DISORDERS OF SKELETAL MUSCLES

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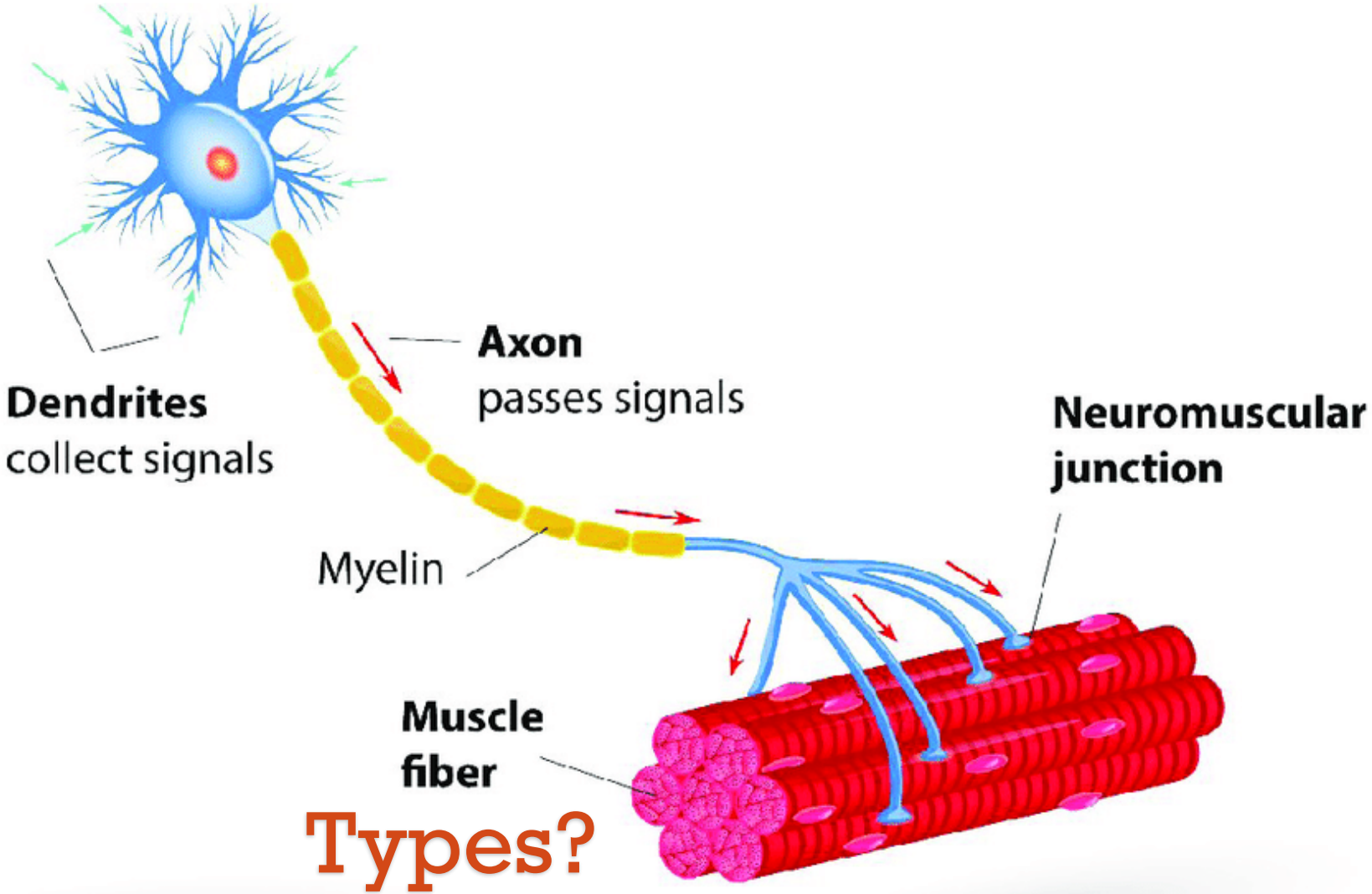
9-3-2025

Motor unit structure



Types?

Table 22.2 Muscle Fiber Types

	Type I	Type II
Action	Sustained force	Fast movement
Activity type	Aerobic exercise	Anaerobic exercise
Power produced	Low	High
Resistance to fatigue	High	Low
Lipid content	High	Low
Glycogen content	Low	High
Energy metabolism	Low glycolytic capacity, high oxidative capacity	High glycolytic capacity, low oxidative capacity
Mitochondrial density	High	Low
Myosin heavy chain gene expressed	*MYH7*	*MYH2*, *MYH4*, *MYH1*
Color	Red (high myoglobin content)	Pale red / tan (low myoglobin content)

MYOPATHY

- Definition : a clinical disorder characterized by primary dysfunction of skeletal muscle.

في فرق "فعظم الأمراض اللي بتصيب العضلات، دون الأعراب العصبية للعضلة أو هيك"

- Primary muscle diseases or myopathies have to be distinguished from secondary neuropathic changes caused by disorders that disrupt muscle innervation.

