Diseases of skeletal muscle

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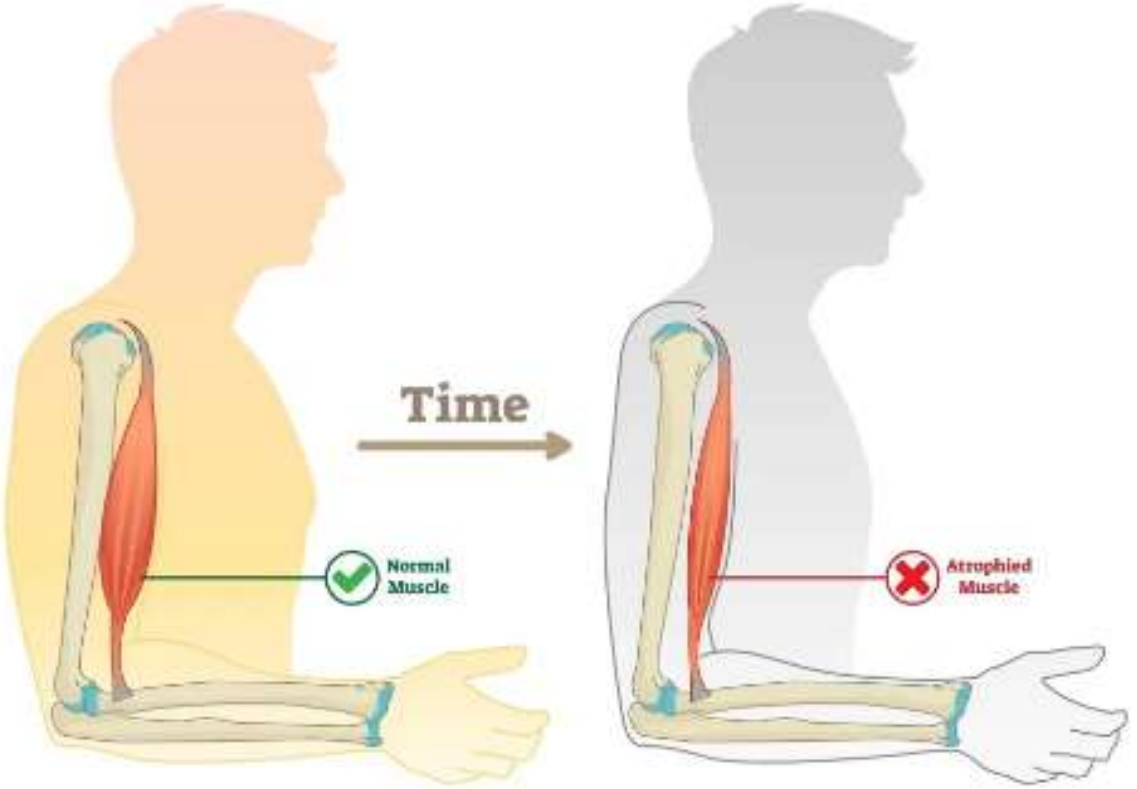
Denervation Atrophy

- Denervation atrophy of skeletal muscle occurs with any disorder that affects motor neurons.

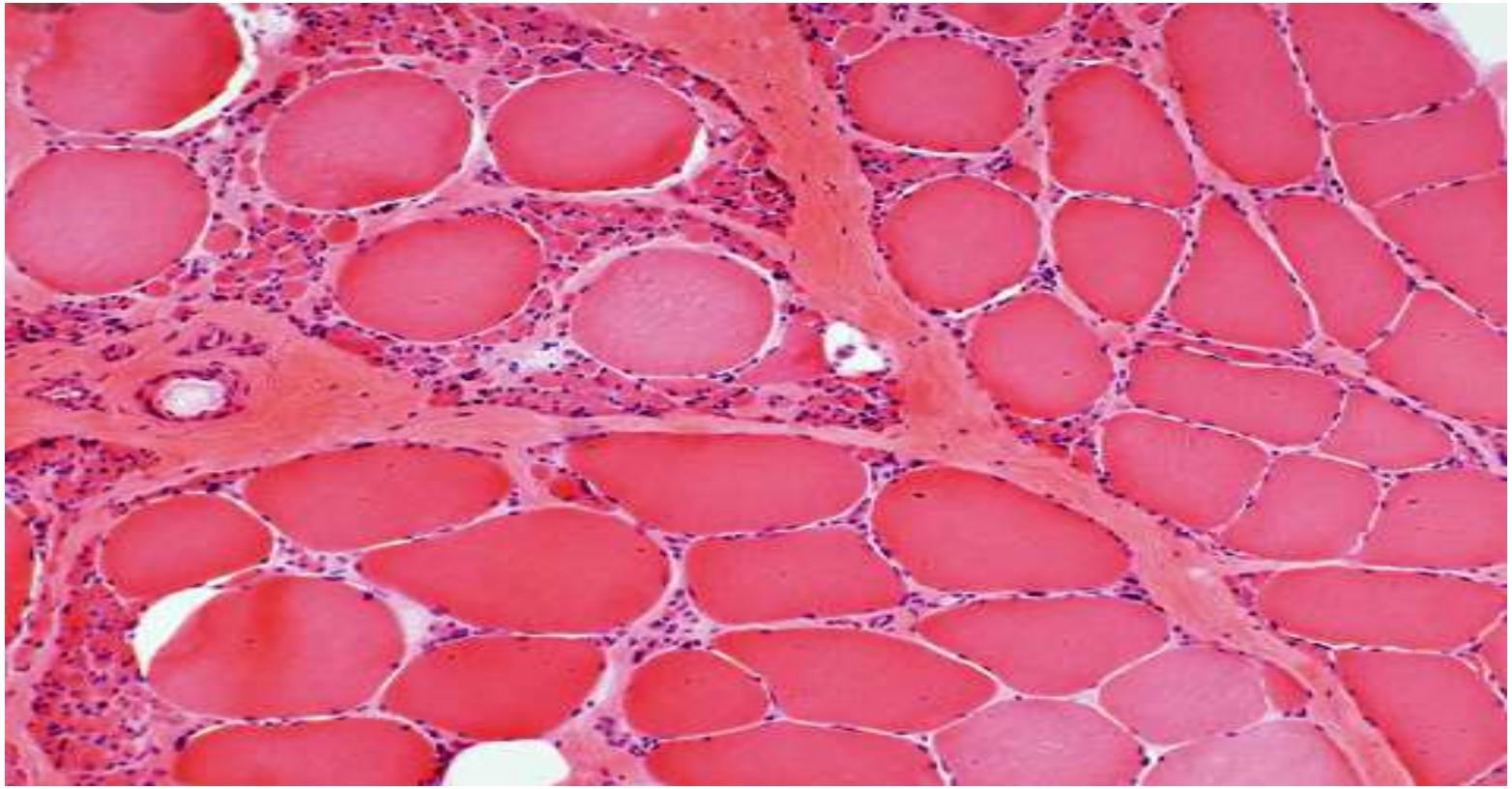


Spinal Muscular Atrophy (Infantile Motor Neuron Disease)

- Spinal muscular atrophy (SMA) refers to a group of autosomal recessive motor neuron diseases with onset in childhood or adolescence.
- All forms of SMA are associated with mutations of the SMN1 gene on chromosome 5.
- The SMN protein is important in axonal transport and neuromuscular junction integrity, so that loss leads to neuronal cell death.

Morphology

- Histology typically exhibits large numbers of extremely atrophic muscle fibers, often involving an entire fascicle of a muscle.

