CHARCOT-MARIE TOOTH DISEASE
GRAND ROUNDS- 06/24/2016

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Charcot-Marie Tooth disease (CMT)

Synonyms

- Charcot–Marie–Tooth neuropathy
- Peroneal muscular atrophy
- Hereditary motor sensory neuropathy (HMSN) type 1
Charcot-Marie Tooth disease (CMT)

**History**

Jean-Martin Charcot (1825–1893)  
Pierre Marie (1853–1940)  
Howard Henry Tooth (1856–1925)
Charcot-Marie Tooth disease (CMT)

Introduction

- CMT is one of the hereditary motor & sensory neuropathies, a group of inherited disorders of the peripheral nervous system characterized by progressive loss of muscle tissue and touch sensation across various parts of the body
Charcot-Marie Tooth disease (CMT)

Epidemiology

- CMT is the most commonly inherited neurological disorder (autosomal dominant or recessive or an X-linked pattern)
- Prevalence: 40 per 100,000 (1 in 2500)
- Males > Females
- Age of onset is variable according to subtype, penetrance, familial phenotype, and ascertainment bias
- CMT is found world wide in people of all races and ethnic groups
- Less common in African Americans
Charcot-Marie Tooth disease (CMT)
Clinical Features

- Affects both motor and sensory nerves
- Symptom onset depends on type of CMT but usually begins in early childhood or early adulthood
- Most CMT1 symptoms start by second decade
Charcot-Marie Tooth disease (CMT)

Clinical Features

- Foot drop (usually the initial symptom)
- High stepped gait
- Frequent falls
- Hammer toes, high arched feet (pes cavus) or flat arched feet (pes planus) are classical
- Muscle wasting
- Weakness in legs later progresses to hands and forearms
- Difficulty with fine motor skills
- Claw hands
- Cramps
- Usually no sensory symptoms in early stages
Charcot-Marie Tooth disease (CMT)

Deformities

Pes cavus

Pes planus

Hammer Toes
Charcot-Marie Tooth disease (CMT)
Clinical Features
Charcot-Marie Tooth disease (CMT)
Clinical Features

Inverted champagne bottle legs (Stork Legs):
- Hypertrophy of the proximal muscles
- Marked peroneal muscle atrophy with tapering of the distal extremities
- Typical of advanced CMT
Charcot-Marie Tooth disease (CMT)  
Clinical Features  

Sensory changes  
- Usually no sensory symptoms in early stages  
- Touch, vibratory and proprioceptive sensations are often damaged  
- Pain is intact  
- Neuropathic pain if present, severity varies (mild to severe and can interfere with daily life activities)  
- Pain due to postural changes, skeletal deformations, muscular fatigue and cramping is fairly common in people with CMT
Charcot-Marie Tooth disease (CMT)

Clinical Features

Other features:

- Weakness in neck and shoulder muscles
- Tremor
- Involuntary grinding of teeth, squinting are prevalent and often go unnoticed by the person affected.
- Breathing difficulties
- Difficulties in hearing and vision
- Scoliosis causing hunching and loss of height
- Malformed hip sockets
- Gastrointestinal problems - difficulty chewing, swallowing
- Difficulty speaking - atrophy of vocal cords
Charcot-Marie Tooth disease (CMT)

Exacerbating Factors

- Emotional stress
- Periods of prolonged immobility
- Pregnancy
- Drugs:
  - Amiodarone, Bortezomib, Cisplatin, carboplatin, Colchicine (extended use), Dapsone, Didanosine, Dichloroacetate, Disulfiram, Gold salts, Leflunomide, Metronidazole/Misonidazole (extended use), Nitrofurantoin, Nitrous oxide (inhalation abuse or vitamin B12 deficiency), Perhexiline (not used in the United States), Pyridoxine (high dose), Stavudine, Suramin, Tacrolimus, Taxols (paclitaxel, docetaxel), Thalidomide, Vincristine, Zalcitabine
Charcot-Marie Tooth disease (CMT)

