males with an X-linked form have a 100% chance of passing on the condition to daughters but a 0% chance of passing it on to sons.

CMT is a genetically heterogeneous condition, with over 90 genes and loci known to cause the condition when mutated. The most common subtype is CMT1A, caused by a duplication of the PMP22 gene. The second most common subtype is CMT1X, caused by a mutation in the GJB1 gene. The most common subtype of axonal CMT (CMT type 2) is CMT2A, caused by mutations in the MFN2 gene. The reciprocal mutation to CMT1A, a deletion of the PMP22 gene, causes hereditary neuropathy with liability to pressure palsies (HNPP), and is the third most common type of CMT overall.[7]

Pathophysiology

The pathophysiology of the different disorders that comprise CMT is dependent on the specific genetic disorder. Genetic mutations primarily affecting the Schwann cell and myelin lead to demyelinating CMT (CMT1), while those affecting axons lead to axonal CMT (CMT2). Clinical disability correlates primarily with axonal loss. Research is focused on understanding the interaction between the Schwann cell and the axon.

Classification

Subtypes of Charcot-Marie-Tooth (CMT) disease

CMT type 1 (CMT1)

- Autosomal dominant with slow nerve conduction velocity, showing demyelination.

CMT type 2 (CMT2)

- Autosomal dominant or recessive inheritance with normal nerve conduction velocity and reduced amplitudes, showing axonal degeneration.

CMT type 4 (CMT4)

- Autosomal recessive inheritance, regardless of nerve conduction study features.

CMT type X

- X-linked inheritance, regardless of nerve conduction study features.

Dominant intermediate CMT (DI-CMT)

- Autosomal dominant inheritance with intermediately slowed nerve conduction velocity of 30-45 m/second in the median or ulnar nerves.

Hereditary motor neuropathy (HMN)

- Only findings of a hereditary motor neuropathy, with little to no sensory involvement.

Hereditary sensory neuropathy (HSN)

- Predominantly and strongly pronounced sensory symptoms and signs, with mild motor deficits.

Hereditary sensory and autonomic neuropathies (HSAN)

- Predominant sensory and autonomic symptoms and signs, possible motor involvement.

Hereditary neuropathy with liability to pressure palsies (HNPP)

- Transient sensory and motor symptoms after minor compression or stretching of a nerve.

THEORY

Case history

Case history #1

A 45-year-old man presents with a bilateral steppage gait (lifting legs up excessively to clear the toes), foot numbness, and difficulty with buttons. His birth history was normal, and early motor milestones were achieved on time. He began walking at 13 months, and was noted to be a 'toe-walker'. As a child he ran towards the middle to the back of his peers and was never able to ice skate because of weak ankles. He first noted problems with walking in his early twenties, tripping often and falling once a month, and has started having problems with his hands in the last 5 years. Nerve conduction studies show symmetrical nerve slowing to 23 m/second (normal >50 m/second) with mildly reduced amplitudes and prolonged distal latencies. Sensory responses are absent. His father was noted to have the same symptoms, and genetic testing reveals a duplication of the PMP22 gene, providing a diagnosis of CMT1A.

Case history #2

A 30-year-old woman presents with severe leg weakness and distal arm weakness. Her birth history was normal and early motor milestones were achieved on time. She began to have trouble with foot-drop and falling in her pre-school and school-age years. The foot-drop and weakness in the proximal muscles progressed through her teens, so that walking up stairs became very difficult. She required a wheelchair for primary ambulation at 20 years of age. On examination, her hands are atrophied and contractures are present, causing an 'en griffe' appearance, and weakness extends proximally. The sensory examination is mostly normal. Nerve conduction studies show no motor or sensory responses. However, she has brought studies from childhood showing normal conduction velocities and severely reduced amplitudes, indicative of axonal degeneration. She has no family history of weakness or neuropathy. Genetic testing reveals a mutation in the MFN2 gene, providing a diagnosis of CMT2A.

Other presentations

The most common features of Charcot-Marie-Tooth (CMT) disease are weakness and atrophy of the lower leg and foot. High-arched feet and hammer toes (pes cavus) are common but not pathognomonic. Most patients present with difficulties in walking, twisting of the ankles, and slapping of the feet. Features are normally symmetrical, although asymmetries may occasionally occur. The majority of patients remain ambulatory, although they may need braces and other assistive devices. Severe cases also exist.

Children with delayed motor milestones, who never ran or ambulated, have a severe early-onset phenotype of CMT1, CMT2, and CMT4 called Dejerine-Sottas syndrome.

Hereditary neuropathy with liability to pressure palsies (HNPP) presents with transient sensory and motor symptoms after minor compression or stretching of a nerve. These symptoms can last for weeks to months and are usually asymmetrical.

Some forms of CMT are solely motor or sensory, and are known as hereditary motor neuropathy and hereditary sensory neuropathy, respectively.

Approach

There are several features characteristic of Charcot-Marie-Tooth (CMT) disease.[8] Affected individuals have typically had difficulty since childhood with balance and with weakness in the ankles. Deep tendon reflexes are usually absent or decreased diffusely in both upper and lower extremities, although the most consistent site is at the Achilles tendon. Nerve conduction studies will show either a reduction in velocity, with decreased amplitudes and prolonged distal latencies in demyelination in CMT1, or decreased amplitudes with normal velocities in the presence of axonal loss in CMT2.

The presence of a peripheral neuropathy with a positive family history and/or abnormal genetic testing is diagnostic. When there is no family history of CMT and genetic testing for the condition is negative, it is often difficult to distinguish between CMT and an acquired inflammatory neuropathy. In these situations, sural nerve biopsy can be used to detect the presence of other disorders instead of CMT.

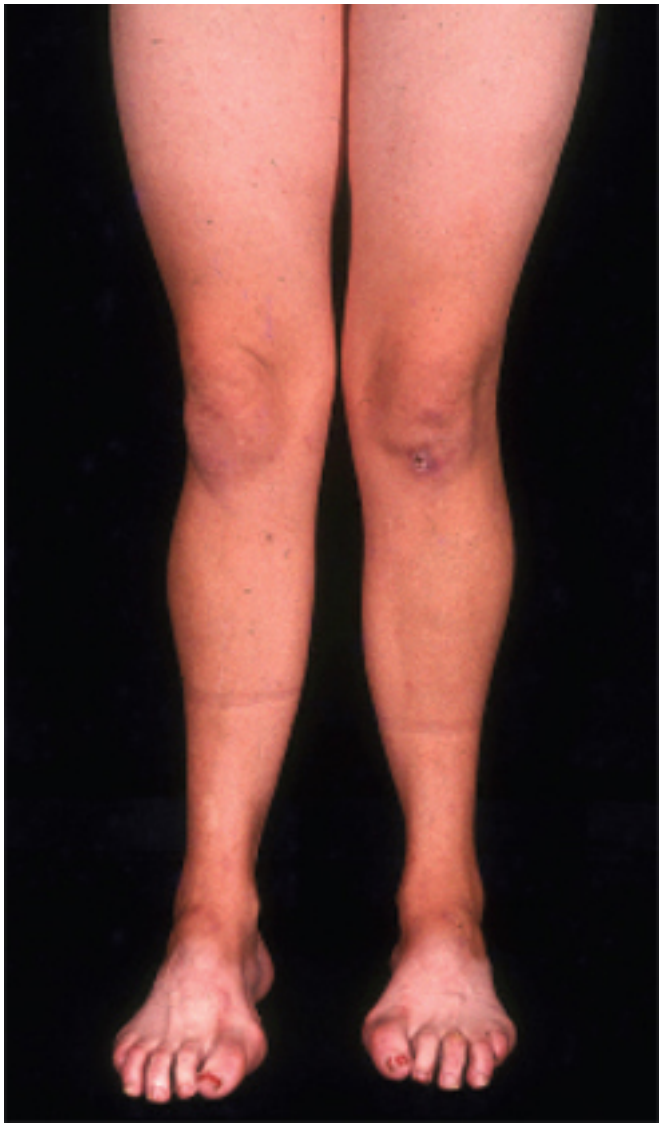
The severity of CMT can be determined using the Charcot-Marie-Tooth Neuropathy Score (CMTNS), a validated measure of impairment for people with the condition.[9] The CMTNS was updated in 2011, creating the CMTNSv2, which decreased ceiling effects of the CMTNS.[10] On a 36-point scale that includes symptoms, clinical findings, and electrophysiology, 0-10 points represents mild impairment, 11-20 points moderate impairment, and ≥21 points severe impairment. A subset of this scale, called the CMT Examination Score (CMTES), was updated in 2020 using Rasch analysis, and can provide a quick analysis of how an individual is doing clinically, using the signs and symptoms of the CMTNS, but not the electrophysiology scores.[11]

Clinical history

To determine if a person has CMT, it is important to obtain a thorough clinical history, including detailed past medical, developmental, and family histories.

Presenting features

- The most common features are weakness and atrophy of the lower leg and foot.



Pes cavus, toe clawing, and bilateral peroneal muscular atrophy in patient with CMT1A

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Most individuals present with difficulties in walking, twisting of the ankles, and slapping of the feet. Nerves to the anterior tibialis muscle are preferentially affected, causing ankle weakness and loss of the ability to dorsiflex the foot.[8] Features are normally symmetrical, although asymmetries may occasionally occur.

- Symptoms occur in a length-dependent manner, as the most distal nerves degenerate (axonal loss) first. Thus, the most distal muscles are affected first, so that the feet are affected before the ankles, which are in turn affected before the hands.[8] Abnormal sensations, such as loss of sensation and burning or tingling in the hands and feet, typically begin at the toes and proceed proximally over time.