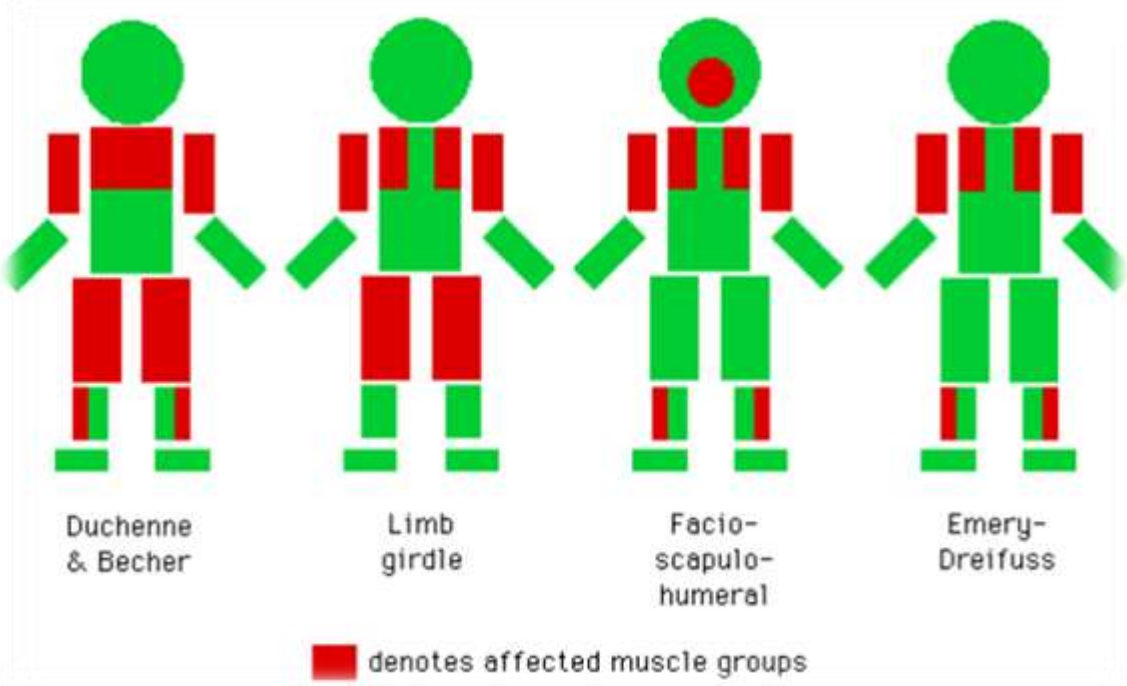


Clinical Course

- The most common form (Werdnig-Hoffmann disease, SMA type 1) presents within the first 4 months of life with hypotonia and death within the first 3 years.
- SMA 2 and SMA 3 present at later ages; SMA 2 patients usually die in childhood (after age 4 years), whereas SMA 3 patients survive into adulthood.

Muscular dystrophies

- These are a heterogeneous group of inherited disorders, often beginning in childhood and characterized clinically by progressive muscular weakness and wasting.



X-Linked Muscular Dystrophy
(Duchenne Muscular Dystrophy and Becker Muscular Dystrophy)

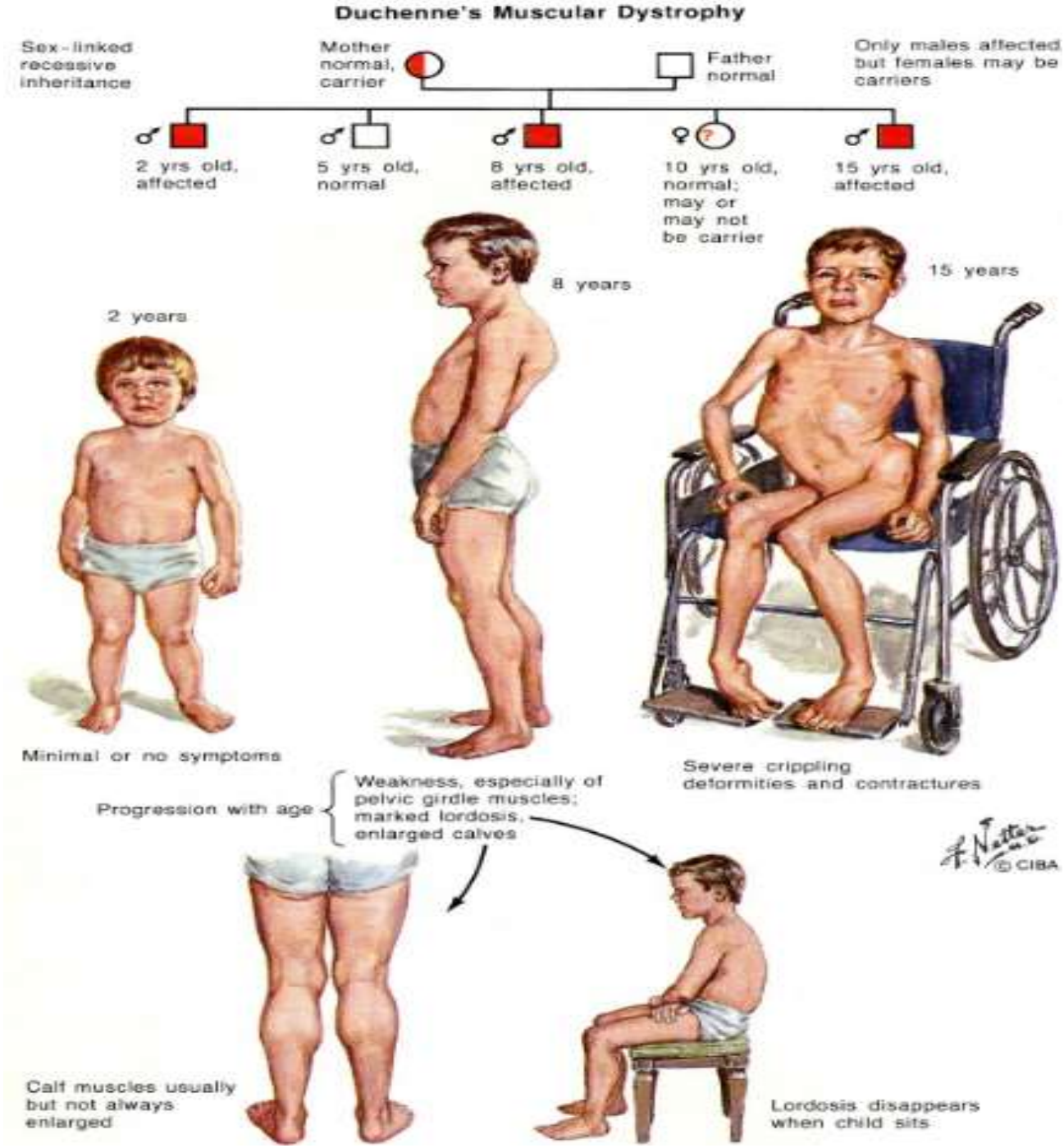
- **Duchenne muscular dystrophy (DMD)** is the most severe and most common form of muscular dystrophy; the incidence is 1 in 3500 live-born males. It is clinically manifest by age 5 years; and patients are wheelchair bound by age 10 to 12 years; the disease progresses relentlessly until death in the early 20s.

- **Becker muscular dystrophy (BMD)** involves the same genetic locus but is less common and less severe, with later onset and a slower rate of progression.

Duchenne Muscular dystrophy

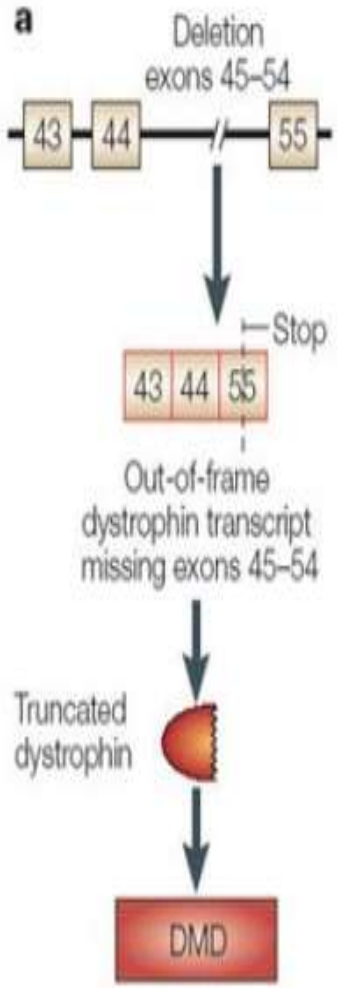
Guillaume Benjamin Amand Duchenne

(French neurologist, 1860s)



