NEURO-MUSCULAR DISEASE IN CHILDREN

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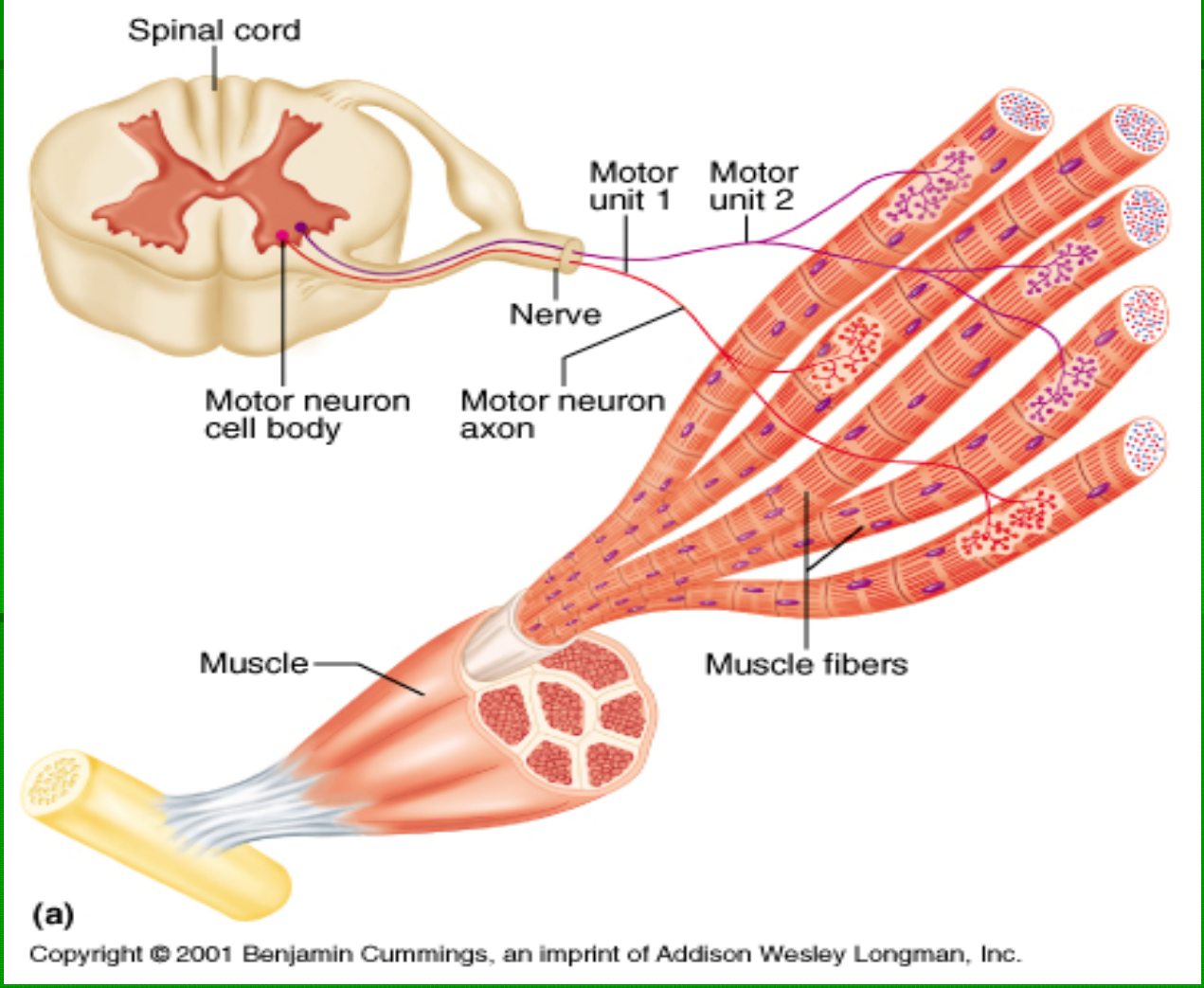
The Neuromuscular pathway



Signs and symptoms

- Hypotonia- not improved with irritation
- Failure to reach milestones
- weakness
- Decreased reflexes

Muscle Diseases

- Duchene's/ Becker's Muscular Dystrophy
- Congenital muscular dystrophy
- Congenital Myopathies
- Myotonic dystrophy
- Inflammatory myopathies
- Metabolic myopathies

