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# Charcot-Marie-Tooth Disease

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**Author and Editor Disclosure**

**Synonyms and related keywords:** hereditary motor sensory neuropathy, HMSN, peroneal muscular atrophy, PMA, CMT





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INTRODUCTION

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## Background

Charcot-Marie-Tooth disease (CMT) is the most common inherited neurologic disorder. CMT is characterized by inherited neuropathies without known metabolic derangements. In 1886, Professor Jean Martin Charcot of France (1825-1893) and his student Pierre Marie (1853-1940) published the first description of distal muscle weakness and wasting beginning in the legs, calling it peroneal muscular atrophy.

Howard Henry Tooth (1856-1926) described the same disease in his Cambridge dissertation in 1886, calling the condition peroneal progressive muscular atrophy. Tooth was the first to attribute symptoms correctly to neuropathy, rather than to myelopathy as physicians had done before him. In 1912, Hoffman identified a case of peroneal muscular atrophy with thickened nerves. This disease was referred to as Hoffman disease and later was known as Charcot-Marie-Tooth-Hoffman disease.

In 1968, CMT was subdivided into 2 types, CMT 1 and CMT 2, based on pathologic and physiologic criteria. CMT has been subdivided further based upon the genetic cause of the disease. With the advent of genetic testing, all the different diseases that fall under the heading of CMT syndrome eventually are likely to become distinguishable.

## Pathophysiology

CMT is a heterogeneous group of genetically distinct disorders with similar clinical presentation. CMT 1 is a disorder of peripheral myelination resulting from a mutation in the peripheral myelin protein-22 (*PMP-22*) gene. Mutations in the gene encoding the major PNS myelin protein, myelin protein zero (MPZ), account for 5% of patients with CMT. The mutation results in abnormal myelin that is unstable and spontaneously breaks down. This process results in demyelination, leading to uniform slowing of conduction velocity.

Slowing of conduction in motor and sensory nerves was believed to cause weakness and numbness. A recent study by Krajewski et al suggests that neurologic dysfunction and clinical disability in CMT 1A are caused by loss or damage to large diameter motor and sensory axons. Pain and temperature sensations usually are not affected because they are carried by unmyelinated (type C) nerve fibers.

In response to demyelination, Schwann cells proliferate and form concentric arrays of remyelination. Repeated cycles of demyelination and remyelination result in a thick layer of abnormal myelin around the peripheral axons. These changes cause what is referred to as an onion bulb appearance.

CMT 2 is primarily a neuronal (ie, axonal) disorder, not a demyelinating disorder. Type 2 results in peripheral neuropathy through direct axonal death and Wallerian degeneration. CMT 3 (also known as Dejerine-Sottas disease) is characterized by infantile onset. Type 3 results in severe demyelination with delayed motor skills and is a much more severe form than type 1. Marked segmental demyelination with thinning of the myelin around the nerve is observed on histological examination. CMT X (X-linked CMT) and CMT 4 are also demyelinating neuropathies.

## Frequency

### United States

Prevalence of CMT is 1 person per 2500 population, or about 125,000 patients in the US. CMT 1 incidence is 15 persons per 100,000 population. CMT 1A incidence is 10.5 persons per 100,000 population, or 70% of CMT 1. CMT 2 incidence is 7 persons per 100,000 population. CMT X represents at least 10-20% of those with the CMT syndrome.

**International**

In Japan, prevalence is reported as 10.8 cases per 100,000 population, in Italy it is reported to be 17.5 cases per 100,000 population, and in Spain it is 28.2 cases per 100,000 population.

## Mortality/Morbidity

Morbidity in CMT is mainly secondary to distal muscle weakness and foot deformities. In rare cases, phrenic nerve involvement of the diaphragm can cause ventilatory difficulties.

## Race

No racial predilection is recognized.

## Sex

No predilection to either sex is known.

## Age

Age of presentation varies depending on the type of CMT. Please refer to the table in the section Causes.



## History

- Patients usually have significant family history of CMT. This history varies, depending on the inheritance and penetrance pattern of the particular disorder. Spontaneous mutations also have been reported.
- Slow progressing weakness beginning in the distal limb muscles, typically in the lower extremities before the upper extremities, generally is noted. A subgroup of patients with CMT 1A can present with proximal muscle wasting and weakness.
- Onset usually is in the first 2 decades of life.
- Patients' initial complaints may be difficulty walking and frequent tripping because of foot and distal leg weakness. Frequent ankle sprains and falls are characteristic.
- Parents may report that a child is clumsy or simply not very athletic.
- As weakness becomes more severe, foot drop commonly occurs. Steppage (ie, gait in which patient must lift the leg in an exaggerated fashion to clear the foot off the ground) also is common.
- Intrinsic foot muscle weakness commonly results in the foot deformity known as pes cavus. Symptoms related to structural foot abnormalities include calluses, ulcers, cellulitis, or lymphangitis.
- Hand weakness results in complaints of poor finger control, poor handwriting, difficulty using zippers and buttons, and clumsiness in manipulating small objects.
- Patients usually do not complain of numbness. This phenomenon may be due to the fact that CMT patients never had normal sensation and, therefore, simply do not perceive their lack of sensation.