VINCISTINE IN CMT PATIENTS

- Acute worsening or onset of weakness in patients after vincristine administration of 2 to 4 mg for adults or 1.5 mg/m² per dose in children
- Most of the patients had undiagnosed demyelinating forms of CMT (e.g., CMT1A)
- Definite high risk for patients with CMT, including those who are asymptomatic and/or undiagnosed.
Charcot-Marie Tooth disease (CMT)
Pathophysiology/Etiology

- Pathophysiology is either a demyelinating process or an axonal process
- Etiology is intragenic mutation and/or DNA duplications or deletions
- More than 50 genes causing CMT have been identified
- Mutations usually affect one of the several myelin genes, but some affect the axon
Charcot-Marie Tooth disease (CMT)  
Pathophysiology/Etiology

- Mutation results in **defects of myelin** structure, maintenance, and formation
- Demyelinating Schwann cells causes **abnormal axon structure and function**
- Some mutations affect the gene MFN2 which codes for mitochondrial protein
- Usually mitochondria travels down the long axons. **Mutated MFN2** causes mitochondria to form large clusters or clots and prevents synapse from functioning
Charcot-Marie Tooth disease (CMT)

Defective Myelin

Defective Axon

http://chronicpainreliefoptions.com/charcot-marie-tooth-a-very-painful-disorder
Charcot-Marie Tooth disease (CMT)

Mode of inheritance

Autosomal Dominant (most common)
Autosomal Recessive
X-linked
Charcot-Marie Tooth disease (CMT)

Classification

- Genetically heterogeneous with more than 50 genes identified to date
- Classified as types 1 through 7
- Each type additionally has many subtypes
- The major division comprises types 1 and 2, which together are the most common hereditary peripheral neuropathies
Charcot-Marie Tooth disease (CMT)

**TYPES**

- CMT1 (Hypertrophic demyelinating)
- CMT2 (Axonal)
- CMT3 (Dejerine-sotta’s disease)
- CMT4 (Refsum’s disease-AR)
- CMT5 (Spastic Paraplegia)
- CMT6 (Optic Atrophy)
- CMT7 (Retinitis Pigmentosa)
Charcot-Marie Tooth disease (CMT)  
Classification-Subtypes