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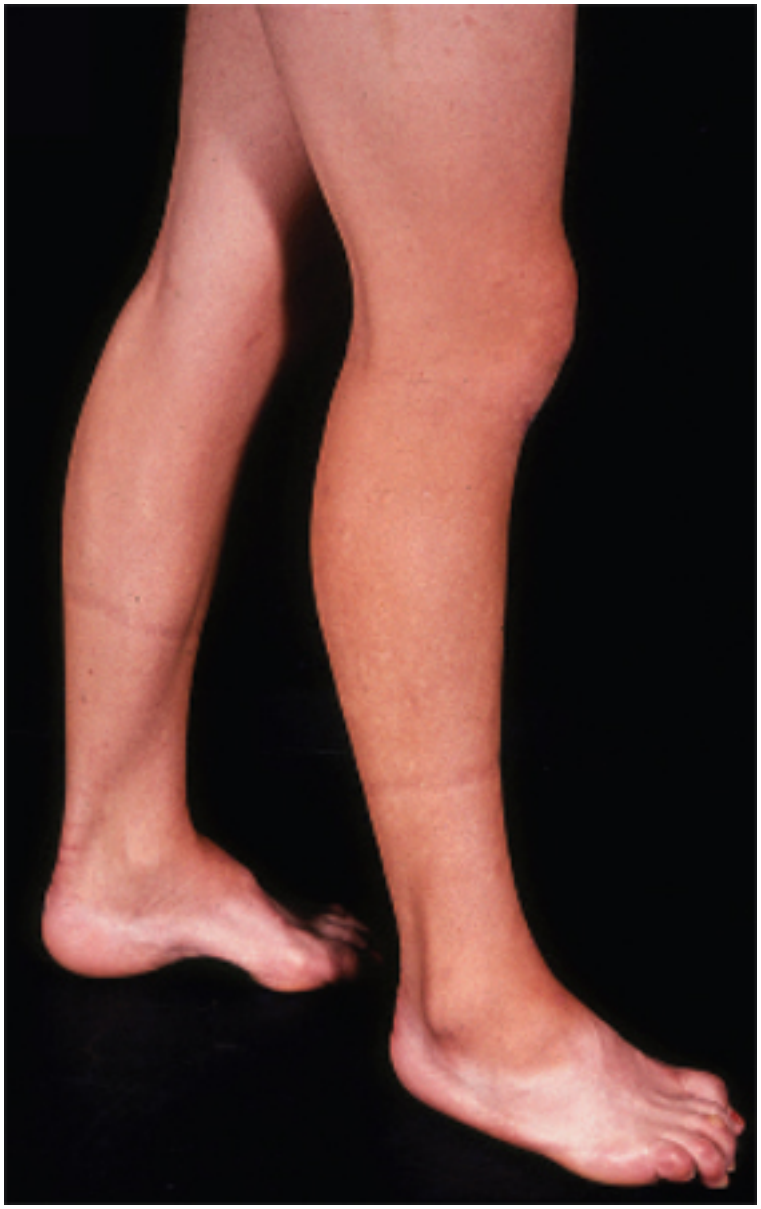

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- Children with delayed motor milestones, who never ran or ambulated, have a severe early-onset phenotype of CMT1, CMT2, and CMT4 called Dejerine-Sottas syndrome. Hereditary neuropathy with liability to pressure palsies (HNPP) presents with transient sensory and motor symptoms after minor compression or stretching of a nerve. These symptoms can last for weeks to months and are usually asymmetrical. Most people with CMT2A have significant motor weakness in the pre-school and school-age years, and will be non-ambulatory by the age of 20 years, although sensory impairment is not affected until later in the disease course. Proximal muscle weakness may also occur in these individuals. Curvature of the spine (kyphoscoliosis) can occur in some people with CMT and is a prominent feature in some forms (e.g., CMT4C due to mutations in SH3TC2).

Past medical history

- Key questions in the developmental history include difficulty with balance or skating as a child, and problems in finding well-fitting shoes owing to high foot arches.
- Past surgical procedures to the feet and ankles should also be noted. Tendon transfers in the feet and Achilles tendon lengthening are common surgeries performed for tight heel cords. Other surgeries include hammer toe straightening, and triple arthrodesis of the ankle.

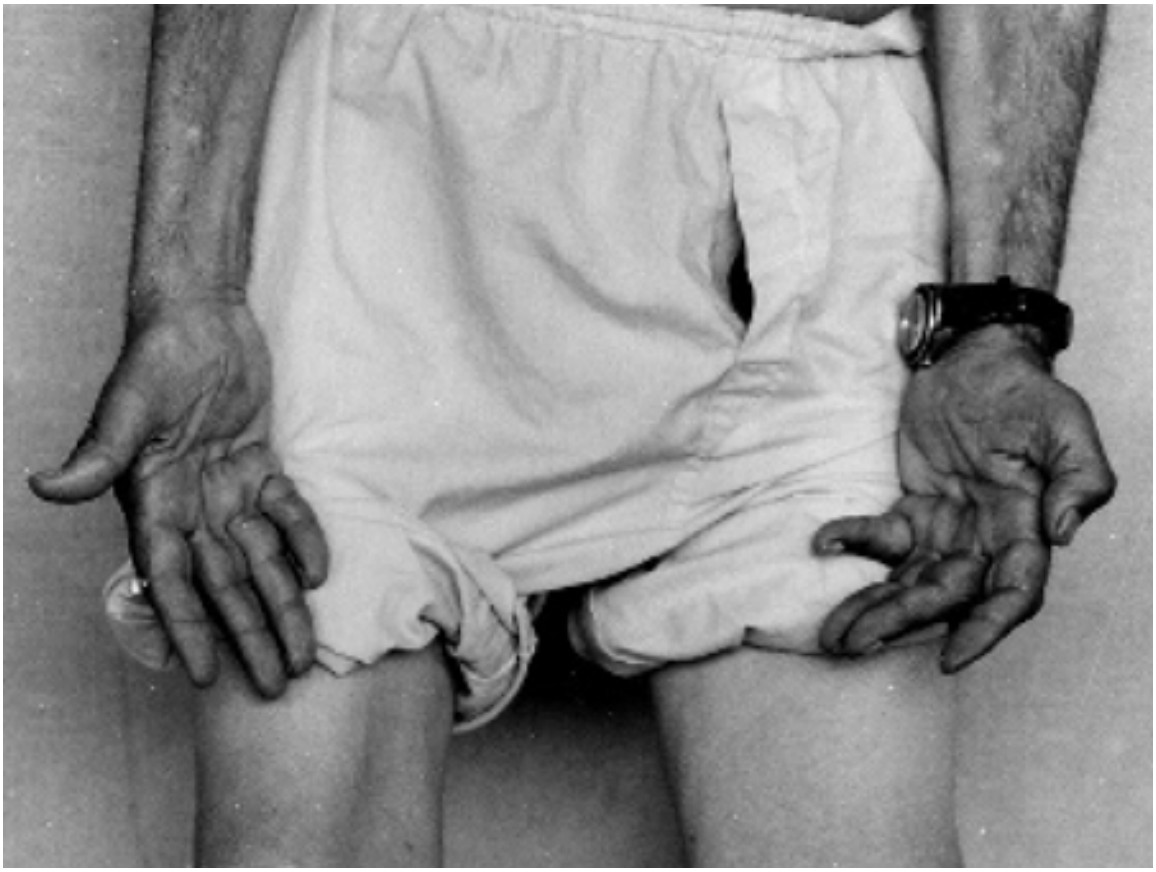
Family history

- As CMT is a hereditary peripheral neuropathy, it is important to obtain a family history going back at least three generations. The majority of affected individuals have a family history of the condition; and a family history of neuropathy, pes cavus (high foot arches with hammer toes), or abnormal gait strongly points to an inherited disorder, particularly CMT.
- It is important to draw a family tree (pedigree) and track both sides of the family for three generations to determine who is affected and what mode of inheritance is present. Questions such as, "did/does this relative have any trouble with walking, balance, tripping, falling, or with their hands or sensations?" should be asked. An autosomal dominant pedigree will have people affected in every generation, and male-to-male transmission can be present. X-linked pedigrees will not have male-to-male transmission, and males are almost always more severely affected than females. Autosomal recessive pedigrees may have only one person or sibling affected.
- Lack of a family history does not preclude the diagnosis, as de novo mutations are relatively common.[12] [13] There is also phenotypic variability such that parents or other family members may be unaware of their disease, and recessive cases can present with no family history.

Physical examination

The neurological examination should test the cranial nerves, strength, sensation, reflexes, co-ordination, and ambulation.

- The cranial nerve examination is typically normal. Some individuals with CMT1B have abnormalities of pupillary constriction, and people with CMT2A may have optic nerve abnormalities.
- Sensory ataxia (i.e., imbalance and in-coordination due to loss of proprioception) may be present.
- Strength is reduced in the distal muscles of the arms and legs (e.g., intrinsic hand and foot muscles, anterior tibialis), with associated atrophy and weakened foot eversion. This clinical observation points to a length-dependent lower motor neuron disorder. Strength is typically maintained in the proximal muscles and in the gastrocnemius muscle.[8]



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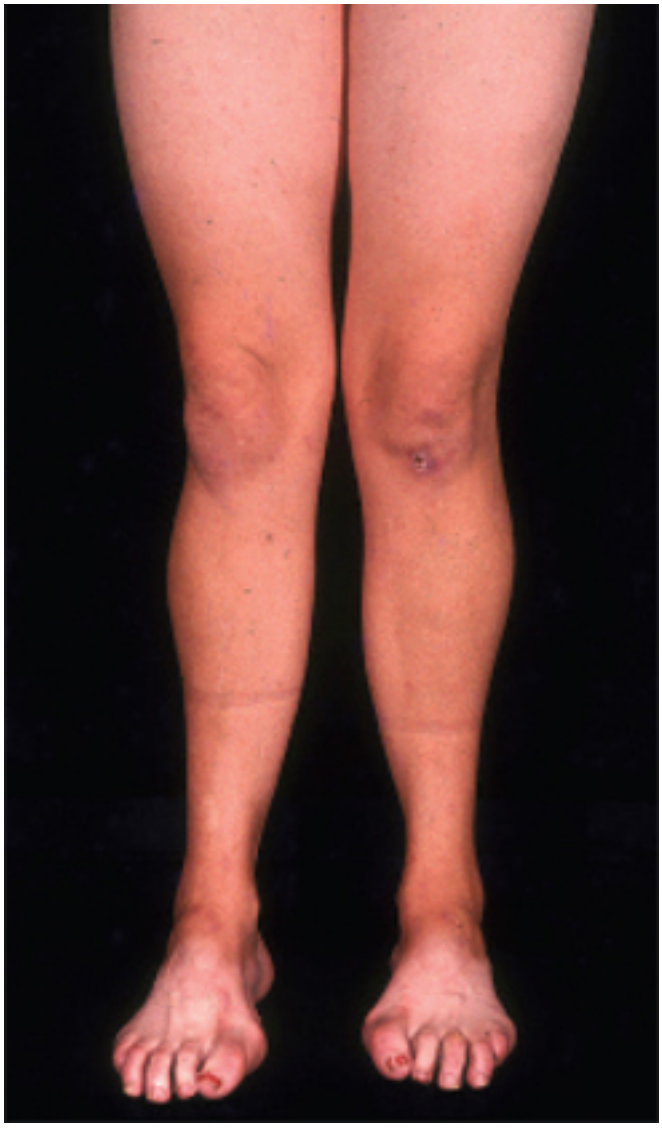