- Both are associated with altered muscle function and morphology, but each has distinctive features

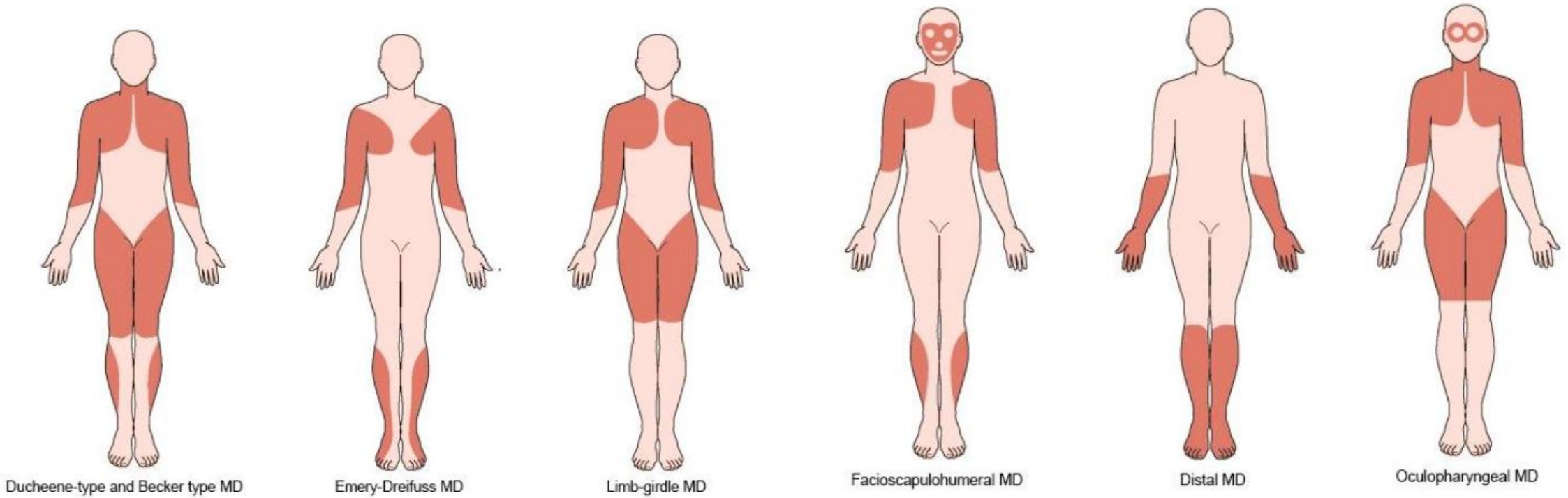
CLASSIFICATION

- Inherited:
  - Dystrophy (Duchenne, Becker).
  - Metabolic
  - Mitochanderial
  - Channelopathies

- Acquired:
  - Inflammatory (dermatomyositis and polymyositis)
  - Infective (viral)
  - Toxic (medication)
  - Systemic (Endocrine disease)

1. 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

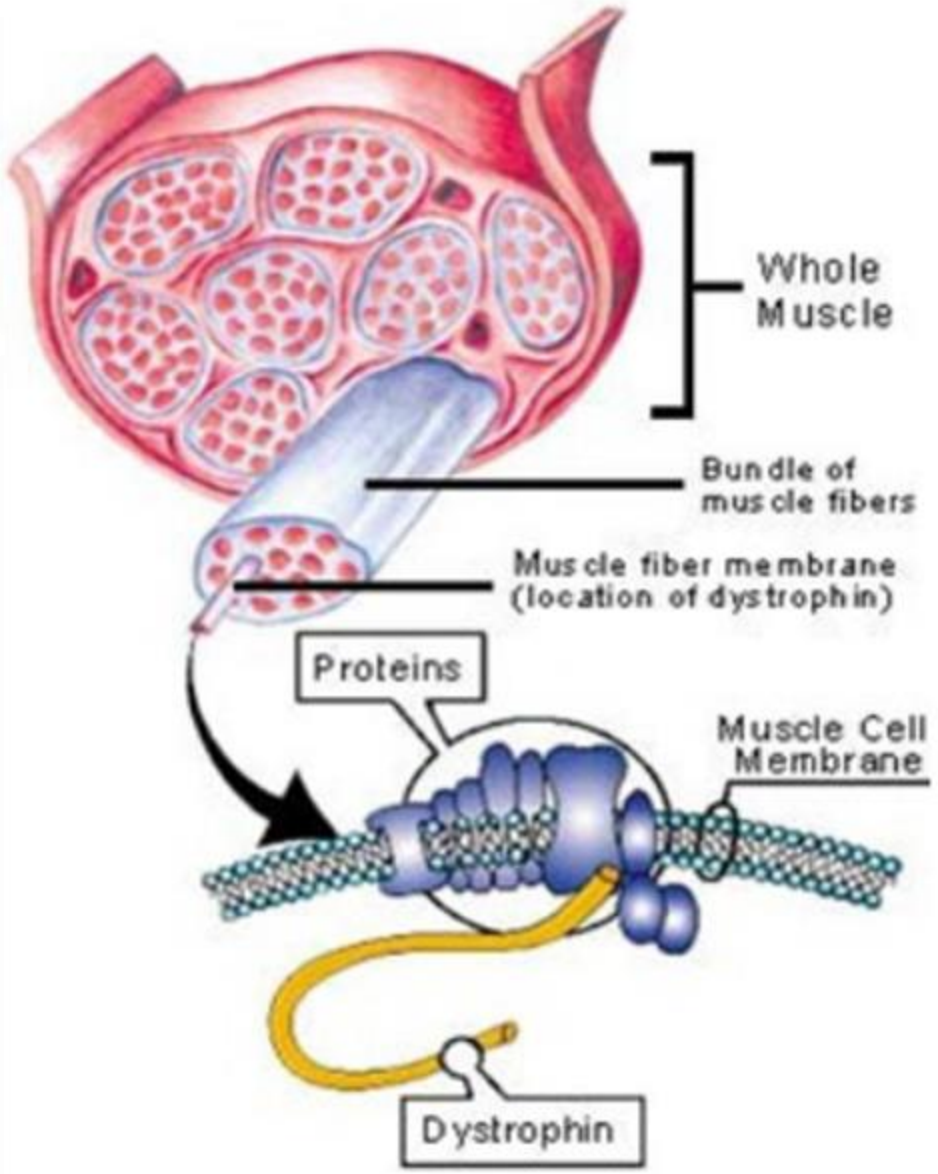
- **Duchenne muscular dystrophy (DMD)** is the most severe and most common form of muscular dystrophy.