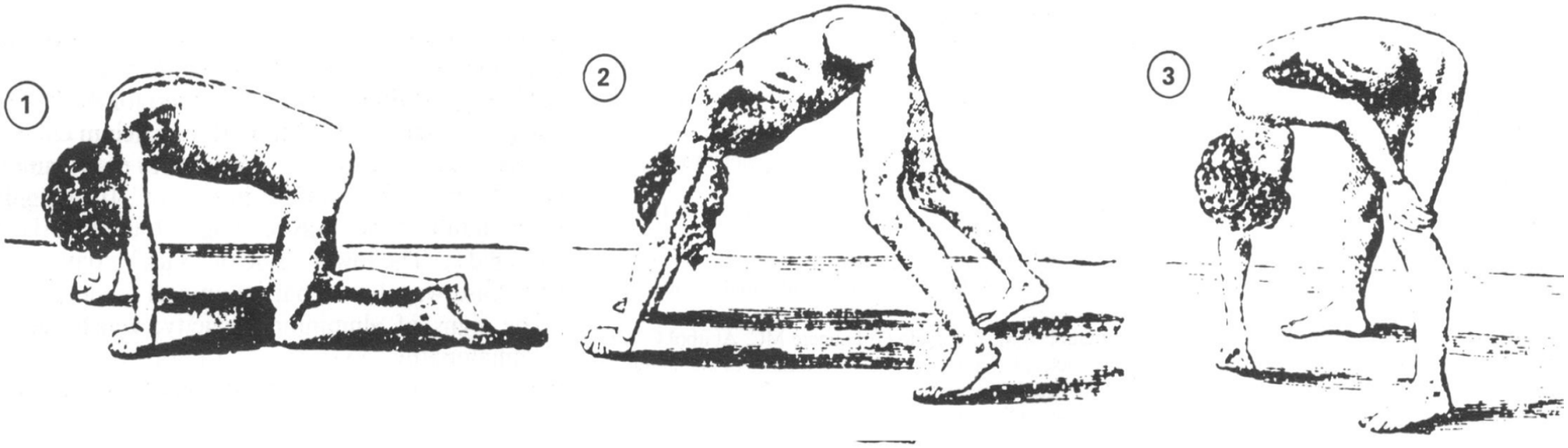
Muscular dystrophies

- 4 criteria- 1. primary myopathies 2. genetically 3. progressive 4. myofiber degeneration at some stage
- Duchene
- Becker
- Emery-Dreifess
- Facioscapulahumoral
- Limb Girdle
- Oculopharyngeal
- Distal
- congenital

Duchene's muscular dystrophy

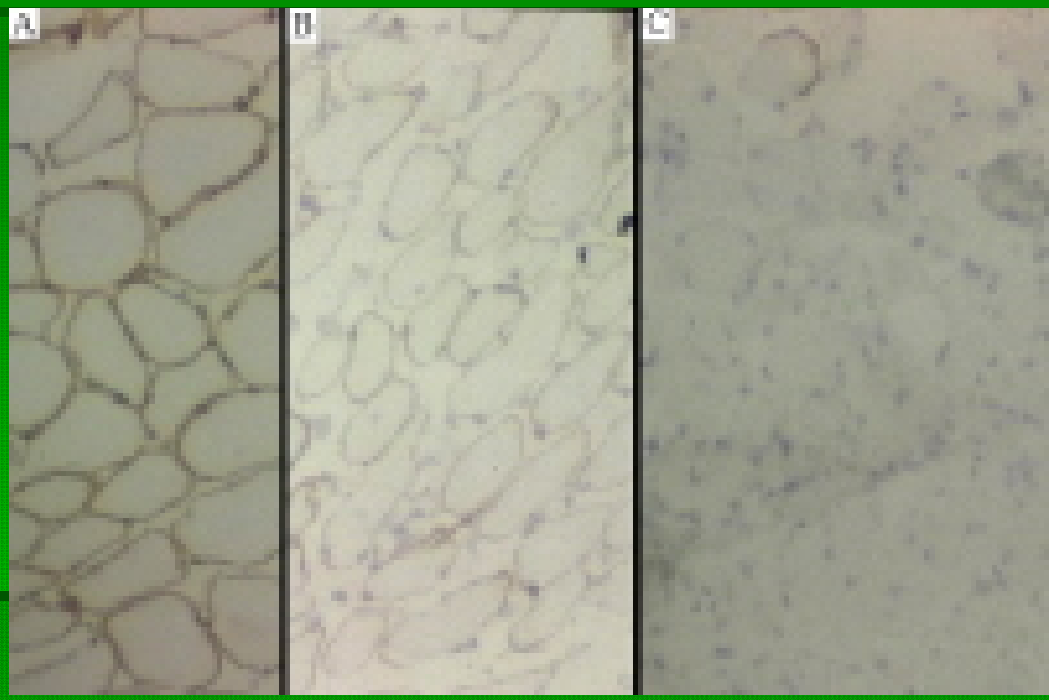
- Most common (1 in 3500 boys)
- X-linked
- Becker’s is more mild form of disease
- Proximal weakness- usually presenting around age 3
- Waddling gait, Gower’s sign
- Muscle psuedohypertrophy
- Wheelchair bound around age 10
- Elevated CK (50-100 fold)
- Dilated cardiomyopathy
- Respiratory problems
- Scoliosis
- Cognitive issues