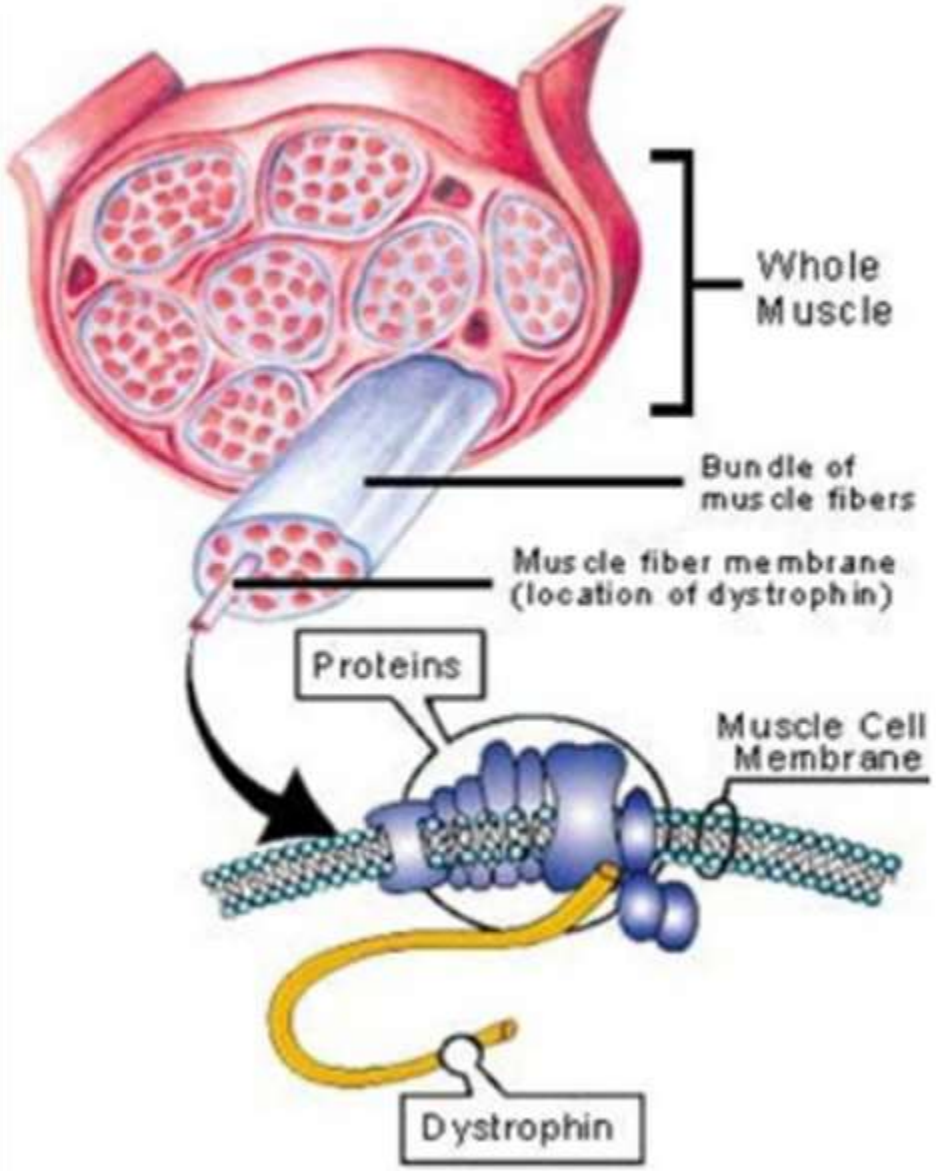
Etiology

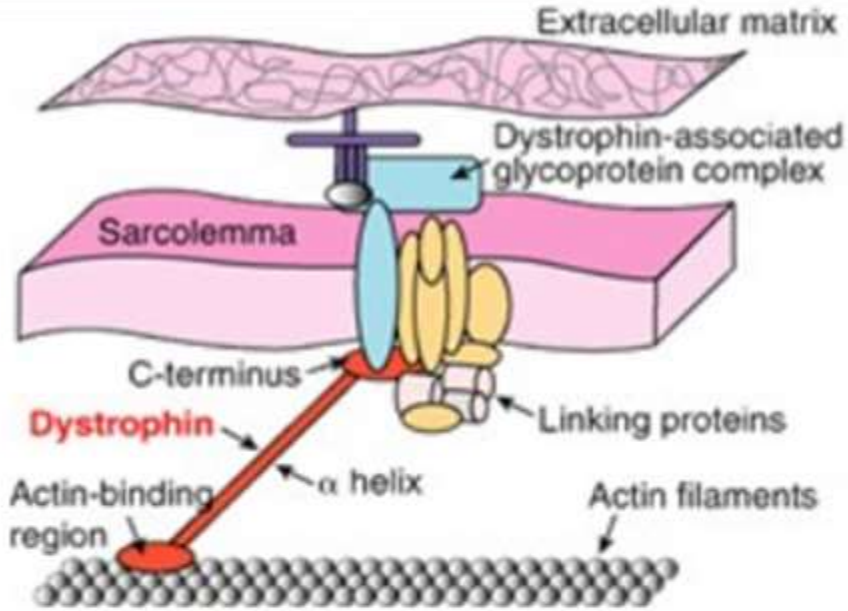
- single gene defect
- Xp21.2 region
- absent dystrophin

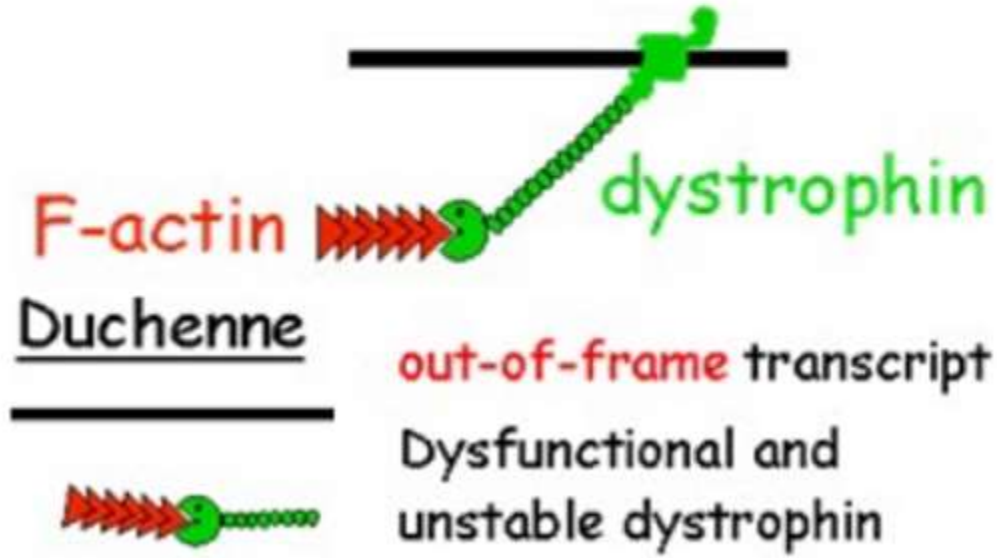


Pathogenesis

- The responsible DMD gene at Xp21 encodes the 427-kD dystrophin protein responsible for transducing contractile forces from the intracellular sarcomeres to the extracellular matrix.
- Most mutations are deletions, with frameshift and point mutations accounting for the rest.
- Muscle from DMD patients has almost no detectable dystrophin; muscle from BMD patients has diminished amounts of dystrophin.