- Pain, both musculoskeletal and neuropathic types, may be present. Muscle cramping is a common complaint.
- Autonomic symptoms usually are absent, but a few men with CMT have reported impotence.

## Physical

- Distal muscle wasting may be noted in the legs, resulting in the characteristic stork leg or inverted champagne bottle appearance.
- Bony abnormalities commonly seen in long-standing CMT disease include the following:
  - Pes cavus (high arch foot), probably analogous to development of claw hand in ulnar nerve lesion, occurs 25% in the first decade of life and 67% in later decades. Other foot deformities also can occur (see Image 1).
  - Spinal deformities (eg, thoracic scoliosis) occur in 37-50% of patients with CMT 1.
- Deep tendon reflexes (DTRs) are diminished markedly or are absent.
- Vibration sensation and proprioception are decreased significantly, although patients usually have no sensory symptoms.
- Patients may have sensory gait ataxia, and Romberg test is usually positive.
- Sensation of pain and temperature usually is intact.
- Essential tremor is present in 30-50% of CMT patients.
- Sensory neuronal hearing loss is observed in 5% of patients.
- Enlarged and palpable peripheral nerves are common.
- Phrenic nerve involvement with diaphragmatic weakness is rare, but it has been described.
- Vocal cord involvement and hearing loss can occur in rare forms of CMT.

## Causes

Hereditary neuropathies are classified by Mendelian Inheritance in Man (MIM).

Charcot-Marie-Tooth Disorders – Genetic and Clinical Feature Comparison

| CMT Type | Chromosome; Inheritance Pattern | Age of Onset | Clinical Features | Average NCVs§ |
|---|---|---|---|---|
| CMT 1A (PMP-22¶ dupl.) | 17p11; AD* | First decade | Distal weakness | 15-20 m/s |
| CMT 1B ($P_0$-MPZ)** | 1q22; AD | First decade | Distal weakness | <20 m/s |
| CMT 1C (non A, non B) | 16p13;AD | Second decade | Distal weakness | 26-42 m/s |

| | | | | |
|---|---|---|---|---|
| CMT 1D (EGR-2)[#] | 10q21; AD | First decade | Distal weakness | 15-20 m/s |
| CMT 1E | 17p11; AD | First decade | Distal weakness, deafness | 15-20 m/s |
| CMT 1F | 8p21; AD | First decade | Distal weakness | 15-20 m/s |
| CMT X (Connexin-32) | Xq13; XD[‡] | Second decade | Distal weakness | 25-40 m/s |
| CMT 2A | 1p36; AD | 10 y | Distal weakness | >38 m/s |
| CMT 2B | 3q; AD | Second decade | Distal weakness, Sensory loss, skin ulcers | Axon loss; Normal |
| CMT 2C | 12q23-q24, AD | First decade | Vocal cord, Diaphragm & Distal weakness | >50 m/s |
| CMT 2D | 7p14; AD | 16-30 y | Distal weakness, upper limb predominantly | Axon loss; N[††] |
| CMT 2E | 8p21; AD | 10-30 y | Distal weakness, lower limb predominantly | Axon loss; N |
| CMT 2F | 7q11-q21; AD | 15-25 y | Distal weakness | Axon loss; N |
| CMT 2G | 12q12-q13; ?AD | 9-76 y | Distal weakness | Axon loss; N |
| CMT 2H | ?; AR[†] | 15-25 y | Distal weakness, Pyramidal features | Axon loss; N |
| CMT 2I | 1q22; AD | 47-60 y | Distal weakness | Axon loss; N |
| CMT 2J | 1q22; AD | 40-50 y | Distal weakness, hearing loss | Axon loss; N |
| CMT 2K | 8q13-q21; AR | <4 y | Distal weakness | Axon loss; N |
| CMT 2L | 12q24; AD | 15-25 y | Distal weakness | Axon loss; N |
| CMT R-Ax (Ouvrier) | AR | First decade | Distal weakness | Axon loss; N |

