CHARCOT-MARIE-TOOTH

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History

- Charcot-Marie-Tooth disease (CMT)
- is the most common inherited neurologic disorder
- CMT was subdivided into 2 types, CMT1 and CMT2, based on pathologic and physiologic criteria.
- CMT has been subdivided further based upon the genetic cause of the disease.

Pathophysiology

- CMT is a heterogeneous group of genetically distinct disorders with similar clinical presentation.

Pathophysiology

- CMT type 1 :
- disorder of peripheral myelination,
- mutation in the peripheral myelin protein-22 (*PMP-22*) gene.
- results in abnormal myelin that is unstable and spontaneously breaks down.
- This process results in demyelination, leading to uniform slowing of conduction velocity

Pathophysiology

- 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.

Pathophysiology

- CMT type 2 :
- primarily a neuronal (axonal) disorder, not a demyelinating disorder.
- results in peripheral neuropathy through direct axonal death and Wallerian degeneration

Pathophysiology

- CMT type 3 :
- Dejerine-Sottas disease; is characterized by infantile onset.
- severe demyelination with delayed motor skills and is much more severe than type 1.
- Marked segmental demyelination with thinning of the myelin around the nerve is observed on histological examination.
- CMT X (X-linked CMT) is also a demyelinating neuropathy phenotypically similar to CMT1,males more severely affected
- CMT 4 also demyelinating neuropathy

Epidemiology

- prevalence : one person per 2,500 population, or about 125,000 people in the United States
- incidence of CMT type 1 is 15 persons per 100,000 population.
- Incidence of CMT type 2 is 7 persons per 100,000 population.
- CMT type1accounts for 2/3 of cases and CMT type 2 about 1/3.

Epidemiology

- No racial predilection
- No gender predilection
- Age of presentation varies depending on type
- onset of CMT 1 - first decade of life ,but disease develops in some patients in young or mid adulthood.
- CMT 2 - usually asymptomatic until later in life, most commonly begin in the second decade .
- CMT 3 - early childhood.

Presentation

- Motor symptoms predominate over sensory symptoms
- Slow progressing weakness
- beginning in the distal limb muscles typically occurring in the lower extremities before the upper extremities

Presentation

- A subgroup of patients with CMT type 1A may present with proximal muscle wasting and weakness
- complain of difficulty walking and frequent tripping due to foot and distal leg weakness.
- Frequent ankle sprains and falls are characteristic

