Muscle Disorders

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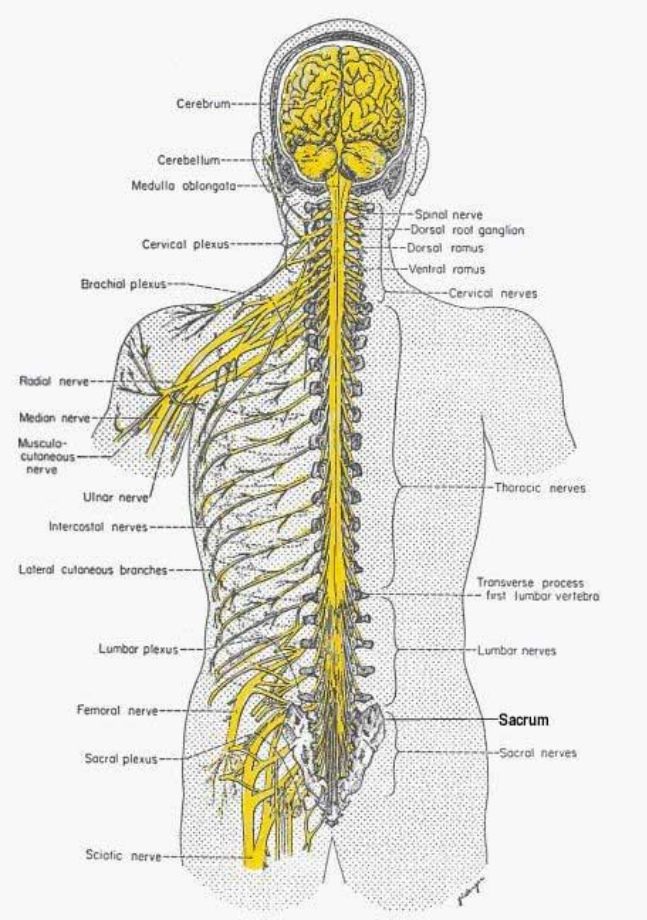
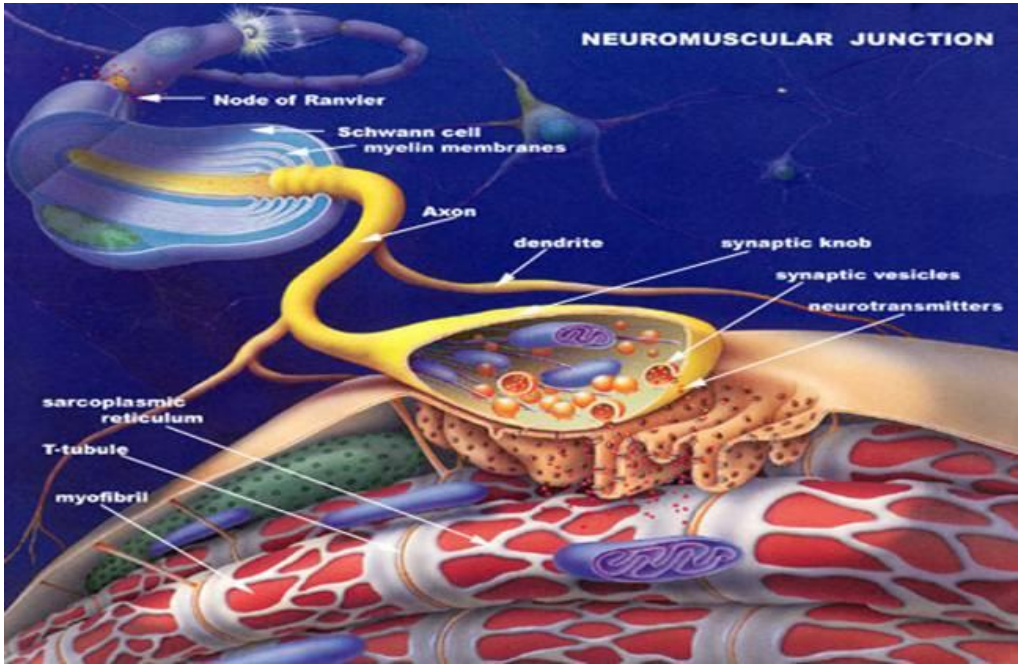
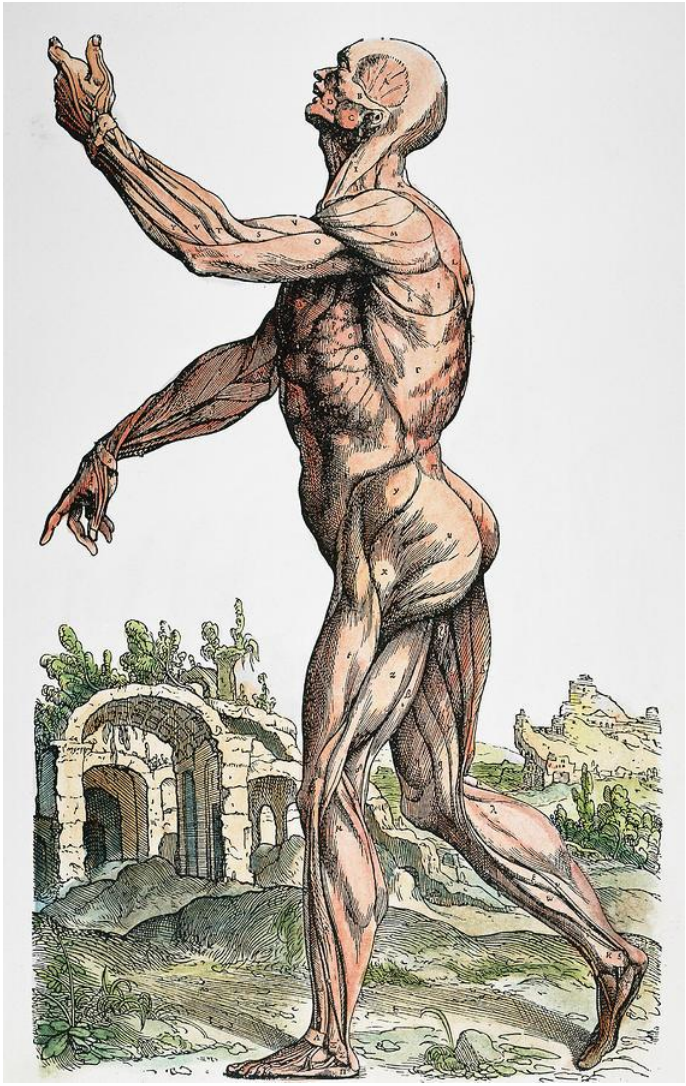
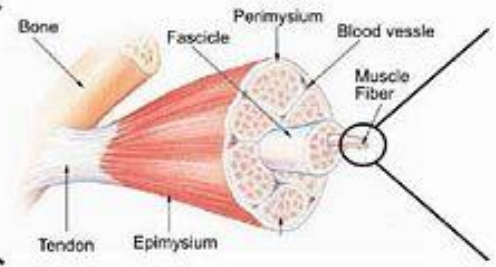

Cerebrum
Cerebellum
Medulla oblongata
Cervical plexus
Brachial plexus
Radial nerve
Median nerve
Muscula-cutaneous nerve
Ulnar nerve
Intercostal nerves
Lateral cutaneous branches
Lumbar plexus
Femoral nerve
Sacral plexus
Sciatic nerve
Spinal nerve
Dorsal root ganglion
Dorsal ramus
Ventral ramus
Cervical nerves
Thoracic nerves
Transverse process first lumbar vertebra
Lumbar nerves
Sacrum
Sacral nerves

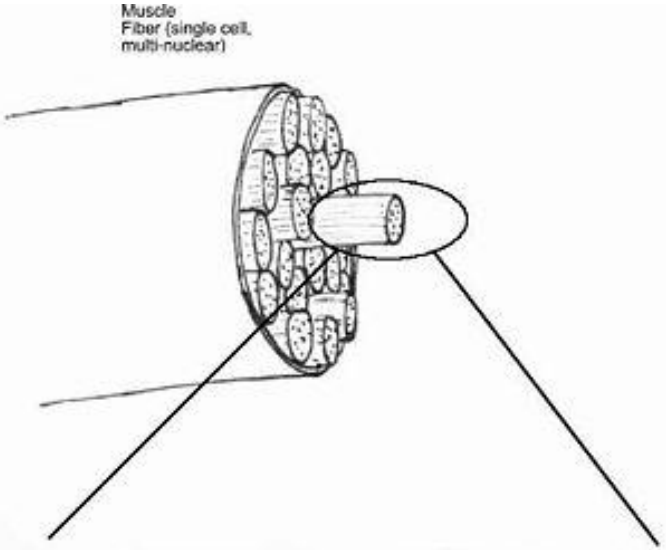

NEUROMUSCULAR JUNCTION
Node of Ranvier
Schwann cell
myelin membranes
Axon
dendrite
synaptic knob
synaptic vesicles
neurotransmitters
sarcoplasmic reticulum
T-tubule
myofibril

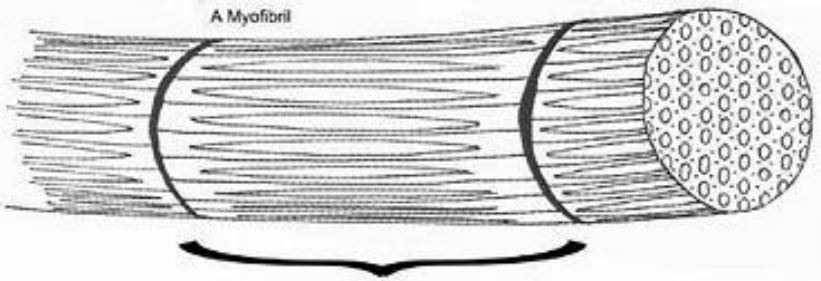
- Voluntary muscles
- Involuntary muscles

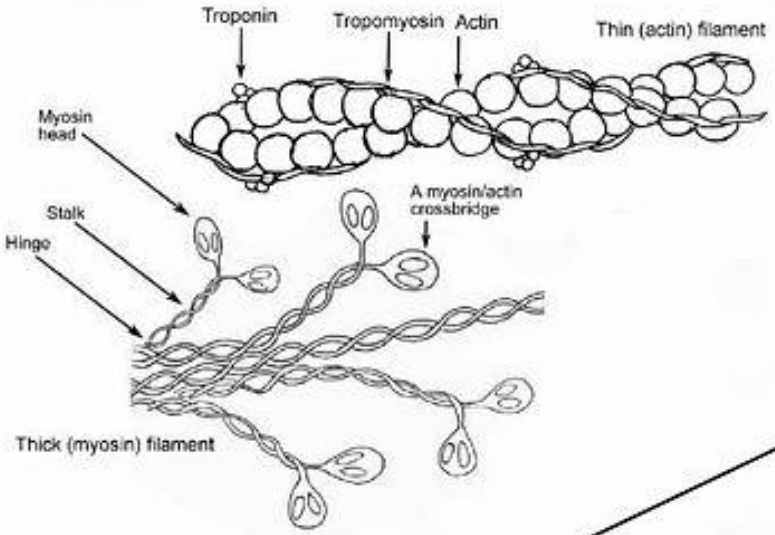
- Skeletal muscle
- Cardiac muscle
- Smooth muscle