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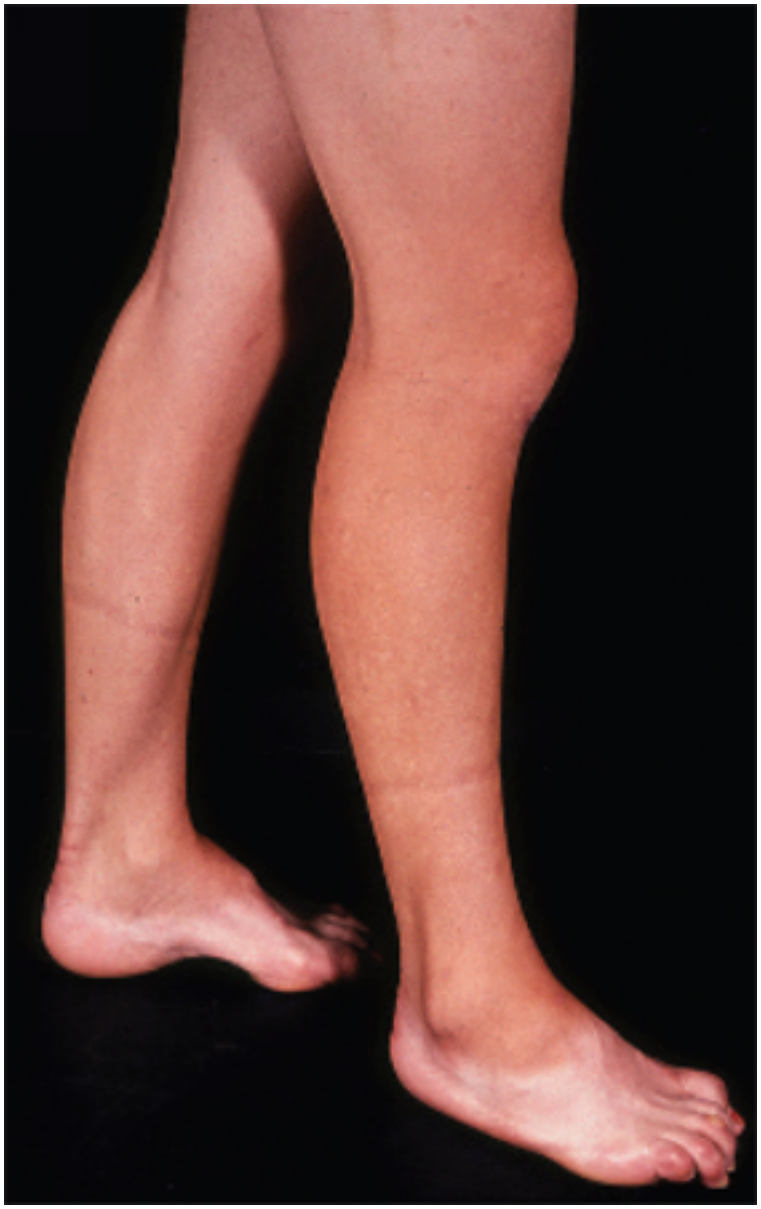
- Sensation corresponding to both small and large sensory nerve fibres is decreased or absent.[8] There is a reduction in pinprick and vibration sensation, which is more pronounced at the toes than in more proximal regions.[8]
- Deep tendon reflexes are diffusely absent (areflexia) or reduced (hyporeflexia).[8] The loss of reflexes may occur in any condition involving nerve damage, but the diffuse nature of the affected sites is not typical of other conditions.
- High-arched feet and hammer toes (pes cavus) are common but not pathognomonic, as pes cavus is seen in a variety of conditions and can be present without a neurological problem. If pes cavus is associated with areflexia, the likelihood of CMT is high. Pes cavus results from muscle imbalance as anterior tibialis and the intrinsic foot muscles are affected with sparing of the gastrocnemius muscle. The stronger pull of gastrocnemius overcomes the weaker pull of anterior tibialis, leading to structural foot deformities.[8]



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- Assessment of the gait reveals slapping of the feet, or loss of a heel-to-toe pattern, and the affected person may walk with a steppage gait (lifting legs up excessively to clear the toes). Toe-walking and the absence of heel-walking result from a tight heel cord, which is due to the nerves to anterior tibialis being preferentially affected, leading to inadequate strength to pull the foot up during ambulation.[8] Patients may require bilateral aids, such as ankle-foot orthoses, to ambulate.

Imaging

A hip x-ray should be considered in all children to screen for hip dysplasia.[14] X-rays of cervical, thoracic, and lumbar spine and pelvis (spinal series) should be considered for children exhibiting signs of scoliosis or kyphosis. Postero-anterior and lateral views are recommended.

Pulmonary function testing

Baseline pulmonary function testing should be undertaken in the following children when they are able to complete this reliably (usually from the age of 5-6 years):[14]

- Children with symptoms of sleep-disordered breathing (e.g., unexplained headaches, daytime somnolence or symptoms of obstructive sleep apnoea).
- Children with recurrent lower respiratory tract infections (>2 courses of antibiotics over 4 months or >2 hospital admissions for a respiratory tract infection in 12 months).
- Children with scoliosis (Cobb angle of >40°).
- All non-ambulant children.

Nerve conduction studies (NCS)

This investigation should be considered for any individual with a suspected neuropathy, as it can confirm the diagnosis of a polyneuropathy and determine if the disorder is primarily motor, sensory, or mixed, and if it affects myelin and the Schwann cell, or the axon. Both motor and sensory nerves should be studied, although it should be noted that interpretation of the results can be difficult, as some forms of CMT show only slight abnormalities on NCS.

The nerve abnormalities are symmetrical, with a similar degree of slowing or reduction in amplitude in all the tested nerves, and sensory nerve responses are typically absent. Demyelination in CMT1 (including CMT1A) is associated with very slow conduction velocities of 15-38 m/second, reduced or absent sensory responses, and prolonged distal latencies. Axonal loss in CMT2 (including CMT2A) is associated with reduced amplitudes (particularly in CMT2A), but with relatively normal conduction velocities of >38 m/second.

In the presence of extreme atrophy in the distal muscles, responses may not be recordable, and it may be necessary to perform the NCS at a more proximal muscle than would typically be used.

Genetic testing

There are more than 90 known genetic causes, and commercial testing is available in the US for most of these.

Genetic testing should be done only after appropriate counselling. The rationales of determining the specific genetic aetiology of the disease include psychological comfort, family planning, the ability to participate in clinical trials, and providing a better knowledge of the natural history of the particular CMT subtype. These considerations should be weighed against potential for discrimination in jobs and insurance, the cost to the individual, the stigma associated with a genetic diagnosis, and family dynamics.

A logical approach based on nerve conduction testing and a genetic history can streamline the genetic testing.[7] [15] Although over 90 genes are known to cause CMT when mutated, about 92% of people with an identifiable mutation will have a mutation in 1 of 4 genes: PMP22 (duplication or deletion), GJB1, MPZ, or MFN2.[16] Phenotypes can help narrow down the subtype of CMT, using the part of the nerve affected (myelin or axon), the mode of inheritance (autosomal dominant, autosomal recessive, or X-linked), and the age of onset (infancy, childhood, adult).[7] Furthermore, genetic testing can be streamlined based on prevalence numbers. Persons with a family pedigree showing a dominant mutation or male-to-male transmission and signs of demyelination on NCS should be tested for CMT1A, the most common form of demyelinating CMT. If there is no duplication of the PMP22 gene indicative of CMT1A, testing for other

myelin gene disorders may be appropriate. If an X-linked disorder is possible, testing for CMT1X with mutations of the GJB1 gene is appropriate. A causative gene mutation is identified in approximately 80% of cases of demyelinating CMT.[17] Persons with an axonal pattern on NCS, with or without a family history, should be tested for mutations in MFN2 causing CMT2A, the most common form of axonal CMT.[13] Only 30% to 40% of cases of axonal CMT will have an identifiable mutation.

Next Generation Sequencing panels allow for rapid and cheap options for testing multiple genes at one time. Nerve conduction studies, family history, and physical examination can help with interpretation of large panel results. For example, if a variant is found in an axonal gene, but the individual has demyelinating CMT, it is unlikely that the axonal gene variant is disease-causing. Exome sequencing is quickly becoming less expensive and more useful in finding new genes in CMT. If a person has negative genetic testing for the most likely known causes of CMT, it may be reasonable to send their DNA and DNA of other affected family members for research or clinical exome testing.

Result reports should be interpreted with caution. The detection of a known gene mutation associated with a dominantly inherited form of CMT is definitely the cause of the condition. However, a single disease-causing mutation in a recessive gene cannot be the cause. Genetic variants of uncertain significance are typically amino acid-changing mutations that have not yet been classified as disease-causing or benign, and can usually only be interpreted by testing the parents and tracking to see if the condition and the variant segregate together. It is always appropriate to call the laboratory that performed the test to ask for clarification and interpretation of the results.

It is recommended to consult with a specialist in a centre that sees many people with CMT to arrange the most efficient and accurate testing. Many specialists would first do a panel and then proceed to exome sequencing if needed.

History and exam

Key diagnostic factors

family history of neuropathy, pes cavus, or abnormal gait (common)

- The majority of individuals have family history of the condition; and family history of neuropathy, pes cavus (high foot arches with hammer toes), or abnormal gait strongly points to an inherited disorder, particularly Charcot-Marie-Tooth disease.
- Lack of family history does not preclude the diagnosis.