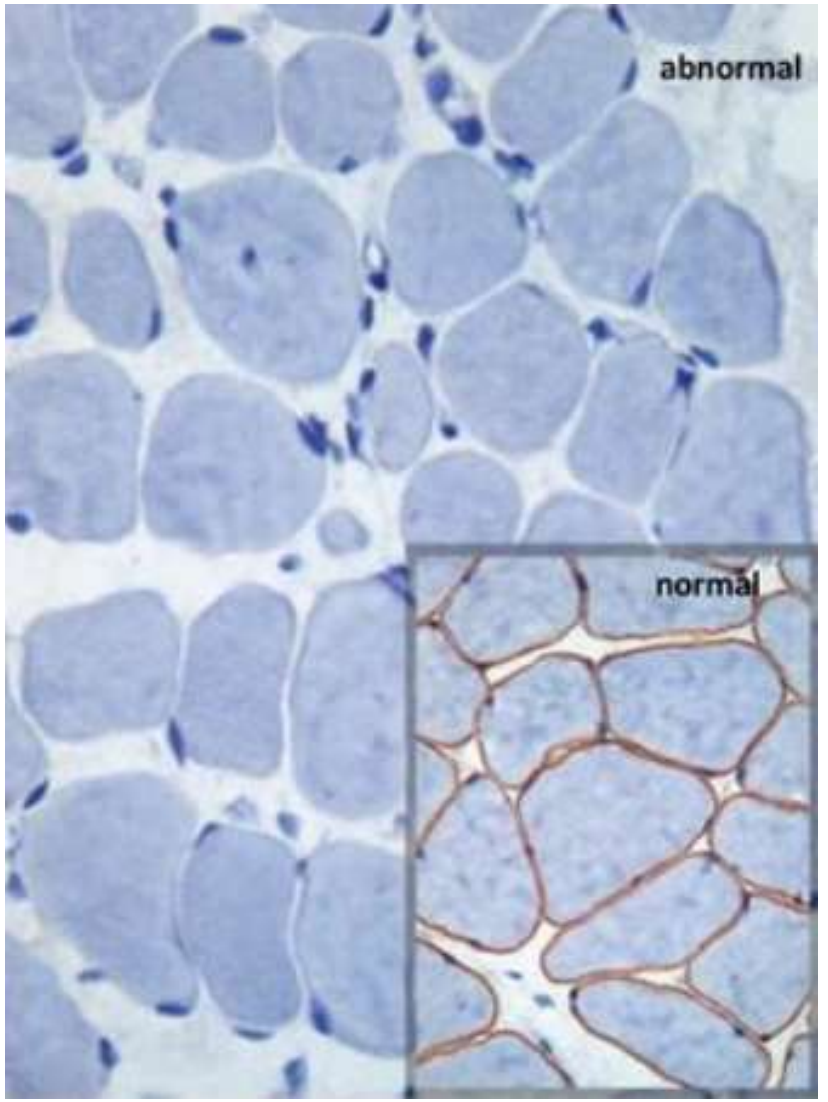

Whole Muscle
Bundle of muscle fibers
Muscle fiber membrane (location of dystrophin)
Proteins
Muscle Cell Membrane
Dystrophin


Extracellular matrix
Dystrophin-associated glycoprotein complex
Sarcolemma
C-terminus
Dystrophin
Linking proteins
α helix
Actin-binding region
Actin filaments


F-actin
dystrophin
Duchenne
out-of-frame transcript
Dysfunctional and unstable dystrophin

Morphology

- DMD cases can exhibit enlarged, rounded, hyaline fibers lacking normal cross striations. Both DMD and BMD muscles show:
- Variation in myofiber diameter, with both small and giant fibers, sometimes with fiber splitting
- Increased numbers of internalized nuclei degeneration, necrosis, and phagocytosis of muscle fibers
- Regeneration of muscle fibers
- Proliferation of endomysial connective tissue
- In late stages, muscles are entirely replaced by fat and connective tissue
- Both type 1 and type 2 fibers are involved, without change in relative distribution.

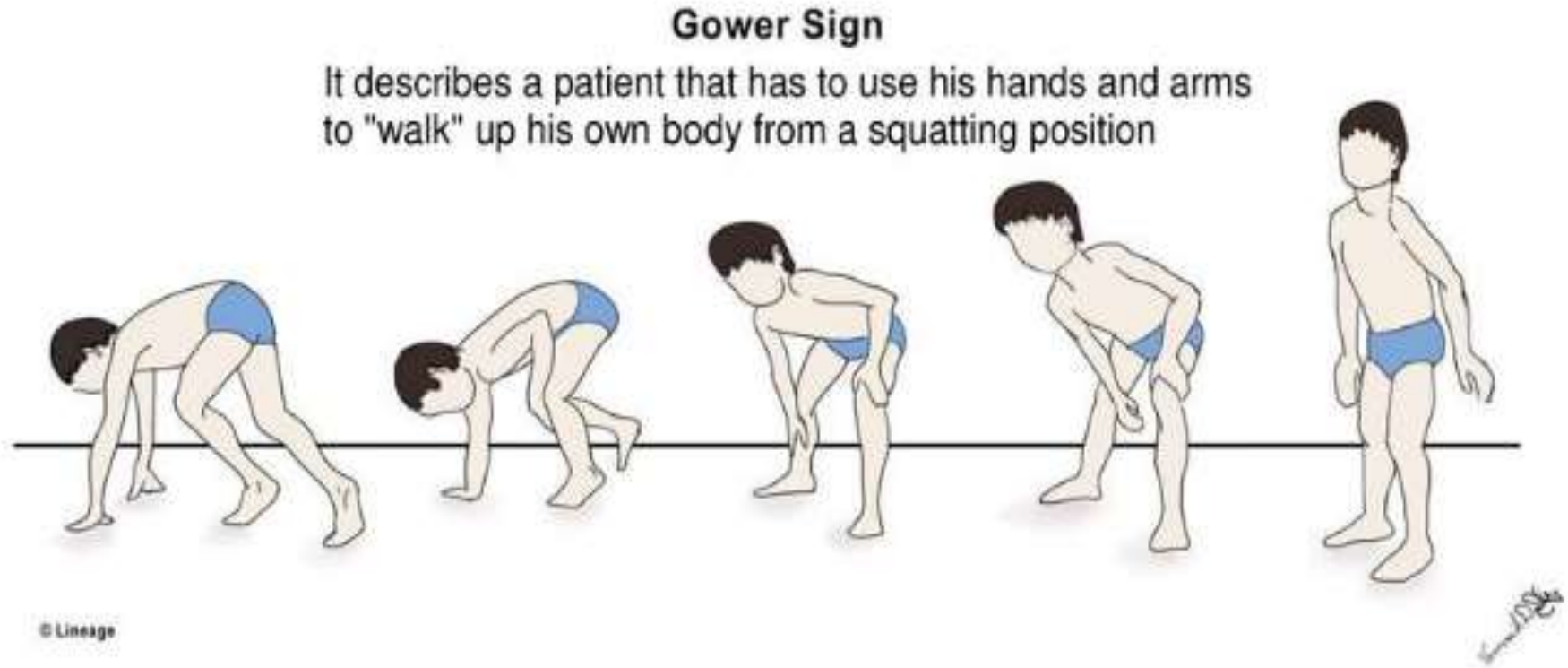


Clinical Course

- Weakness begins in the pelvic girdle muscles, extending to the shoulder girdle; the lower leg is hypertrophied associated with weakness (pseudo hypertrophy).
- Pathologic changes are also found in the heart (failure and arrhythmia), and cognitive impairment is a component of the disease.
- Female carriers and affected males are at risk for developing dilated cardiomyopathy.
- Death results from respiratory insufficiency, pulmonary infection, and cardiac decompensation.