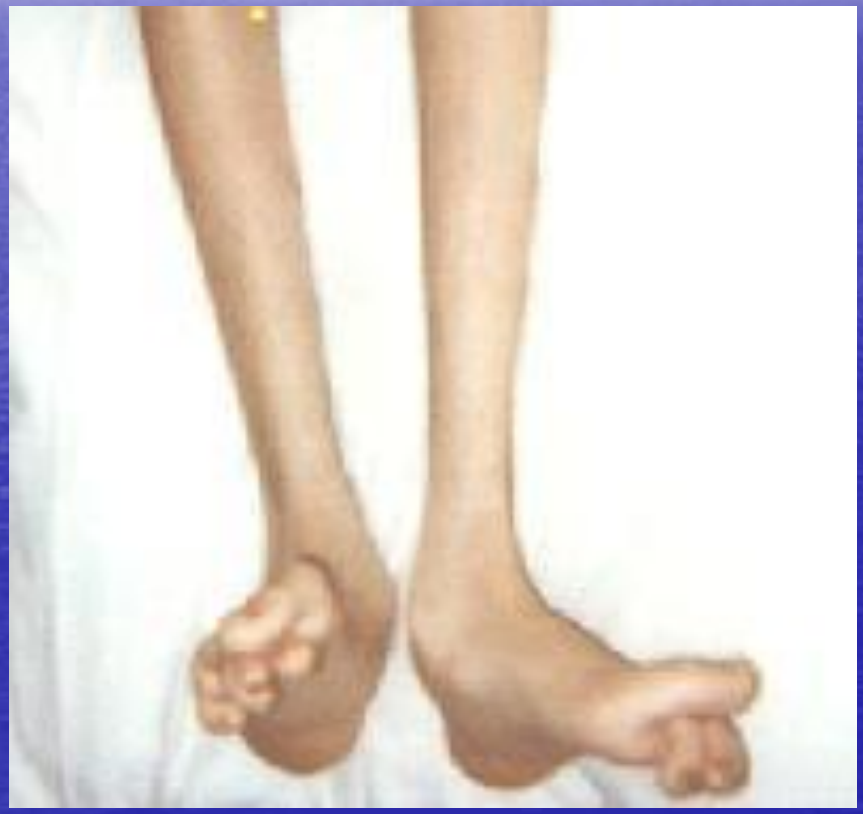
Presentation

- Foot drop commonly occurs.
- Steppage (ie, gait in which the individual must lift the leg in an exaggerated fashion to clear the foot off of the ground) also is common

Presentation

- Intrinsic foot muscle weakness commonly results in the foot deformity known as pes cavus
- Hammertoes and high arches
- Symptoms related to structural foot abnormalities include calluses, ulcers, cellulitis, cold feet, hair loss ,leg edema and lymphangitis

Foot Deformities



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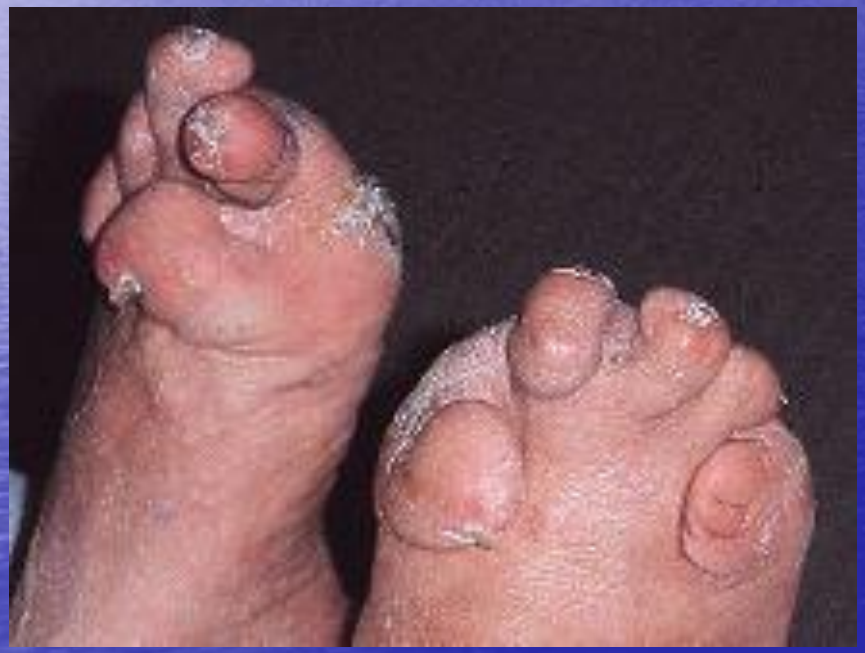

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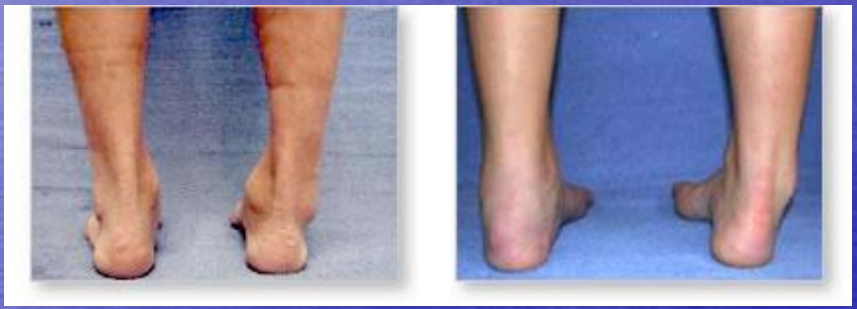

These are the appearance of the feet from behind in two patients with a high arch, with the heel twisted inwards. The foot on the left in both patients has already undergone surgical correction and is straight.