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Clinical features</th>
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</thead>
<tbody>
<tr>
<td>CMT1</td>
<td></td>
<td></td>
<td>Onset in first or second decade</td>
</tr>
<tr>
<td>CMT1A</td>
<td>PMP22</td>
<td>17p11.2-p1</td>
<td>Motor symptoms predominate (clumsy walking)</td>
</tr>
<tr>
<td>CMT1B</td>
<td>MPZ</td>
<td>1q22</td>
<td>Gradual loss of proprioception and vibration</td>
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<tr>
<td>CMT1C</td>
<td>LITAF</td>
<td>16p.13.1-p12.3</td>
<td>Ambulation usually maintained</td>
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<tr>
<td>CMT1D</td>
<td>EGR2</td>
<td>10q21.1-q22.1</td>
<td>Normal life expectancy</td>
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<tr>
<td>CMT1E</td>
<td>PMP22</td>
<td>17p11.2-p1</td>
<td>Palpable enlargement of the peripheral nerves</td>
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<tr>
<td>CMT1F</td>
<td>NEFL</td>
<td>8p21</td>
<td>NCV slowed to &lt;60 percent normal</td>
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<tr>
<td>Roussy-Levy</td>
<td>MPZ</td>
<td>1q22</td>
<td>CMT1 features plus: Postural tremor and gait ataxia</td>
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<tr>
<td>CMTX1</td>
<td>GJB1</td>
<td>Xq13.1</td>
<td>Symptoms more prominent in males</td>
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<td></td>
<td></td>
<td></td>
<td>Symptomatic in second decade</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Loss of ankle reflexes</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>NCV moderately slowed</td>
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<tr>
<td>CMT2</td>
<td></td>
<td></td>
<td>Onset in second or third decade</td>
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<tr>
<td>CMT2A</td>
<td>MFN2</td>
<td>1p36.2</td>
<td>Sensory symptoms predominate</td>
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<tr>
<td>CMT2B</td>
<td>RAB7</td>
<td>3q21.3</td>
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<tr>
<td>CMT2C</td>
<td>TRPV4</td>
<td>12q24.1</td>
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<tr>
<td>CMT2D</td>
<td>GARS</td>
<td>7p15</td>
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<td>CMT2E</td>
<td>NEFL</td>
<td>8p</td>
<td></td>
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<tr>
<td>CMT2F</td>
<td>HSPB1</td>
<td>7q11.23</td>
<td>Onset before age 5 years</td>
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<tr>
<td>CMT2G</td>
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<td>12q12-q13</td>
<td>Rapid progression of weakness below the knee</td>
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<tr>
<td>CMT2I</td>
<td>MPZ</td>
<td>1q22</td>
<td>Loss of ambulation by mid-teens</td>
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<td>CMT2K</td>
<td>GDAP1</td>
<td>8q13-q21.1</td>
<td>NCV normal or mildly reduced</td>
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<tr>
<td>CMT2L</td>
<td>HSPB8</td>
<td>12q24.23</td>
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<td>Early onset</td>
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<td>Not known</td>
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<td>Onset before age 5 years</td>
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<td>Rapid progression of weakness below the knee</td>
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<td>Loss of ambulation by mid-teens</td>
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<td></td>
<td>NCV normal or mildly reduced</td>
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<tr>
<td>CMT3</td>
<td></td>
<td></td>
<td>Severe, early onset</td>
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<tr>
<td>Dejerine-Sottas syndrome</td>
<td>PMP22</td>
<td>17p11.2-p1</td>
<td>Hypotonia in early infancy</td>
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<tr>
<td></td>
<td>MPZ</td>
<td>1q22</td>
<td>Initial sensory loss and distal weakness</td>
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<tr>
<td></td>
<td>EGR2</td>
<td>10q21.1-q22.1</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Congenital hypomyelinating neuropathy</td>
<td>PMP22</td>
<td>17p11.2-p1</td>
<td>NCV profoundly slowed (10m/sec)</td>
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<tr>
<td></td>
<td>MPZ</td>
<td>1q22</td>
<td>Profound hypotonia and contractures at birth</td>
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<td></td>
<td>EGR2</td>
<td>10q21.1-q22.1</td>
<td>Feeding difficulties</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Respiratory distress</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Death in infancy</td>
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<tr>
<td></td>
<td></td>
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<td>NCV extremely slowed or absent</td>
</tr>
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</table>

Vocal cord paralysis-CMT 2C
# Charcot-Marie Tooth disease (CMT)

## Classification-Subtypes

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Clinical features</th>
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<tbody>
<tr>
<td>CMT4</td>
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<tr>
<td>CMT4A</td>
<td>GDAP1</td>
<td>8q13-q21.1</td>
<td>Onset in early childhood, Distal weakness, Mild sensory loss, Rapidly progressive, Incapacity in first decade</td>
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<tr>
<td>CMT4B1</td>
<td>MTMR2</td>
<td>11q22-23</td>
<td>Onset at age 2 to 4 years, Distal and proximal weakness, Moderate sensory loss, Frequent involvement of cranial nerves</td>
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<tr>
<td>CMT4B2</td>
<td>SBF2</td>
<td>11p15</td>
<td>Onset in first two decades, Initial distal weakness, Proximal weakness after several years</td>
</tr>
<tr>
<td>CMT4B3</td>
<td>SBF1</td>
<td>22q13.33</td>
<td>Onset mean age 8 years, Slowly progressive leg weakness and gait difficulty, Areflexia and sensory loss (vibration/position &gt; pain/temperature), Pes planus</td>
</tr>
<tr>
<td>CMT4C</td>
<td>SH3TC2</td>
<td>5q32</td>
<td>Severe spinal deformities and weakness, Onset in childhood and adolescence</td>
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<tr>
<td>CMT4D</td>
<td>NDRG1</td>
<td>8q24.3</td>
<td>Early onset neuropathy, Muscle weakness and wasting, Skeletal deformities, Sensory loss, Neural deafness in second or third decade, NCV severely reduced</td>
</tr>
<tr>
<td>CMT4E</td>
<td>EGR2</td>
<td>10q21.1-22.1</td>
<td>Distal weakness at birth, Onset in early childhood, Distal muscle weakness, Severe sensory loss, Absent sensory and motor evoked response on NCV</td>
</tr>
<tr>
<td>CMT4F</td>
<td>PRX</td>
<td>19q13.1-13.2</td>
<td>Onset in early childhood, Distal muscle weakness, Severe sensory loss, Absent sensory and motor evoked response on NCV</td>
</tr>
<tr>
<td>CMT4H</td>
<td>FGD4</td>
<td>12p11.2</td>
<td>Severe demyelinating neuropathy, Unsteady gait</td>
</tr>
<tr>
<td>CMT4I</td>
<td>FIG4</td>
<td>6q21</td>
<td>Childhood or adult onset, Widespread denervation</td>
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<tr>
<td>CMT5</td>
<td></td>
<td></td>
<td>Spastic paraparesis, Sensory neuropathy</td>
</tr>
<tr>
<td>CMT6</td>
<td></td>
<td></td>
<td>Optic atrophy, Motor sensory neuropathy</td>
</tr>
<tr>
<td>CMT7</td>
<td></td>
<td></td>
<td>Retinitis pigmentosa, Motor sensory neuropathy</td>
</tr>
</tbody>
</table>
CMT1