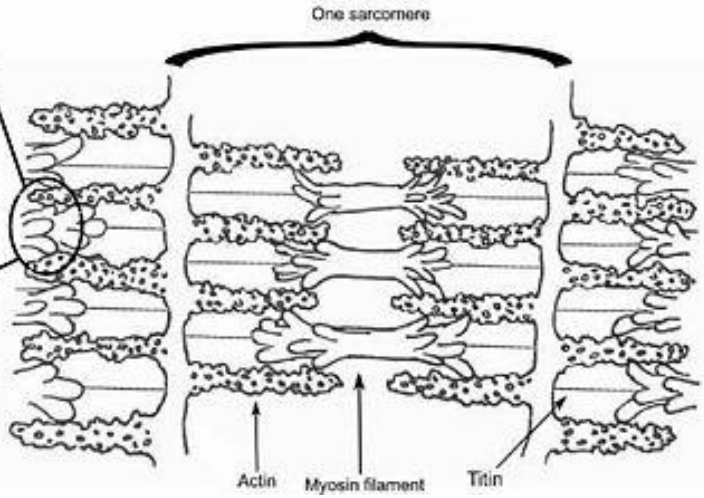


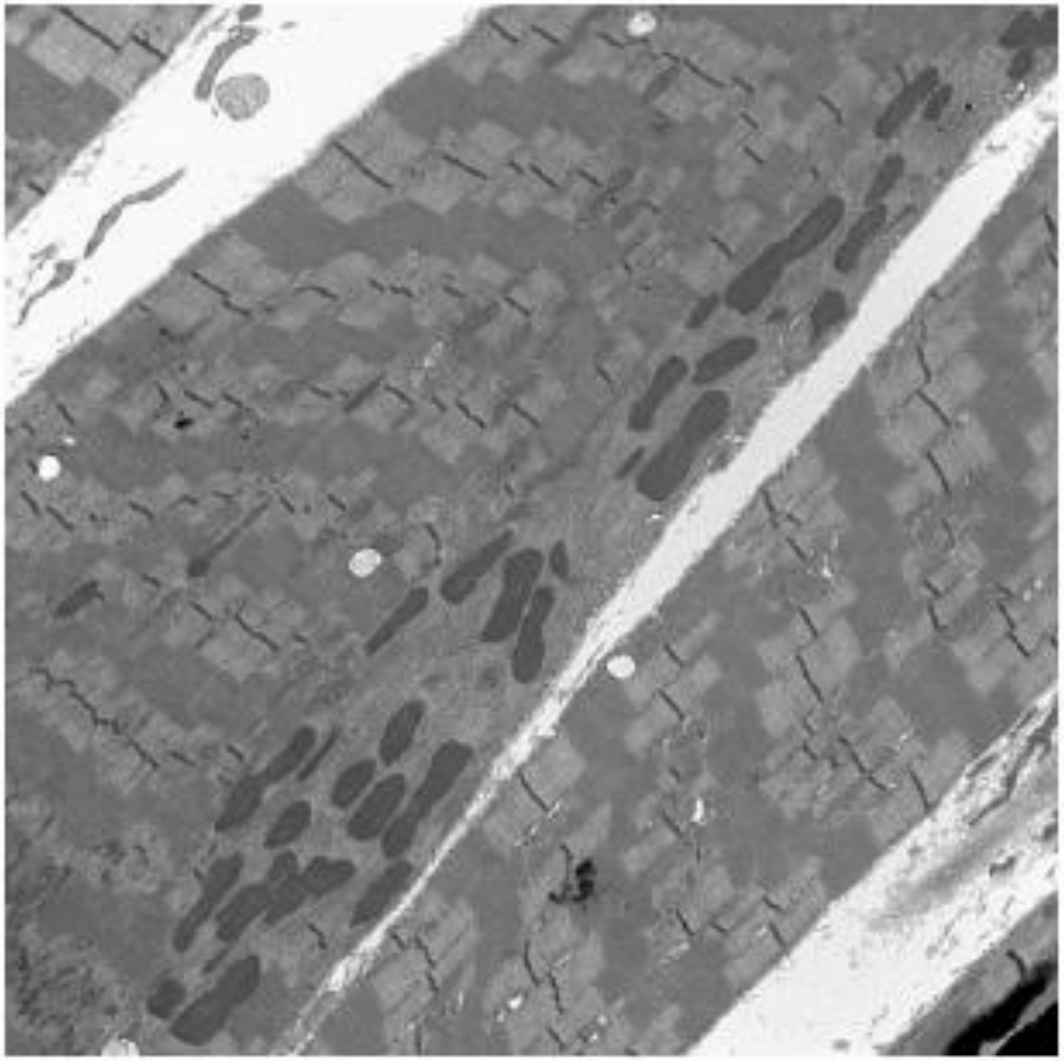

Bone
Fascicle
Perimysium
Blood vessle
Muscle Fiber
Tendon
Epimysium

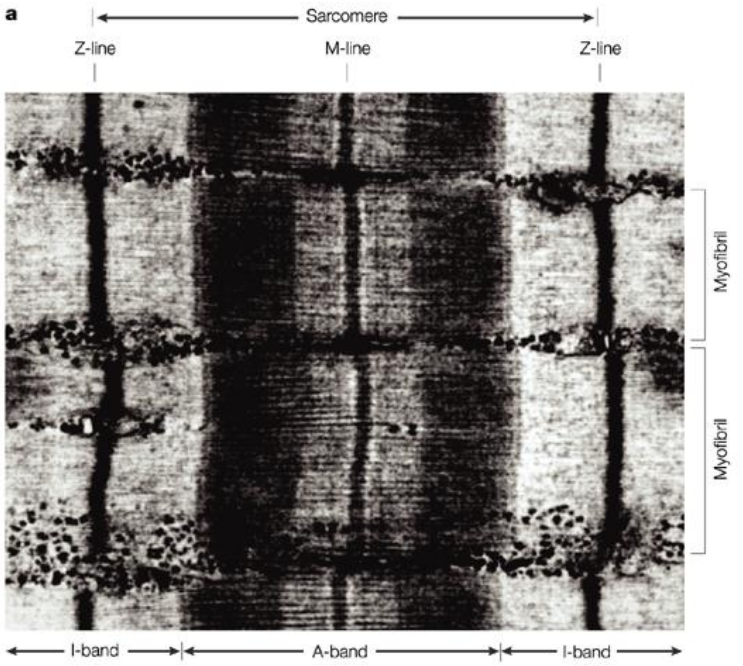

Muscle Fiber (single cell, multi-nuclear)


A Myofibril


Troponin
Tropomyosin
Actin
Thin (actin) filament
Myosin head
Stalk
Hinge
A myosin/actin crossbridge
Thick (myosin) filament

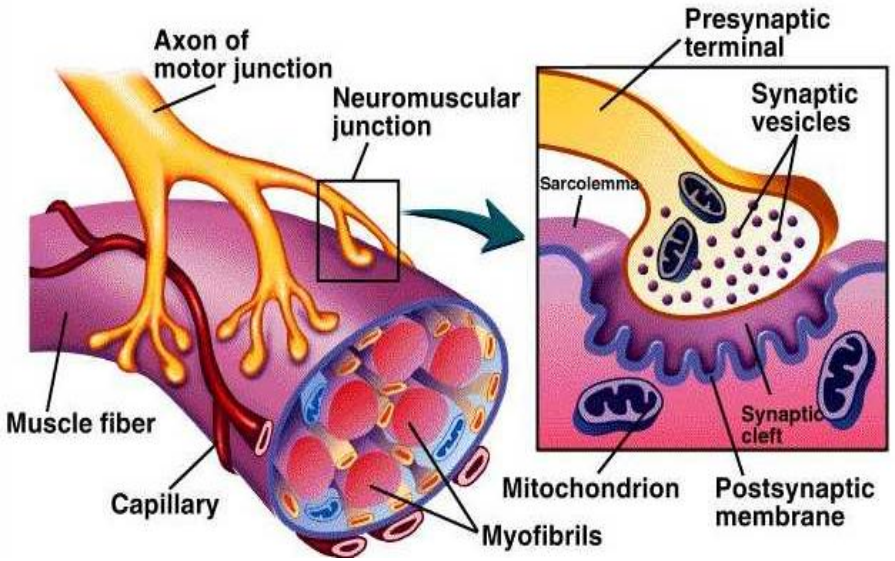

One sarcomere
Actin
Myosin filament
Titin

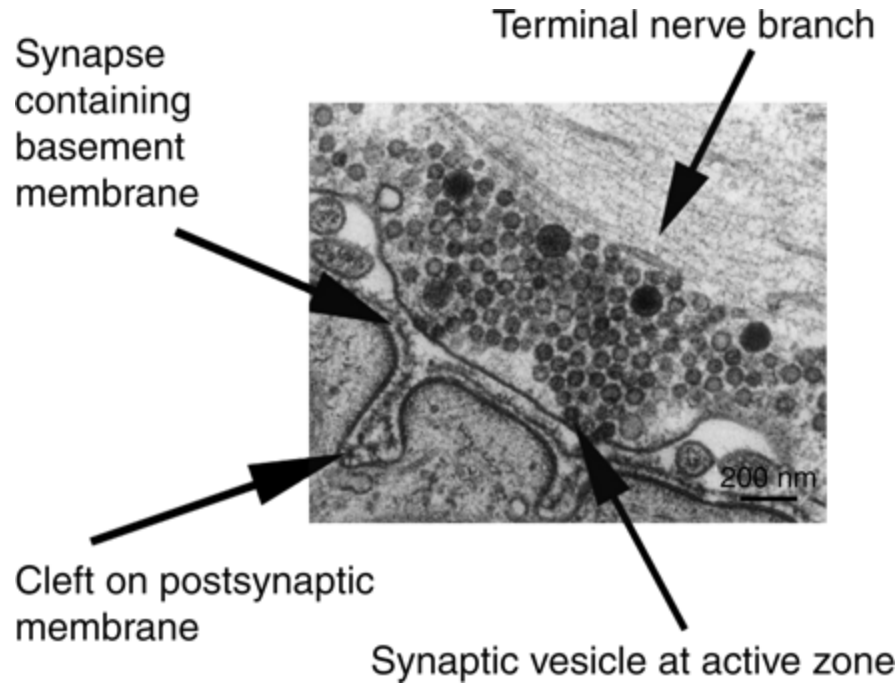



a
Sarcomere
Z-line
M-line
Z-line
Myofibril
Myofibril
I-band
A-band
I-band

How does skeletal muscle work?

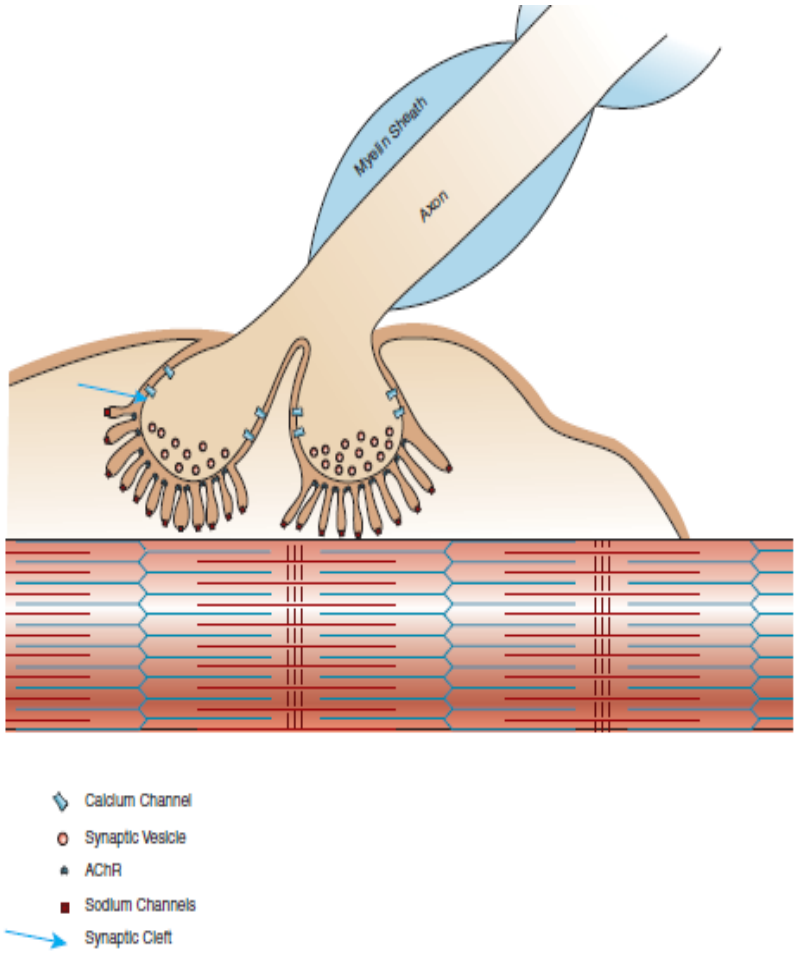
- The impulse arrives at the end bulb, chemical transmitter is released from vesicles
- Each of which contains 5,000 - 10,000 molecules of **acetylcholine** and diffuses across the neuromuscular cleft.



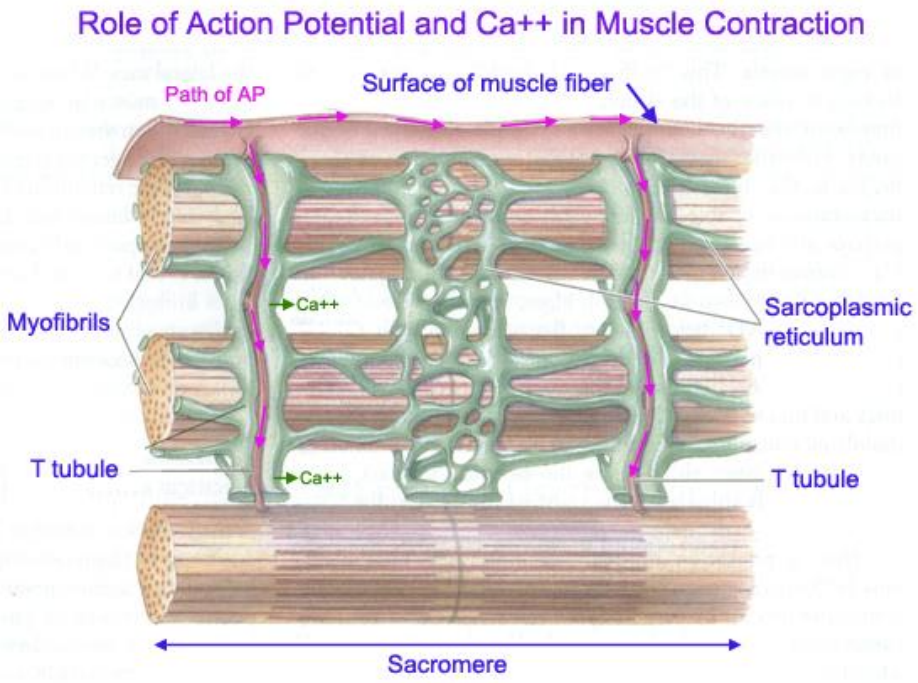


How does skeletal muscle work?