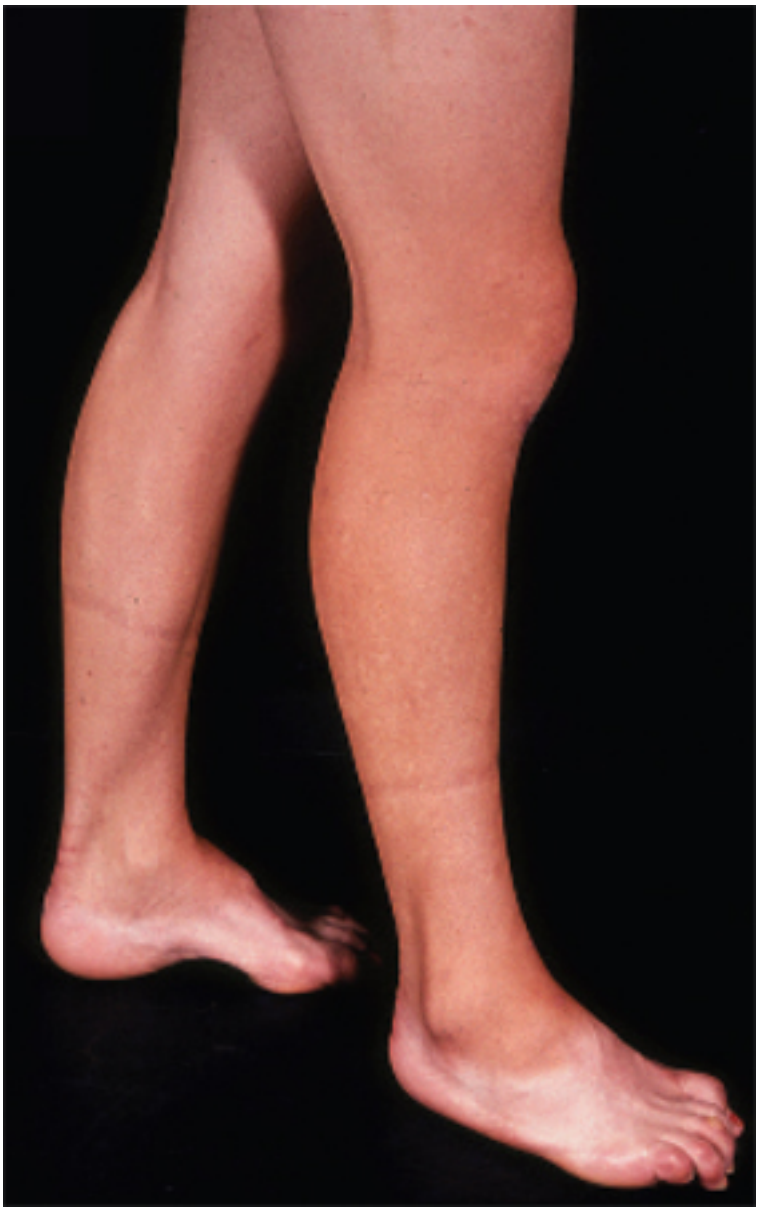
walking difficulties (common)

- The most common features are weakness and atrophy of the lower leg and foot. Most people present with difficulties in walking, twisting of the ankles, and slapping of the feet.
- Features are normally symmetrical, although asymmetries may occur. The majority of individuals remain ambulatory, although they may need braces and other assistive devices.

pes cavus (common)

- High-arched feet and hammer toes (pes cavus) are common but not pathognomonic, as pes cavus is seen in a variety of conditions and can be present without a neurological problem. If pes cavus is associated with areflexia, the likelihood of Charcot-Marie-Tooth disease is high. Pes cavus results

from muscle imbalance as anterior tibialis and the intrinsic foot muscles are affected with sparing of the gastrocnemius muscle. The stronger pull of gastrocnemius overcomes the weaker pull of anterior tibialis, leading to structural foot deformities.[8]



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steppage gait (common)

- Assessment of the gait reveals slapping of the feet, or loss of a heel-to-toe pattern, and the person may walk with a steppage gait (lifting legs up excessively to clear the toes).

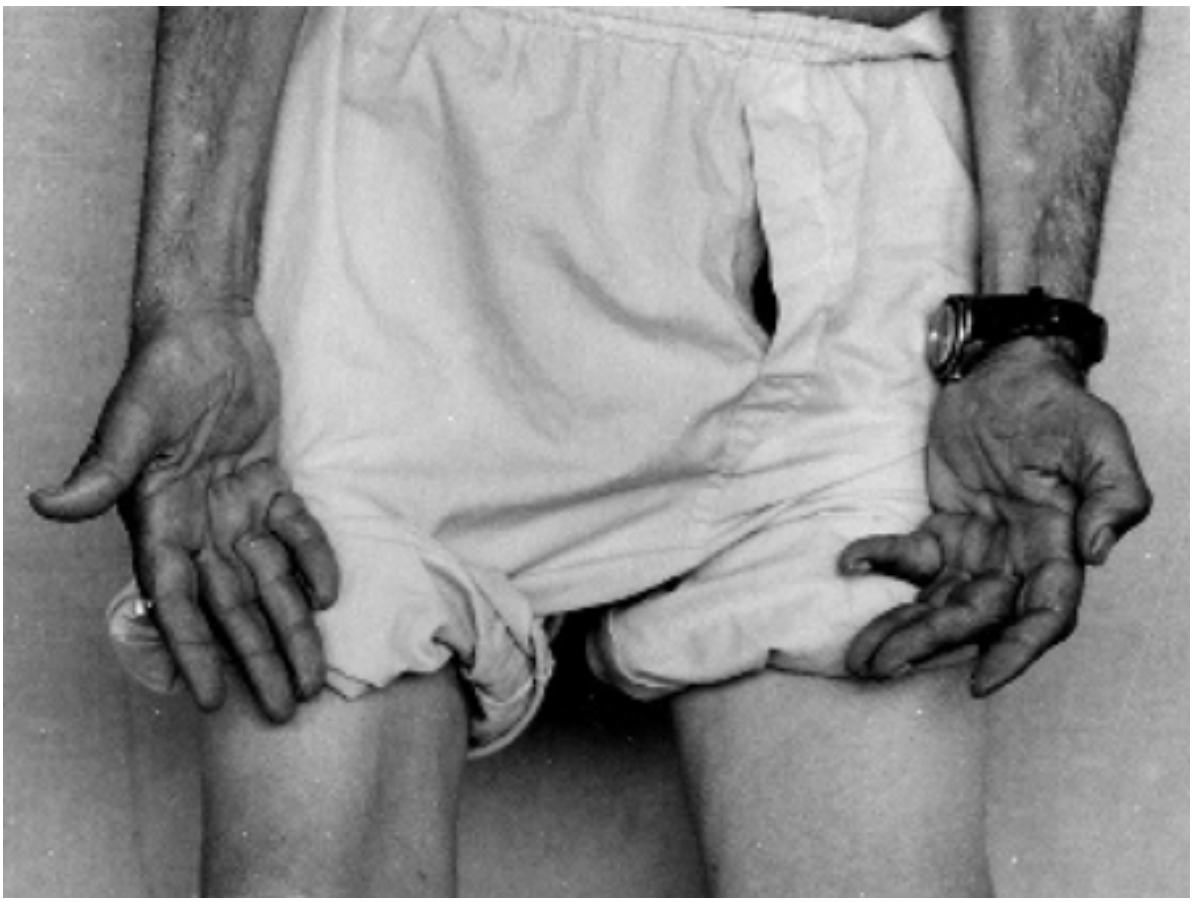
diffuse deep tendon hyporeflexia or areflexia (common)

- Deep tendon reflexes are diffusely absent (areflexia) or reduced (hyporeflexia).[8] The loss of reflexes may occur in any condition involving nerve damage, but the diffuse nature of the affected sites is not

typical of other conditions. As Charcot-Marie-Tooth disease progresses in a length dependent manner, the loss of reflexes often follows the same pattern, with areflexia at the Achilles tendon being universal.

reduced muscle strength (common)

- Strength is reduced in the distal muscles of the arms and legs (e.g., intrinsic hand and foot muscles, anterior tibialis) with associated atrophy and weakened foot eversion. This clinical observation points to a length-dependent lower motor neuron disorder.
- The most distal nerves degenerate (axonal loss) first. Thus, the most distal muscles are affected first, so that the feet are affected before the ankles, which are in turn affected before the hands, and strength is typically maintained in the proximal muscles and the gastrocnemius muscle strength is usually greater in comparison to the anterior tibialis.[8]



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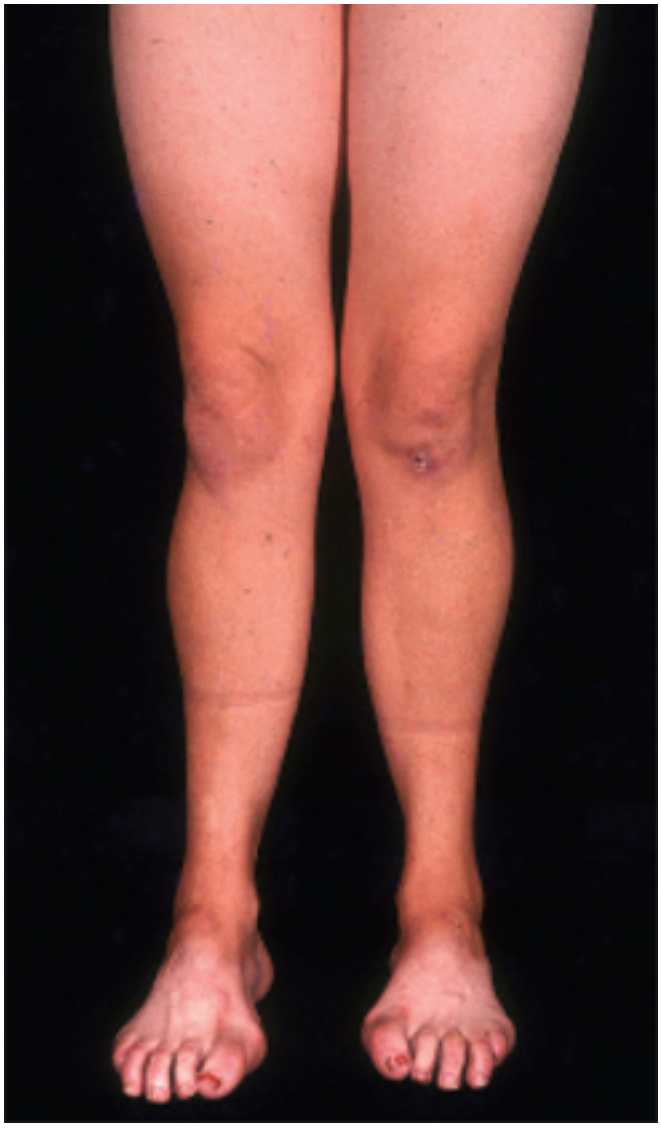

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reduced sensation (common)

- Sensation corresponding to both small and large sensory nerve fibres is decreased or absent.[8] There is a reduction in pinprick and vibration sensation, which is more pronounced at the toes than in more proximal regions.[8]

transient sensory symptoms (uncommon)

- Hereditary neuropathy with liability to pressure palsies presents with transient sensory and motor symptoms after minor compression or stretching of a nerve. These symptoms can last for weeks to months and are usually asymmetrical.

transient motor symptoms (uncommon)

- Hereditary neuropathy with liability to pressure palsies presents with transient sensory and motor symptoms after minor compression or stretching of a nerve. These symptoms can last for weeks to months and are usually asymmetrical.