Gower's sign



Dystrophin

- Mutation in dystrophin gene
- A cytoskeletal protein, critical in stabilizing the link between the sarcolemmal membrane and the extracellular matrix
- Without dystophin, there is sarcolemma breakdown and then muscle cell death



Duchene's Muscular dystrophy

- Diagnosed by clinical picture and elevated CK
- Molecular diagnosis available
- Muscle biopsy usually not needed
- Treatment consists of physical therapy, orthopedics, cardiology and pulmonary therapies
- Corticosteroids can help preserve ambulation
- Gene therapy in future

Congenital muscular dystrophy

- Heterogeneous group of disorders
- Most are automsomal recessive
- Weakness and hyporeflexia in first year of life
- Elevated CK (not as high as Duchene's)
- Muscle biopsy shows signs of myofibrillar necrosis and regeneration, along with endomysial fibrosis and deposition of fat
- Some die in infancy and others may live into adulthood with minimal disability
- Merosin (alpha-2 chain of laminin2) positive or merosin deficient
- Many are associated with CNS abnormalities (cobblestone lissencephaly, MR, seizures, white matter changes)
- Fukyama type, Muscle-eye-brain disease, Walker-Warburg syndrome, Ulrich form

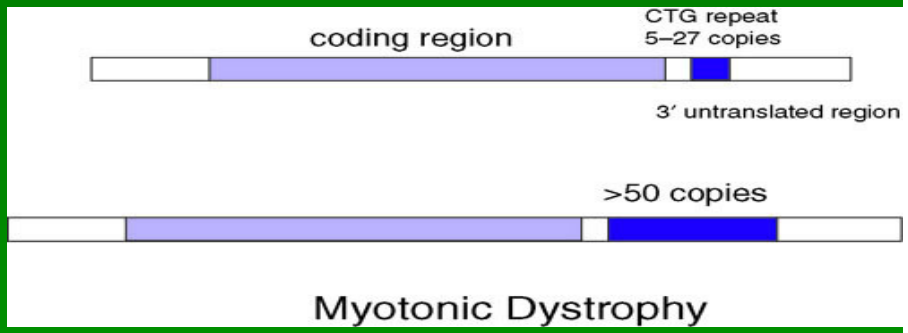
Congenital myopathies

- Onset in early life with hypotonia, hyporeflexia, generalized weakness that is more often proximal than distal, and poor muscle bulk
- Often with dysmorphic features that may be secondary to the weakness
- Relatively nonprogressive
- Hereditary
- Unique morphological features on histochemical or ultrastructural examination of the muscle biopsy sample that originate within the myofiber
- Myopathies with protein accumulation
  - Nemaline myopathy
  - Myosin storage myopathy
  - Cap disease
  - Reducing body myopathy
- Myopathies with cores
  - Central core disease
  - Core-rod myopathy
  - Multiminicore disease
- Myopathies with central nuclei
  - Myotubular myopathy
  - Centronuclear myopathy
- Myopathies with fiber size variation
  - Congenital fiber type disproportion

Myotonic dystrophy I

- Most common form of muscular dystrophy among whites
- Prevalence 3-5/100,000
- Usually appears in late adolescence or early adult life
- Can present at birth (congenital myotonic dystrophy) or during the first decade (juvenile myotonic dystrophy) (20%)
- Myotonia with a dystrophic process of muscle with multisystem involvement
- Caused by a CTG trinucleotide expansion on chromosome 19q13.3

Pathogenesis



- Gene is DMPK which encodes a serine-threonine protein kinase (myotonia protein kinase [DMK])
- The trinucleotide repeat does not affect the coding portion of the gene (transcribed to RNA but not to protein)
- Explanation for clinical manifestations of DM1 is multifactorial
- Study on mice showed abnormal accumulation of abnormally expanded RNA molecules resulted in defective splicing of the skeletal muscle chloride channel pre-mRNA (Mankodi et al, 2002)
- The loss of chloride channel protein from the sarcolemma may lead to channel dysfunction and membrane hyperexcitability, resulting in myotonia