- Ach binds receptor sites in the membrane of the muscle & increase membrane permeability to **sodium**,
- Sodium then diffuses in & the membrane potential becomes less negative,
- If the threshold potential is reached, an **action potential** occurs, an impulse travels along the muscle cell membrane

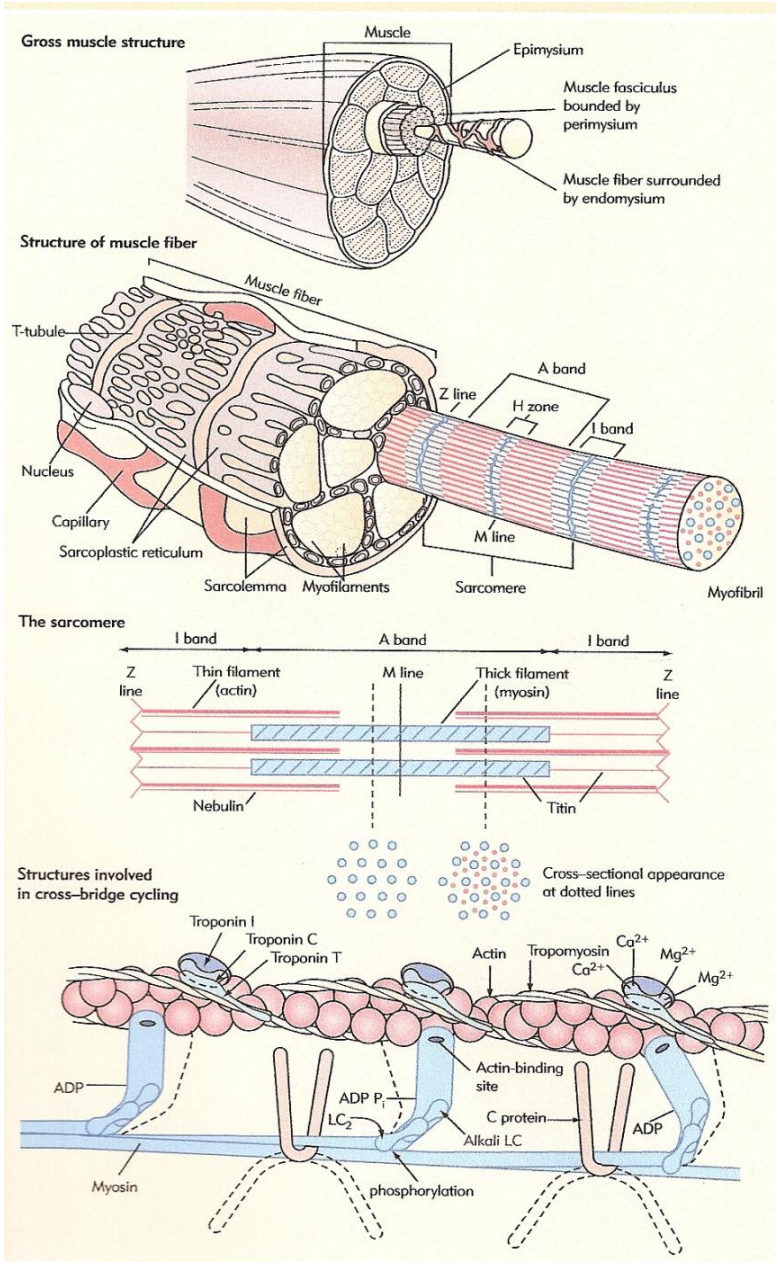


How does skeletal muscle work?



- The impulse travels along the **sarcolemma** and down the **T-tubules**.
- From the T-tubules , the impulse passes to the **sarcoplasmic reticulum.**
- As the impulse travels along the Sarcoplasmic Reticulum (SR)
- As a result, **calsium** diffuses out of the SR and among the myofilaments.

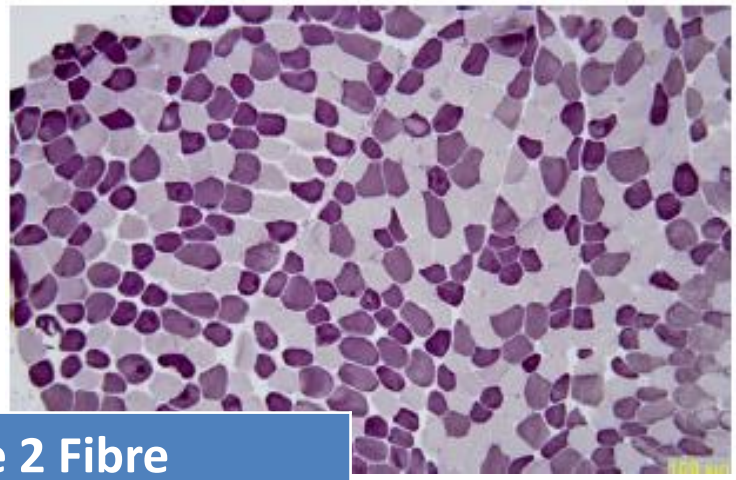
How skeletal muscle work?



Calcium fills the binding sites in the **troponin** molecules. This alters the shape and position of the troponin which in turn causes movement of the attached **tropomyosin** molecule.

- Movement of tropomyosin permits the **myosin head** to contact actin.
- Contact with actin causes the myosin head to swivel.
- At the end of the swivel, ATP fits into the binding site,breaks the bond between the myosin and actin. The myosin head then swivels back.
- As it swivels back, the ATP breaks down to ADP & P and the cross-bridge again binds to an actin molecule.

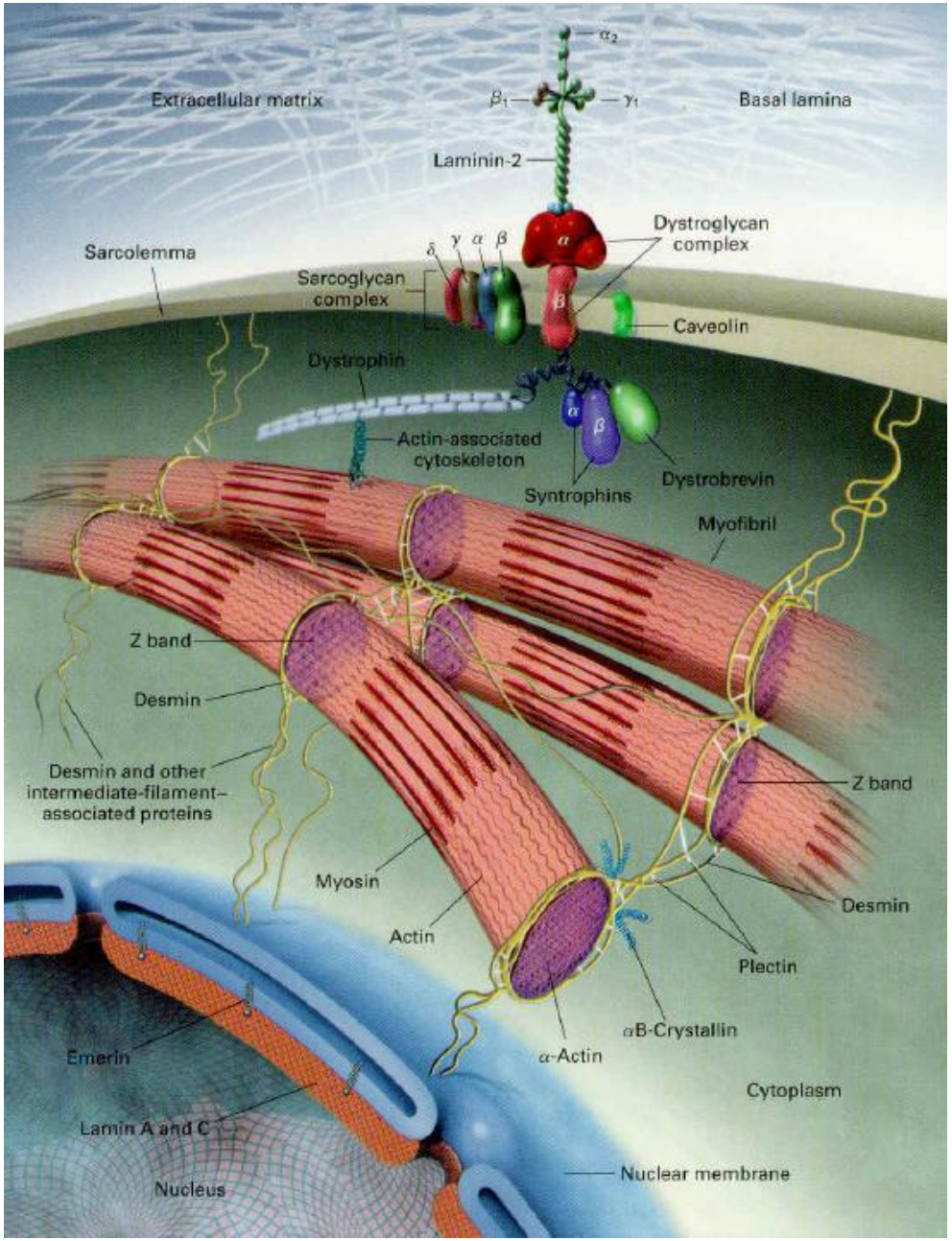
Muscle Fibers



	Type 1 Fibre	Type 2 Fibre
Capillary density	High	Low
Mitocondrial density	High	Low
Oxidative capasity	High	Low
Glicolytic capasity	Low	High
Major storage fuel	Triglicerides	Creatine phosphate, glycogen
Activity used for	Aerobic	Anaerobic
Contraction time	Slow	Fast
Resistansce to fatıgue	High	Low
Maximum duration of use	Hours	Minutes
Activity	Weight lifting, slow walking	Running

Sarcolemmal proteins

- There are lots of proteins which help muscle structure stabilisation, efficient contraction and enduration
- The most important one is Dystrophin
- Muscle contractil protein Actin is connected with sarcolemmal and nuclear membrane proteins.
- Other proteins are sarkoglycans, dystroglycans, lamnin, desmin, emerin.
- Every defect that influence this structure cause instability and contraction dysfunction.



Muscle Disorders Etiology

- **Muscular Diseases**
  - **Muscular Dystrophies**
  - **Inflammatory Myopathies** (Infectious, Autoimmun)
  - **Metabolic Myopathies**
    - Glycogen storage defects
    - Disorders of lipid metabolism
  - **Mitochondrial Myopathies**
  - **Endocrine Myopathies** (e.g., hypothyroidism)
  - **Toxic or Drug Induced Myopathies**
  - **Electrolyte imbalance** (Hyperkalemia, Hypokalemia, Hypophosphatemia, Hypercalcemia)

- **Disorders of Neuromuscular Transmission**

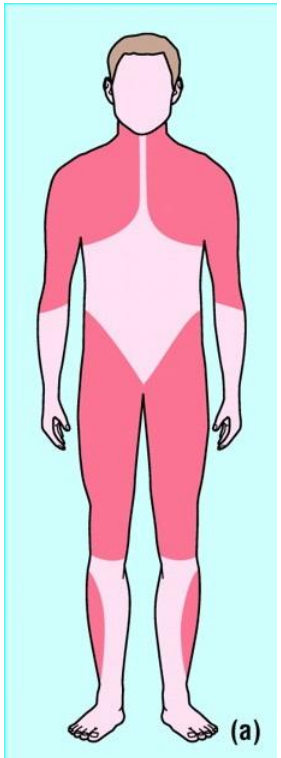
Muscular Dystrophies

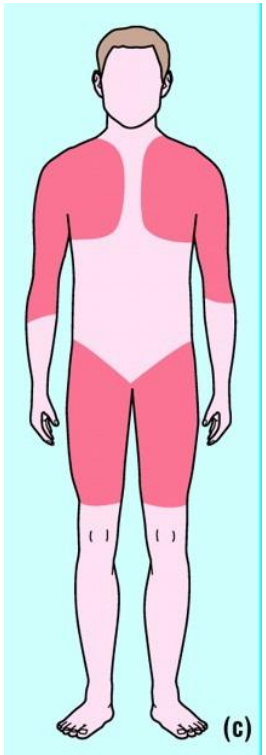
Limb Girdle Distribution

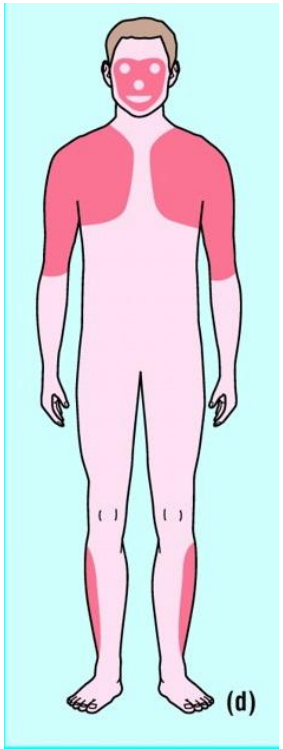
- DMD (X Linked recessive) (a)
- BMD (X Linked recessive)
- LGMD (OD , OR) (c)

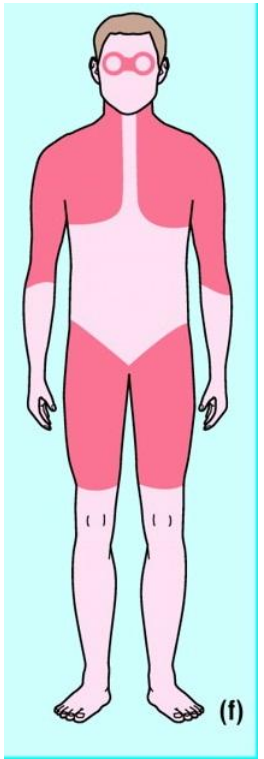
Special Distribution

- Fascioskapulohumoral Dystrophy (OD) (d)
- Myotonik Dystrophy (OD)
- Oculopharingeal Dystrophy (f)