Other diagnostic factors

past surgery to feet and ankles (common)

- Tendon transfers in the feet are common, owing to tight heel cords. Other surgeries include hammer toe straightening and triple arthrodesis of the ankle.

balance difficulties in childhood (common)

- There may be a history of difficulty with balance or skating as a child, and problems in finding well-fitting shoes owing to high foot arches.

ankle weakness (common)

- Nerves to the anterior tibialis muscle are preferentially affected, causing ankle weakness and loss of the ability to dorsiflex the foot.[8]

sensory abnormalities in hands and feet (common)

- The most distal nerves are affected first, and abnormal sensations, such as loss of sensation and burning or tingling in the hands and feet, typically begin at the toes and proceed proximally over time.

toe-walking (common)

- Toe-walking and the absence of heel-walking result from a tight heel cord, due to the nerves to anterior tibialis being preferentially affected, leading to inadequate strength to pull the foot up during ambulation.[8]

delayed motor milestones (uncommon)

- Children with delayed motor milestones, who never ran or ambulated, have a severe early-onset phenotype of CMT1, CMT2, and CMT4 called Dejerine-Sottas syndrome. Late-normal age of walking is common (12-14 months).

sensory ataxia (uncommon)

- Imbalance and in-coordination due to loss of proprioception may be present.

kyphoscoliosis (uncommon)

- Curvature of the spine (kyphoscoliosis) can occur in some individuals with Charcot-Marie-Tooth disease and is a prominent feature in some forms (e.g., CMT4C due to mutations in SH3TC2).

Risk factors

Strong

family history of neuropathy, pes cavus (high foot arches with hammer toes), or abnormal gait

- Charcot-Marie-Tooth (CMT) disease is a genetic condition and there are no known risk factors for the condition, other than a family history. Depending on the inheritance pattern of the CMT subtype, the risk of passing the condition on to the next generation differs.
- In autosomal dominant forms (most CMT1 and CMT2), one parent with the genetic disorder is sufficient to pass on the condition, and each child has a 50% chance of inheriting the disorder. In autosomal recessive forms (CMT4), both parents carry one genetic mutation, but do not have clinical manifestations of the disease, as they have one working copy of the gene. In such cases, each child has a 25% chance of getting the disorder, a 50% chance of being a carrier, and a 25% chance of inheriting two working copies of the gene and being an unaffected non-carrier.
- Females with an X-linked form of CMT have a 50% chance of passing on the condition, and males with an X-linked form have a 100% chance of passing on the condition to daughters but a 0% chance of passing it on to sons.

Investigations

1st test to order

Test	Result
nerve conduction studies (NCS) • This investigation should be considered for any person with a suspected neuropathy, as it can confirm the diagnosis of a polyneuropathy and determine if the disorder primarily affects myelin and the Schwann cell, or the axon (i.e., whether the disorder is primarily motor, primarily sensory, or mixed). Both motor and sensory nerves should be studied, although interpretation of the results can be difficult as some types of Charcot-Marie-Tooth (CMT) disease show only slight abnormalities on NCS. • The nerve abnormalities are symmetrical, with a similar degree of slowing or reduction in amplitude in all the tested nerves, and sensory nerve responses are typically absent. CMT1 is associated with demyelination, and CMT2 is associated with axonal loss. • In the presence of extreme atrophy in the distal muscles, responses may not be recordable, and it may be necessary to perform the NCS at a more proximal muscle than would typically be used.	**conduction velocities of 15-38 m/second, reduced or absent sensory responses, and prolonged distal latencies in demyelination; reduced amplitudes and normal conduction velocities (>38m/second) in axonal loss**

Other tests to consider

Test	Result
genetic testing • Persons with a family pedigree showing a dominant mutation or male-to-male transmission and signs of demyelination on nerve conduction studies (NCS) should be tested for CMT1A, the most common form of demyelinating Charcot-Marie-Tooth (CMT) disease. If there is no duplication of the PMP22 gene indicative of CMT1A, testing for other myelin gene disorders may be appropriate. If an X-linked disorder is possible, testing for CMT1X with mutations of the GJB1 gene is appropriate. A causative gene mutation is identified in approximately 80% of cases of demyelinating CMT.[17] Individuals with an axonal pattern on NCS, with or without family history, should be tested for CMT2A, the most common form of axonal CMT.[13] Only 30% to 40% of cases of axonal CMT will have an identifiable mutation. Genetic testing has >99% sensitivity for each subtype of CMT. Next Generation Sequencing panels will now look at 30-100 hereditary neuropathy-associated genes at one time, relatively quickly and cheaply. Exome sequencing is quickly becoming less expensive and more useful in finding new genes in CMT. If a person has negative genetic testing for the most likely known causes of CMT, it may be reasonable to send their DNA and the DNA of other affected family members' for research or clinical exome testing.	**gene mutation associated with specific CMT subtype**
hip x-ray • Hip x-ray should be considered in all children to screen for hip dysplasia.[14]	**normal or hip dysplasia**
x-rays of cervical, thoracic, and lumbar spine and pelvis • Spinal and pelvic x-rays should be considered for children exhibiting signs of scoliosis or kyphosis. Postero-anterior and lateral views are recommended.	**normal or scoliosis/ kyphosis**
nerve ultrasound • Nerve ultrasounds may be useful for people who do not want to undergo NCS or electromyography (EMG), or if there is a question about Charcot-Marie-Tooth (CMT) versus a different neuropathy. People with CMT, particularly demyelinating forms of CMT (with CMT1A being the most well studied) will have increased nerve CSA compared to controls.[18]	**normal or possibly increased nerve cross sectional area (CSA) if demyelinating neuropathy**
nerve biopsy • Nerve biopsies may be useful if genetic testing finds one or more variants of uncertain significance in a gene that has specific microscopic nerve lesions to elucidate the pathogenicity of the variant.[19] They are also useful to distinguish between a genetic neuropathy and a non-genetic neuropathy, such as one caused by vasculitis.[20]	**specific genes and their corresponding nerve lesions: PMP22 (CMT1A/CMT1E): Onion bulbs; PMP22 (HNPP): Tomaculae; MPZ (CMT1B): Uncompacted Myelin, myelin out foldings, Onion bulbs; EGR2 (CMT1D): Very severe demyelination, dysmyelination, or no myelination; GJB1 (CMT1X): Clusters of regeneration; MTMR2, MTMR13, FDG4 (CMT4B1,**

Test	Result
	CMT4B2, CMT4H): Myelin in- and out-foldings; SH3TC2 (CMT4C): Basal proliferation (onion bulbs), Unmyelinated fibers involvement; INF2 (CMT-DIE): Proliferation of actin filaments, Unmyelinated fibers involvement; NDRG1 (CMT4D): Adaxonal deposits; PRX (CMT4F): Abnormal paranodal loops, Dysjunction of Cajal bands; NEFL (CMT2E/CMT1F): Giant axons; MFN2 (CMT2A): Mitochondrial anomalies; GDAP1 (CMT4A): Mitochondrial anomalies; LMNA (AR-CMT2A): Severe rarefaction of large myelinated fibers, with no cluster of regeneration.
pulmonary function testing • Baseline pulmonary function testing should be undertaken in the following children when they are able to complete this reliably (usually from the age of 5-6 years): children with symptoms of sleep-disordered breathing (e.g., unexplained headaches, daytime somnolence or symptoms of obstructive sleep apnoea); children with recurrent lower respiratory tract infections (>2 courses of antibiotics over 4 months or >2 hospital admissions for a respiratory tract infection in 12 months); children with scoliosis (Cobb angle of >40°); all non-ambulant children.[14]	**normal or reduced vital capacity**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Diabetic neuropathy	• The most common cause of neuropathy, normally seen in adults.	• Fasting plasma glucose: ≥7 mmol/L (≥126 mg/dL). • Oral glucose tolerance test: 2-hour post-glucose load ≥11.1 mmol/L (≥200 mg/dL). • HbA1c: >42 mmol/mol (>6%).
Chronic inflammatory demyelinating polyneuropathy	• Symmetrical polyneuropathy involving both distal and proximal muscles. Usually more rapidly progressive than Charcot-Marie-Tooth disease, with an acute onset.	• Sural nerve biopsy: may show inflammation in addition to demyelination.
Acquired peripheral neuropathy	• Causes include toxins, hypothyroidism, vitamin deficiencies, and renal failure. • As with Charcot-Marie-Tooth (CMT) disease, deep tendon reflexes are diffusely absent or reduced. • Timeline of symptom onset and the past medical history help to differentiate this condition from CMT.	• Investigations and results dependent on the underlying cause. • Fasting plasma glucose: ≥7 mmol/L (≥126 mg/dL) in diabetes mellitus. • Oral glucose tolerance test: 2-hour post-glucose load ≥11.1 mmol/L (≥200 mg/dL) in diabetes mellitus. • Urea and creatinine: may show chronic renal impairment. • Liver function tests: deranged in hepatitis, toxin ingestion. • Thyroid function tests: thyroid-stimulating hormone (TSH) elevated, free thyroxine (T4) and free triiodothyronine (T3) reduced in hypothyroidism. • Erythrocyte sedimentation rate and C-reactive protein: elevated in systemic lupus erythematosus, mononeuritis multiplex. • Serum B12: reduced in vitamin B12 deficiency.
Hereditary spastic paraplegia (HSP)	• Spasticity, hyper-reflexia, and Babinski's signs are indicative of an upper motor neuron lesion. Central nervous system manifestations, including upper motor neuron signs,	• Genetic testing: specific gene mutation known to cause HSP. • MRI: atrophy of spinal cords, possible atrophy of cerebral cortex.

Condition	Differentiating signs / symptoms	Differentiating tests
	are uncommon in Charcot-Marie-Tooth disease.	
Spinocerebellar degeneration	• Ataxia is a major component of the symptomatology, but some patients have an associated neuropathy.	• MRI: spinocerebellar degeneration.

Screening

Although Charcot-Marie-Tooth (CMT) disease is a relatively common condition, there are no general-population screening programmes in place. Adults at risk as a result of a positive family history may be screened, but screening of asymptomatic individuals should only be performed after genetic counselling so that an informed decision can be made regarding testing.

Nerve conduction studies

Screening an at-risk individual by testing a single nerve is possible for some forms of CMT. For example, in CMT1A, if a family member has had genetic testing revealing a duplication of the PMP22 gene, the patient can have a single motor nerve (e.g., median or ulnar nerve) velocity measured. If the velocity is profoundly slowed, this provides a strong indication of CMT1A, whereas if it is normal, this excludes the possibility of CMT1A. For other forms of the condition, abnormal conditions may only be suggestive, and genetic testing may be warranted.