Positive Gower sign in Duchenne and Becker muscular dystrophy

...due to proximal lower limb muscle weakness
...not only in Duchenne & Becker



- Decreased heart function
- Cardiomyopathy

Rimeporide

Heart failure

- Weak diaphragm

Rimeporide

ER002

Respiratory failure

- Loss of muscle mass
- Inflammation
- Fibrosis

Rimeporide

ER002

Requires wheelchair

TABLE 27-4 Other Selected Muscular Dystrophies

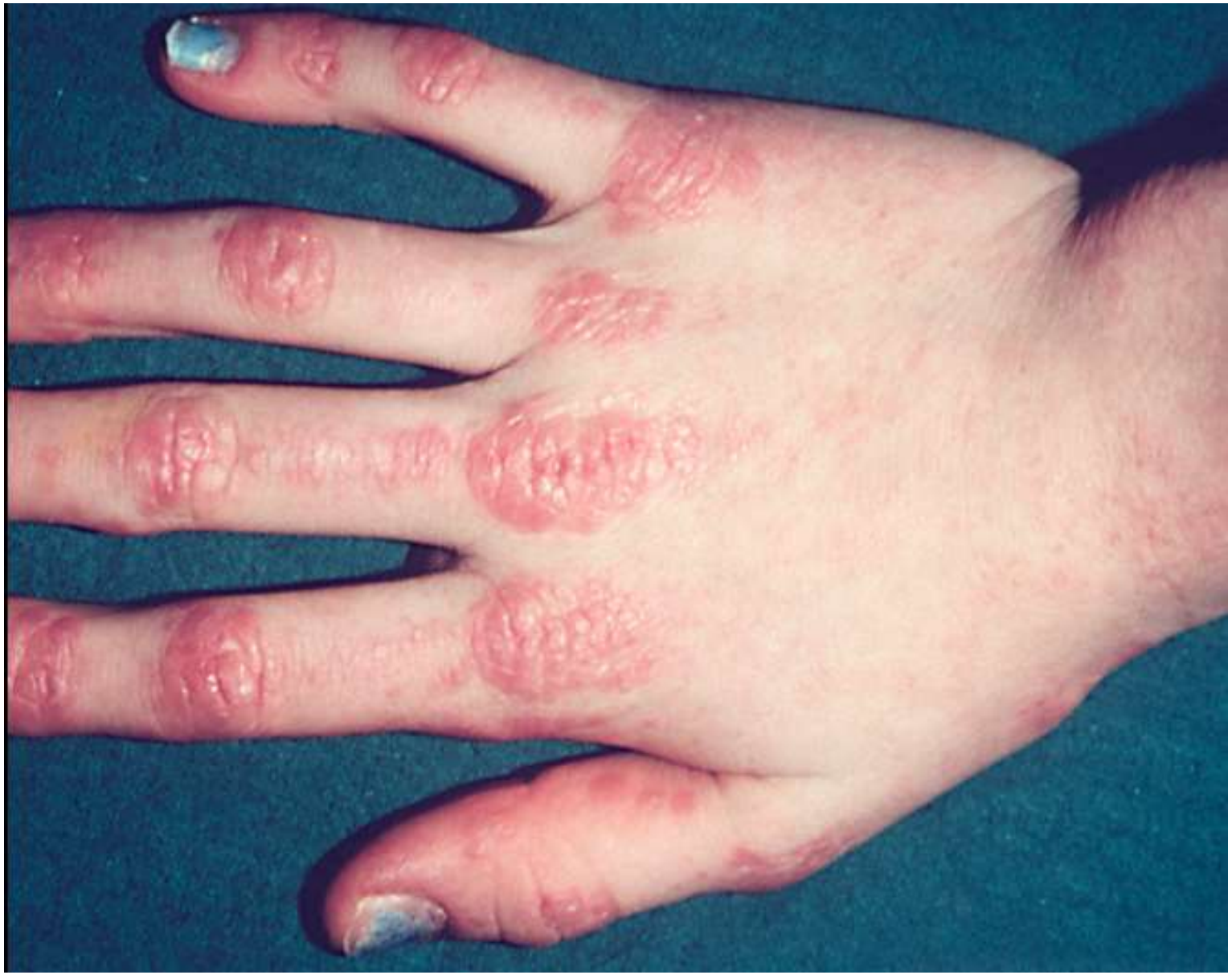
Disease and Inheritance	Gene and Locus	Clinical Findings	Pathologic Findings
Fascioscapulohumeral muscular dystrophy; autosomal dominant	Type 1A—deletion of variable number of 3.3-kilobase subunits of a tandemly arranged repeat *(D4Z4)* on 4q35 Type 1B *(FSHMD1B)*—locus unknown	Variable age at onset (most commonly 10-30 years); weakness of muscles of face, neck, and shoulder girdle	Dystrophic myopathy, often associated with inflammatory infiltrates in muscle
Oculopharyngeal muscular dystrophy; autosomal dominant	Poly(A)-binding protein-2 *(PABP2)* gene; 14q11.2–q13	Onset in mid-adult life; ptosis and weakness of extraocular muscles; difficulty in swallowing	Dystrophic myopathy, but often including rimmed vacuoles in type 1 fibers
Emery-Dreifuss muscular dystrophy; X-linked	Emerin (*EMD1*) gene; Xq28	Variable onset (most commonly 10-20 years); prominent contractures, especially of elbows and ankles	Mild myopathic changes; absent emerin by immunohistochemistry
Congenital muscular dystrophies; autosomal recessive (also called muscular dystrophy, congenital, subtypes MDC1A, MDC1B, MDC1C)	Type 1A (merosin-deficient type)—laminin α2 (merosin) gene; 6q22–q23) Type 1B—locus at 1q42; gene unknown Type 1C; fukutin-related protein gene; 19q13.3	Neonatal hypotonia, respiratory insufficiency, delayed motor milestones	Variable fiber size and extensive endomysial fibrosis
Congenital muscular dystrophy with CNS malformations (Fukuyama type); autosomal recessive	Fukutin; 9q31	Neonatal hypotonia and mental retardation	Variable muscle fiber size and endomysial fibrosis; CNS malformations such as polymicrogyria
Congenital muscular dystrophy with CNS and ocular malformations (Walker-Warburg type)	Protein *O*-mannosyl transferases (*POMT1*, 9q34.1; *POMT2*, 14q24.3)	Neonatal hypotonia and mental retardation with cerebral and ocular malformations	Variable muscle fiber size and endomysial fibrosis; CNS and ocular malformations

Inflammatory Myopathies

- Noninfectious Inflammatory Myopathies are a heterogeneous group of immune-mediated disorders characterized by skeletal muscle inflammation and injury.