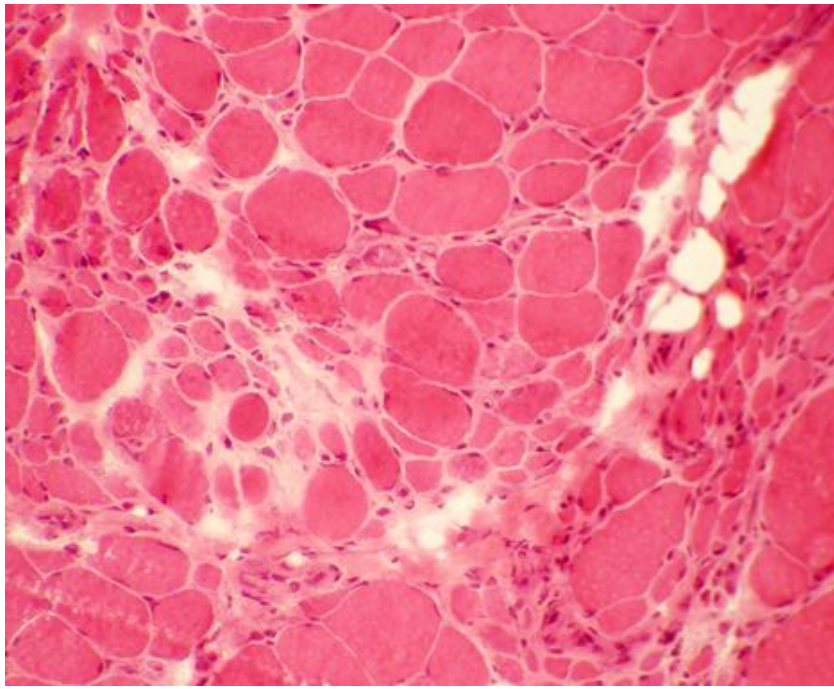


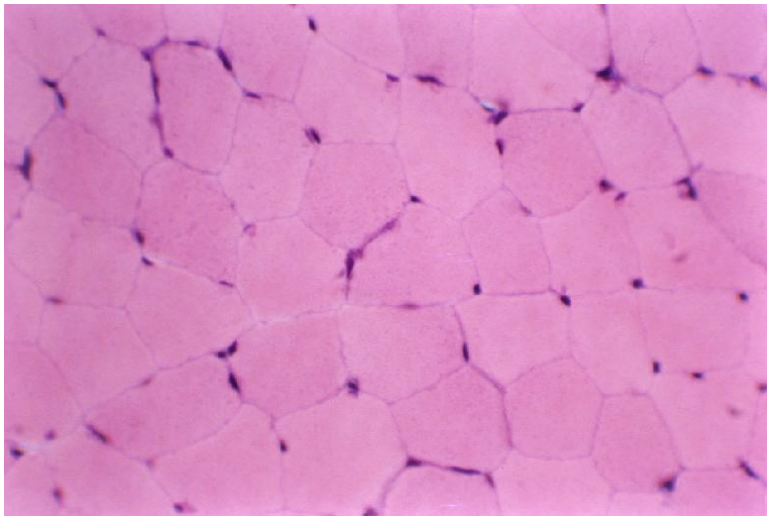


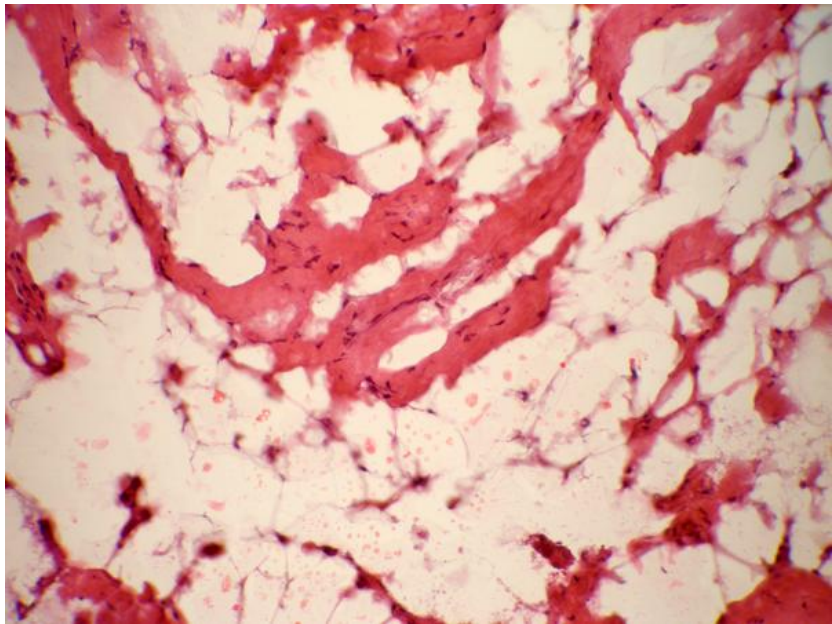


Dystrophic Muscle

- Different size fibres
- Necrotic small fibers
- Increase in fat and connective tissue

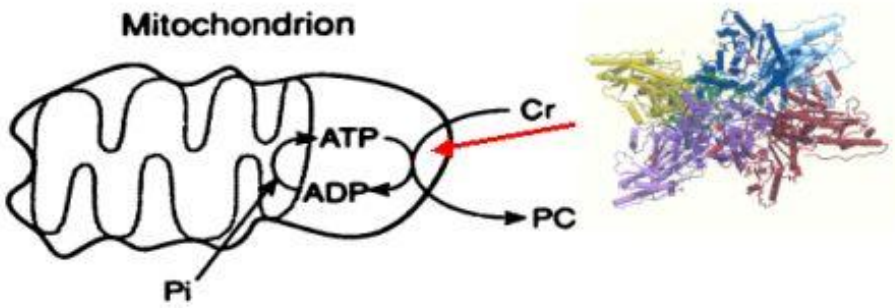






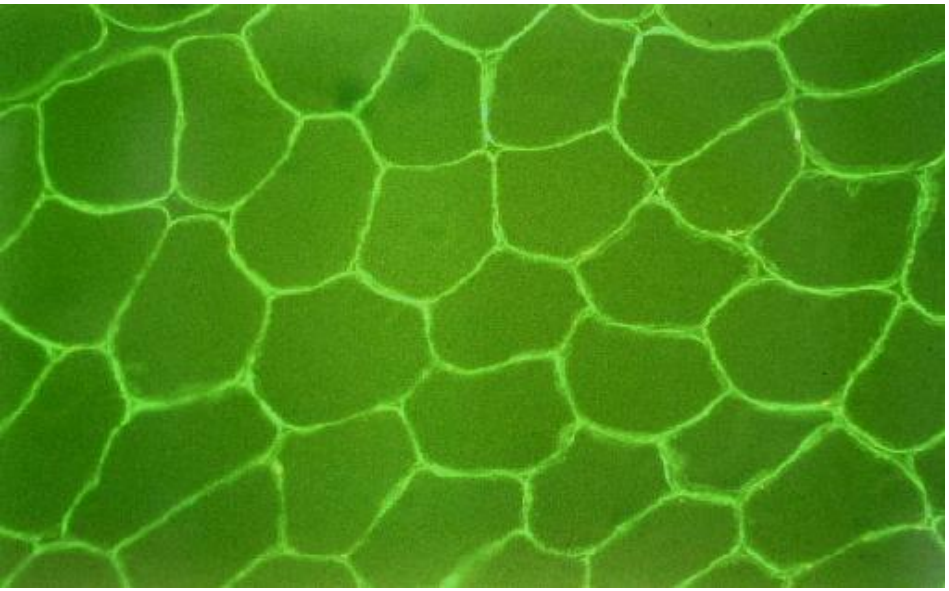
Dystrophic Features

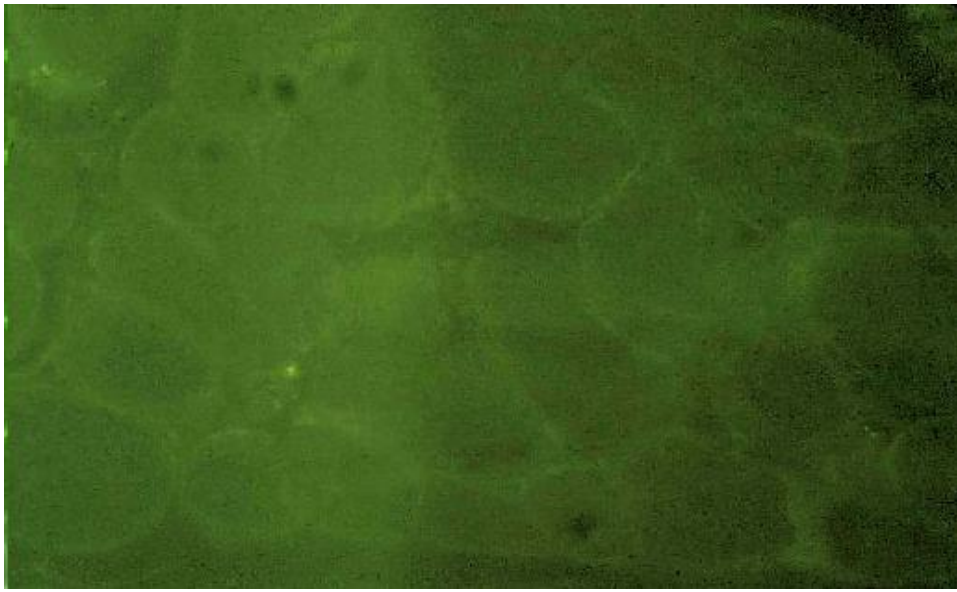
- Progressive weakness
- Skeletal muscle degeneration
- Difficulty in movements
- Difficulty in eating and respiration
- Heart muscle involvement
- High creatine kinase



Duchenne Muscular Dystrophy

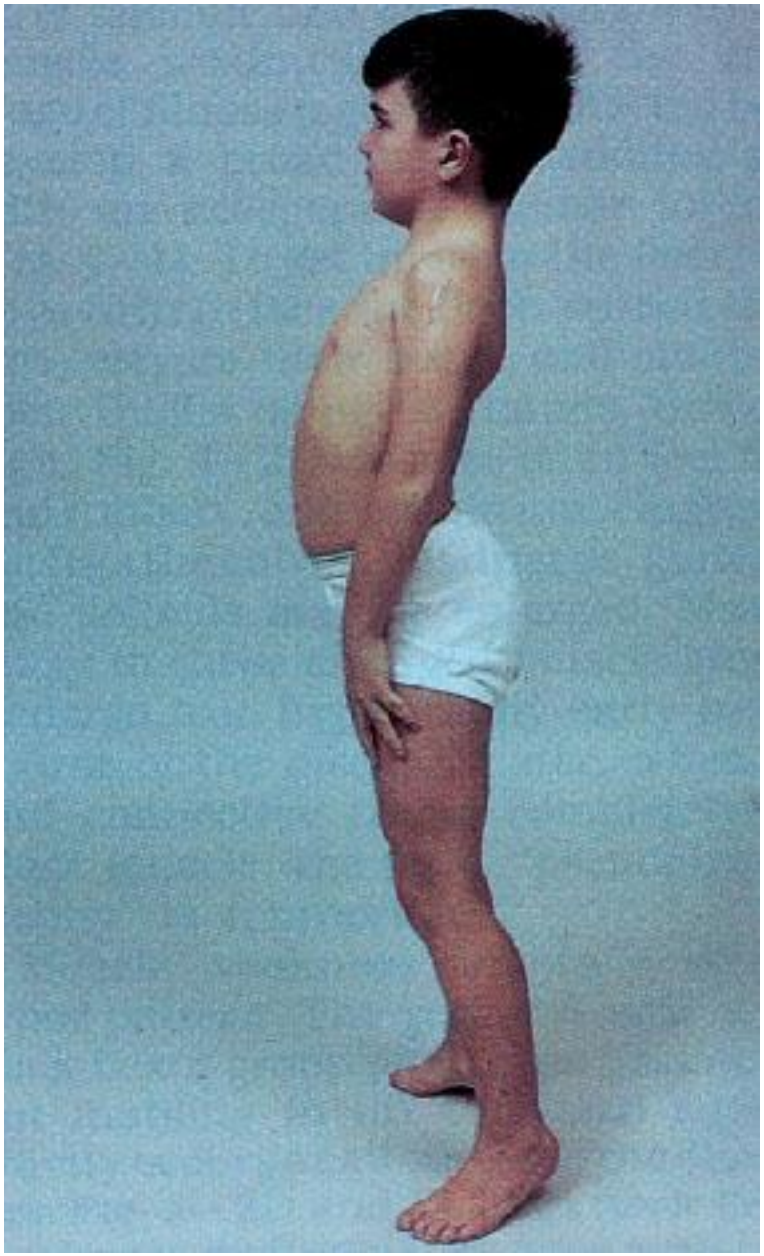
- X linked resessive (Xp21), dystrophin gene mutation
- Complete loss of sarkolemmal protein distrophin and muscle degeneration
- The incidence is around 1 in 3,600 boys.
- Females are rarely affected and are more often carriers