Genetic testing

After a patient has been diagnosed with CMT, and a specific mutation has been identified, other family members can be tested for the same mutation. The mutation should be the same throughout the family.

Genetic testing may be considered if the individual is interested in family planning, natural history information, or inclusion in clinical trials. Neurotoxic chemotherapy drugs (e.g., paclitaxel, cisplatin, and vincristine) can cause severe neuropathy and should be avoided in CMT. Therefore, if a person at risk of CMT is diagnosed with cancer, it may be reasonable to have genetic testing to determine the risk of exacerbating a neuropathy.

Not all individuals will want to have genetic testing. It is always an optional test, and individuals should only have genetic testing once informed of the implications. It is worth noting that in the US, life, disability, and long-term-care insurances can be difficult or near-impossible to obtain if a person is asymptomatic but has a positive genetic test, which indicates that the condition will appear in the future. The results of the testing will probably have an emotional impact on the individual, either through blaming the parents for passing on the condition, or feelings of guilt for passing it on to a child. Although genetic testing has become less expensive, some local funding/insurance may not cover the costs; this should always be checked before ordering the test. Genetic counsellors are knowledgeable about the process and should be consulted whenever possible, both for genetic testing and for providing information and support to people with a family history or signs of a genetic condition.

Screening of minors

Asymptomatic minors should not receive genetic testing or nerve conduction studies without careful consideration and discussion with a physician, nurse, or genetic counsellor.[21] Reasons for this include the

social and psychological consequences. As there is no treatment for CMT at this time, testing minors may not provide significant medical benefit. However, if a child is symptomatic and requires therapy and bracing, it is appropriate to obtain a definitive diagnosis of CMT. This also eliminates unnecessary testing for other conditions, and assists the parents in making appropriate life plans.

Approach

Although there is no cure for Charcot-Marie-Tooth (CMT) disease and therapy is supportive, there are several treatment recommendations aimed at helping patients with the condition. Proper bracing and/or orthopaedic surgery of the feet can allow increased mobility and independence.

Physiotherapy and exercise

Low-impact exercises, such as cycling and swimming, as well as physiotherapy sessions, increase energy as well as reducing fatigue and pain.[22] The addition of a stretching programme, which may include yoga, enables a greater range of motion over time. Strength training of proximal/core muscles should be encouraged, starting at low resistance and gradually building up. Progressive resistance exercise of the ankle dorsiflexors is recommended to improve muscle strength and slow progression of muscle weakness.[14] Physiotherapy should be on a fixed schedule that the patient can ease into and modify as required. Exercise programmes should include rest days to encourage recovery.[14] Exercise should cease temporarily and exercise regimen should be modified, if there are any signs of exercise-induced muscle damage.[14]

Balance re-training, core strengthening, postural strengthening, and age-appropriate recreational activities may all be used to improve balance.[14]

Cramps are treated by stretching of involved muscle groups.[14]

Occupational therapy

Over time, patients lose intrinsic hand muscle strength, and can develop contractures of the fingers. Modifications in activities of daily living are thus often required. An occupational therapist can provide an assortment of tools - such as writing instruments, eating utensils, button hooks, and sock helpers - to enable better daily functioning. Adapted keyboard settings and voice-to-text software may be beneficial for children with impaired upper limb function.[14]

The occupational therapy input is tailored to the individual needs of the patient and modified as these needs change over time.

Bracing

Patients of all ages should be evaluated for appropriate bracing. Gait and mobility aids should be prescribed by a qualified health professional with experience in their provision.[14] Children with foot drop, who have recurrent trips and falls, or who have ankle instability may benefit from ankle-foot orthoses (AFOs). Children with foot pain may benefit from foot orthoses.[14] An orthotist aligns the hindfoot in the neutral position, and then posts the forefoot so it is parallel to the ground.[23] Once proper alignment has been achieved, patients often find their gait, and balance are improved, reducing the risk of falls. Posture can be improved and fatigue is reduced. Alignment of the feet also helps to reduce stress on the ankles, knees, hips, and back. With good bracing, orthopaedic surgery can be delayed, or the need for such surgery eliminated altogether. Bracing can improve the quality of life of patients with CMT and it is important that the right brace is fitted to each patient. Children with impaired mobility should wear well-fitting, supportive footwear.[23]

Patients with CMT require a stronger design of bracing than those with drop-foot from other causes. Carbon fibre ankle-foot orthoses (AFO) have been used instead of the traditional plastic AFO, as they

are lighter and achieve increased strength and stability. AFO devices usually necessitate a shoe insert to create lateral stability, and provide a cushion that allows the foot to rest comfortably and be supported. It is important to consult with a knowledgeable orthotist. While prefabricated AFOs are cheaper, many patients require custom-fitted braces. Patients with CMT have reported that they appreciate the durability of their braces, but often find them uncomfortable, painful, or the cause of abrasions to their feet/legs.[24] Braces that are uncomfortable or that do not fit properly will not be worn, limiting the function of the patient. The other factor that keeps people from using braces is that they do not like their appearance, in particular teenagers. Dealing with this concern requires sensitive counselling with the family.

While night splinting is sometimes suggested for increasing range of motion at the ankle, two randomised studies did not find any statistically significant benefits.[25] These studies were small and used prefabricated splints. Future studies analysing the effectiveness of other interventions, such as serial removable night casting made from moulds of the patient's legs, may be warranted.

Orthopaedic surgery

The musculoskeletal features of CMT can be as problematic as the weakness. While properly fit AFOs are recommended as the first-line for preventing or delaying surgeries, the hammer toes and high arch to the foot can make it difficult to utilise bracing. The inward or outward turning of the foot (equinovalgus and equinovarus deformities) can keep the foot from being flat on the floor. Some patients will require orthopaedic surgery at some point to correct the foot deformities associated with CMT, or for secondary complications, such as a knee or hip replacement in osteoarthritis. It is important to consult with a surgeon who has experience with patients with CMT as their needs are not typically seen in other conditions.[26]

Common surgeries include tendon transfers, heel-cord prolongation, and/or hammer toe straightening.[27] These surgeries have better long-term effects than other procedures, including triple arthrodesis (ankle fusion), as the latter has been shown to break down over time and cause pain subsequent to arthritis formation at the ankle joint, though this procedure may be appropriate with accompanying soft tissue and tendon transfers in an older person who has painful arthritic joints.[26]

Surgery also has risks, including, but not limited to: pain, infection, nerve injury, possibilities of future corrective surgeries, and possible adverse reactions to anaesthesia (not elevated over general population risks).[28] [29]

The progressive nature of CMT should be remembered. Surgery is not always corrective, and, even if it is, the clinical feature in question may regress in the future.[30] Even after surgery, most patients will still need to wear an AFO for ambulation.

Treatment of underlying concomitant conditions affecting ambulation

Diabetes mellitus (DM) has been shown to exacerbate CMT.[31] Being in good glycaemic control leads to better outcomes for people with CMT than those with poor glycaemic control.[31]

Spine issues, including spinal stenosis or lumbar radiculopathy, can impair ambulation for all people. For people with CMT who have seemingly superimposed secondary spinal deficits, appropriate physiotherapy and surgical referral can be made. Thought should be given to the intervention and how it could impact the underlying neuropathy.

Neurotoxical medicines should be undertaken with a critical eye on the risk: benefit ratio. The chemotherapeutic agent vincristine can occasionally induce atypical and more severe neuropathy symptoms than would occur without the drug.[32]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing		(summary)
all patients		
	1st	**physiotherapy and exercise**
	plus	**occupational therapy**
	adjunct	**bracing**
	adjunct	**orthopaedic surgery**
	adjunct	**treatment of underlying concomitant conditions**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

all patients

1st **physiotherapy and exercise**

» Low-impact exercises, such as cycling and swimming, as well as physiotherapy sessions, increase energy as well as reducing fatigue and pain.[22] The addition of a stretching programme, which may include yoga, enables a greater range of motion over time. Strength training of proximal/core muscles should be encouraged, starting at low resistance and gradually building up. Progressive resistance exercise of the ankle dorsiflexors is recommended to improve muscle strength and slow progression of muscle weakness.[14] Physiotherapy should be on a fixed schedule that the patient can ease into and modify as required. Exercise programmes should include rest days to encourage recovery.[14] Exercise should cease temporarily and exercise regimen should be modified, if there are any signs of exercise-induced muscle damage.[14] Balance re-training, core strengthening, postural strengthening, and age-appropriate recreational activities may all be used to improve balance.[14] Cramps are treated by stretching of involved muscle groups.[14]

plus **occupational therapy**

Treatment recommended for ALL patients in selected patient group

» Over time, patients lose intrinsic hand muscle strength and can develop contractures of the fingers. Modifications in activities of daily living are thus often required. An occupational therapist can provide an assortment of tools - such as writing instruments, eating utensils, button hooks, and sock helpers - to enable better daily functioning. Adapted keyboard settings and voice-to-text software may be beneficial for children with impaired upper limb function.[14] The occupational therapy input is tailored to the individual needs of the patient and modified as these needs change over time.

adjunct **bracing**

Treatment recommended for SOME patients in selected patient group

Ongoing

» Patients of all ages should be evaluated for appropriate bracing. Gait and mobility aids should be prescribed by a qualified health professional with experience in their provision.[14] Children with foot drop, who have recurrent trips and falls, or who have ankle instability may benefit from ankle-foot orthoses (AFOs). Children with foot pain may benefit from foot orthoses.[14] An orthotist aligns the hindfoot in the neutral position, and then posts the forefoot so it is parallel to the ground.[23] Once proper alignment has been achieved, patients often find their gait and balance are improved, reducing the risk of falls. Posture can be improved, and fatigue is reduced. Alignment of the feet also helps to reduce stress on the ankles, knees, hips, and back. Properly made custom foot orthoses have also been shown to help with foot pain.[33] With good bracing, orthopaedic surgery can be delayed, or the need for such surgery eliminated altogether. Bracing can improve the quality of life of patients with Charcot-Marie-Tooth (CMT) and it is important that the right brace is fitted to each patient. Children with impaired mobility should wear well-fitting, supportive footwear.[14]