| | | | | |
|---|---|---|---|---|
| CMT R-Ax (Moroccan) | 1q21; AR | Second decade | Distal weakness | Axon loss; N |
| Cowchock syndrome | Xq24-q26 | First decade | Distal weakness, deafness, mental retardation | Axon loss; N |
| HNPP‖ (PMP-22)<br>Or tomaculous neuropathy | 17p11; AD | All ages | Episodic weakness and numbness | Conduction Blocks |
| Dejerine-Sottas-syndrome (DSS) or HMSN 3 | $P_0$; AR<br>PMP-22; AD<br>8q23; AD | 2 y | Severe weakness | <10 m/s |
| Congenital hypomyelination (CH) | $P_0$, EGR2 or PMP-22<br>AR | Birth | Severe weakness | <10 m/s |
| CMT 4A | 8q13; AR | Childhood | Distal weakness | Slow |
| CMT 4B<br>(Myotubular in-related protein-2) | 11q23; AR | 2-4 y | Distal & proximal weakness | Slow |
| CMT 4C | 5q23; AR | 5-15 y | Delayed walking | 14-32 m/s |
| CMT 4D (Lom)<br>(N-myc Downstream-Regulated Gene 1) | 8q24; AR | 1-10 y | Distal muscle wasting, foot and hand deformities | 10-20 m/s |
| CMT 4E (EGR2) | 10q21; AR | Birth | Infant hypotonia | 9-20 m/s |
| CMT 4G | 10q23.2; AR | 8-16 years | Distal weakness | 9-20 m/s |
| CMT 4H | 12p11.21-q13.11; AR | 0-2 years | Delayed walking | 9-20 m/s |
| CMT 4F | 19q13; AR | 1-3 y | Motor delay | Absent |

*Autosomal dominant

†Autosomal recessive

‡X-linked dominant

§Nerve conduction velocities

||Hereditary neuropathy with liability to pressure palsy

¶Peripheral myelin protein

#Early growth response

**Myelin protein zero

††Normal

- The above classification is the most specific, up to date, and comprehensive classification. In the past, CMT was classified as hereditary motor and sensory neuropathy (HMSN). Hereditary neuropathy with diffusely slow nerve conduction velocity (hypertrophic neuropathy) is HMSN I.
    - HMSN I (CMT 1) with different subclassifications
    - HMSN III (Dejerine-Sottas disease, hypertrophic neuropathy of infancy, congenital hypomyelinated neuropathy) - Autosomal recessive inheritance
    - HMSN IV (Refsum syndrome - phytanic acid excess) - Autosomal recessive inheritance - tetrad of peripheral neuropathy, retinitis pigmentosa, cerebellar signs, and increased cerebrospinal fluid (CSF) protein
- Hereditary motor and sensory neuropathy with normal or borderline abnormal nerve conduction velocity (neuronal or axonal type)
    - HMSN II (CMT 2)
        - CMT 2A - Chromosome 1(p35-36) - Typical type, no enlarged nerves, later onset of symptoms, feet more severely affected than hands
        - CMT 2B - Chromosome 3(q13-22) - Typical type with axonal spheroids
        - CMT 2C - Not linked to any known loci; diaphragm and vocal cord weakness
        - CMT 2D - Chromosome 7(p14) - Muscle weakness and atrophy is more severe in hands than feet
        - Autosomal recessive CMT 2
    - HMSN V (ie, spastic paraplegia) - Normal upper limbs and no sensory symptoms
- Roussy-Levy syndrome - Autosomal dominant with essential tremor
- HMSN VI - With optic atrophy
- HMSN VII - With retinitis pigmentosa
- Prednisone-responsive hereditary neuropathy

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DIFFERENTIALS

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## Other Problems to be Considered

Acquired nongenetic causes of peripheral neuropathies
Alcoholism
Vitamin B-12 deficiency
Thyroid disease

Diabetes mellitus
HIV infection
Vasculitis
Leprosy
Neurosyphilis
Amyloid associated with chronic inflammation
Occult malignancy
Heavy-metal intoxication
Chronic inflammatory demyelinating polyneuropathy
Motor neuropathy with multiple conduction block
Other genetic neuropathies
Familial brachial plexus neuropathy (ie, hereditary neuralgic amyotrophy)
Autosomal recessive genetic disorders, such as Refsum disease or metachromatic leukodystrophy
X-linked recessive genetic disorders such as adrenomyeloneuropathy or Pelizaeus-Merzbacher disease
Amyloid neuropathies
Hereditary ataxias with neuropathy (eg, Friedreich ataxia)
Blindness, seizures, dementia, and mental retardation are not part of CMT syndrome.