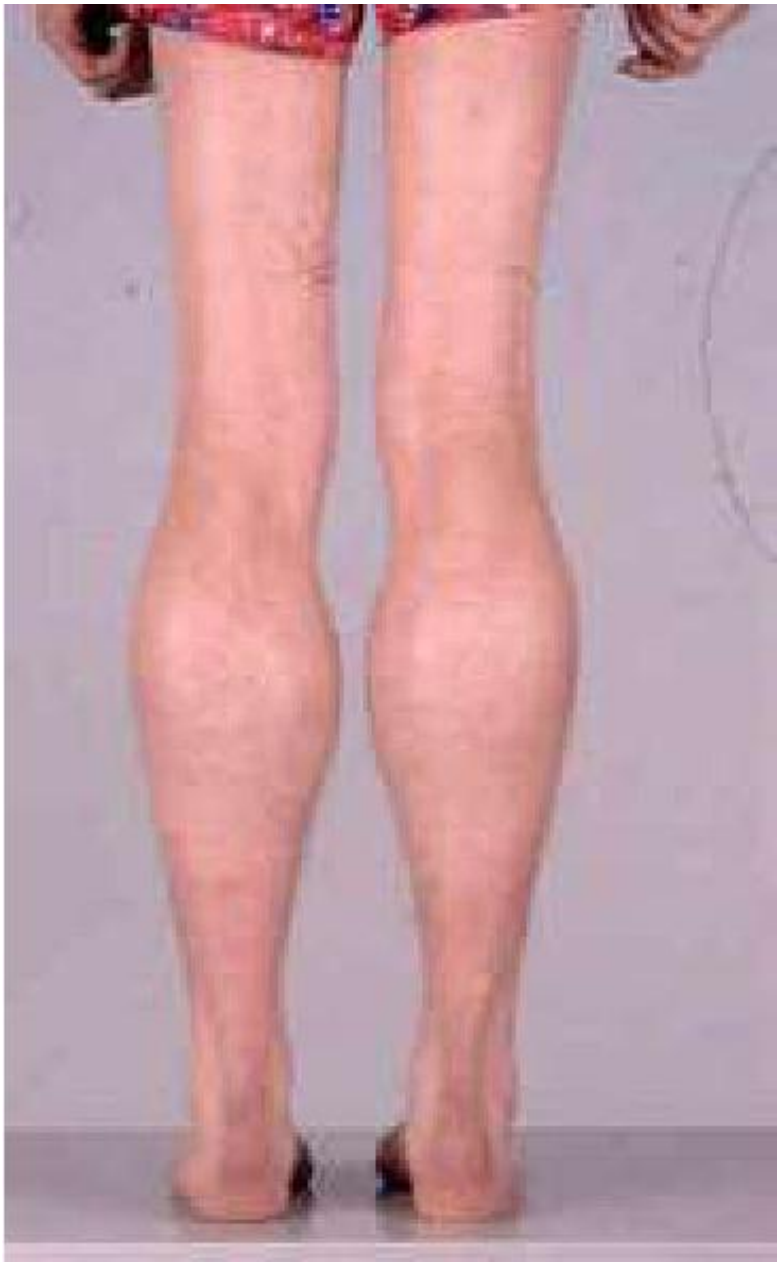


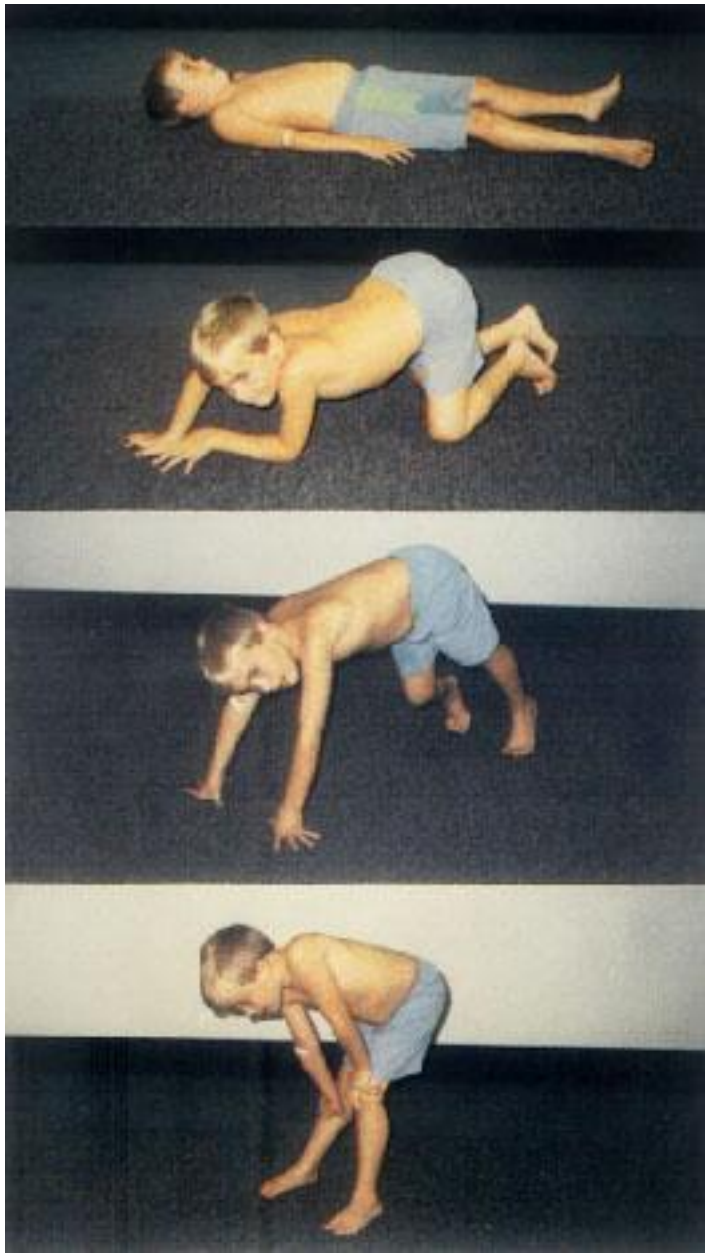


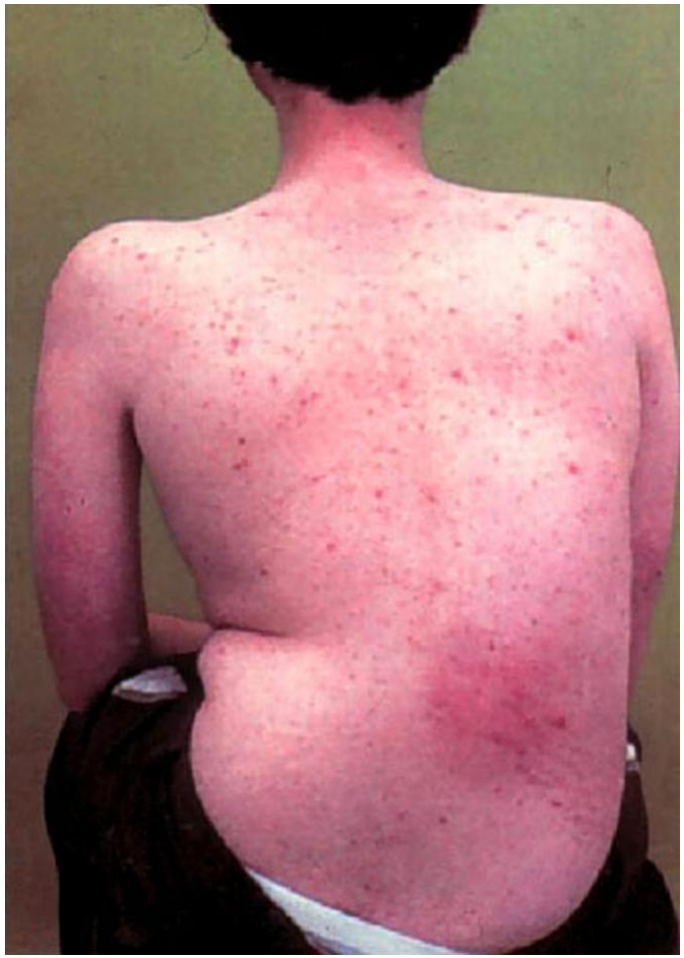
Duchenne Muscular Dystrophy

- Symptoms usually appear in male children before age 5 (especially 2-3 yo)
- Progressive proximal muscle weakness of the legs and pelvis
- Cause difficulty in walking and frequent drops
- Eventually this weakness spreads to the arms, neck, and other areas.
- As the condition progresses, muscle tissue experiences wasting and is eventually replaced by fat and fibrotic tissue
- Pseudohypertrophy (enlargement of calf and deltoid muscles),
- Hyperlordotic posture, walking like a duck and Gower's sign
- wheelchair dependent by age 12
- Cardiac involvement and scoliosis
- The average life expectancy for patients is around 25









Becker Muscular Dystrophy

- Parsial loss of sarkolemmal protein distrophin
- X linked resessive
- Symptoms usually appear in men at about ages 5–25, but may sometimes begin later
- Slowly progressive muscle weakness (Difficulty running, hopping, jumping) difficulty walking, toe-walking , frequent falls
- The pattern of symptom development resembles that of DMD, but with a later, and much slower rate of progression
- Loss of ambulation may not occur until the person is in his fifties

DMD and BMD

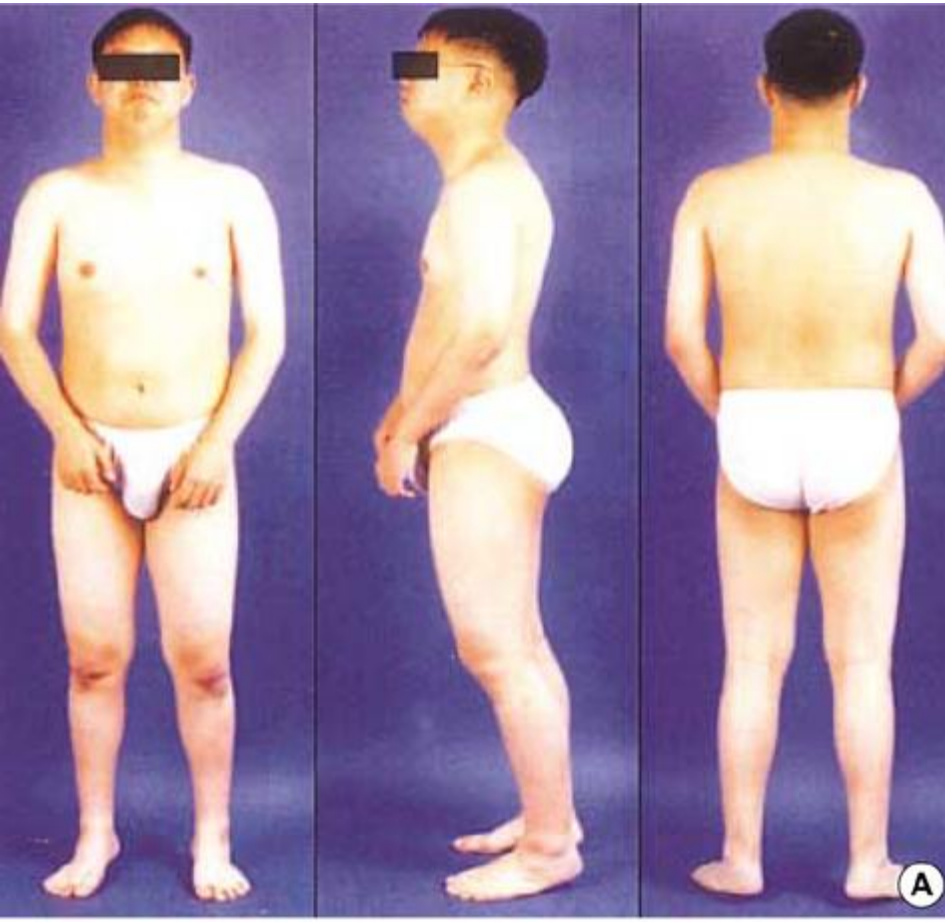
Diagnosis

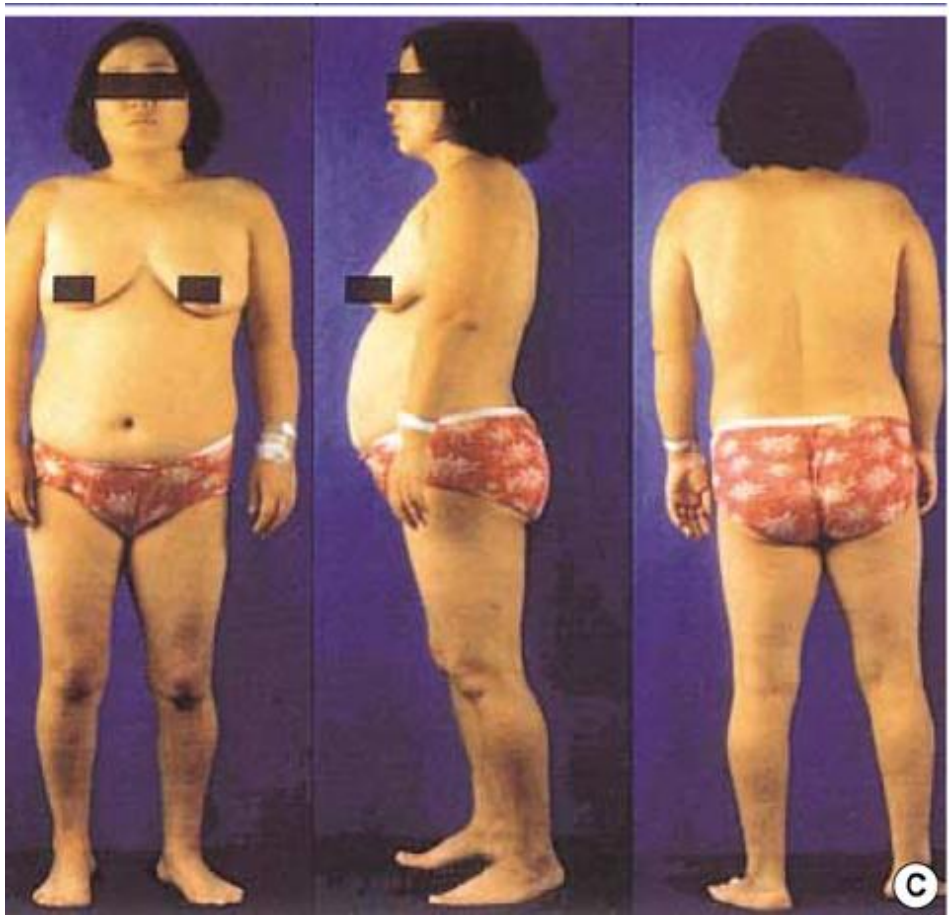
- High CK
- Genetic analysis
  - %70 deletion
  - %30 single nucteotid mutation
- Muscle Biopsy
- Prenatal diagnosis: corionic villus sampling