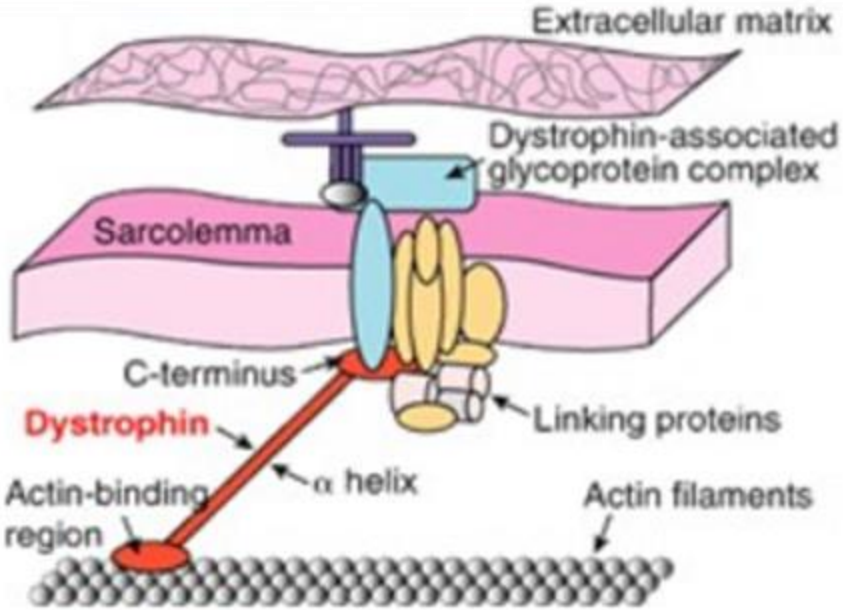
- Clinically manifest by age 5 years; and patients are wheelchair bound by age 10 to 12 years; the disease progresses relentlessly until death in the early 20s.

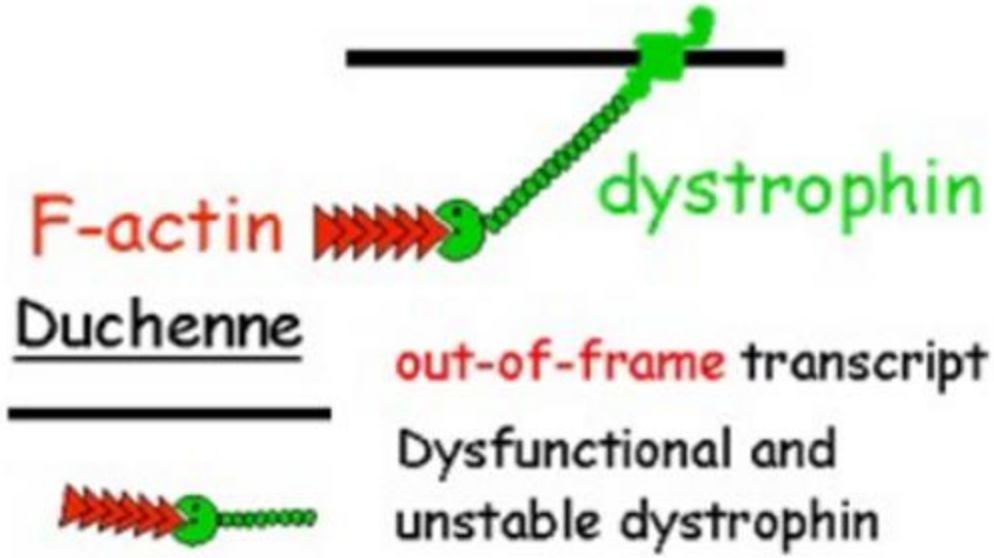
- **Becker muscular dystrophy (BMD)** involves the same genetic locus but is less common and less severe, with later onset and a slower rate of progression.