Genetics

- Autosomal dominant with variable penatrance
- Normal people have 5 to 37 repeats
- In families with DM1, there is amplication of the repeats in the next generation (anticipation)
- CTG repeat expansion occurs to a greater degree in egg than in sperm
- Borderline premutation- 38 to 49 copies (small possibility of expansion)
- Carrier premutation- 50 to 80 copies (mildly symptomatic or no symptoms)- no cardiac problems
- Full mutation- above 80 copies
- Positive correlation with increased number of repeats and earlier age of disease onset (not possible to predict age)

Clinical

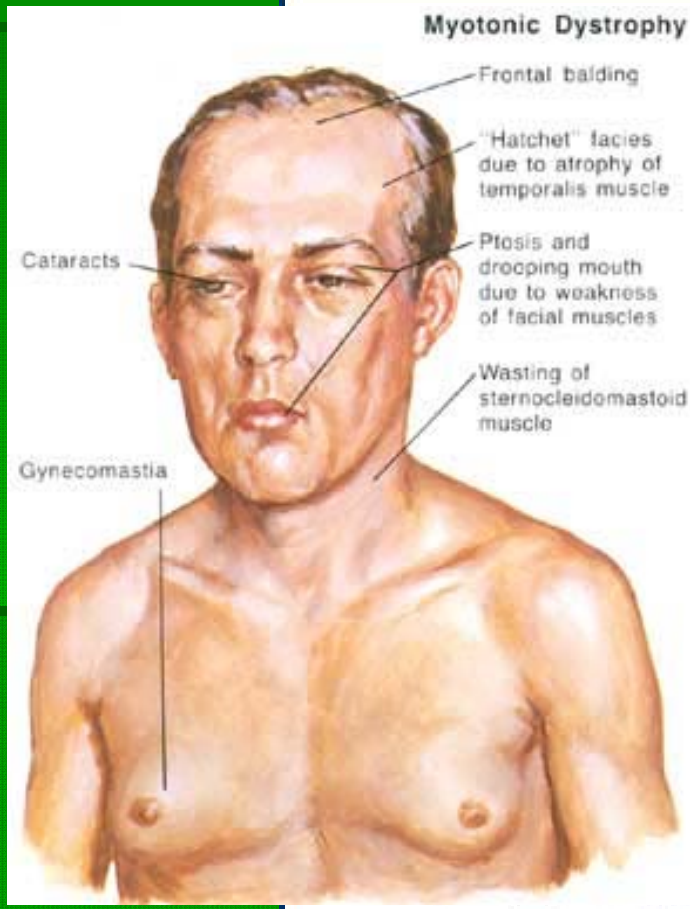
- Myotonia- percussion and grip
- Stiffness that improves with repeated contractions
- Weakness (face, distal>proximal)
- Weakness progresses over time as myotonia improves
- Atrophy (face and sternocleidomastoid affected first)
- Hatchet face (long face with shrinkage of masseter and temporal muscles)
- Cheshire cat smile
- Dysarthria, swallowing difficulties and mild external ophthalmoplegia may be seen

Associated features

- Hearing loss
- Polyneuropathy (large myelinated fibers)
- Smooth muscle involvement of pharynx, esophagus and GI tract
- Myotonia of anal sphincter
- Excessive daytime sleepiness
- Cardiomyopathy and conduction defects-
  - prolonged PR interval (70%)
  - arrhythmias, mainly atrial flutter (15%)
- Immunologic abnormalities- increased catabolism of IgG (1/3)

Associated symptoms

- Endocrinopathies-
  - frontal baldness
  - loss of body hair
  - testicular atrophy, infertility
  - hypothyroidism
  - growth hormone secretion disturbances
  - insulin-resistant diabetes (6.5-20%)
- Ophthalmology- cataracts after age 10
- Cognitive deficits in 80%
- Older adults have frontal and temporal lobe cognitive decline


Myotonic Dystrophy
Frontal balding
"Hatchet" facies due to atrophy of temporalis muscle
Cataracts
Ptosis and drooping mouth due to weakness of facial muscles
Wasting of sternocleidomastoid muscle
Gynecomastia