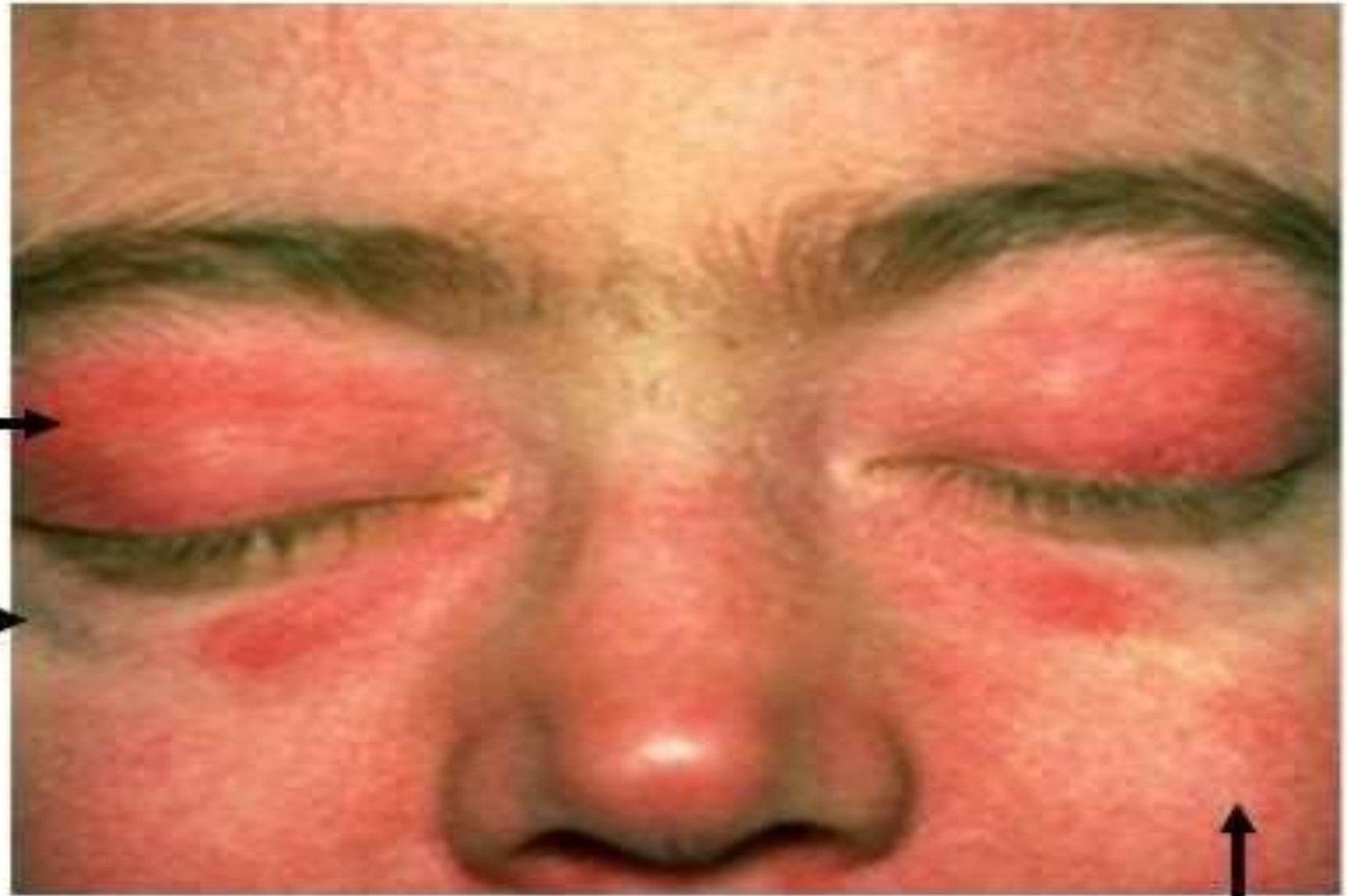
Dermatomyositis

- Involves skin and muscle. Classically, discoloration of upper eyelids and periorbital edema accompanies or precedes weakness; scaling, erythematous patches are also present over knuckles, elbows, and knees (Grotton lesions).
- Muscle weakness is slow in onset and bilaterally symmetric, affecting proximal muscles first; dysphagia occurs in a third of patients.
- Interstitial lung disease, vasculitis, and myocarditis can also be present. Nearly 25% of adult patients have cancer; juvenile patients more characteristically exhibit gastrointestinal symptoms, and a third have calcinosis.
- Capillaries appear to be the primary target of immunologic attack. Immune suppressive therapy is beneficial.



Gottron's papules. Discrete erythematous papules overlying the metacarpal and interphalangeal joints in a patient with juvenile dermatomyositis

Heliotrope Rash



Polymyositis

- It is similar to dermatomyositis but lacks cutaneous involvement; it occurs primarily in adults.
- The pathogenesis involves cytotoxic T-cell–driven myocyte damage; various autoantibodies against tRNA synthetases are also present.
- Immune suppressive therapy is beneficial.

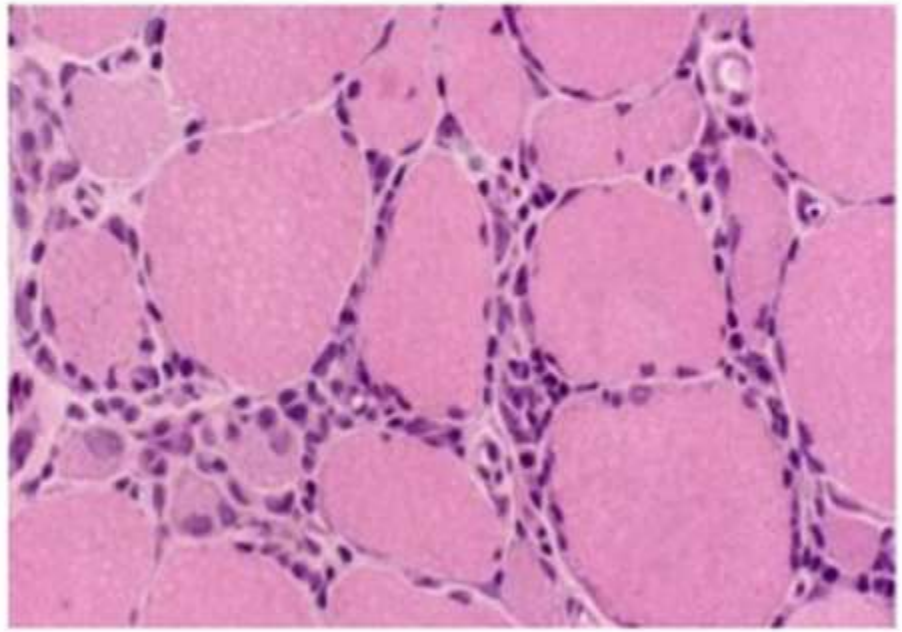
Inclusion body myositis

- begins with distal muscle involvement, especially extensors of the knee and flexors of the wrists, and can be asymmetric. It has an insidious onset, typically affecting individuals older than 50 years. Although cytotoxic CD8þ T cells are present, immunosuppressive therapy is generally not beneficial.
- Intracellular depositions of b-amyloid protein and hyperphosphorylated tau proteins suggest abnormal protein folding as an etiology.

Morphology

- **Dermatomyositis:** Perivascular inflammatory infiltrates are associated with scattered necrotic muscle fibers and muscle fiber atrophy, especially at the periphery of fascicles (“perifascicular atrophy”)—likely related to hypoperfusion.
- **Polymyositis:** There is endomysial inflammation and scattered necrotic muscle fibers, but no apparent vascular injury (perifascicular atrophy).
- **Inclusion body myositis:** Endomysial inflammatory infiltrates are associated with diagnostic “rimmed vacuoles”—clear cytoplasmic vacuoles in myocytes surrounded by a thin rim of basophilic material; myocytes can also contain amyloid deposits highlighted by Congo red staining.