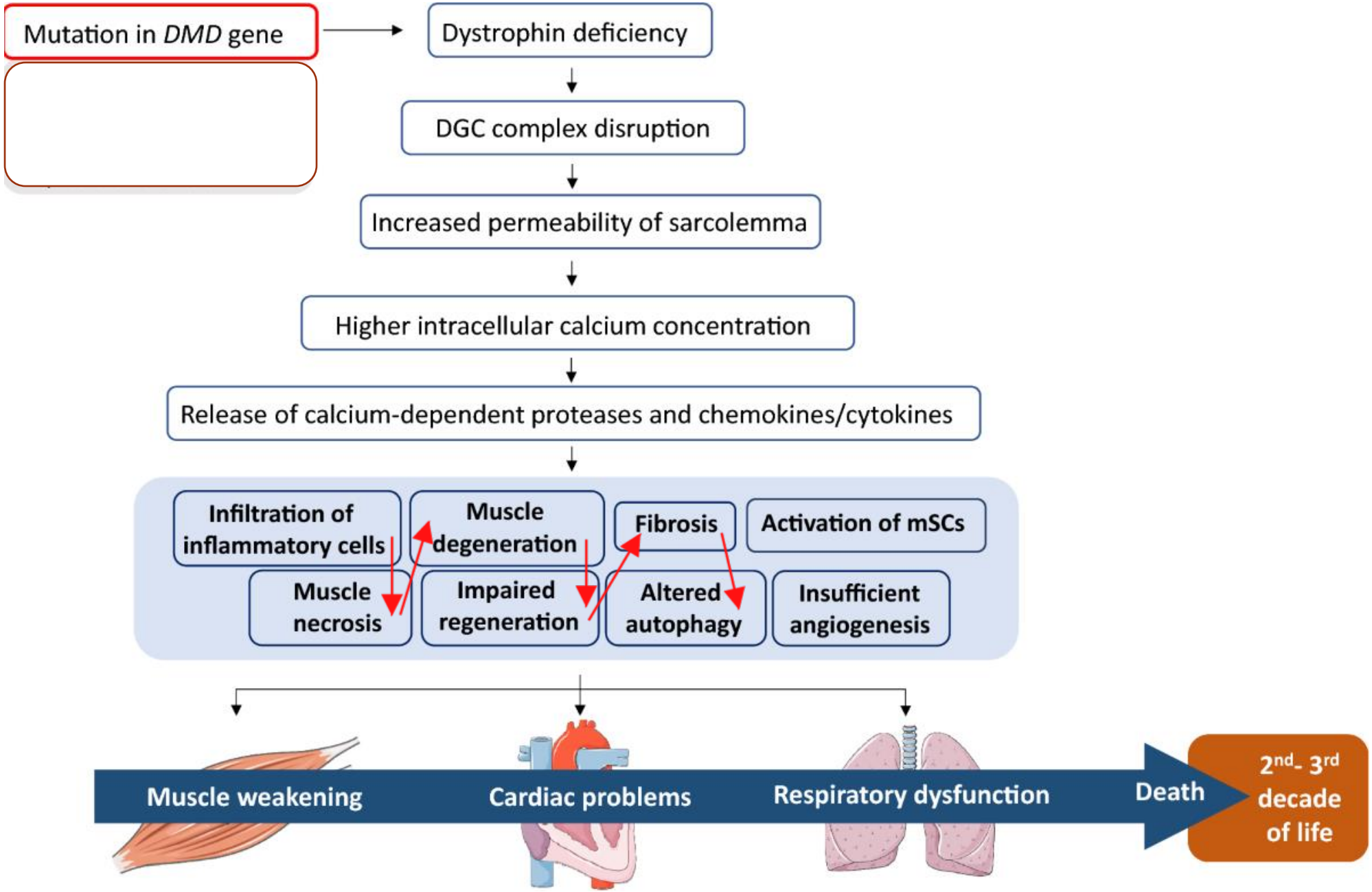
PATHOGENESIS

- The responsible DMD gene at Xp21 encodes the 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