## Lab Studies

- Results of all routine laboratory tests are within the reference range in CMT. Special genetic tests are available for some types of CMT.
    - CMT 1A: Pulsed field gel electrophoresis or a specialized fluorescent in situ hybridization (FISH) assay is the most reliable genetic test, but it is not widely available. DNA-based testing for the PMP-22 duplication (CMT 1A) is widely available and detects more than 98% of patients with CMT 1A (see Image 2). Point mutations in the *PMP-22* gene cause fewer than 2% of cases of CMT 1A and are identified by this technique. Approximately 70-80% of cases of CMT 1 are designated CMT 1A, caused by alteration of the *PMP-22* gene (chromosomal locus 17p11).
    - CMT 1B: Genetic testing is performed primarily on a research basis, but it is available from a few commercial laboratories. Approximately 5-10% of CMT 1 is designated CMT 1B and is caused by a point mutation in the myelin P0 protein (*MPZ*) gene (chromosomal locus 1q22).
    - CMT 1C and CMT 1D: Very rarely, mutations occur in the *EGR2* (early growth response 2) gene or the *LITAF* gene, causing CMT 1D and CMT 1C, respectively, for which molecular genetic testing is also available clinically.
    - CMT 2: The 4 subtypes of CMT 2 are indistinguishable clinically and are distinguished solely based on genetic linkage findings. Relative proportions of CMT 2A, 2B, 2C, and 2D have not been determined yet. The chromosomal loci for CMT 2A, CMT 2B, CMT 2C, CMT 2D, CMT 2E, CMT 2F, CMT 2G, and CMT 2L have been mapped, but the genes have not been identified. Molecular genetic testing is clinically available for CMT 2A, 2B1, 2E, and 2F only.
    - CMT X: Molecular genetic testing of the *GJB1* (Cx32) gene detects about 90% of cases. Such testing is clinically available.
    - Genetic testing is not available currently for other types of CMT.

## Imaging Studies

- High-resolution ultrasonography of the median nerve and other peripheral nerves may serve as an adjunct to

electrodiagnosis in CMT 1A.

## Other Tests

- Nerve biopsy rarely is indicated to diagnose CMT, especially since the advent of genetic testing. Biopsies sometimes are performed in cases of diagnostic dilemmas. Findings vary in different types of CMT.
    - In CMT 1, peripheral nerves contain few myelinated fibers, and intramuscular nerves are surrounded by rich connective tissue and hyperplastic neurilemma. Lengths of myelin are atrophic along the fibers. Concentric hypertrophy of the lamellar sheaths is seen. Onion bulb formation, made up of circumferentially directed Schwann cells and their processes, frequently is observed.
    - In CMT 2, axon loss with Wallerian degeneration generally is found.
    - In CMT 3, or Dejerine-Sottas disease, demyelination with thinning of the myelin sheath is observed.
    - Inflammatory infiltrate, indicating an autoimmune demyelinating process, should not be present.

## Procedures

- Electromyography/nerve conduction study
    - Perform electromyography/nerve conduction studies (EMG/NCS) first if CMT is suggested. Findings vary depending on the type of CMT.
    - In demyelinating types, like CMT 1, diffuse and uniform slowing of nerve conduction velocities is observed (see Image 3).
    - Harding and Thomas criteria for diagnosing CMT 1 include median motor nerve conduction velocity less than 38 meters per second (m/s) with compound motor action potential (CMAP) and amplitude of at least 0.5 millivolts (mV). No focal conduction block or slowing should be present unless associated with other focal demyelinating processes.
    - All nerves tested, both sensory and motor, show the same degree of marked slowing.
    - Absolute values vary, but they are approximately 20-25 m/s in CMT 1 and less than 10 in Dejerine-Sottas and congenital hypomyelination. Slowing of nerve conduction also can be found in asymptomatic individuals.
    - In neuronal (ie, axonal) types of CMT, nerve conduction velocity usually is normal, but markedly low amplitudes are noted in both sensory (ie, sensory nerve action potential [SNAP]) and motor nerve (ie, CMAP) studies.
    - In neuronal (ie, axonal) types, increased insertional activity is evident with fibrillation potentials and positive sharp waves seen. Motor unit potentials show decreased recruitment patterns and neuropathic changes in morphology.

## Histologic Findings

- In CMT 1, peripheral nerves contain few myelinated fibers and intramuscular nerves are surrounded by a rich connective tissue and hyperplastic neurilemma, and lengths of myelin are atrophic along the fibers.
- Concentric hypertrophy of the lamellar sheaths is seen. Formation of the typical onion bulb, made up of circumferentially directed Schwann cells and their processes, is noted.
- In CMT 2, axonal degeneration is observed.

- In CMT 3, Dejerine-Sottas disease, demyelination with thinning of the myelin sheath can be seen.
- No inflammatory infiltrate should be present, indicating autoimmune demyelinating process.

TREATMENT

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## Rehabilitation Program

**Physical Therapy**

Daily heel cord stretching exercises are desirable to prevent Achilles tendon shortening. Special shoes with good ankle support may be needed. Physical therapy can assist with ambulation and provide necessary evaluation and training with orthoses, such as an ankle-foot orthosis (AFO). Patients often require an AFO to correct foot drop and aid walking.

Some patients require the use of forearm crutches or a cane for improved gait stability, but fewer than 5% of patients need wheelchairs. Advise patients with CMT about weight management, as obesity makes ambulation more difficult. Encourage exercise within each individual patient's capability. Most patients with CMT usually remain physically active.