Congenital myotonic dystrophy

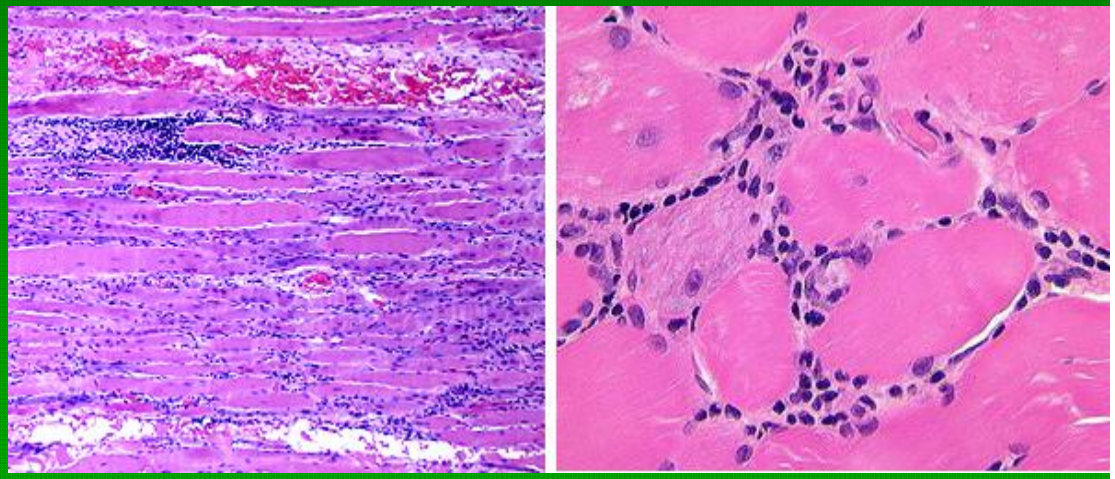
- Almost always transmitted by mother (15-20%)
- The greater the CTG expansion in the mother, the higher the probability of the offspring being affected (>100 copies=62% risk)
- GTG repeats usually >730 copies
- Polyhydramnios
- Prematurity (50%)
- Arthrogryposis
- Perinatal asphyxia common
- Weak suck

Congenital Myotonic Dystrophy

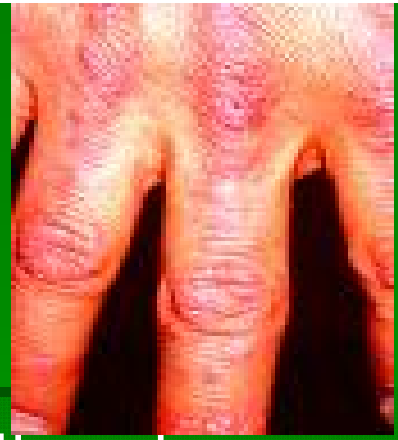
- Hypotonia, especially involving neck muscles
- Facial diplegia (87%)
- Delayed motor development (87%)
- Mental retardation (68%)
- Clinical myotonia is absent in 1st year- 12% of 1 to 5 year old children
- In 1st year- respiratory insufficiency, dysphagia and aspiration, and problems with GI motility (16% mortality)
- After 1st year- appear to improve for a few years, only to deteriorate gradually with features of the adult form of disease

Inflammatory Myopathies

- Associated with a presumed immunologic attack
- Polymyositis, Dermatomyositis and infectious myositis
- Elevated CK with muscle weakness and pain



Dermatomyositis



- Muscle pain and weakness associated with rash
- Can be acute or insidious
- Erythematous, scaly discoloration of eyelids which then spreads to cheeks and extensor surfaces of joints (Grotton rash), elbows and knees
- Increased ESR and WBC
- May have positive ANA
- MRI- increased signal in T2 with normal T1
- Treatment- prednisone or other immunosuppressives

Polymyositis

- Uncommon in children
- Chronic inflammatory process of muscles
- Cell mediated disease with abnormal T lymphocytes
- Can begin as early as 1yo
- Can look like muscular dystrophy- more rapid onset
- Antibodies to myosin in 90%
- Course is generally downhill

Metabolic myopathies

- Muscle phosphorylase deficiency (McArdle's)- onset in childhood with painful muscle cramps and weakness after exertion
- Congenital defect of phosphofructokinase (Glycogenosis type VII)- easy fatigability and weakness of stiffness induced by exertion
- Phosphoglyceromutase deficiency- life long history of muscle pain, cramps and weakness after exercise and MR
- Aldolase A deficiency- unexplained episodes of jaundice and anemia and markedly elevated CK

Disorders of neuromuscular junction

- Myasthenia gravis
- Botulism
- Lambert-Eaton

Myasthenia Gravis

- Autoimmune disease in which antibodies are directed against acetylcholine receptor antibodies which impair neuromuscular transmission and produce weakness

Types

- Neonatal- transplacental passage of antibodies to baby
- Juvenile- <18yo, F>M
- Adult onset (early or late)
- Congenital- not autoimmune
  -defects in proteins at NMJ
  - can be presynaptic, synaptic or postsynaptic

Generalized Myasthenia Gravis

- Eye findings (ptosis or extraocular muscle weakness) most common- 50% at presentation and 90% at some time during illness
- Double vision
- Pupil is always spared
- Bulbar symptoms are the next most common symptom
- Nasal speech
- Dysphagia
- Jaw weakness