Prognosis and Treatment

- Prognosis depends on distrophin protein amount.
- **Treatment**:
  - Corticosteroids increase independent walking period and time to wheelchair dependence.
  - Physiotherapy
  - Surgery for skeletal deformities

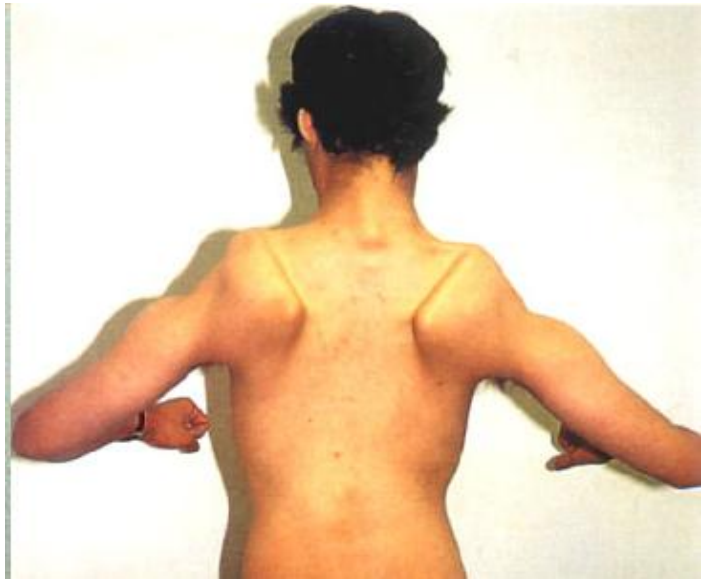
Limb Girdle Muscular Dystropies (LGMD)

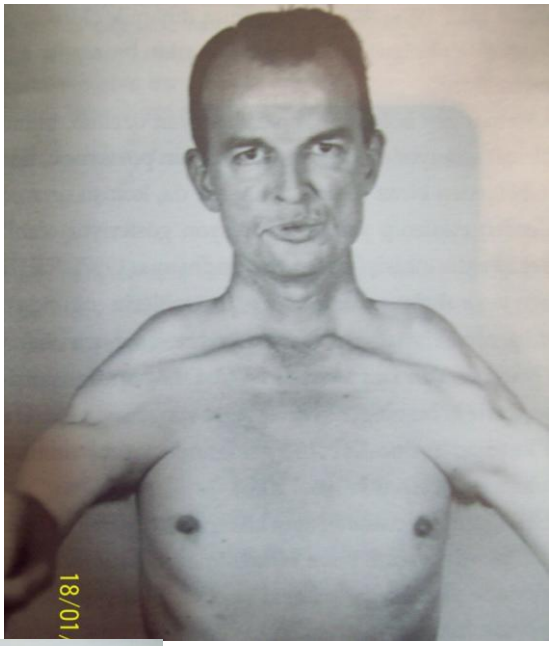




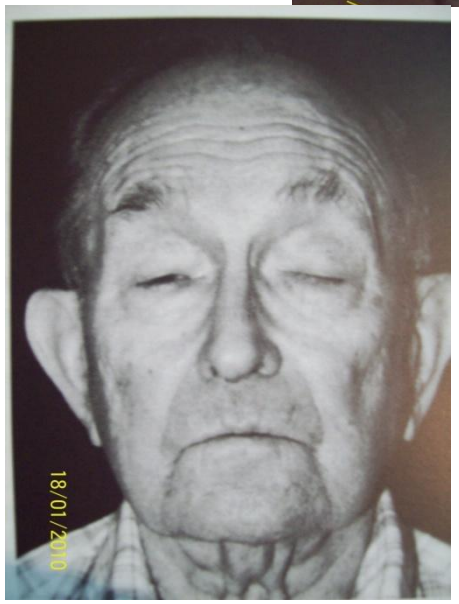
Dystrophies with spescial distribution

Fascioscapulohumeral Musculer Dystrophy



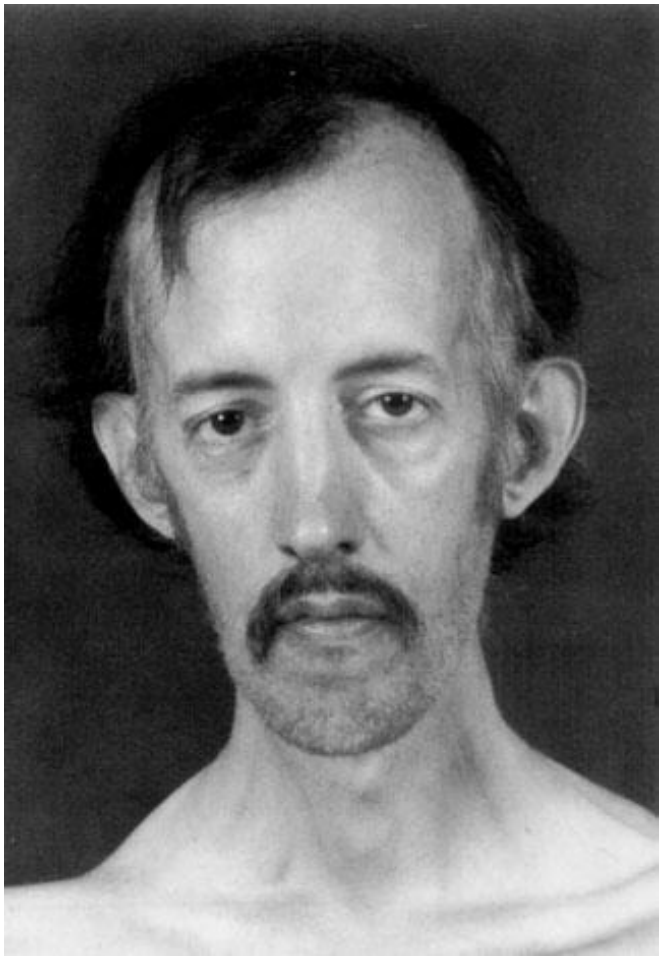


Oculopharingeal dystrophy

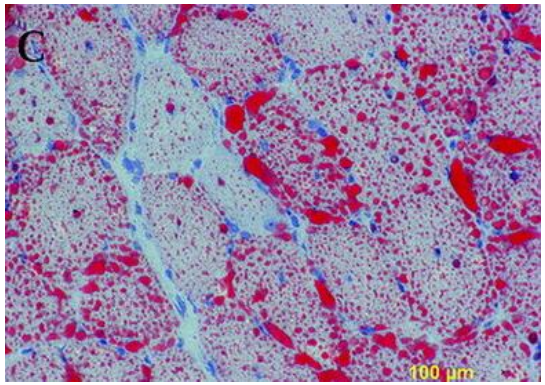


Dystrophies with special distrubition
Myotonic Dystrophy

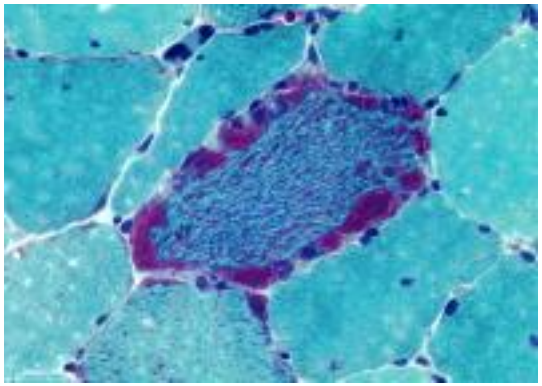
- Increase in CTG repeat in Miyotonin gene on 19. chromosome. OD
- Most frequent muscular dystrophy of adults. 13,5/100.000
- Myotonin responsible with cell shape, aktin-myosin contractility regulation, voltage depented channel modulation.
- Clinic:
  - Symmetrical weakness
  - Atrophy
  - Myotonia
  - Systemic features:insulin resistans, cataract, hypogonadism, frontal alopesia
  - Typhical face with temporal, masetter, levator ve palpebral muscle involvement.



- **Metabolic Myopathies**
  - Glycogen storage defects
  - Disorders of lipid metabolism

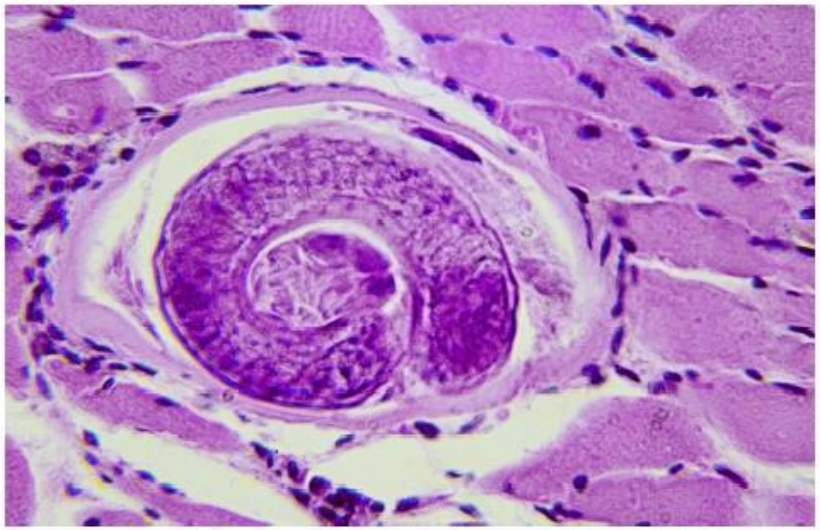


- **Mitochondrial Myopathies**
- Kearns-Sayre sydrome
- MELAS
- MERRF
- MNGIE



Inflammatory Myopathies

- Infectious
  - Viral
  - Bacterial
  - Fungal
  - Protozoal
  - Helmitic (trishinosis, cysticercosis)
- Otoimmun
  - Dermatomyositis
  - Polimyositis



Otoimmun Inflammatory Myopaties Dermatomyositis

- Dermatomyositis is an idiopathic inflammatory myopathy (IIM) with characteristic cutaneous findings.
- Dermatomyositis is considered to be the result of a humoral attack against the muscle capillaries and small arterioles.
- Dermatomyositis and polymyositis are twice as common in women as in men
- An association between dermatomyositis and cancer has long been recognized

The characteristic and possibly pathognomonic cutaneous features of dermatomyositis are a heliotrope (ie, blue-purple) discoloration on the upper eyelids (see the first image below) and a raised, violaceous, scaly eruption on the knuckles (ie, Gottron papules; see the second image below).

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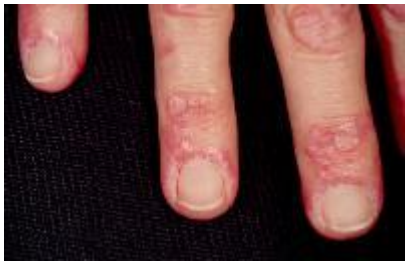
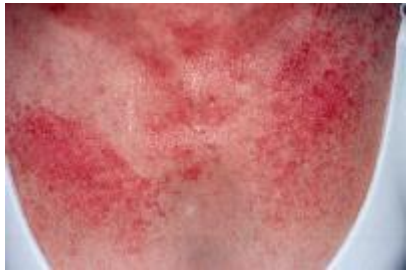
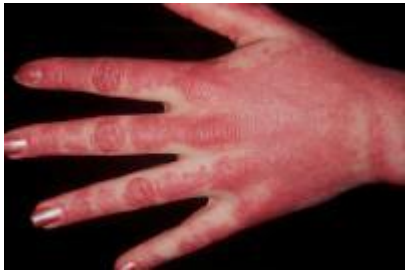


malar erythema, in a photosensitive distributionon the extensor surfaces





Otoimmun Inflammatory Myopaties
Polymyositis

- Polymyositis is an idiopathic inflammatory myopathy
- Polymyositis and dermatomyositis have many shared clinical features. Both are inflammatory myopathies that present as symmetrical proximal muscle weakness
- Muscles usually painless
- Dysphagia (30%)
- Polymyositis is an immune-mediated syndrome secondary to defective cellular immunity
- Incidence of lung, bladder, and non-Hodgkin lymphoma may be increased in patients with polymyositis, especially in the first year after diagnosis

Toxic or Drug Induced Myopathies

Statins

- Discuss as cause myopathy via mitochondirial dysfunction
- Asymptomatik increase in CK / myalgia/ myopathy/ rabdomyolisis
- Avoid high doses and polypharmacy

Steroids

- Cause selective Type 2 fibre atrophy and Na channel dysfunction, muscle inexitability/rabdomyolisis
- Proximal involvement in lower extremities is common