Hand Deformities

Presentation

- Hand weakness results in complaints of poor finger control, poor handwriting, difficulty using zippers and buttons, and clumsiness in manipulating small objects

- Pain, both musculoskeletal and neuropathic types, may be present. Muscle cramping is a common complaint

Presentation

- Spinal deformities (eg, thoracic scoliosis) occur in 37-50% of patients with CMT type 1
- Deep tendon reflexes (DTRs) are markedly diminished or absent.
- Vibration sensation and proprioception are decreased significantly, but patients usually have no sensory symptoms until adulthood,
- But mild diffuse sensory loss is common inCMT1 and there is a definite sensory loss in CMT3, and some patients have marked sensory ataxia.

Presentation

- Sensation of pain and temperature is usually intact.
- Essential tremor is present in 30-50% of patients with CMT.
- Sensory neuronal hearing loss is observed in 5% of patients.
- Enlarged and palpable peripheral nerves are common in more than 25% of patients CMT1and are often visible in the superficial cervical nerves and palpable in the arms

Presentation

- Phrenic nerve involvement with diaphragmatic weakness is rare but has been described.
- Vocal cord involvement and hearing loss can occur in rare forms of CMT.

Diagnosis

- workup : tests that address causes of neuropathies, such as endocrinologic, infectious, and immunologic abnormalities; vitamin and nutritional deficiencies; and nerve compression
- CSF protein is elevated in most but not all cases of CMT 3
- Special genetic tests are available for some types of CMT.
- DNA-based testing for the PMP-22 duplication (CMT 1A) is widely available and detects more than 98% of patients with CMT 1A

Diagnosis

Genetic testing is performed primarily on a research basis

- For CMT X: DNA-based testing detects a mutation in the connexin 32 gene. The test detects 100% of cases and is available commercially

Diagnosis

- Nerve biopsy rarely is indicated to diagnose CMT, especially since the advent of genetic testing.
- Biopsies sometimes are performed in cases of diagnostic dilemmas.

Diagnosis

- Electromyography/nerve conduction study
- Perform electromyography/nerve conduction studies (EMG/NCS) first if CMT is suggested.
- In demyelinating types, diffuse and uniform slowing of nerve conduction velocities is observed

Diagnosis

- Harding and Thomas criteria for diagnosing CMT 1 include median motor nerve CV less than 38 meters per second (m/s) with 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.

Diagnosis

- All nerves tested, both sensory and motor, show the same degree of marked slowing

  In neuronal (ie, axonal) types of CMT, nerve conduction velocity usually is normal, but markedly low amplitudes are noted in both SNAP and CMAP
- In neuronal (ie, axonal) types, increased insertional activity is evident with fibrillation potentials and positive sharp waves

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).

Rehabilitation Program

- 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

Rehabilitation Program

- **Occupational Therapy:**
- 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 training regarding importance of career and employment implications may be needed because of persistent weakness of hands and/or feet

Medical Care

- 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.
- Improved understanding of the genetics and biochemistry of the disorder offers hope for an eventual treatment.

Medical Care

- Patients often are evaluated and treated symptomatically by a team that includes a neurologist, physiatrist, orthopedic surgeon, physical therapist, and occupational therapist

Surgical Care

- Orthopedic surgery is required to correct severe pes cavus deformities, scoliosis, and other joint deformities.
- Treatment is determined by the age of the patient and the cause and severity of the deformity.

Surgical Care

- Surgical procedures consist of the following 3 types:
  - Soft tissue (plantar fascia release, tendon release or transfer)
  - Osteotomy (metatarsal, midfoot, calcaneal)
  - Joint stabilizing

Pain

- Pain may result from joint deformities or compensatory overuse of certain muscle groups.
- Some types of pain may respond to nonsteroidal anti-inflammatory drugs (NSAIDs).
- Dysesthetic pain may occur but is not typical; it responds to antidepressants, such as amitriptyline, desipramine, or paroxetine, and to anticonvulsants, such as gabapentin or carbamazepine.