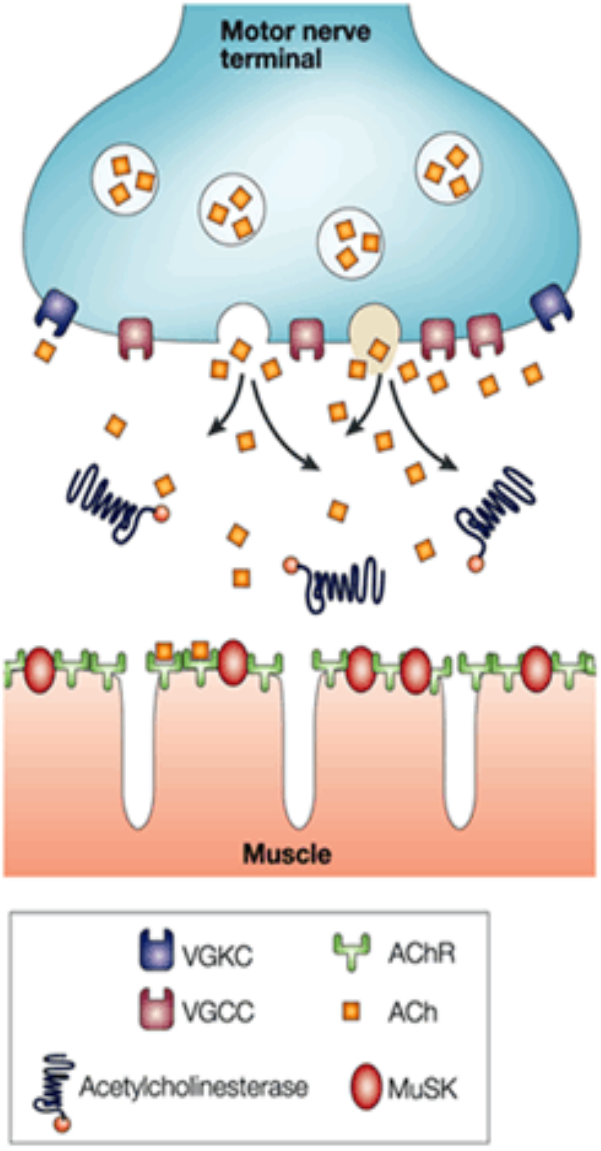
Muscle weakness

- Fluctuates and progressively worsens over the course of the day
- Fatigability
- Painless
- Variable distribution and severity (may be asymmetric)
- Distal weakness less common
- Legs usually affected later
- Most common muscles- jaw closure, neck flexors, deltoids, triceps
- Respiratory muscles may be affected
- Bowel and bladder spared

Physical exam

- Pupils unaffected
- Fatigability- sustained upgaze, count to 100, repetitively testing proximal limb or neck flexors
- Subtle weakness- functional testing
- Ice bag test
- DTRs preserved
- No sensory findings

Fatigability



Nature Reviews | Immunology

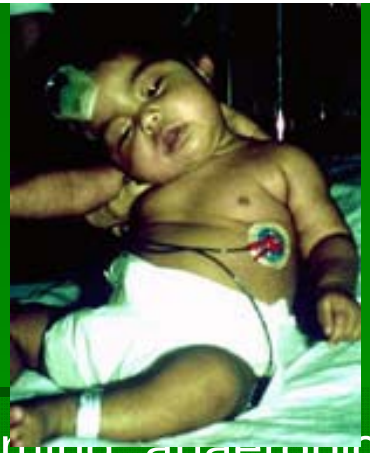
MG treatment

- Anticholinesterase inhibitors
- Remission induction- steroids, IVIG, plasmaphoresis, immunosuppresives
- thymectomy

Drugs and MG

- A number of drugs have the *potential* to impair neuromuscular transmission and worsen MG
- Antirheumatic: Penicillamine, chloroquine
- Antibiotics: amionglycosides> macrolides, floroquinolones
- Antiarrythmics: beta blockers, calcium channel blockers, procainamide
- Anesthetic agents: Non-depolarizing agents (vecuronium, pancuronium), succinylcholine
- Magnesium
- phenytoin
- Carnitine
- Ace inhibitors