» Patients with CMT require a stronger design of bracing than those with drop-foot from other causes. Carbon fibre AFO have been used instead of the traditional plastic AFO, as they are lighter and achieve increased strength and stability. AFO devices usually necessitate a shoe insert to create lateral stability, and provide a cushion that allows the foot to rest comfortably and be supported.It is important to consult with a knowledgeable orthotist. While prefabricated AFOs are cheaper, many patients require custom-fitted braces. Braces that are uncomfortable or that do not fit properly will not be worn, limiting the function of the patient. The other factor that keeps people from using braces is that they do not like their appearance, in particular teenagers. Dealing with this concern requires sensitive counselling with the family.

adjunct **orthopaedic surgery**

Treatment recommended for SOME patients in selected patient group

» Some patients will require orthopaedic surgery at some point to correct the foot deformities associated with Charcot-Marie-Tooth (CMT), or for secondary complications, such as a knee or hip replacement in osteoarthritis. It is important to consult with a surgeon who has experience

Ongoing

with patients with CMT as their needs are not typically seen in other conditions.[26]

» Common surgeries include tendon transfers, heel-cord prolongation, and/or hammer toe straightening.[27] These surgeries have better long-term effects than other procedures, including triple arthrodesis (ankle fusion), as the latter has been shown to break down over time and cause pain subsequent to arthritis formation at the ankle joint, though this procedure may be appropriate with accompanying soft tissue and tendon transfers in an older person who has painful arthritic joints.[26]

» The progressive nature of CMT should be remembered. Surgery is not always corrective, and, even if it is, the clinical feature in question may regress in the future.[30] Even after surgery, most patients will still need to wear an ankle-foot orthosis for ambulation.

adjunct **treatment of underlying concomitant conditions**

Treatment recommended for SOME patients in selected patient group

» Diabetes mellitus has been shown to exacerbate at least one type of Charcot-Marie-Tooth (CMT), CMT1A.[31] Being in good glycaemic control leads to better outcomes for people with CMT than those with poor glycaemic control.[31]

» Spine issues, including spinal stenosis or lumbar radiculopathy, can impair ambulation for all people. For people with CMT who have seemingly superimposed secondary spinal deficits, appropriate physiotherapy and surgical referral can be made. Thought should be given to the intervention and how it could impact the underlying neuropathy.

» Neurotoxic medicines should be undertaken with a critical eye on the risk: benefit ratio. The chemotherapeutic agent vincristine can occasionally induce atypical and more severe neuropathy symptoms than would occur without the drug.[32]

Emerging

PXT-3003 (baclofen/naltrexone/sorbitol)

PXT-3003 is being investigated for the treatment of CMT1A. This compound combines three drugs currently approved for other indications: baclofen, naltrexone, and sorbitol.[34] Pre-clinical trials showed decreased PMP22 mRNA levels on transgenic rats. A treatment trial of 80 patients with CMT1A found good safety/tolerability of the drug and some improvement in strength and function in the high-dose group compared with placebo. Additional trials are necessary to determine if this decreases disability in people with CMT1A, and trials are planned for the near future.[35]

Antisense oligonucleotides

A preclinical study found that the PMP22 antisense oligonucleotide (ASO) reversed CMT1A phenotypes in two different CMT1A animal models. ASOs are able to bind specific RNA and block the production of the protein related to that DNA and RNA. In CMT1A, there is an over-expression of PMP22 and the ASO may be able to reduce this expression. Preclinical and clinical trials need to be undertaken with care, because too little PMP22 production causes hereditary neuropathy with liability to pressure palsies (HNPP).[36] Although it may take a number of years to determine if this has a beneficial effect in patients with CMT1A, ASOs could potentially be the first treatment that directly attacks the cause of the disease and stops disease progression.[36] DTx-1252 is one such ASO that has received orphan drug designation by the Food and Drug Administration (FDA). It utilises a small interfering RNA (siRNA) to target the PMP22 duplication and reduce the amount of PMP22 protein produced. Mouse models show normalised myelin levels and increased functionality.

Gene therapy

Loading of a complete gene or a target gene into an adeno-associated virus (AAV) vector is being developed for multiple forms of CMT, including CMT1A and CMT1X. The goal is having a functional gene inserted into the nerves to replace the defective copy (in the case of CMT1X) or to add a different gene (e.g., NTF3) thought to increase nerve health (in the case of CMT1A).[37] NT3 is expressed by the myelin sheath and allows for survival and differentiation along the nerve. Trials are ongoing for AAV-NTF3.[38] AAV2/9 vectors are being developed for delivery of small hairpin RNAs to reduce PMP22 expression in CMT1A.[39]

Sorbitol inhibitors

CMT caused by the gene recessive sorbitol dehydrogenase (SORD) causes SORD deficiency, and people are found to have increased serum sorbitol levels, roughly 20 times normal levels.[40] Clinical trials are ongoing to reduce the sorbitol levels. Govorestat (AT-007), an experimental aldose reductase inhibitor, is being administered via oral liquid suspension in clinical trials to determine the efficacy of reduction of sorbitol levels on functional outcomes.[41]

Primary prevention

Primary prevention can only be achieved through pre-natal and pre-implantation genetic testing in couples with a known genetic mutation. However, if this is the choice of the family, genetic counselling is warranted for any family considering these options. It should be emphasised that most people with the condition are capable of leading fulfilling and productive lives, and ambulate independently throughout life.

Patient discussions

Patients should have appropriate bracing to increase ambulation. Low-impact exercises, such as cycling and swimming, as well as physiotherapy and yoga, help some patients to feel better and improve cardiac health.

The only medications known to cause a worsening of symptoms are neurotoxic chemotherapy drugs (e.g., paclitaxel, cisplatin, and vincristine), which may cause acute paralysis. Use of these medications should be discussed with a physician to weigh the risks and benefits. Other drugs may have an association with muscle weakness or neuropathy, but no others have been definitively linked to neurotoxicity, and the risks and benefits of the medication should be discussed between a patient and their doctor.[45]

The Charcot-Marie-Tooth Association (CMTA) is an active patient-run US organisation that provides support, as well as supports research into the condition. Patients can sign up for the newsletter or get involved in other ways. [Charcot-Marie-Tooth Association (CMTA)] (http://www.cmtausa.org) The Hereditary Neuropathy Foundation is also an active patient-run organisation providing support and supporting research into CMT. [Hereditary Neuropathy Foundation] ()

Monitoring

Monitoring

Patients should be followed up every 1-2 years to assess for symptom progression. Evaluation should include a neurology examination (with use of the Charcot-Marie-Tooth disease Neuropathy Score [CMTNS]) or CMT Exam Score [CMTES]), possibly electrophysiology (nerve conduction studies), genetic counselling, and rehabilitative evaluation.[9][10] [11] All patients with CMT should be checked annually for evidence of diabetes mellitus, and treated for the condition promptly if it is present, as it can exacerbate the symptoms of CMT1A and possibly other forms of the condition.

Research into CMT is ongoing, and new updates and trials are common. Physicians should be aware of updates and be able to explain research or clinical trials that may be of assistance to the patient.

Complications

Complications	Timeframe	Likelihood
osteoarthritis	**long term**	**medium**
Due to the weakness of the ankles, degenerative arthritis of the ankle, knee, or hip may develop over years and require joint replacements.		
pain	**long term**	**medium**
Neuropathic (burning, tingling, shooting) pain may occur as a result of the neuropathy, while bone and joint pain may result from pressure on the feet. Muscle cramps and restless legs may also occur. Neuropathic pain can be treated with gabapentin, pregabalin, duloxetine, and amitriptyline.[14] [44] Topical lidocaine patches may help localised pain.[44] Potentially addictive medications, such as narcotics, opioids, and muscle relaxants, should be avoided when possible. Non-pharmaceutical approaches should be used in conjunction with medications for pain lasting >6 months, ideally within a specialised multidisciplinary team.[14] Joint, bone, and muscle pains require different approaches and should be treated appropriately.		

Prognosis

Charcot-Marie-Tooth (CMT) disease is a progressive condition, and the subtypes show different disease courses. Symptoms of the condition do not remit, and often worsen over time. There are no effective therapies, other than bracing and orthopaedic corrective surgery, and there is no cure.

CMT1A

CMT1A is the most common form of CMT, and as such has considerable natural history data. One study investigated this condition using the Charcot-Marie-Tooth Neuropathy Score (CMTNS) as a measure of longitudinal data and found that, as a group, people with the disorder progressed at a rate of 0.7 points per year, leading to a difference in impairment over a 2-year period.[42] It also found that individuals with CMT1A

without concomitant illnesses, such as diabetes mellitus or a second form of CMT, rarely become wheelchair-dependent, with 95% remaining ambulatory.

Symptoms of CMT1A begin between the first and second decades. Orthotics or ankle-foot orthoses are usually required within two decades of symptom onset, and orthopaedic surgery may be required from the first to the sixth decade. Symptoms progress in a length-dependent manner, so that the feet are affected before the ankles, which are in turn affected before the hands, and there is usually no proximal muscle involvement. Patients are likely to require life-long bracing and may require aids for utility function over time.

CMT2A

CMT2A is usually more severe than CMT1A. Most individuals affected with CMT2A have significant motor weakness in the pre-school and school-age years, and will be non-ambulatory by the age of 20 years.[43] Sensory impairment is not affected until later in the disease course. Severe muscle atrophy of the distal legs and arms and proximal muscle weakness may occur. Some cases of CMT2A are associated with optic nerve atrophy and/or respiratory insufficiency due to weakness of the diaphragm, and the latter may lead to premature death. Many of the severe forms of CMT follow this disease course.