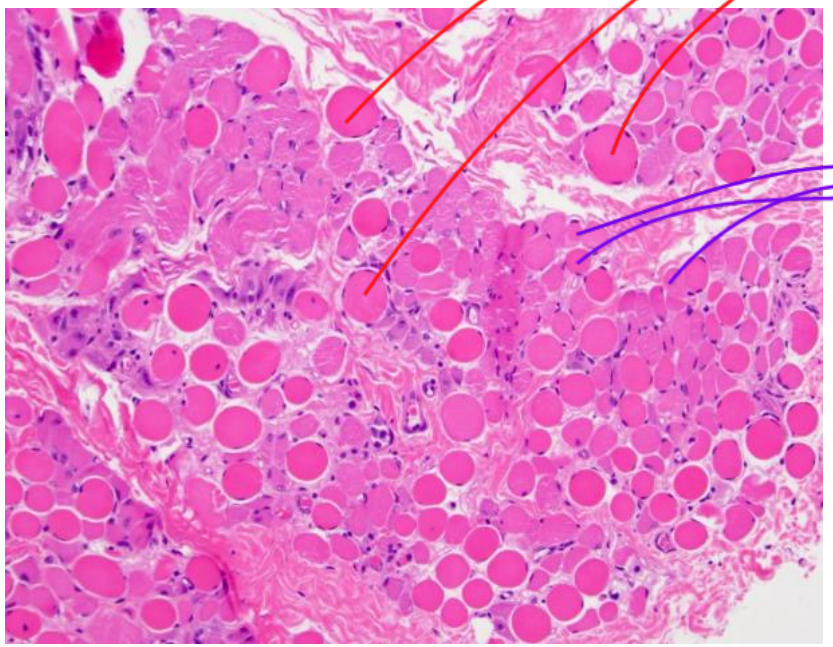

Mutation in *DMD* gene
Dystrophin deficiency
DGC complex disruption
Increased permeability of sarcolemma
Higher intracellular calcium concentration
Release of calcium-dependent proteases and chemokines/cytokines
Infiltration of inflammatory cells
Muscle degeneration
Fibrosis
Activation of mSCs
Muscle necrosis
Impaired regeneration
Altered autophagy
Insufficient angiogenesis
Muscle weakening
Cardiac problems
Respiratory dysfunction
Death
2nd- 3rd decade of life

MICROSCOPIC FEATURES

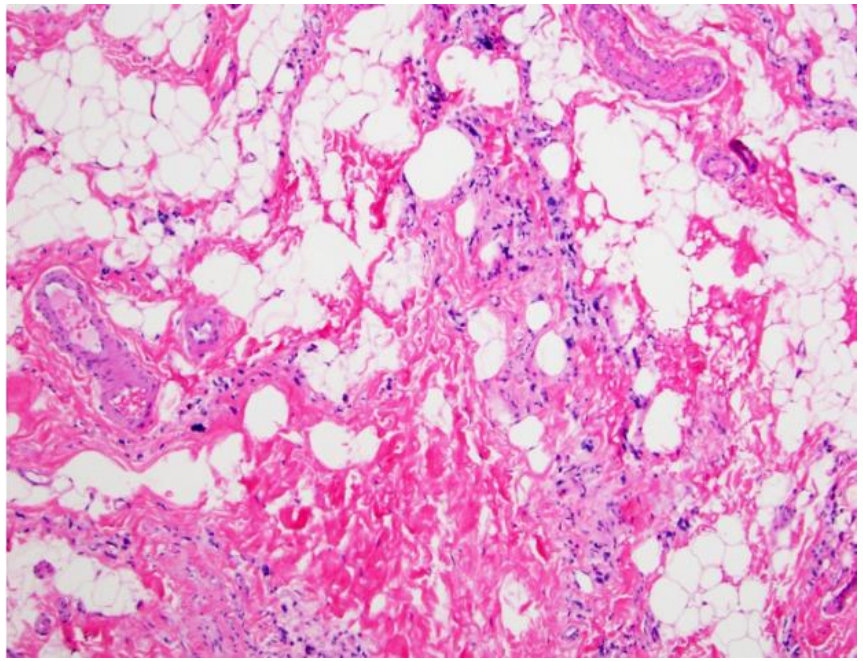
- X linked dystrophinopathies include similar histologic changes with difference in severity.

- Variation in myofiber size with small atrophic fibers admixed with large, rounded, hypertrophic fibers
- Increased internal nuclei
- Myofiber splitting, necrosis, phagocytosis and regeneration "Inflammation".
- Increased endomysial fibrosis and fatty replacement of muscle "Non functional".