Infantile Botulism



- caused by a neurotoxin produced by the spore-forming, anaerobic, gram-positive bacilli *Clostridium botulinum*, which is found globally in soil
- The toxin irreversibly binds to presynaptic cholinergic receptors at motor nerve terminals and is subsequently internalized.
- Once inside the cytosol, the toxin behaves as a protease, damaging an integral membrane protein of acetylcholine-containing vesicles, disrupting exocytosis and inhibiting the release of the acetylcholine that is needed to excite muscle
- Soil and honey contamination are the two recognized sources of botulinum spores (A history of honey consumption is seen in 15 percent of the botulism cases reported to the CDC)
- Presents at 6 weeks to 6 months

Infantile botulism

TABLE 1
Signs and Symptoms of Infant Botulism at Hospital Admission

Signs and symptoms	Incidence (%)
Weakness or floppiness	88
Poor feeding	79
Constipation	65
Lethargy/decreased activity	60
Weak cry	18
Irritability	18
Respiratory difficulties	11
Seizures	2

Reprinted with permission from Schreiner MS, Field E, Ruddy R. Infant botulism: a review of 12 years' experience at the Children's Hospital of Philadelphia. Pediatrics 1991;87:161.

Infantile Botulism

- Treatment is supportive
- use of botulinum immune globulin in infants has successfully reduced the time spent in the hospital and the need for mechanical ventilation and tube feeding
- prognosis is excellent, with a case-fatality rate of less than 2 percent
- Recovery results from the regeneration of nerve terminals and motor endplates.
- Diaphragmatic function returns before peripheral muscle recovery.

Peripheral Neuropathies

- Guillian- Barre syndrome (AIDP)
- CIDP
- Hereditary motor and sensory neuropathy (CMT)

Guillian-Barre syndrome (AIDP)

- Acquired, immune mediated polyradiculoneuropathy causing dysfunction, segmental demyelination and/or axonal degeneration is peripheral nerves, spinal sensory and motor nerve roots, and cranial nerves
- 1-2/100,000 per year
- Previous infection in 2/3 of children (URI or AGE)
- Most frequent between ages 4 and 9
- Associated with pain and parasthesias
- Usually symmetric ascending paralysis
- Ataxia (44%)
- CN involvement

GBS

- Can have papilledema
- Can have impaired vital capacity
- Dysautonomia
- Sphincter disturbances in 1/3
- Decreases or absent reflexes
- Increased CSF protein- may have small increase in WBC
- EMG- conduction block and prolonged F-waves
- Treatment- IVIG or plasma exchange
- Recovery usually is 2 months- may take up to 18 months

CIDP

- Childhood incidence of 0.5/100,000 per year
- Like GBS but slower progression
- CSF- albumino-cytologic dissociation
- Treatment- steroids, IVIG, plasma exchange, immunosuppresives

Hereditary motor and sensory neuropathy

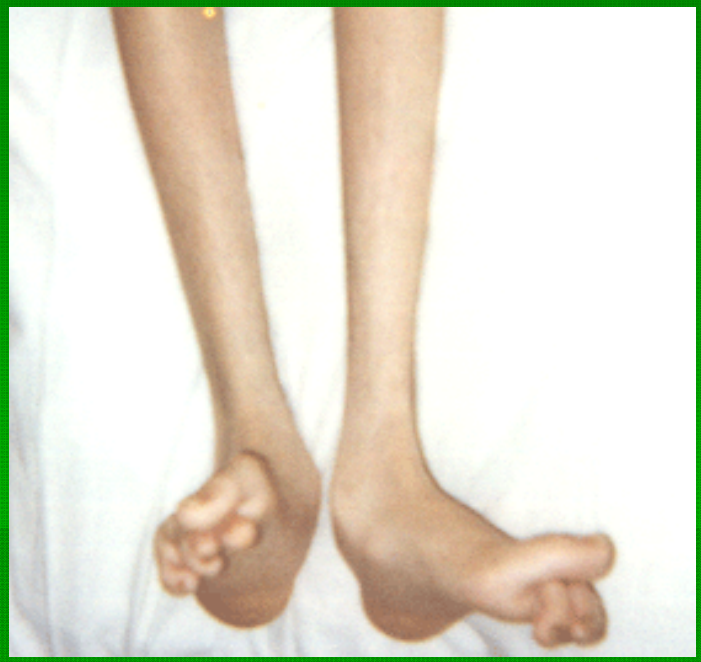
- Also called Charcot-Marie-Tooth disease (CMT)
- Peroneal muscular atrophy
- CMT1- AD

  - extensive segmental demyelination and remyelination of peripheral nerves

  - thickening of peripheral nerves
- CMT2- less common axonal form
- CMT3 (Dejerine-Sottas syndrome)- most severe demyelinating form

CMT 1

- Bimodal age distribution- 1st 2 decades or after 5th decade
- Can have sxs before age 1
- Peroneal muscles affected 1st
- Pes cavus, scolioisis, contractures, absent ankle jerks
- Decreased sensation
- Increased CSF protein
- Decreased NCVs
- Slowly progressive