**Occupational Therapy**

An occupational therapist may recommend use of adaptive equipment for activities of daily living (ADL) and self-care. Fitting of a proper orthosis and keeping the wrist and hand in functional position may be required. Vocational and avocational training regarding importance of career and employment implications may be needed because of persistent weakness of hands and/or feet.

## Medical Issues/Complications

- Currently, no treatment exists to reverse or slow the natural disease process for the underlying disorder. Nothing can correct the abnormal myelin, prevent its degeneration, or prevent axonal degeneration.
- Stem-cell therapies and gene transfer therapies are the most promising forms of treatment for the cure of CMT. Some promising results on the effect of antiprogesterone therapy and ascorbic acid treatment for CMT 1A have been reported in animal CMT 1A models. Progesterone receptor antagonists can reduce PMP22 overexpression and clinical severity in a CMT 1A rat model. Furthermore, ascorbic acid treatment reduced premature death and demyelination in a CMT 1A mouse model. There is also the prospect of developing drugs to reduce the effects of PMP22 overexpression in gene duplications by downregulation via the promoter. Improved understanding of the genetics and biochemistry of the disorder offers hope for an eventual treatment.
- Patients often are evaluated and managed symptomatically by a team that includes a physiatrist, neurologist, orthopedic surgeon, and physical and occupational therapists.

## Surgical Intervention

Orthopedic surgery may be required to correct severe pes cavus deformities, scoliosis, and other joint deformities.

## Consultations

Consult specialist in neurogenetics to order specific genetic tests and proper genetic counseling.

Avoid drugs and medications known to cause nerve damage (eg, vincristine, isoniazid, nitrofurantoin). Identify the cause of any pain as accurately as possible. Musculoskeletal pain may respond to acetaminophen or nonsteroidal anti-inflammatory agents. Neuropathic pain may respond to tricyclic antidepressants or antiepileptic drugs like carbamazepine or gabapentin.

Dyck et al (1982) and Ginsberg et al (2004) have described a few individuals with CMT 1 and sudden deterioration in whom treatment with steroids (prednisone) or intravenous immunoglobulin produced variable levels of improvement. Sahenk et al (2003) are studying the effects of neurotrophin-3 on individuals with CMT 1A. Passage et al (2004) reported benefit from ascorbic acid (vitamin C) in a mouse model of CMT 1.

**Drug Category: *Nonsteroidal anti-inflammatory drugs***

Have analgesic, anti-inflammatory, and antipyretic activities. Their mechanism of action is not known, but they may inhibit cyclo-oxygenase activity and prostaglandin synthesis. Other mechanisms may exist as well, such as inhibition of leukotriene synthesis, lysosomal enzyme release, lipoxygenase activity, neutrophil aggregation, and various cell-membrane functions.

| | |
|---|---|
| **Drug Name** | Ibuprofen (Motrin, Ibuprin) |
| **Description** | DOC for patients with mild to moderate pain. Inhibits inflammatory reactions and pain by decreasing prostaglandin synthesis. |
| **Adult Dose** | 200-400 mg PO q4-6h while symptoms persist; not to exceed 3.2 g/d |
| **Pediatric Dose** | <6 months: Not established<br>6 months to 12 years: 4-10 mg/kg/dose PO tid/qid<br>>12 years: Administer as in adults |
| **Contraindications** | Documented hypersensitivity; peptic ulcer disease, recent GI bleeding or perforation, renal insufficiency, or high risk of bleeding |
| **Interactions** | Coadministration with aspirin increases risk of inducing serious NSAID-related adverse effects; probenecid may increase concentrations and, possibly, toxicity of NSAIDs; may decrease effect of hydralazine, captopril, and beta-blockers; may decrease diuretic effects of furosemide and thiazides; may increase PT when taking anticoagulants (instruct patients to watch for signs of bleeding); may increase risk of methotrexate |

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| | toxicity; phenytoin levels may be increased when administered concurrently |
| **Pregnancy** | B - Usually safe but benefits must outweigh the risks. |
| **Precautions** | Category D in third trimester of pregnancy; caution in congestive heart failure, hypertension, and decreased renal and hepatic function; caution in anticoagulation abnormalities or during anticoagulant therapy |