MORPHOLOGY

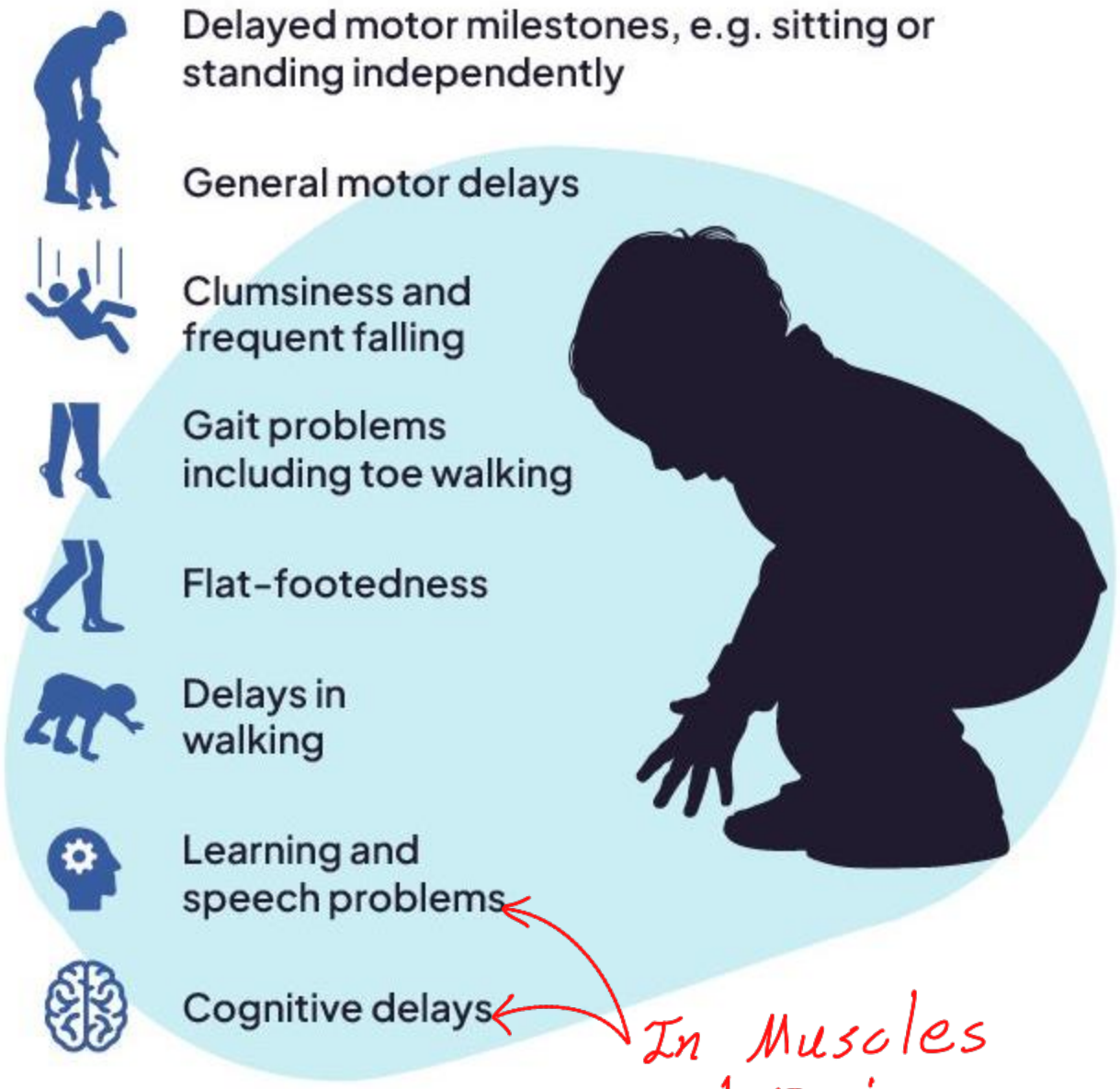


variation in myofiber size with small atrophic fibers admixed with large rounded hypertrophic fibers and increased internal nuclei.



End stage changes in muscle including endomysial fibrosis, fatty replacement and widespread atrophic myofibers.

Clinically


Delayed motor milestones, e.g. sitting or standing independently
General motor delays
Clumsiness and frequent falling
Gait problems including toe walking
Flat-footedness
Delays in walking
Learning and speech problems
Cognitive delays
In Muscles and Brain

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.