Endocrine Myopathies

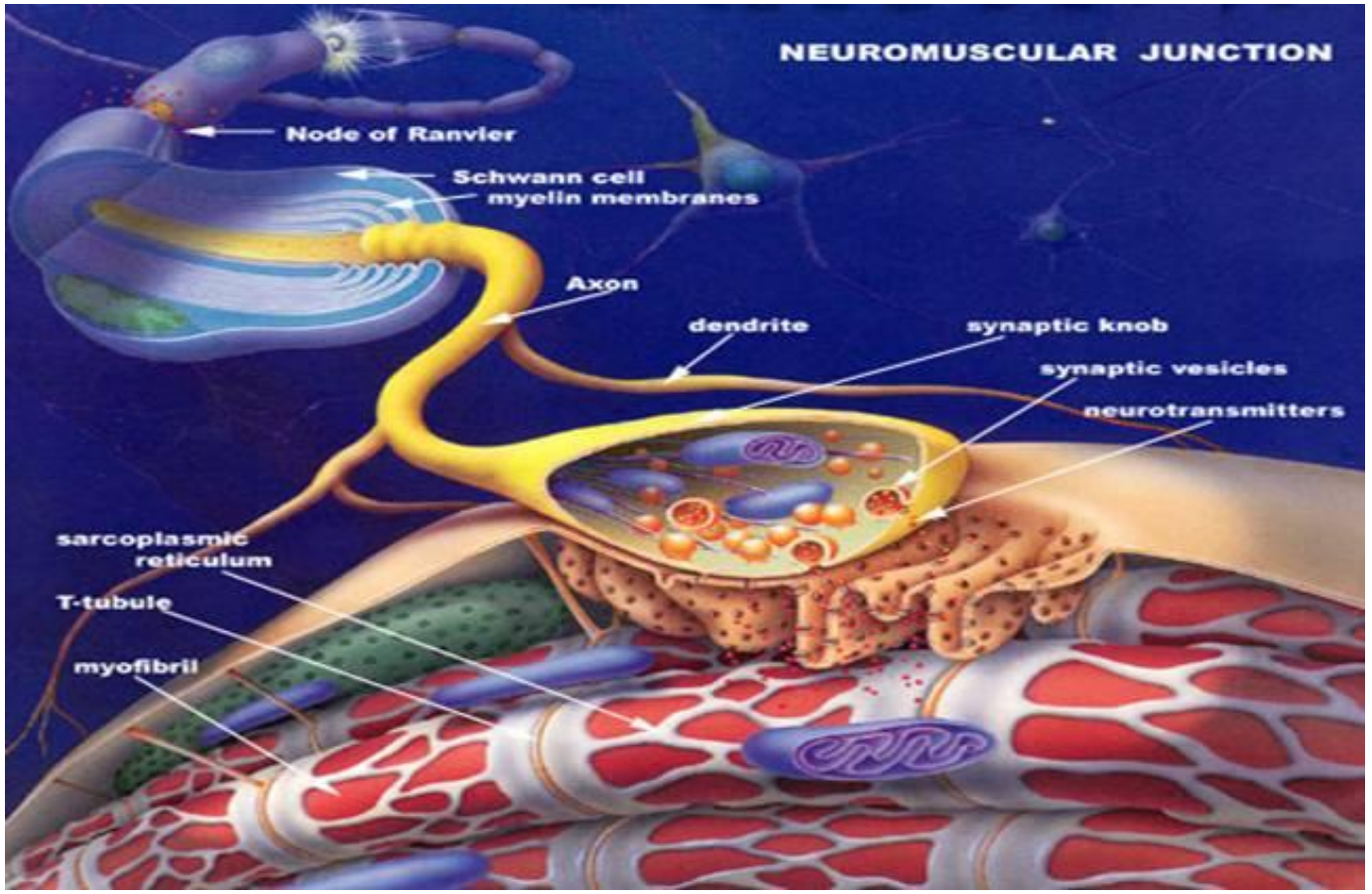
Hypothyroidism

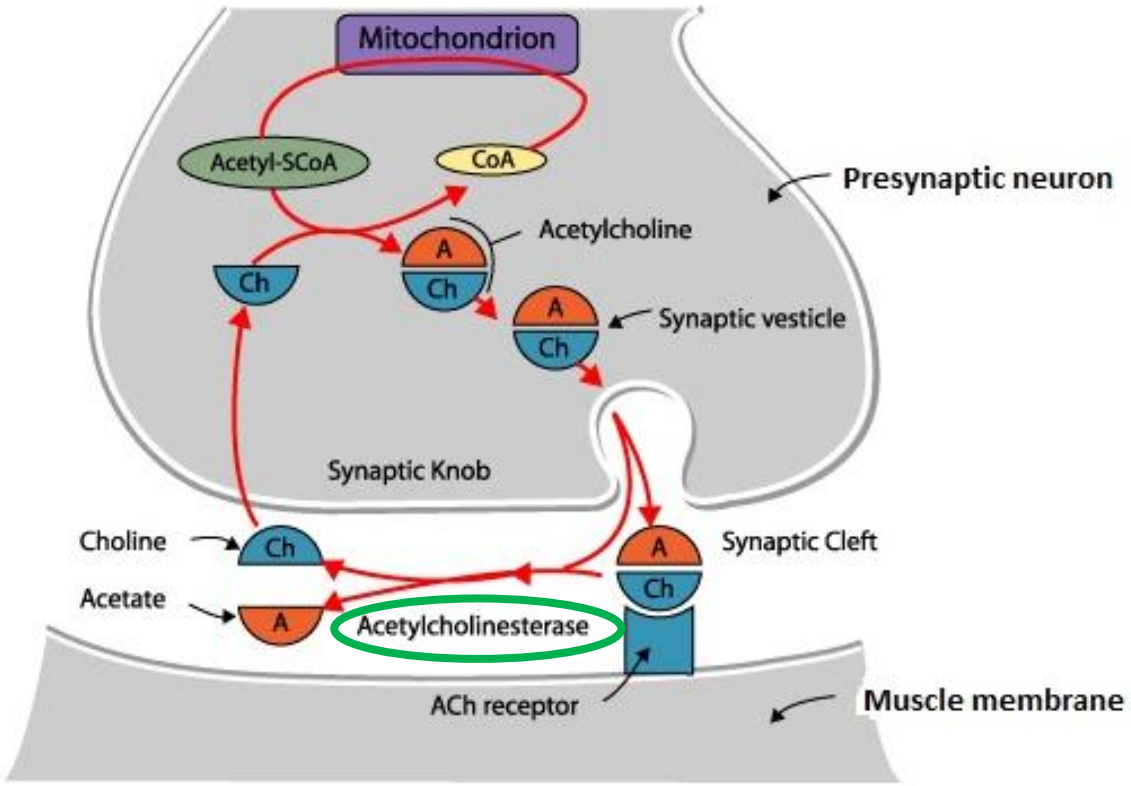
-Proximal weakness

-CK may be high

-Rarely rabdomyolisis

Neuromuscular Junction





ACh molecules are hydrolyzed by the enzyme acetylcholinesterase (AChE), which is abundantly present at the NMJ

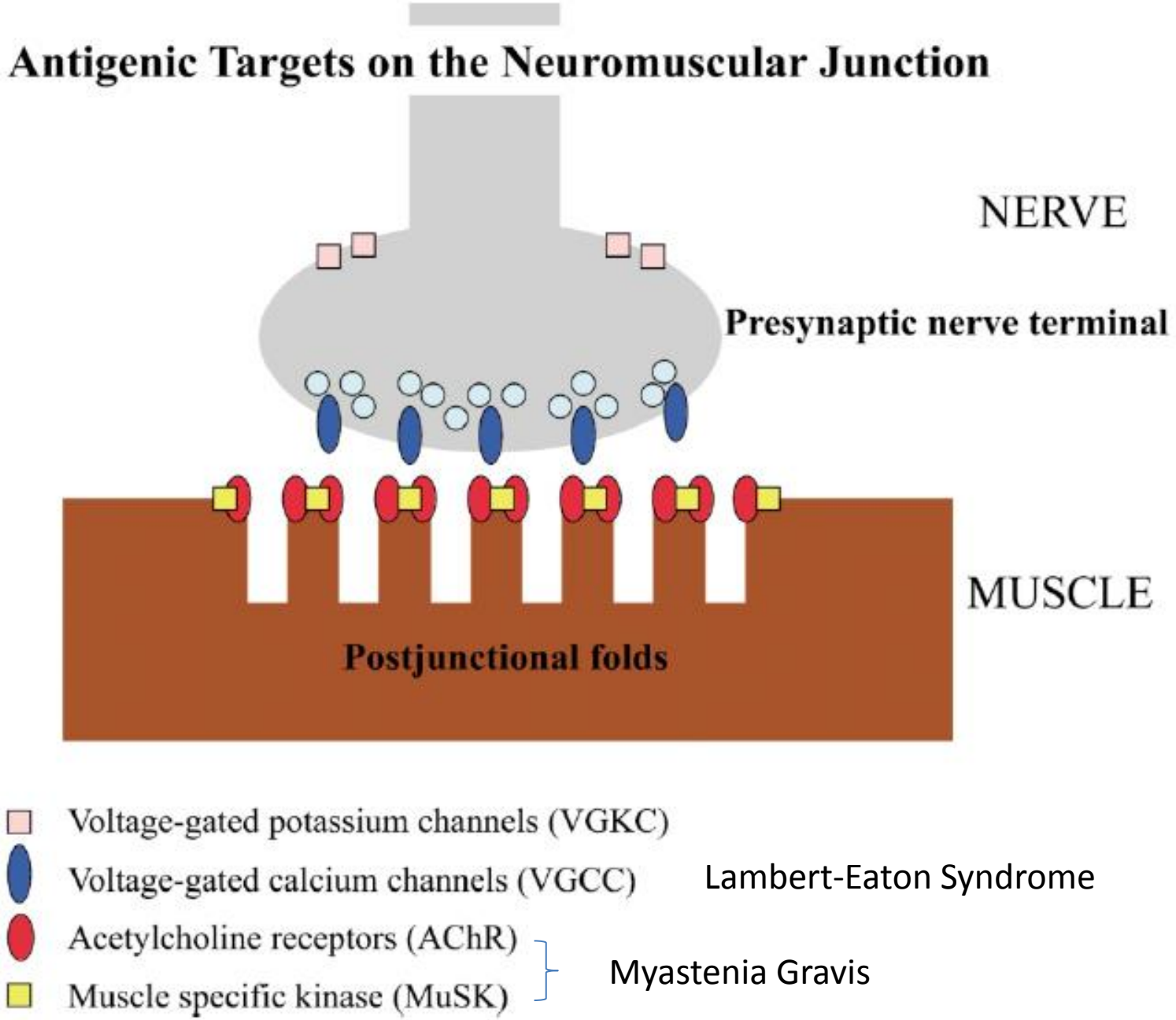
Neuromuscular Junction Disorders

Aquired

- Autoimmun
  - Myastenia Gravis
  - Lambert Eaten Myastenic Syndrome
- Botilism
- Drugs and Toxins
- Metabolic

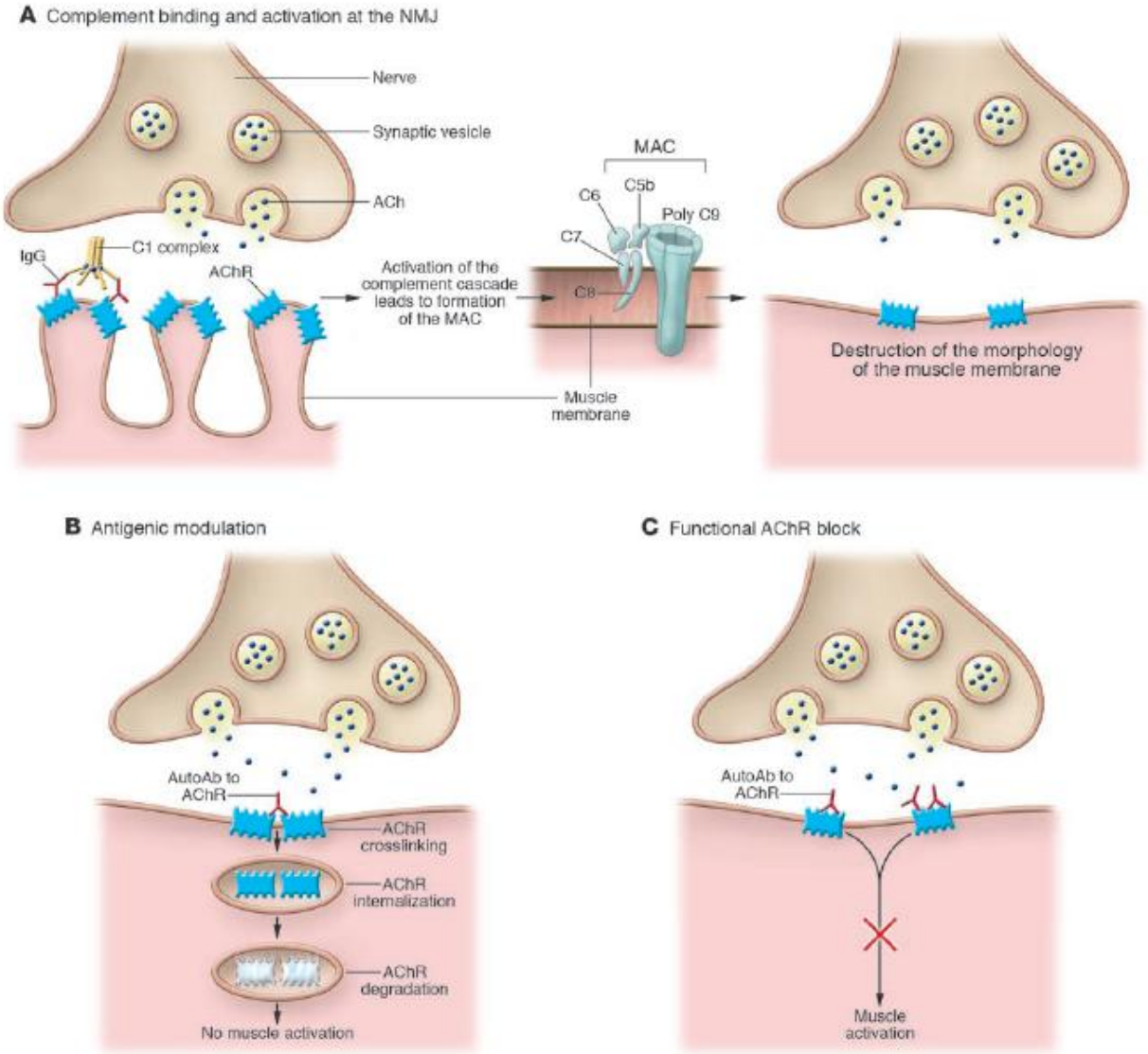
Congenital and Familial

Presynaptic, synaptic or postsynaptic mutations


Antigenic Targets on the Neuromuscular Junction
NERVE
Presynaptic nerve terminal
MUSCLE
Postjunctional folds
Voltage-gated potassium channels (VGKC)
Voltage-gated calcium channels (VGCC)
Acetylcholine receptors (AChR)
Muscle specific kinase (MuSK)
Lambert-Eaton Syndrome
Myastenia Gravis