- Demyelinating disorder of peripheral nerves
- Subtypes: 1A, 1B, 1C, 1D, 1E, 1F
- Type 1A: 70 to 80 percent of CMT1 cases and 40-50% of all CMT patients

Clinical features:
- Symptoms typically start in the early second decade, but can manifest in infancy as well
- Foot drop
- Clumsy walking/difficulty running
- Sensory loss is gradual and mainly involves proprioception and vibration
- Deformities
CMT1

Physical findings:

Early changes:
- Loss of reflexes, pes cavus foot deformity, and hammer toes
- Distal calf muscle atrophy often occurs, causing the classic "stork leg deformity."

Later changes:
- Atrophy of the intrinsic hand and foot muscles
- Palpable enlargement of the peripheral nerves secondary to nerve hypertrophy
- Kyphosis or scoliosis often develops.
CMT1

- Life expectancy: normal
- Disease exacerbation can occur in pregnancy, an effect that may be mediated by increased plasma progesterone
- Sleep apnea can associate (in one study, 11 of 14 patients found to have sleep apnea)
CMT1

SUB TYPES

CMT1A:

- Associated with a 1.5 Mb duplication or, less commonly, a point mutation of the peripheral myelin protein 22 (PMP22) gene on chromosome 17p11.2-p1
- Duplication leads to overexpression of PMP22 and it gets inserted in the myelin sheath
- Point mutations alter distribution of the protein and therefore PMP22 partially accumulates in the Schwann cells
- Interestingly, patients with a 1.5 Mb deletion at this site develop hereditary neuropathy with pressure palsy (HNPP)
CMT1

CMT1B:
- Originally known as peroneal muscular atrophy
- **Point mutations** in the myelin protein zero (MPZ) gene on chromosome 1q22, which cause **overexpression** of the major myelin structural protein resulting in **malfuctioning** of myelin

**Myelin protein-zero is normally expressed on the cell membrane of Schwann cells, and plays a major role in myelin membrane adhesion**

CMT1E:
deafness is common
Gene is either PMP22 or PO
CMT1

Roussy-Levy syndrome:

- CMT type 1 phenotype
- First described in 1926
- Manifestations include postural tremor, gait ataxia, distal muscle atrophy, pes cavus, areflexia, and mild distal sensory loss
- One family: Mutation in the extracellular domain of the MPZ gene, indicating type 1B disease
- Another family: Partial duplication at chromosome 17p11.2, indicating type 1A disease
It takes patience to listen..