| | |
|---|---|
| **Drug Name** | Naproxen (Naprelan, Naprosyn, Anaprox) |
| **Description** | For relief of mild to moderate pain; inhibits inflammatory reactions and pain by decreasing activity of cyclo-oxygenase, which results in a decrease of prostaglandin synthesis. |
| **Adult Dose** | 500 mg PO followed by 250 mg q6-8h; not to exceed 1.25 g/d |
| **Pediatric Dose** | <2 years: Not established<br>>2 years: 2.5 mg/kg/dose PO; not to exceed 10 mg/kg/d |
| **Contraindications** | Documented hypersensitivity; peptic ulcer disease; recent GI bleeding or perforation; renal insufficiency |
| **Interactions** | Coadministration with aspirin increases risk of inducing serious NSAID-related side effects; probenecid may increase concentrations and, possibly, toxicity of NSAIDs; may decrease effect of hydralazine, captopril, and beta-blockers; may decrease diuretic effects of furosemide and thiazides; may increase PT when taking anticoagulants (instruct patients to watch for signs of bleeding); may increase risk of methotrexate toxicity; phenytoin levels may be increased when administered concurrently |
| **Pregnancy** | B - Usually safe but benefits must outweigh the risks. |
| **Precautions** | Category D in third trimester of pregnancy; acute renal insufficiency, interstitial nephritis, hyperkalemia, hyponatremia, and renal papillary necrosis may occur; patients with preexisting renal disease or compromised renal perfusion risk acute renal failure; leukopenia occurs rarely, is transient, and usually returns to normal during therapy; persistent leukopenia, granulocytopenia, or thrombocytopenia warrants further evaluation and may require discontinuation of drug |

**Drug Category:** ***Cyclooxygenase-2 inhibitors***

Although increased cost can be a negative factor, the incidence of costly and potentially fatal GI bleeds is clearly less with COX-2 inhibitors than with traditional NSAIDs. Ongoing analysis of cost avoidance of GI bleeds will further define the populations that will find COX-2 inhibitors the most beneficial.

| | |
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| **Drug Name** | Celecoxib (Celebrex) |
| **Description** | Inhibits primarily COX-2. COX-2 is considered an inducible isoenzyme, induced during pain and inflammatory stimuli. Inhibition of COX-1 may contribute to NSAID GI toxicity. At therapeutic concentrations, COX-1 isoenzyme is not inhibited, thus GI toxicity may be decreased. Seek lowest dose of celecoxib for each patient. |
| **Adult Dose** | 200 mg/d PO qd; alternatively, 100 mg PO bid |
| **Pediatric Dose** | Not established |
| **Contraindications** | Documented hypersensitivity |
| **Interactions** | Coadministration with fluconazole may cause increase in celecoxib plasma concentrations because of inhibition of celecoxib metabolism; coadministration of celecoxib with rifampin may decrease celecoxib plasma concentrations |

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| **Pregnancy** | C - Safety for use during pregnancy has not been established. |
| **Precautions** | May cause fluid retention and peripheral edema; caution in compromised cardiac function, hypertension, conditions predisposing to fluid retention; severe heart failure and hyponatremia, because may deteriorate circulatory hemodynamics; NSAIDs may mask usual signs of infection; caution in the presence of existing controlled infections; evaluate symptoms and signs suggesting liver dysfunction or in cases of abnormal liver lab results |

**Drug Category: *Analgesics***

Pain control is essential to quality patient care. Analgesics ensure patient comfort and have sedating properties, which are beneficial for patients who experience pain.

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| **Drug Name** | Acetaminophen (Tylenol) |
| **Description** | DOC for pain in patients with documented hypersensitivity to aspirin or NSAIDs, with upper GI disease, or who are taking oral anticoagulants. |
| **Adult Dose** | 325-650 mg PO q4-6h or 1000 mg tid/qid; not to exceed 4 g/d |
| **Pediatric Dose** | <12 years: 10-15 mg/kg/dose PO q4-6h prn; not to exceed 2.6 g/d<br>>12 years: 325-650 mg PO q4h; not to exceed 5 doses in 24 h |
| **Contraindications** | Documented hypersensitivity; known G-6-P deficiency |
| **Interactions** | Rifampin can reduce analgesic effects of acetaminophen; coadministration with barbiturates, carbamazepine, hydantoins, and isoniazid may increase hepatotoxicity |
| **Pregnancy** | B - Usually safe but benefits must outweigh the risks. |
| **Precautions** | Hepatotoxicity possible in chronic alcoholics following various dose levels; severe or recurrent pain or high or continued fever may indicate a serious illness; APAP is contained in many OTC products and combined use with these products may result in cumulative APAP doses exceeding recommended maximum dose |

**Drug Category: *Tricyclic antidepressants***

A complex group of drugs that has central and peripheral anticholinergic effects, as well as sedative effects. They have central effects on pain transmission, blocking the active re-uptake of norepinephrine and serotonin.