Diagnostic guidelines

Europe

Differential diagnosis of acquired and hereditary neuropathies in children and adolescents-consensus-based practice guidelines (https://register.awmf.org/de/leitlinien/detail/022-027)

Published by: Society for Neuropediatrics (GNP); German Society for Pediatric and Adolescent Medicine (DGKJ); German Society for Neurology (DGN); German Society for Human Genetics (GfH); German Society for Clinical Neurophysiology (DGKN); German Society for Neuropathology and Neuroanatomy (DGNN); Society for Pediatric Radiology (GPR); Austrian Society for Pediatric and Adolescent Medicine (ÖGKJ); Swiss Society for Neuropediatrics (SGNP); Swiss Society of Pediatrics (SGP)

Last published: 2021

Treatment guidelines

International

Clinical practice guideline for the management of paediatric Charcot-Marie-Tooth disease (https://jnnp.bmj.com/content/93/5/530.long)

Published by: Paediatric CMT Best Practice Guidelines Consortium

Last published: 2022

Online resources

1. Charcot-Marie-Tooth Association (CMTA) (http://www.cmtausa.org) *(external link)*

2. Hereditary Neuropathy Foundation (https://www.hnf-cure.org) *(external link)*

Key articles

- Saporta AS, Sottile SL, Miller LJ, et al. Charcot-Marie-Tooth disease subtypes and genetic testing strategies. Ann Neurol. 2011 Jan;69(1):22-33. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21280073?tool=bestpractice.bmj.com)
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Images

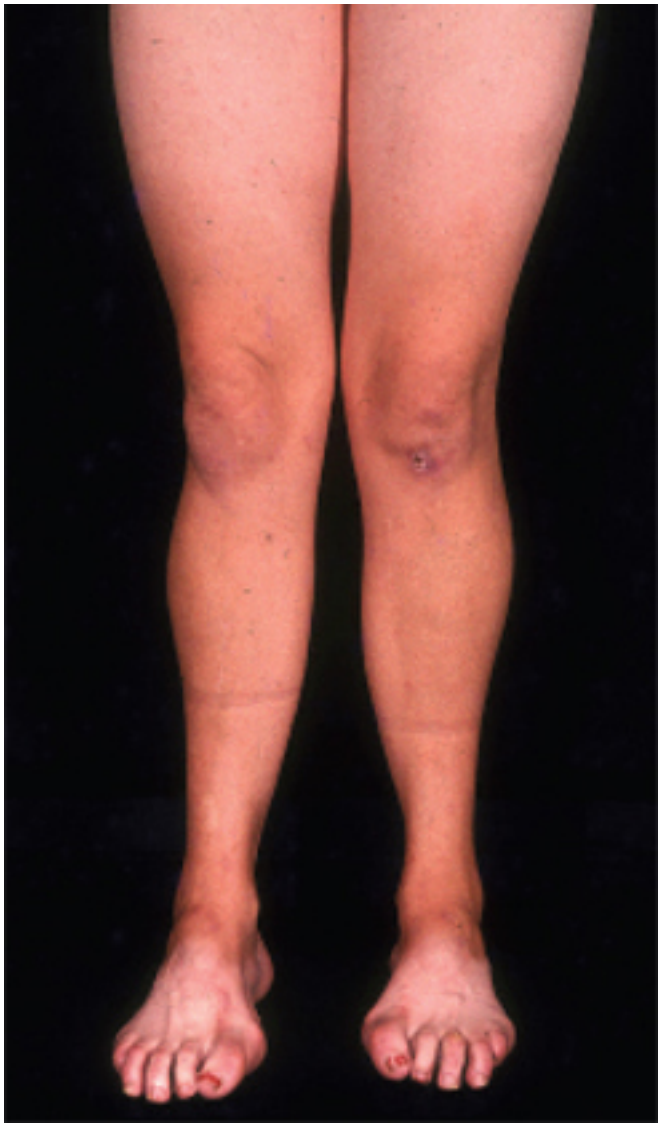

Figure 1: Pes cavus, toe clawing, and bilateral peroneal muscular atrophy in patient with CMT1A

Adapted from Berciano J, Gallardo E, Garcia A, et al. Charcot-Marie-Tooth disease type 1A duplication with severe paresis of the proximal lower limb muscles: a long-term follow-up study. J Neurol Neurosurg Psychiatry. 2006 Oct;77(10):1169-76

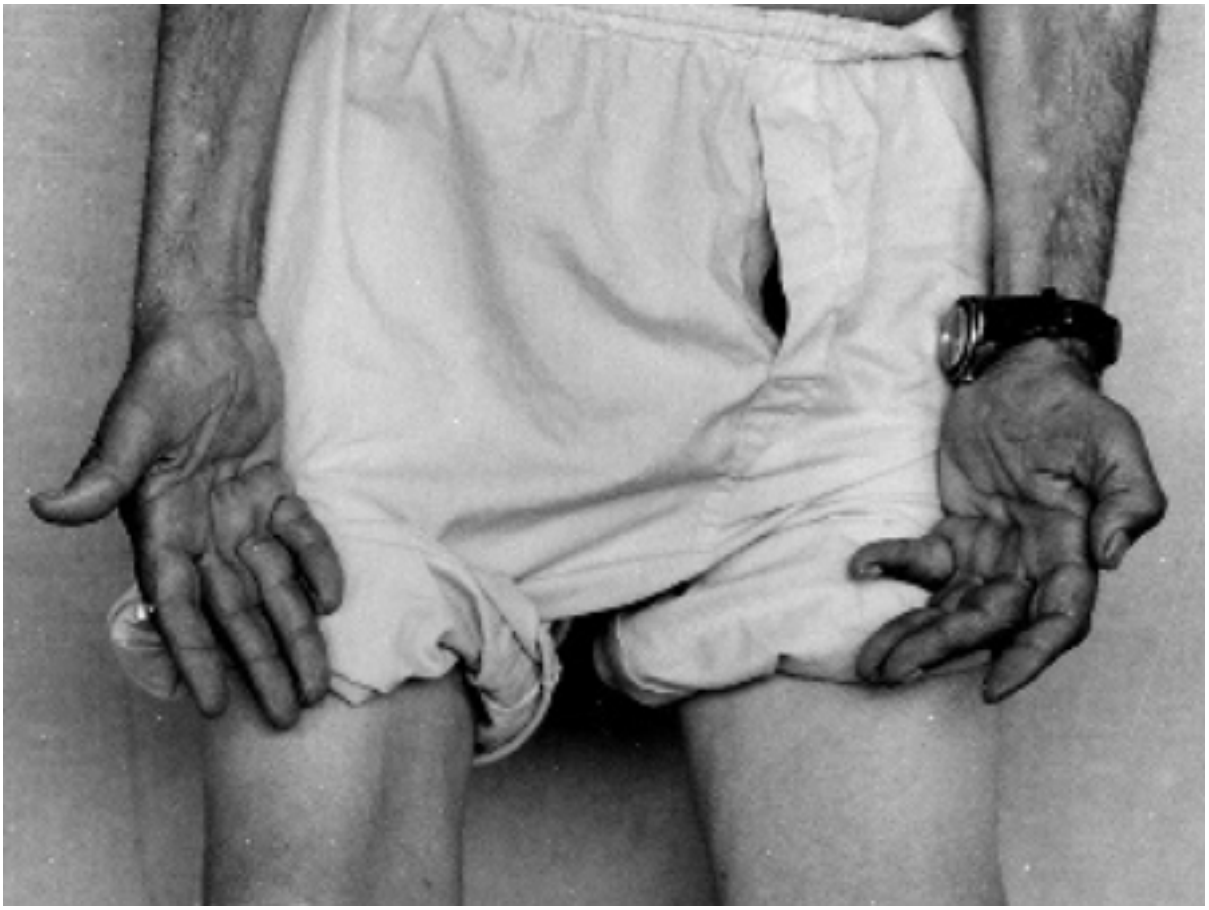

Figure 2: Wasting of hand muscles in patient with CMT1A

Adapted from Berciano J, Gallardo E, Garcia A, et al. Charcot-Marie-Tooth disease type 1A duplication with severe paresis of the proximal lower limb muscles: a long-term follow-up study. J Neurol Neurosurg Psychiatry. 2006 Oct;77(10):1169-76

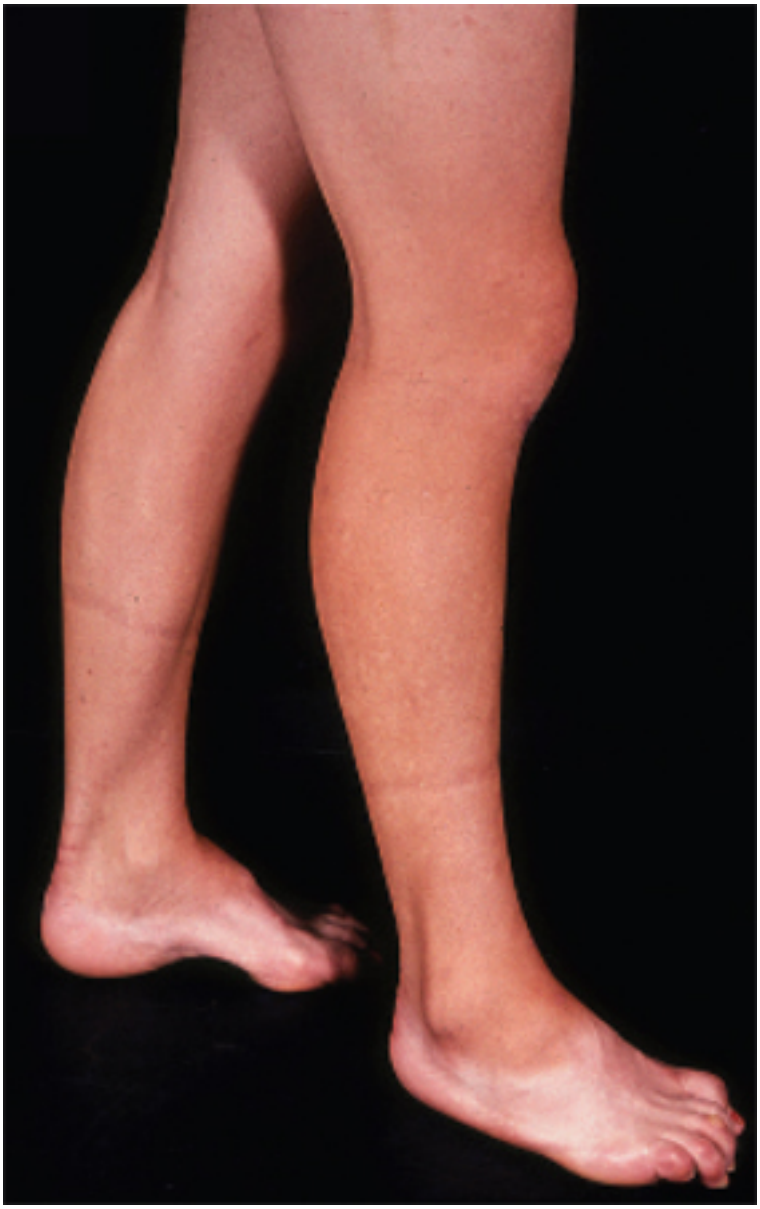

Figure 3: Pes cavus, toe clawing, and bilateral peroneal muscular atrophy in patient with CMT1A

Adapted from Berciano J, Gallardo E, Garcia A, et al. Charcot-Marie-Tooth disease type 1A duplication with severe paresis of the proximal lower limb muscles: a long-term follow-up study. J Neurol Neurosurg Psychiatry. 2006 Oct;77(10):1169-76

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Figure 1 – BMJ Best Practice Numeral Style

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