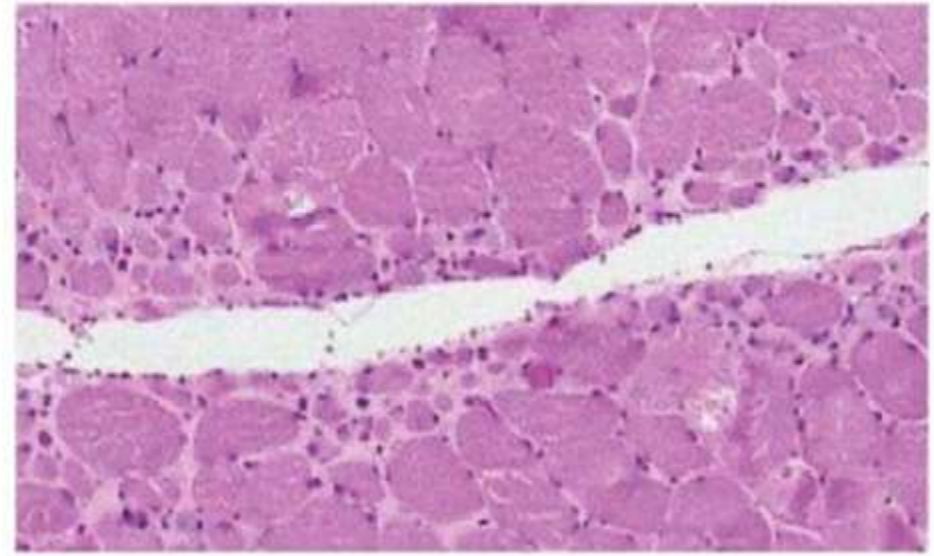
Polymyositis Histopathology



http://emedicine.medscape.com/article/335925-workup

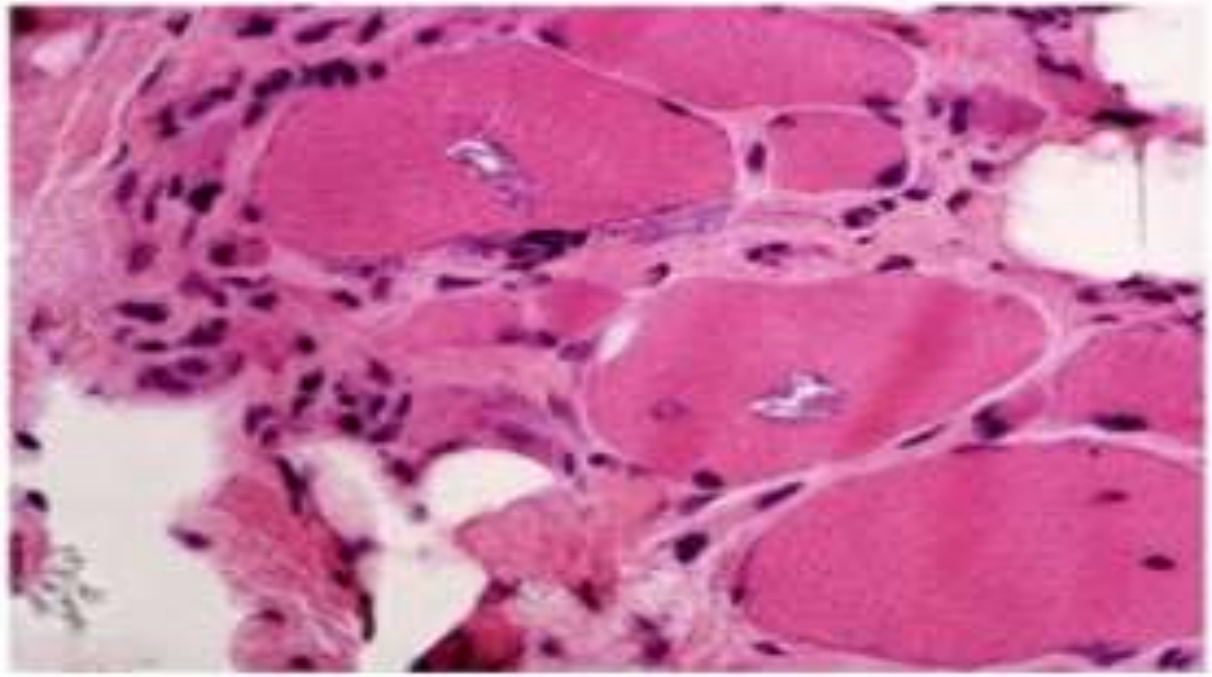
Dermatomyositis Histopathology

Figure 2a

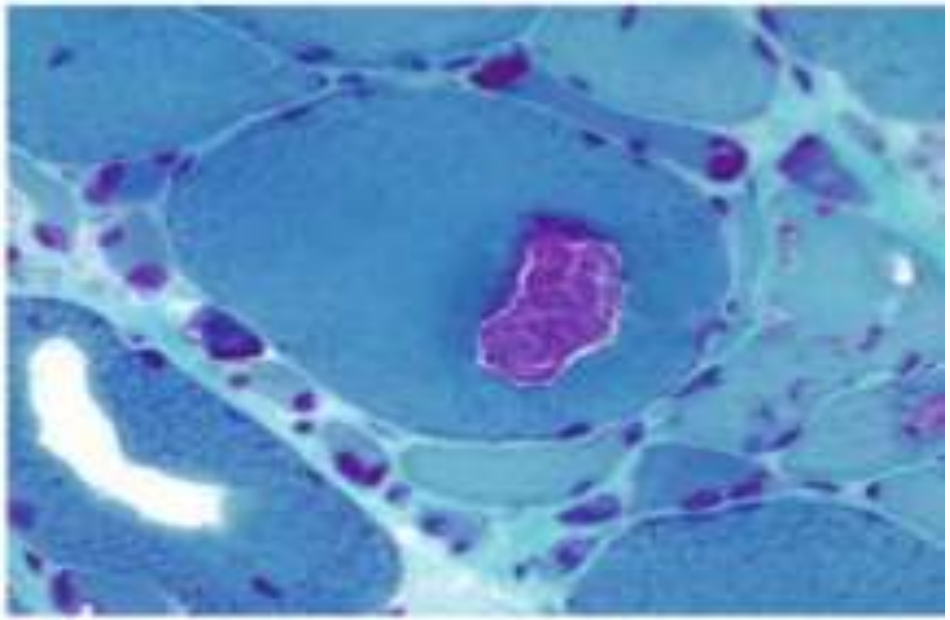


Dimachkie MM, Barohn RJ. Idiopathic inflammatory myopathies. *Semin Neurol*

Inclusion body myositis



Basophilic rimmed vacuoles

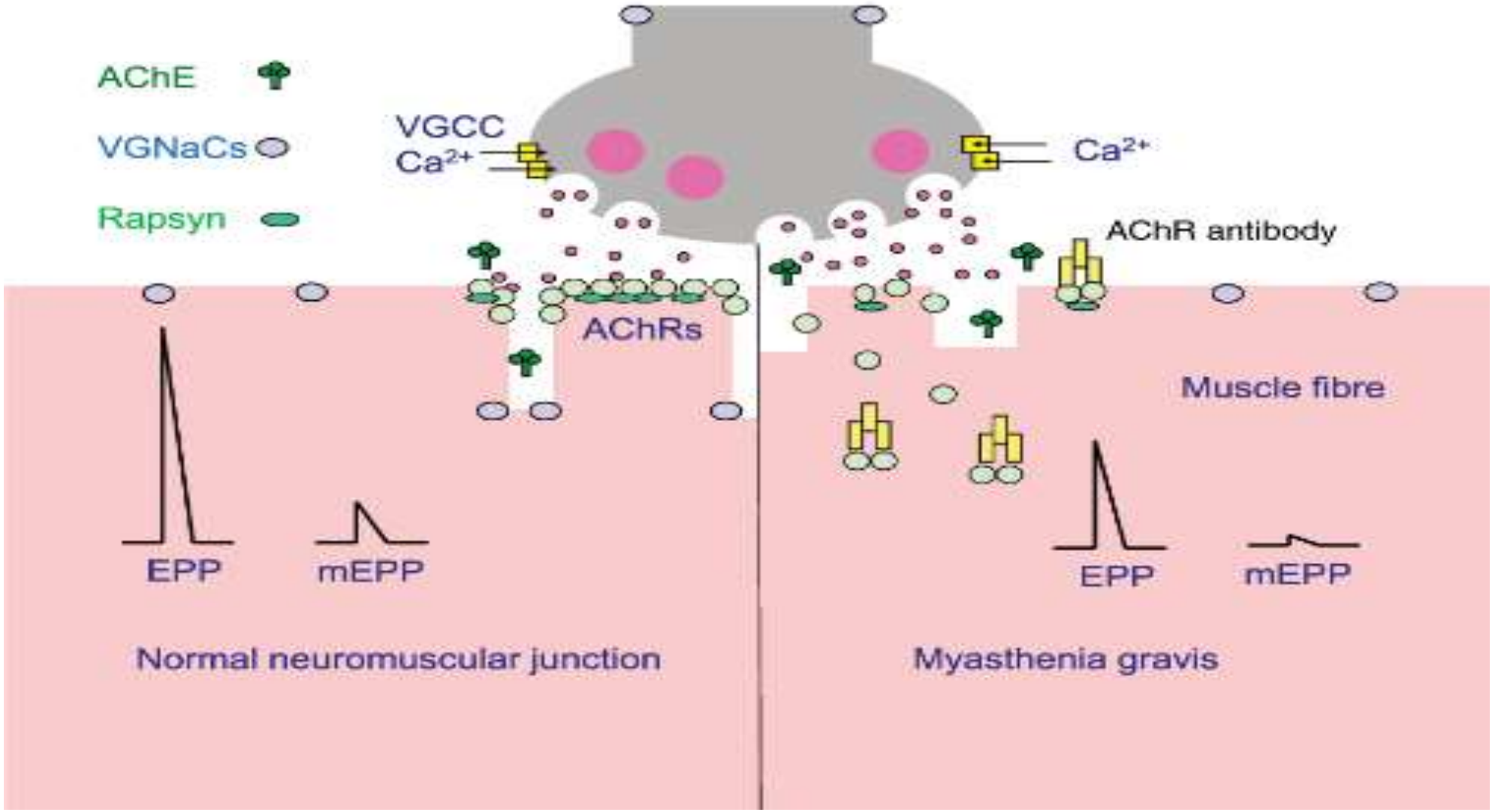


Vacuole filled with granules

Vacuolated muscle fibres infiltrated with CD8/MHC-1complexes. Beta-amyloid deposits and cytochrome oxidase negative fibres may be seen.

Diseases of the Neuromuscular Junction Myasthenia Gravis

- Myasthenia gravis is due to autoantibodies directed against skeletal muscle acetylcholine receptors (AChR); it is more common in women younger than 40 years, but it has equal gender predilection in older age groups.
- Pathogenesis:
- AChR autoantibodies can mediate complement fixation and direct postsynaptic membrane damage leads to down-regulation of the AChR, or block ACh binding.