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| **Drug Name** | Amitriptyline (Elavil) |
| **Description** | Analgesic for certain chronic and neuropathic pain. Inhibits membrane pump responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neuron. |
| **Adult Dose** | 30-100 mg/d PO qhs |
| **Pediatric Dose** | <12 years: Not established<br>>12 years: Administer as in adults |
| **Contraindications** | Documented hypersensitivity; patient has taken MAO inhibitors in past 14 d; has history of seizures, cardiac arrhythmias, glaucoma, and urinary retention |
| **Interactions** | Phenobarbital may decrease effects; coadministration with CYP2D6 enzyme system inhibitors (eg, cimetidine, quinidine) may increase levels; inhibits hypotensive effects of guanethidine; may interact with thyroid medications, alcohol, CNS depressants, barbiturates, and disulfiram |
| **Pregnancy** | D - Unsafe in pregnancy |

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| **Precautions** | Caution in cardiac conduction disturbances and history of hyperthyroidism, renal or hepatic impairment; avoid using in elderly patients |

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| **Drug Name** | Nortriptyline (Pamelor) |
| **Description** | Has demonstrated effectiveness in the treatment of chronic pain. By inhibiting the re-uptake of serotonin and/or norepinephrine by the presynaptic neuronal membrane this drug increases the synaptic concentration of these neurotransmitters in the central nervous system. Pharmacodynamic effects, such as the desensitization of adenyl cyclase and down-regulation of beta-adrenergic receptors and serotonin receptors, also appear to play a role in its mechanisms of action. |
| **Adult Dose** | 25 mg PO tid/qid, up to 150 mg/d |
| **Pediatric Dose** | <12 years: Not established<br>>12 years:<br>25-35 kg: 10-20 mg/d PO<br>35-54 kg: 25-35 mg/d PO |
| **Contraindications** | Documented hypersensitivity; narrow-angle glaucoma; do not administer to patients who have taken MAO inhibitors in past 14 d |
| **Interactions** | Cimetidine may increase nortriptyline levels when used concurrently; nortriptyline may increase prothrombin time in patients stabilized with warfarin |
| **Pregnancy** | D - Unsafe in pregnancy |
| **Precautions** | Caution in cardiac conduction disturbances and history of hyperthyroidism, renal or hepatic impairment; due to pronounced effects in cardiovascular system, best to avoid in elderly patients |

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| **Drug Name** | Doxepin (Sinequan) |
| **Description** | Inhibits histamine and acetylcholine activity and has proven useful in treatment of various forms of depression associated with chronic and neuropathic pain. |
| **Adult Dose** | 10-150 mg/d PO hs or divided bid/tid |
| **Pediatric Dose** | <12 years: Not recommended<br>>12 years: 25-50 mg/d PO hs or bid/tid and increase gradually to 100 mg/d |
| **Contraindications** | Documented hypersensitivity; urinary retention; acute recovery phase following myocardial infarction; glaucoma |
| **Interactions** | Decreases antihypertensive effects of clonidine but increases effects of sympathomimetics and benzodiazepines; effects of desipramine increase with phenytoin, carbamazepine, and barbiturates |
| **Pregnancy** | C - Safety for use during pregnancy has not been established. |
| **Precautions** | Caution in cardiovascular disease, conduction disturbances, seizure disorders, urinary retention, hyperthyroidism, and patients receiving thyroid replacement |

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| **Drug Name** | Desipramine (Norpramin) |
| **Description** | May increase synaptic concentration of norepinephrine in CNS by inhibiting reuptake by presynaptic neuronal membrane. May have effects in the desensitization of adenyl cyclase, down-regulation of beta-adrenergic receptors, and down-regulation or serotonin receptors. |

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| **Adult Dose** | 75 mg/d PO initially in equally divided doses and increase gradually prn; not to exceed 300 mg/d<br>Elderly patients: 25-100 mg/d PO; not to exceed 150 mg/d |
| **Pediatric Dose** | <6 years: Not established<br>6-12 years: 1-5 mg/kg/d PO in equally divided doses; not to exceed 5 mg/kg qd<br>>12 years: 25-50 mg/d PO, initially and increase gradually to 100 mg/d prn; not to exceed 150 mg/d; give in single or equally divided doses |
| **Contraindications** | Documented hypersensitivity; narrow-angle glaucoma, recent postmyocardial infarction; patients currently receiving MAO inhibitors or fluoxetine or who have taken them in the previous 2 wk |
| **Interactions** | Decreases antihypertensive effects of clonidine but increases effects of sympathomimetics and benzodiazepines; effects of desipramine increase with phenytoin, carbamazepine, and barbiturates |
| **Pregnancy** | C - Safety for use during pregnancy has not been established. |
| **Precautions** | Caution in cardiovascular disease, conduction disturbances, seizure disorders, urinary retention, hyperthyroidism, and patients receiving thyroid replacement |

**Drug Category: *Anticonvulsants***

Used to manage pain and provide sedation in neuropathic pain.

