CHARCOT-MARIE-TOOTH DISEASE

BY- SACHIN SARASWAT
LA3 C-O- 206(1)

Charcot-Marie Tooth disease (CMT)

Synonyms

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

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 .

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

Clinical Features

- Affects both motor and sensory nerves

- Symptom onset depends on type of CMT but us begins in early childhood or early adulthood

- Most CMT1 symptoms starts by second decade .

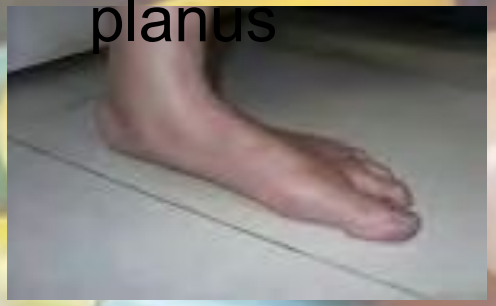
Clinical Features

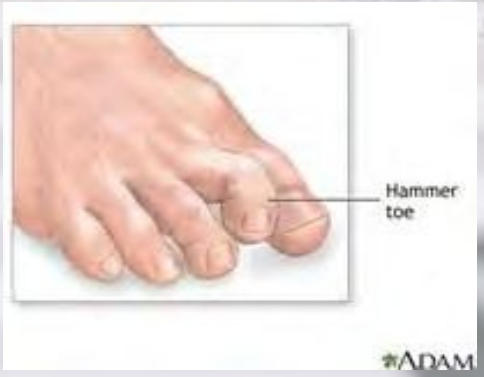
- Foot drop (usually the initial symptom)
- High stepped gait
- Frequent falls
- Hammer toes, high arched feet (pes cavus) or flat arched feet (pes planus) are classical
- Muscle wasting
- Weakness in legs later progresses to hands and forearms
- Difficulty with fine motor skills
- Claw hands
- Cramps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