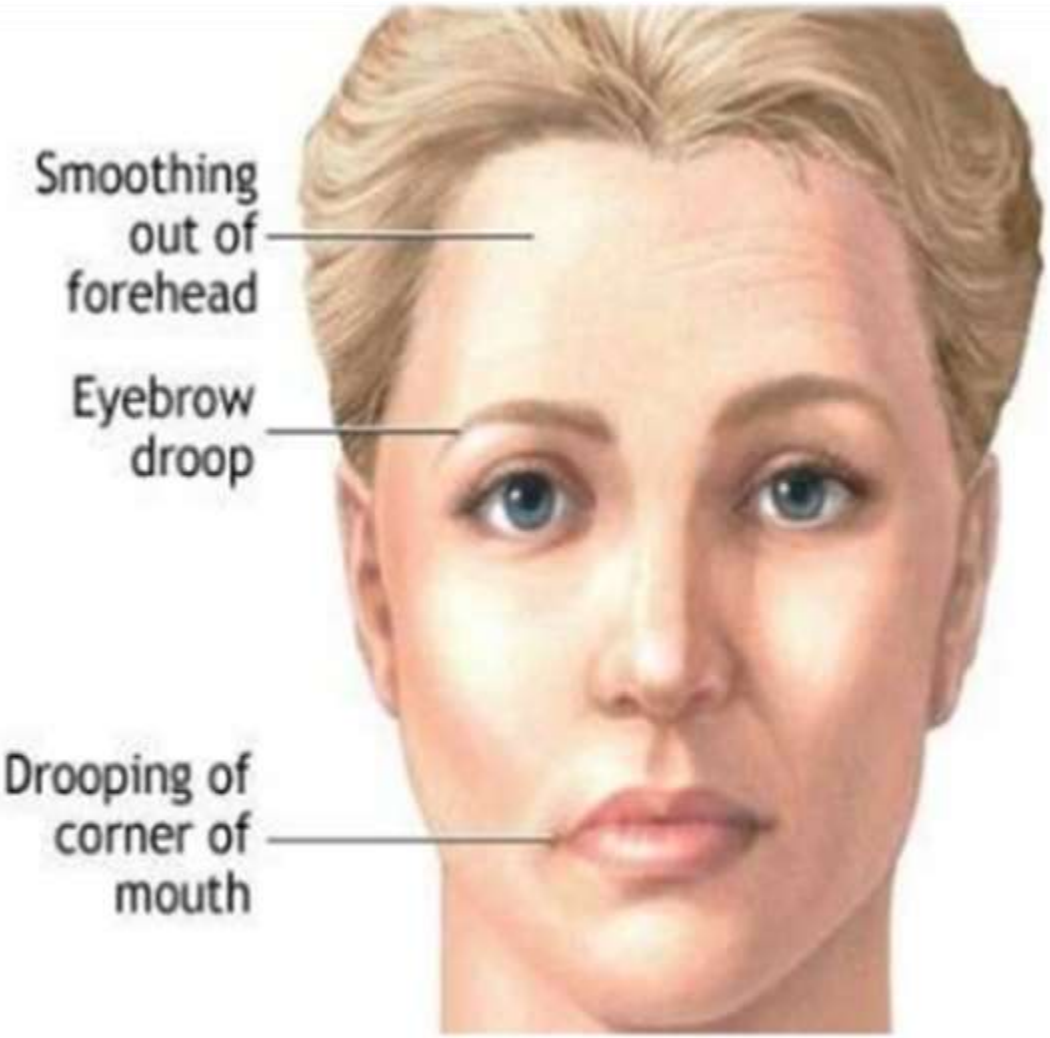

AChE
VGNaCs
Rapsyn
VGCC
Ca2+
Ca2+
AChR antibody
AChRs
Muscle fibre
EPP
mEPP
EPP
mEPP
Normal neuromuscular junction
Myasthenia gravis

Morphology

- Light microscopic examination of muscle is ordinarily unremarkable; ultra-structurally, junctional folds are greatly reduced at the neuromuscular junction, and there is diminished AChR expression.

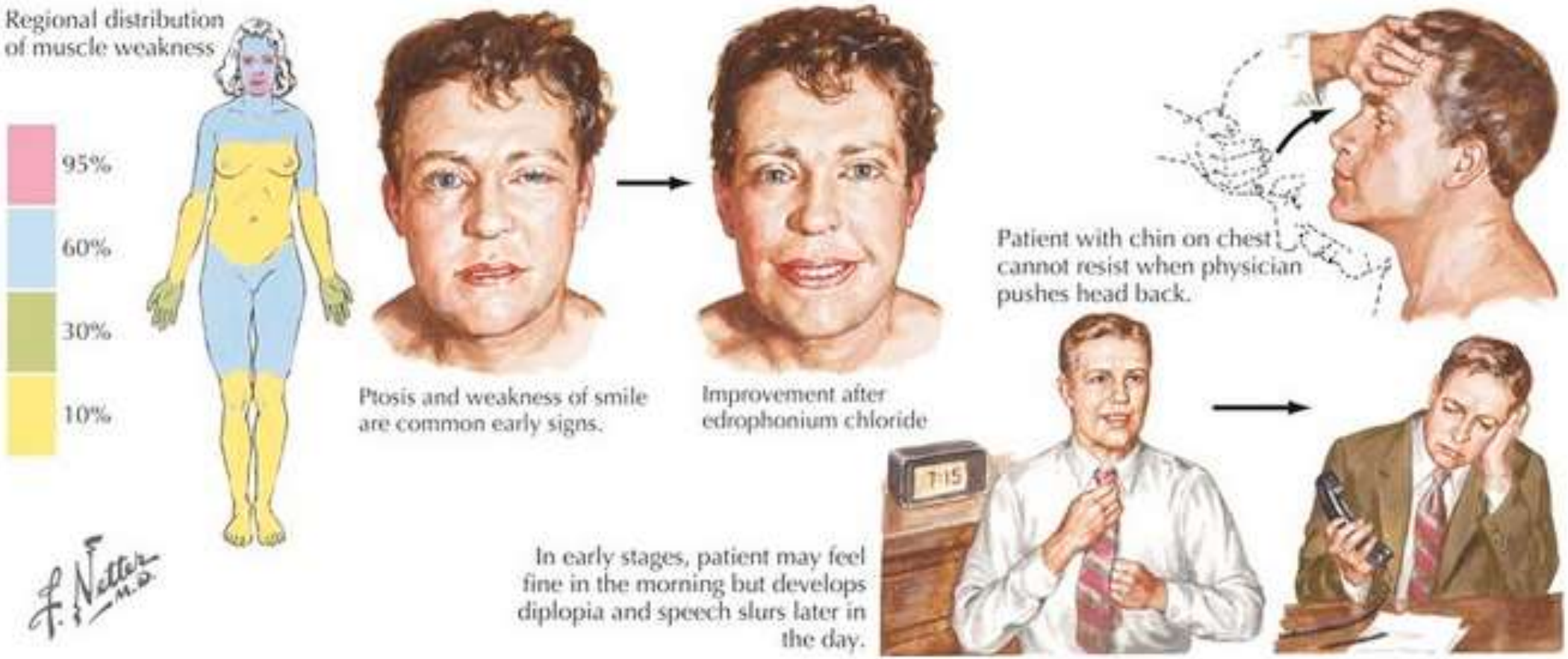
Clinical Course

- Patients classically present with easy fatigability, ptosis, and diplopia; symptoms worsen with repeated stimulation.
- Treatments include anticholinesterase agents, prednisone, and plasmapheresis.
- Thymic hyperplasia occurs in 65% of patients and thymomas in 15%; thymic resection can improve symptoms.



SYMPTOMS:

- The first noticeable symptom is weakness of the **eye muscles,** difficulty in swallowing and slurred speech may also be the first signs.
- Muscles that control eye and eyelid movement, facial expressions**, chewing, talking and swallowing** becomes weaker.
- The muscles that control **breathing** and neck and limb movements can also be affected.


Regional distribution of muscle weakness
95%
60%
30%
10%
F. Netter M.D.
Ptosis and weakness of smile are common early signs.
Improvement after edrophonium chloride
Patient with chin on chest cannot resist when physician pushes head back.
In early stages, patient may feel fine in the morning but develops diplopia and speech slurs later in the day.
7:15

Lambert-Eaton Myasthenic Syndrome

- Lambert-Eaton myasthenic syndrome presents with weakness and autonomic dysfunction. Most cases (i.e., 60%) are paraneoplastic and are classically associated with small cell lung carcinoma; the syndrome can also occur in the absence of malignancy.
- The causal autoantibody is directed against a pre-synaptic voltage-gated calcium channel; each presynaptic action potential releases fewer synaptic vesicles than normal; as compared to myasthenia gravis, neurotransmission improves with repeated stimulation.