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| **Drug Name** | Gabapentin (Neurontin) |
| **Description** | Membrane stabilizer, a structural analogue of the inhibitory neurotransmitter gamma-amino butyric acid (GABA), which paradoxically is thought not to exert effect on GABA receptors. Appears to exert action via the alpha(2)delta1 and alpha(2)delta2 sub unit of the calcium channel. |
| **Adult Dose** | 300-3600 mg PO in 3-4 divided doses |
| **Pediatric Dose** | <12 years: Not established<br>>12 years: Administer as in adults |
| **Contraindications** | Documented hypersensitivity |
| **Interactions** | Antacids may reduce bioavailability of gabapentin significantly (administer at least 2 h following antacids); may increase norethindrone levels significantly |
| **Pregnancy** | C - Safety for use during pregnancy has not been established. |
| **Precautions** | Adjust dose in patients with renal insufficiency<br>If creatinine clearance is 30-60 mL/min, dose should be 300 mg bid; if 15-30 mL/min, 300 mg qd; if <15 mL/min, 300 mg qod; in hemodialysis patients, administer 200-300 mg after each dialysis |

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FOLLOW-UP

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## Further Outpatient Care

- Patients should have regular follow-up visits to check for deterioration in function and development of contractures. This follow-up allows early detection of complications. Proper interventions early in the disease course help to avoid significant and permanent functional limitations.

## Deterrence

- Regular and proper follow-up and therapeutic interventions are necessary to avoid joint contractures and deformities.
- Proper genetic counseling helps parents understand the risk of having a child with this disorder and gives them a chance to make informed decisions on having children.

## Complications

- Due to loss of protective sensation distally in all 4 limbs, patients with CMT are susceptible to skin breakdown or burns, nonhealing foot ulcers, and, in severe cases, bony deformities of bilateral feet. As mentioned previously, orthoses are required for treatment of foot drop or to accommodate bony foot deformities. If not fit properly, the orthoses themselves become a source of skin breakdown secondary to associated distal sensory impairment.
- Maternal CMT increases the risk for complications during delivery, which is linked to a higher occurrence of emergency interventions during birth.

## Prognosis

- Prognosis for the different types of CMT varies and depends on the clinical severity (see the table in the section Causes).
- Generally, CMT is a slowly progressive neuropathy, causing eventual disability secondary to distal muscle weakness and deformities.
- CMT usually does not shorten the expected life span.
- Shy et al developed the CMT neuropathy score, which is a modification of total neuropathy score. This has been shown to be a validated measure of length-dependent axonal and demyelinating CMT disability and can be investigated as an end point for longitudinal studies and clinical trials of CMT.

## Patient Education

- Genetic counseling is the process of providing individuals and families with information on the nature, inheritance patterns, and implications of genetic disorders to help them make informed medical and personal decisions. Offer patients with CMT genetic counseling so that they can make informed decisions regarding potential risk of passing the disease to their children.
- Drugs and medications such as vincristine, isoniazid, paclitaxel, cisplatin, and nitrofurantoin are known to cause nerve damage and should be avoided.
- Routine exercise within the individual's capability is encouraged; many individuals remain physically active.
- Obesity should be avoided because it makes walking more difficult.
- Daily heel-cord stretching exercises are warranted to prevent Achilles tendon shortening.

MISCELLANEOUS

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## Medical/Legal Pitfalls

- Failure to make proper diagnosis, including the genetic pattern, has significant medicolegal concerns.
- Informing the parents about the genetic nature of the disease and the possibility of having a child with the disorder is medicolegally important.

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MULTIMEDIA

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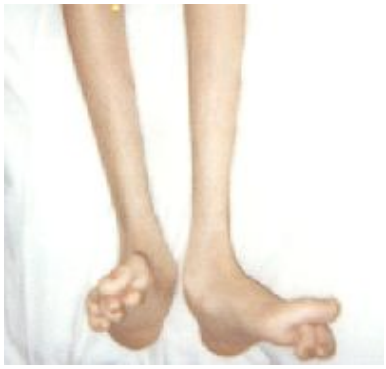
Media file 1: **Foot deformities in a 16-year-old boy with Charcot-Marie-Tooth disease type 1A.**



View Full Size Image

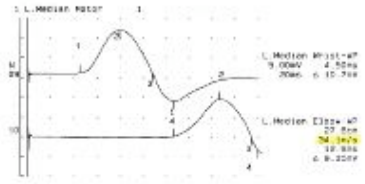
Media type: Photo

Media file 2: **Charcot-Marie-Tooth disease type 1A DNA test showing duplication in the short arm of chromosome 17 (A) compared with normal (B).**


View Full Size Image

Media type: Photo

Media file 3: **Nerve conduction study showing decreased nerve conduction velocity in the median nerve in an 18-year-old woman with Charcot-Marie-Tooth disease type 1.**



View Full Size Image

Media type: Graph

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Charcot-Marie-Tooth Disease excerpt

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