Deformities

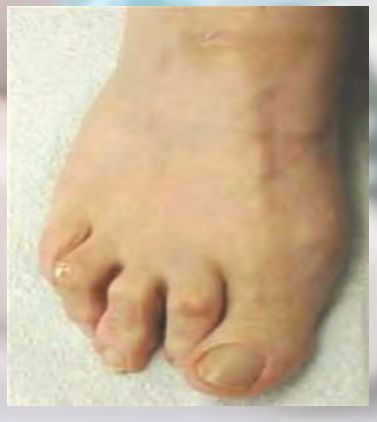
Pes cavus

Pes planus





Hammer Toes



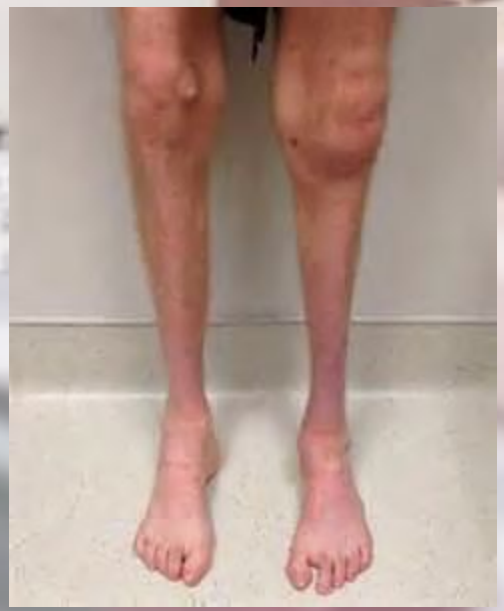
Clinical Features

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



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

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

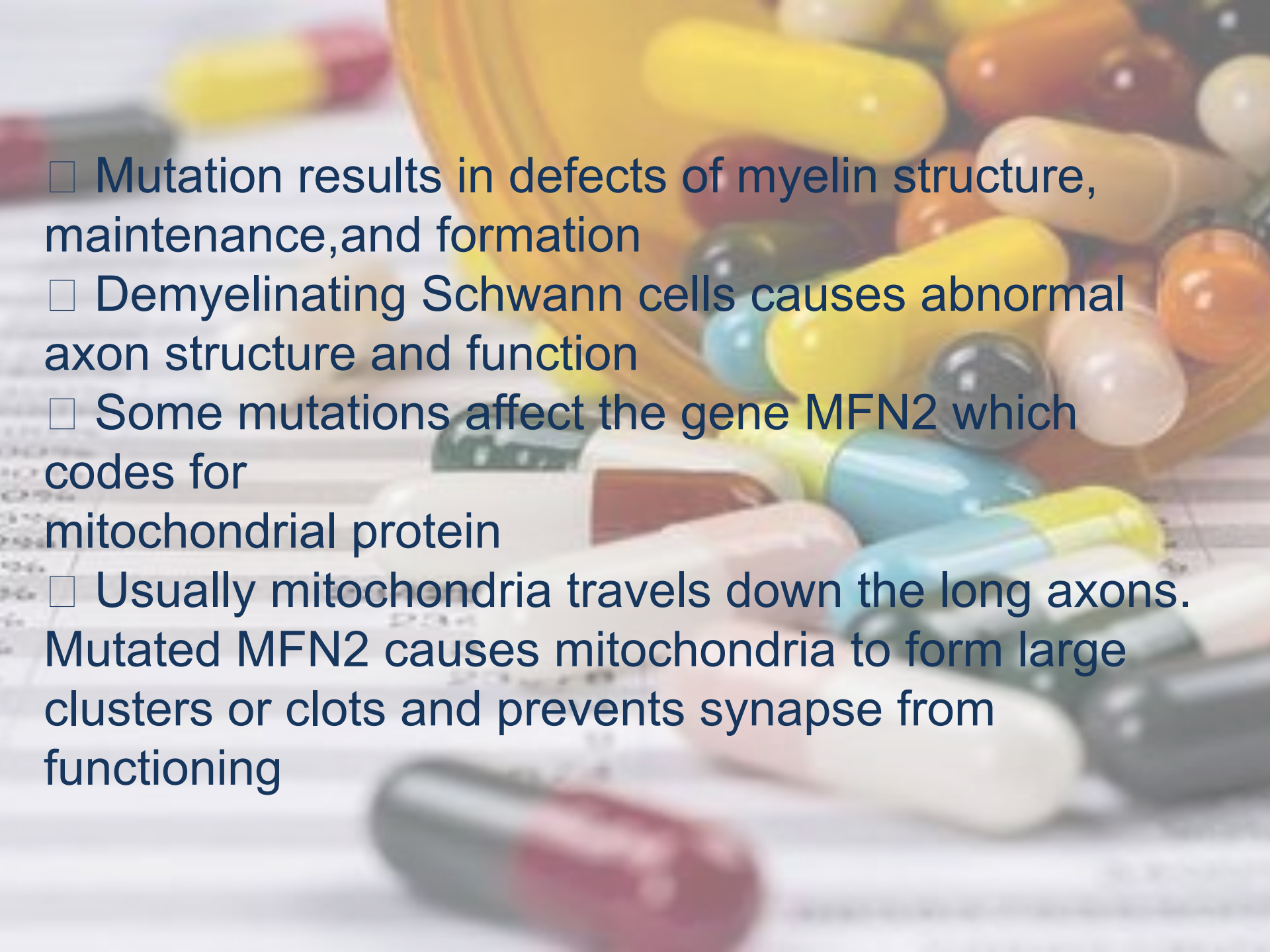
Exacerbating Factors

- 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 theUnited States), Pyridoxine (high dose), Stavudine, Suramin, Tacrolimus, Taxols (paclitaxel, docetaxel), Thalidomide, Vincristine, Zalcitabine

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



- 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

Defective Myelin

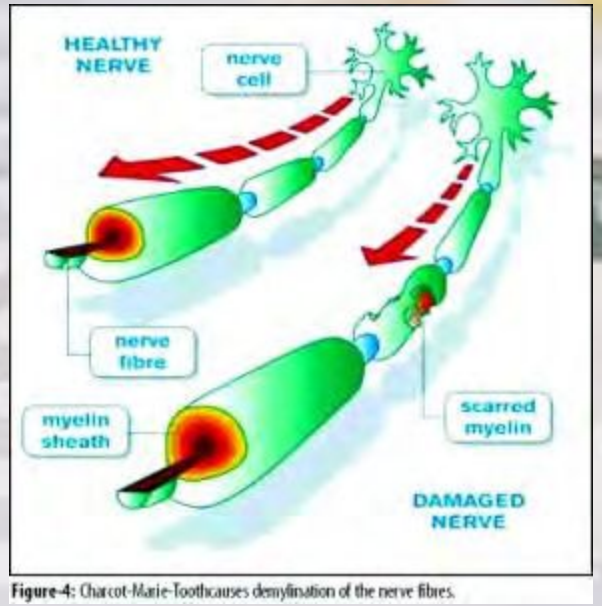
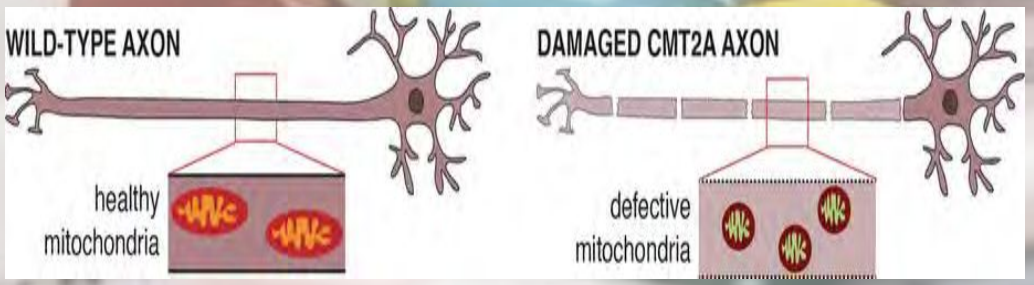


Figure-4: Charcot-Marie-Toothcauses demyliination of the nerve fibres.