It takes skill to pretend you're listening.

www.iLikeitFunny.com
NO, REALLY, YOUR LECTURE IS INTERESTING

PLEASE GO ON.
CMT2

- Hereditary motor sensory neuropathy (HMSN) type 2
- Synonym: Axonal CMT
- More heterogeneous disorder than CMT1

**Classic features:**

- distal weakness, atrophy, sensory loss, decreased deep tendon reflexes, and variable foot deformity
- The onset of symptoms usually is in the second decade of life
- The clinical course is similar to that of CMT1, but sensory symptoms, with loss of vibration and proprioception, typically predominate over motor symptoms, and peripheral nerves are not palpably enlarged. Distal trophic ulcerations in the feet may occur.
CMT2

Early-onset form: before 5 years old
- Rapidly progressive with loss of strength below the knees by the second decade
- Sensory symptoms are present but overshadowed by the motor weakness
- Ambulation often is lost by mid-teens

Late-onset form: between 35 to 85 years of age (median age 57)
- 6 families identified so far
- Genetically heterogeneous
- Autosomal dominant inheritance was demonstrated in two of the families, while inheritance patterns were unclear in the remaining four families
CMT2

Genetics of CMT2

- Heterogeneous
- Majority are autosomal dominant
- Mitochondrial fusion protein mitofusin 2 (MFN2) gene mutations, most common cause of the CMT2 phenotype, accounting for approximately one-third of autosomal dominantly inherited CMT2 cases
- Some MFN2 mutations cause early onset CMT2, autosomal recessive inheritance
Other Genes:

- MPZ gene mutations
- GARS-autosomal dominant mutations-CMT2D
  (**same gene for HMN too)
- NEFL gene mutations, both autosomal dominant and recessive
- Dynamin 2 (DNM2) gene mutations
- MME gene mutations, autosomal recessive CMT2
- X-linked and autosomal recessive inheritance
CMT2

SUB TYPES

- CMT2A: most common CMT2 phenotype and maps to chromosome 1p35-36. Gene is mitochondrial fusion protein mitofusin 2 (MFN2)

- Other subtypes:
  - CMT2B
  - CMT2C → Vocal Cord Paralysis
  - CMT2D → Arms>legs
  - CMT2E, CMT2F, CMT2G, CMT2I, CMT2K, CMT2L, CMT2S
CMT3

HMSN/CMT3

- Genetically heterogeneous.
- Severe, early-onset peripheral neuropathies
- Inability of the Schwann cells to produce normal myelin, resulting in *thin, poorly formed myelin*

- **Two diseases:**
  1. Dejerine-Sottas syndrome
  2. Congenital hypomyelinating neuropathy
CMT3
Dejerine-Sottas syndrome

- Severe demyelinating neuropathy **clinically evident in early infancy** because of hypotonia

- Delayed motor development, prominent sensory loss, distal followed by proximal weakness, absent reflexes, ataxia, and profound slowing of nerve **conduction velocities to ≤10 m/sec** Scoliosis appears early and progresses with time, and contractures develop

- Progression is slow, **often with ambulation maintained through adult life**
CMT3
Dejerine-Sottas syndrome

Genetics:
- Mutations in the PMP22 gene (as in CMT1A), the MPZ gene (as in CMT1B) and the EGR2 gene (as perhaps occurs in CMT1C)
- Autosomal recessive and several dominant heterozygous forms have been described

Histology:
- Thin myelin sheaths and large onion bulb formation

EMG/NCS:
- Profound slowing of nerve conduction velocities to ≤10 m/sec
CMT3

Congenital hypomyelinating neuropathy

- Presents at birth with profound hypotonia and contractures
- Feeding difficulties and respiratory distress often lead to death in infancy
- Spontaneous improvement in motor function with increasing age have been reported in several cases
- One patient completely recovered by four months
CMT3

Congenital hypomyelinating neuropathy

Genetics:
- genetically heterogeneous
- mutations in PMP22 gene, MPZ gene mutations, early growth response 2 gene (EGR2) and the myotubularin related 2 gene (MTMR2)
- most cases-autosomal dominant, but rare autosomal recessive cases have been reported

Histology:
- absent myelin without evidence of inflammation, myelin breakdown, or onion bulbs.