Myastenia Gravis

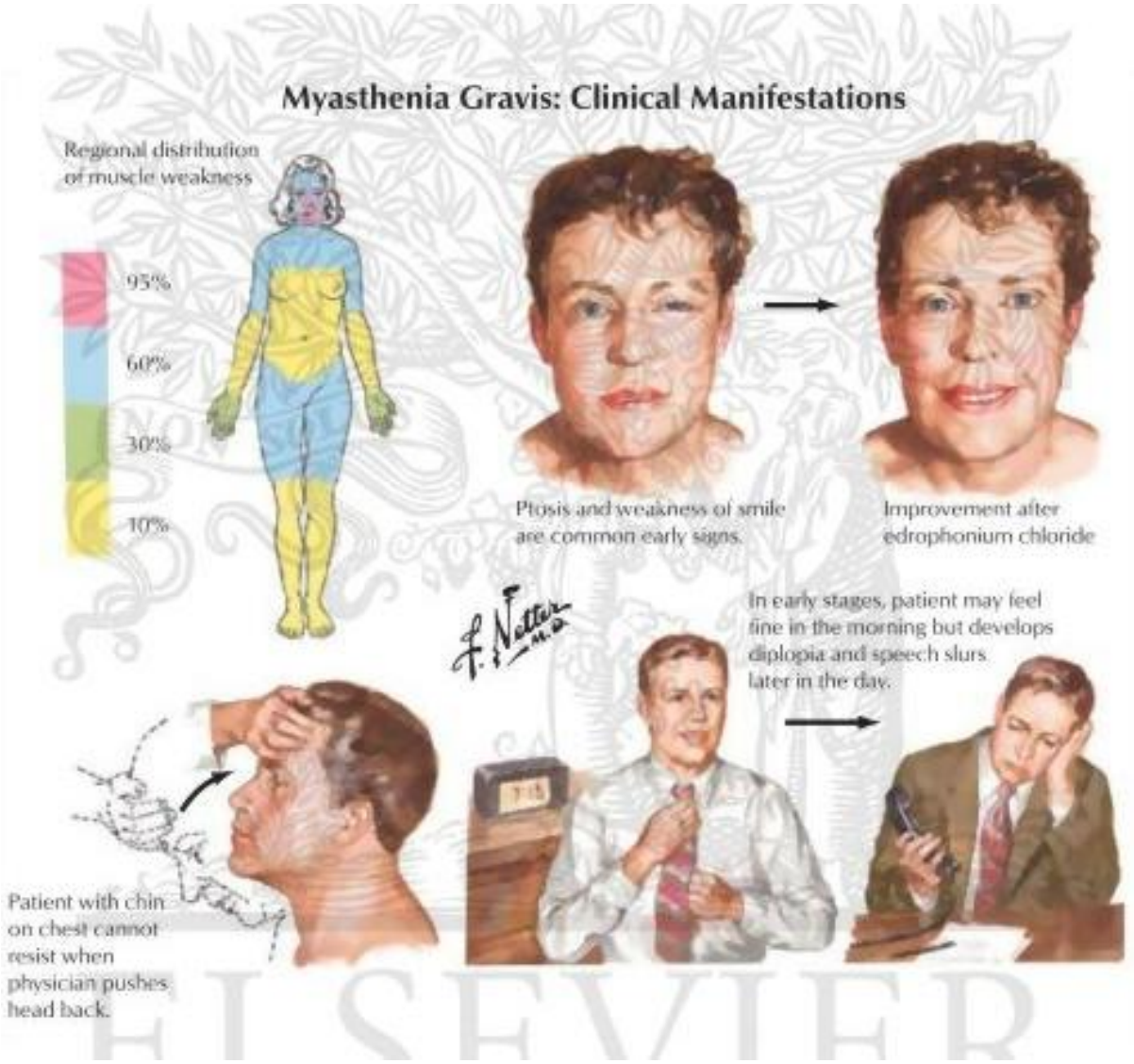
- Related with antibodies against **postsynaptic** membrane receptors
- Most common antibodies are against **Acetyl Choline Receptor** (%85-90)
- Second common antibody is **Anti MUSK** antibody
- Other antibodies anti Titin, anti Ryanodin

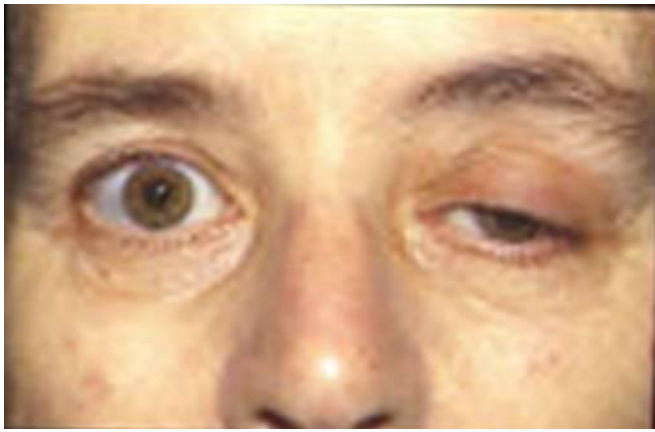


In MG, there is **a reduction in the number of AChRs** available at the muscle endplate and **flattening of the postsynaptic folds**

Myastenia Gravis

- The severity of the weakness typically fluctuates over hours being least severe in the morning and worse as the day progresses; it is increased by exertion and alleviated by rest.
- Extraocular muscle weakness (ptosis , diplopia) is present initially in 2/3 of all patients and occurs during the course of illness in 90%. (Ocular MG)
- Weakness tends to spread from the ocular to facial to bulbar muscles and then to truncal and limb muscles (Generalized MG)
- Atrophy not common in myastenia gravis


Myasthenia Gravis: Clinical Manifestations
Regional distribution of muscle weakness
95%
60%
30%
10%
Ptosis and weakness of smile are common early signs.
Improvement after edrophonium chloride
In early stages, patient may feel fine in the morning but develops diplopia and speech slurs later in the day.
Patient with chin on chest cannot resist when physician pushes head back.
F. Netter M.D.
ELSEVIER



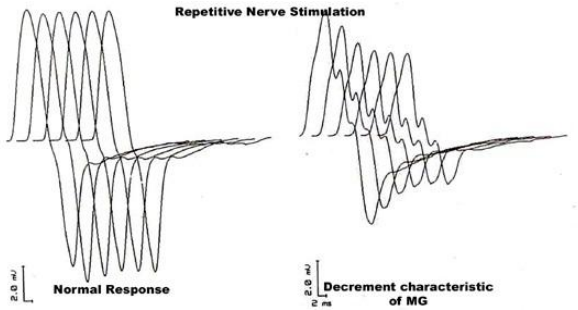
Myastenia Gravis

- Prevelance: 1/10.000-20.000
- F/M: 2/1
- Thymic abnormalities are common
  - Thymic hyperplasia is observed in %50-70 of MG patients
  - Thymoma in %10

- Other autoimmun disease are also common in MG patienst
  - Thyroid diseases in %15
  - Rheumatoid arthritis, lupus, polymyositis, pernicious anemia in %5

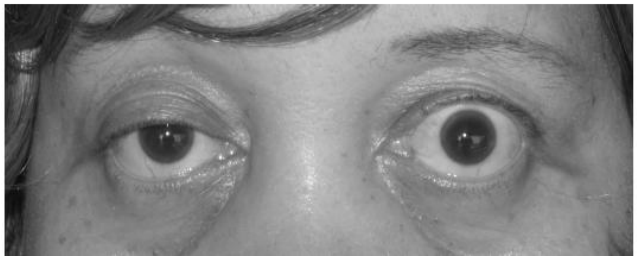
Diagnosis

- **Clinical clues:**
  - Increasing in fatıgue and symptoms at the end of the day
  - Fluctuation in sypmtoms with tiredness
- **Antibody test**
- **EMG**
  - Repetetive stimulation
  - Single Fibre EMG



- **Response to cholinesterase inhibitor injection**

a



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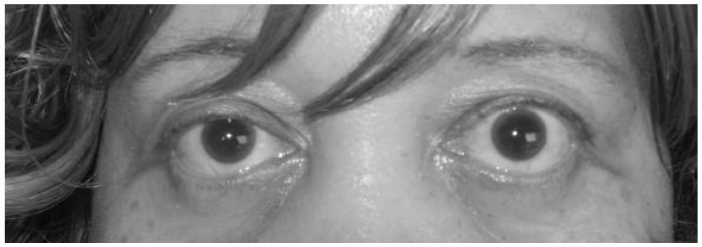

Myastenia Gravis Treatment

Mechanism	**Treatment**
• Neuromuscular modulation	Cholinesterase inhibitors (increase Ach)
• Immunomodulation	Thymectomy Plasmapheresis IV ımmunglobulin
• Immunosuppression	Steroids Immunosuppressan drugs

Lambert-Eaton Myastenic Syndrome

- **Presynaptic** autoimmun disorder
- Antibodies against voltage gated Ca channels (VGCC)
- Proximal weakness in lower extremities
- Repetetive movements increase strenght
- Malignancy in %50 of patients. Especially small cell lung cancer (SCLC)
- Autonomic dysfunction signs (dry mouth, constipation, ımpotence)

Botulismus

- Botulism is an acute neurologic disorder due to a neurotoxin produced by *Clostridium botulinum*.
- The toxin binds irreversibly to the **presynaptic membranes of peripheral neuromuscular** and **autonomic nerve junctions**.
- Toxin binding blocks acetylcholine release
- Resulting in symmetical weakness, flaccid paralysis and often respiratory
- Bulbar muscle ınvolvement cause dysphagia and ocullar muscle involvement cause diplopia.
- Autonomic findings
- Foodborne botulism and wound botulism source of adult botulismus
- The incubation period is usually 18-36 hours after following consumption of contaminated food products
- Treatment: Supportive treatment (for respiration and feeding) + antitoxin

Drugs

- **Antibiotics**
  - Aminoglycosides
- D-penisilamin
- Iodine IV contrast agents
- Magnesium
- Lithium
- Cardiac drugs
  - Quinine
  - Lidocain
  - Beta-Blockers
  - Ca channel blockers
- Diazepam
- Curare

Metabolic

- Thyroid disease
- Hypocalsemia
- Hypomagnesemia
- Hypokalemia

Approach to the Patient with Neuromuscular Disease

Distribution of Weakness

Asymmetry/Symmetry
Distal / Proximal
Face & Periocular
Bulbar
Respiratory
Limb-Girdle Syndromes
Selective involvement

Time Course

Acute
Episodic
Fatigue
· Myasthenia
Onset of weakness
· Congenital
· Infantile
Hereditary

Familiy History

Approach to the Patient with Neuromuscular Disease

Muscle Features

Crapms

Atrophy

Pseudohypertorphy

Myotonia

Fatigue and exercise intolerance

- After 20 min. exercise → lipid metabolism disorder?
- In first 5 min.→ glycogen metabolism disorder?

Cardiac muscle involvement

Systemic Features

Endocrine

Gastro-Intestinal

Infections

Reumathologic

Paraneoplastic

Skeletal

Skin

Testing in Neuromuscular Disease—Lab features and Electrodiagnosis

- Laboratory - creatinkinase (CK)
- Electromyography
- Genetic investigation
- Muscle biopsy

- EMG
  - Neuromuscular junction disorders
  - Myopatic disorder
- Genetic Investigation
  - İmportant in DMD
- Pathology
  - Dystrophinopathy
  - Glycogen Storage
  - Immune & Inflammatory
  - Inclusion bodies
  - Lipid Disorders
  - Mitochondrial Disorders

Goals

- Muscle fibre types
- Dystrophin related myopathies
- Neuromuscular junction disorders
- Pre and postsynaptic disorders
- Myastenia Gravis