Defective Axon



Mode of inheritance

Autosomal Dominant(most common)

Autosomal Recessive

X-linked

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

TYPES OF CMT

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

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

Diagnosis

- Nerve Biopsy: Not necessary for diagnosis

-Fiber type grouping, a similarly non-specific finding which is evidence of a cycle of denervation/reinnervation

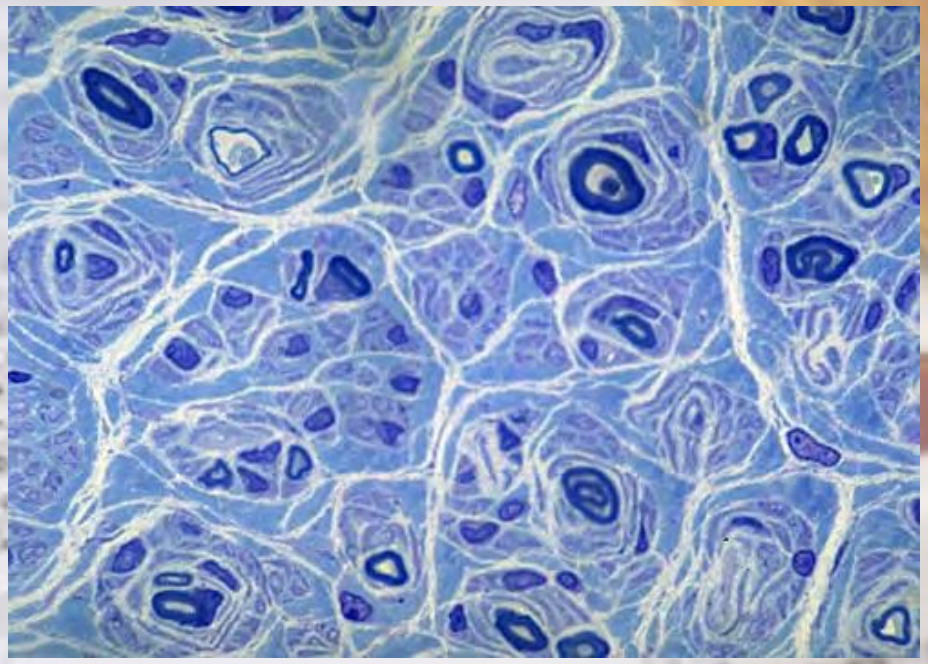
-Type 1 reveals demyelination and multiple layers of remyelination, called “onion bulb”

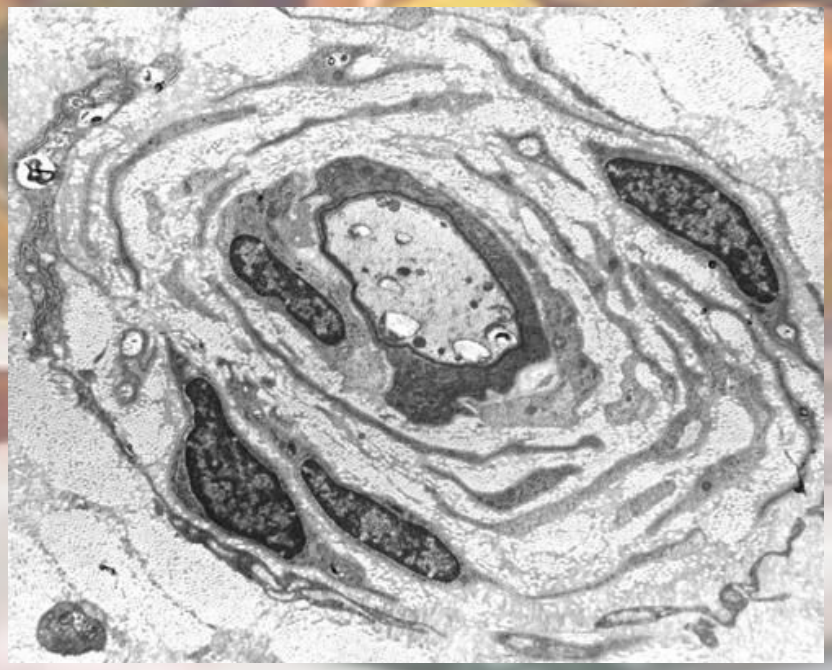
-Type 2 reveals axon loss with wallerian degeneration

-Type 3 reveals demyelination with thinning of the myelin sheath

**There should be no inflammatory infiltrate indicating an autoimmune demyelinating process.

Diagnosis





“Onion bulbs”

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

Treatment

Treatment of CMT hereditary neuropathy is symptomatic and Supportive. A Cure is not available so it is important to minimize or Stall the symptoms Comprehensive treatments include physical therapy, shoe orthotics, leg braces and surgery to correct deformities Complementary therapies may help psychologically. relieve pain and discomfort, and improve overall quality of life. Vocational counseling, anticipating progression of the disorder, may be useful for young patients.

- Surgery

If foot deformities are severe, corrective foot surgery may help alleviate pain and improve your ability to walk Surgery cant improve weakness or loss of sensation

Potential future treatments

Researchers are investigating a number of potential therapies that nay one day treat Charcot-Marie-Tooth disease Potential include medications and In vitro procedure that may help to prevent passing the disease to future generations

THANK YOU