EMG/NCS:
- Conduction velocities are either absent or extremely slow
Charcot-Marie Tooth disease (CMT)

Hereditary neuropathy with liability to pressure palsies (HNPP)

- Focal episodes of weakness or sensory loss and focal slowing of motor nerve conduction velocities.
- Test for PMP22 deletion and point mutations
Charcot-Marie Tooth disease (CMT) Diagnosis

Clinical History (including family history):
- Weakness in muscles of legs/arms, foot drop, deformities (pes cavus, pes planus, and hammer toes)
- Family history of high arched feet (lack of family history does not rule out CMT)
- Usually no sensory symptoms reported

Physical Examination:
- Distal weakness, proximal hypertrophy
- Foot deformities, Inverted champagne bottle legs (Stork Legs)
- DTRs reduced or absent in CMT patients
- Decreased vibratory and proprioception on exam
Charcot-Marie Tooth disease (CMT) Diagnosis

Symptoms and signs alone do not lead to diagnosis
EMG/NCS and genetic testing are needed to confirm the diagnosis
Nerve biopsy is not indicated
Charcot-Marie Tooth disease (CMT)

Diagnosis

EMG/NCS:

CMT1:
-diffusely and equally decreased conduction velocities in demyelinating form
-In every nerve tested, both sensory and motor, roughly the same degree of marked slowing is found
-CMT1 median motor NCV is around 15-25 m/s
-consider testing of family members as needed
Charcot-Marie Tooth disease (CMT)

Diagnosis

EMG/NCS:

CMT2: Normal or mildly reduced nerve conduction velocity (>38 m/sec) with decreased amplitude

- CMTX: 25-40 m/sec
- Distal intermediate CMT: 15-50 m/sec
- Dejerine-Sottas syndrome: <10 m/sec
Charcot-Marie Tooth disease (CMT) Diagnosis

- Nerve Biopsy: Not necessary for diagnosis
  - Fiber type grouping, a similarly non-specific finding which is evidence of a cycle of denervation/reinnervation
  - Type 1 reveals demyelination and multiple layers of remyelination, called “onion bulb”
  - Type 2 reveals axon loss with wallerian degeneration
  - Type 3 reveals demyelination with thinning of the myelin sheath

**There should be no inflammatory infiltrate indicating an autoimmune demyelinating process.**
Charcot-Marie Tooth disease (CMT)

Diagnosis

“Onion bulbs”
Charcot-Marie Tooth disease (CMT)

Diagnosis

- **Genetic testing:** DNA testing can give a definitive diagnosis, but not all the genetic markers for CMT are known.

**Advantages:**
- Can simplify the diagnosis of CMT by avoiding uncomfortable and invasive procedures such as electromyography and nerve biopsy respectively.
- Early diagnosis can facilitate early interventions such as physical therapy.

**Disadvantages:**
- Often will **not** affect the management for individual patients with CMT.
- Cost
Charcot-Marie Tooth disease (CMT)

Genes

CMT1:
- PMP22 (CMT1A and CMT1E)
- MPZ (CMT1B)
- LITAF (CMT1C)
- EGR2 (CMT1D)
- NEFL (CMT1F)
Charcot-Marie Tooth disease (CMT)

**Genes**

**CMT2:**
- MFN2 and KIF1B (CMT2A)
- RAB7A (CMT2B)
- LMNA (CMT2B1)
- TRPV4 (CMT2C)
- BSCL2 and GARS (CMT2D)
- NEFL (CMT2E)
- HSPB1 (CMT2F)
- MPZ (CMT2I and CMT2J)
- GDAP1 (CMT2K); and HSPB8 (CMT2L)
- DNM2 gene mutations
Algorithm for Genetic Testing in suspected CMT patients

A

Intermediate MNCV (35< and ≤45 m/s)

- Symptom onset: classic
  - Male to male transmission?
    - No: Test for GJB1 (Cx32) CMT1X
    - Yes: Male to male transmission?
      - Yes: Test for MPZ CMT1B
      - No: Test for GJB1 (Cx32) CMT1X
      - Negative: Affected parent/child?
        - No: Test for recessive forms
        - Yes: Research Testing (including dominant intermediate forms)
      - Negative: Research Testing (including dominant intermediate forms)
    - Negative: Test for MPZ CMT1B
  - Negative: Test for MPZ CMT1B