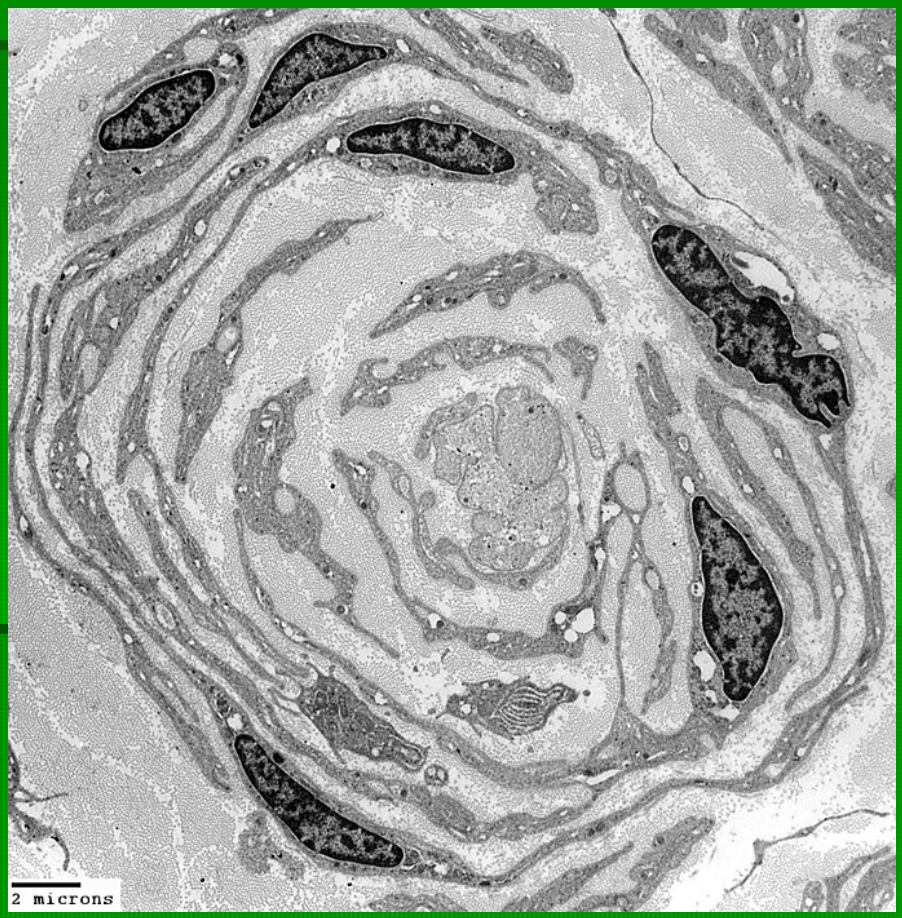


CMT 2

- Genetically heterogeneous
- Axonal degeneration of peripheral nerves
- Clinical picture similar to CMT 1 with slower progression

CMT 3 (Dejerine-Sottas Disease)

- Onset of sxs in infancy or early childhood progressing to severe disability
- AD or AR
- Hypotonia, muscle atrophy and weakness
- Facial weakness
- Very slow NCVs



Anterior horn cell disease

- Spinal Muscular Atrophy
- Infection (polio, enteroviruses, rabies)

Spinal Muscular Atrophy

- AR
- 1 in 10,000-25,000
- Mutation in SMN1- 2 copies
- SMA 1 (Wednig-Hoffman)- ¼
- SMA 2- ½
- SMA 3 (Kugleburg Welander)
- Symmetric proximal weakness
- Atrophy
- Diaphragm spared until late
- Cardiac and smooth muscle spared
- Tongue fasciculation
- Absent DTR's
- Some sensory symptoms

- Blood marker for SMN1 gene
- CK- normal or mild elevation
- EMG- fibs and fasics
- Biopsy- dennervation atrophy

SMA 1

- Acute and rapidly progressive
- Almost always fatal by 3yo

SMA 2

- Symptoms by 18 months
- Tremor in upper extremities
- CK increased up to 5x normal
- May have gastroc hypertrophy

SMA 3

- Present 18 months to adult
- Proximal muscle weakness
- Impaired joint mobility

Poliomyelitis

- Affects motor units of spinal cord and brain
- Mostly affects anterior horns cells
- Clinically ranges from non specific febrile illness to a severe and potentially fatal paralytic disease
- Paralytic polio follows aseptic meningitis
- Pain, fasciculations, twitching and decreased DTR's
- Polio-like syndrome- seen with west nile virus and other viruses