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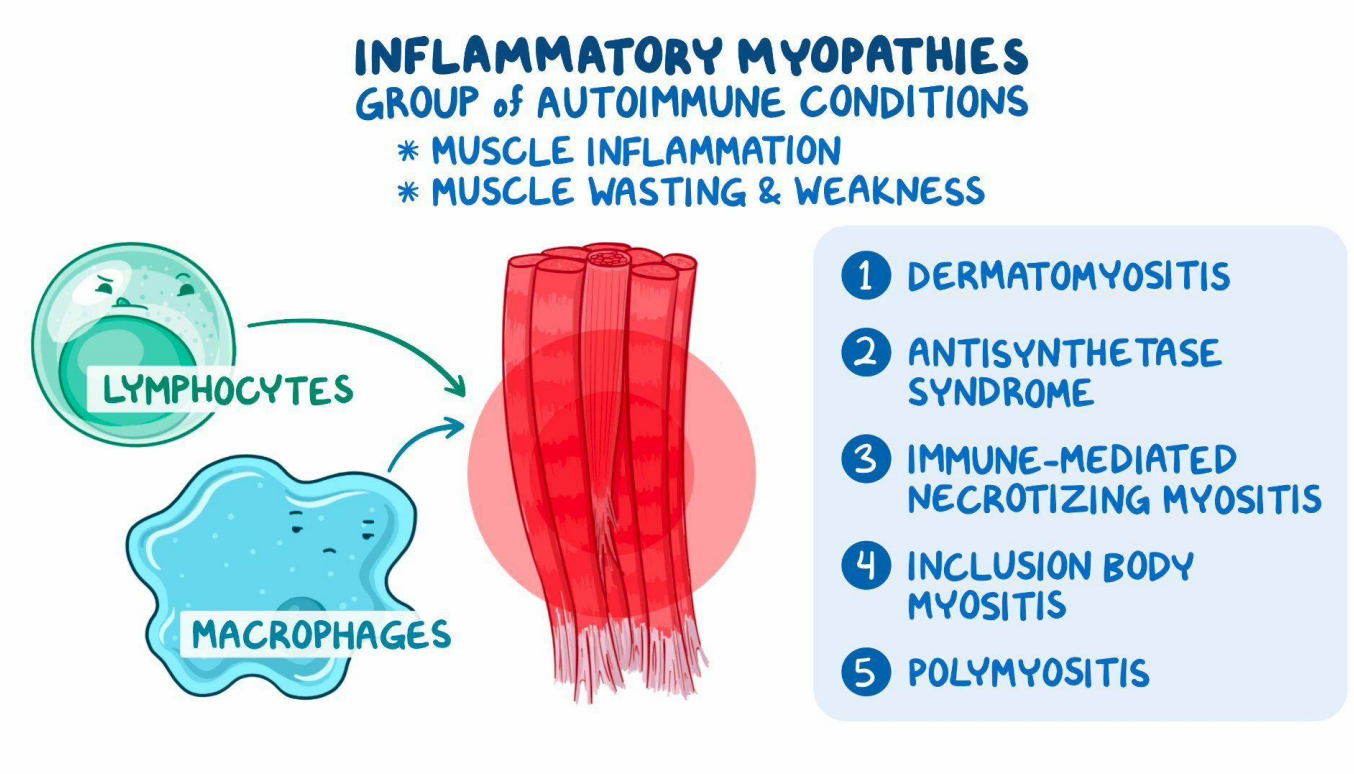
TABLE 27-4 Other Selected Muscular Dystrophies

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

2. INFLAMMATORY MYOPATHIES

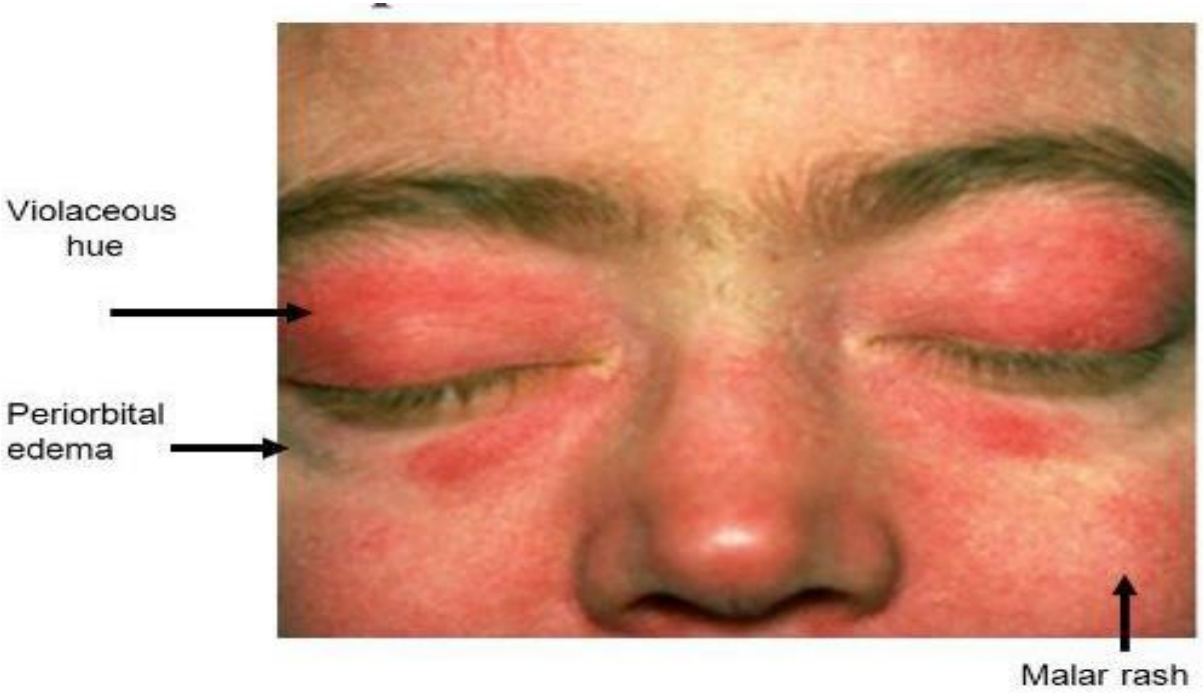
- a heterogeneous group of immune-mediated disorders characterized by skeletal muscle inflammation and injury.