B

Normal MNCV (>45 m/s)

- Symptom onset: Infancy or Severe in Childhood
  - Male to male transmission?
    - Yes: Test for MFN2 CMT2A
    - No: Pure motor upper>lower limb onset?
      - Yes: Test for NFEL (rare) CMT2E
      - No: Test for GARS CMT2D
        - Yes: Affected parent/child?
          - Yes: Test for recessive forms
          - No: Research testing
        - No: Research testing
      - Negative: Test for GARS CMT2D
      - No: Test for NFEL (rare) CMT2E
      - No: Test for GDAP1 (rare) CMT2K
        - Yes: Affected parent/child?
          - Yes: Test for recessive forms
          - No: Research testing
        - No: Research testing
Charcot-Marie Tooth disease (CMT)

Diagnosis

Genetic screening for relatives: optional

Genetic counseling:

- Prenatal testing for pregnancies at increased risk is possible for some types of CMT only if the disease-causing mutation in the family is already known
Charcot-Marie Tooth disease (CMT) Management

- No cure
- No disease-modifying therapy is available
- Supportive care
- Genetic counselling
- Most important goal for patients with CMT is to maintain movement, muscle strength, and flexibility
- **PT/OT** and moderate activity are usually recommended, but *overexertion should be avoided*
- Daily stretching exercises early in the course of the disease may help delay ankle contractures
Charcot-Marie Tooth disease (CMT) Management

- **Orthoses (bracing):** to help stabilize ankles
- Ankle-foot orthoses (AFOs)
- Appropriate footwear
- **Podiatrist** referral as indicated
- **Orthopedic surgery** (straightening and pinning the toes, lowering the arch, and sometimes, fusing the ankle joint to provide stability)
- **Fall precautions**
- **Avoid exacerbating factors** (*Emotional* stress, periods of prolonged immobility, pregnancy, medications like vincristine)
Charcot-Marie Tooth disease (CMT)
Management-Research

*Progesterone antagonist*: used in animal models reduced overexpression of PMP22 and slowed disease progression

*Ascorbic acid (vitamin C):*
- promote myelination and appeared promising in an animal model of CMT1A
- Ascorbic acid therapy reduced the expression of PMP22
- remyelination, amelioration of the CMT1A phenotype, and prolonged lifespan
- However, there was no clear benefit of ascorbic acid in a 12 month randomized controlled trial of 81 children with CMT1A or in a similar trial of 179 adults with CMT1A
- Since disease progression in CMT1A is typically slow, trials with longer treatment periods may be necessary to detect benefit
Charcot-Marie Tooth disease (CMT) Management-Research

Neurotrophin-3 (NT3):
- Improved axonal regeneration and associated myelination in both a xenograft model of Schwann cells with a PMP22 duplication and in a mouse model with a PMP22 point mutation
- A single-blinded pilot clinical trial involving eight patients with CMT1A found that NT3 treatment for six months was associated with improved sural nerve myelinated fiber regeneration compared with placebo treatment.
- Clinical applicability of these observations remains to be proven.
Charcot-Marie Tooth disease (CMT)
Management-Research

Anesthesia:
- Regional anesthesia has been controversial
- may have an increased susceptibility to further nerve damage with the use of local anesthetic agents
- a number of small case series and case reports have described uneventful outcomes with regional anesthesia, including both peripheral nerve and neuraxial blocks
Charcot-Marie Tooth disease (CMT) Research

**PUBMED ID: 25519680**


An exploratory randomised double-blind and placebo-controlled phase 2 study of a combination of baclofen, naltrexone and sorbitol (PXT3003) in patients with Charcot-Marie-Tooth disease type 1A


**Clinical Trials.gov**

Active study: NCT02579759

Phase III Trial Assessing the Efficacy and Safety of PXT3003 in CMT1A Patients (PLEO-CMT) (PLEO-CMT)
I won’t do it
I can’t do it
I want to do it
How do I do it?
I’ll try to do it
I can do it
I will do it
YES, I DID IT
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Thank you