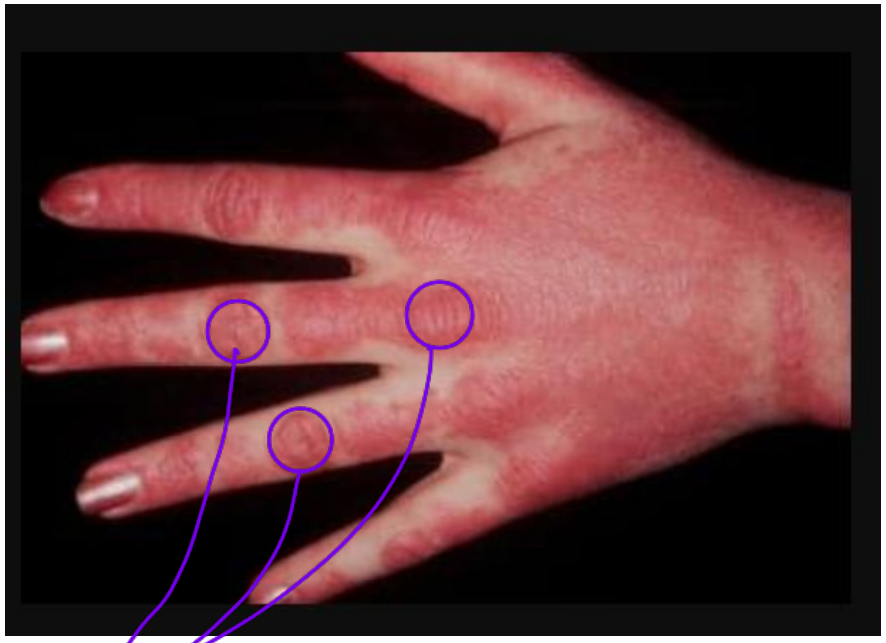
DERMATOMYOSITIS.

- Idiopathic process that leads to an inflammatory myopathy with skin manifestations.
- Dermatomyositis is the most common form of inflammatory myopathy in children and associated with HLA DQA1.
- Pathogenesis include attack on the endothelium of the capillaries of myofibers, with deposition of complement on the vessel walls and eventual formation of membrane attack complex that lead to perivascular inflammation.
- Histologically : Perifascicular atrophy is the hallmark of dermatomyositis

The classic symptoms are a rash followed by mild to severe myopathy



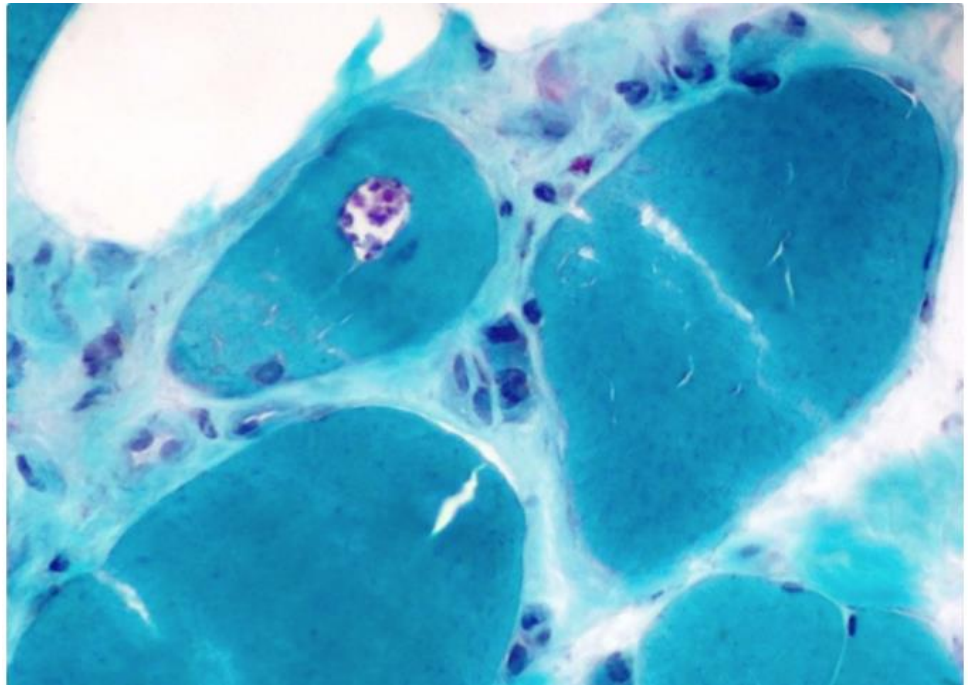
#helicotrophic (violaceous, purple-blue) with edema over the upper eyelids



#Gottron's papules: erythematous papules on the dorsum of MCP or interphalangeal joints

INCLUSION BODY MYOSITIS.

- inflammatory myopathy of predominantly skeletal muscle usually seen in ages 50+
- The main histologic finding is rimmed vacuoles with accumulation of specific proteins.



Trichrome Stain

3. 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.

- Treatments include anticholinesterase agents, prednisone, and plasmapheresis.
- Thymic hyperplasia occurs in 65% of patients and thymomas in 15%; thymic resection can improve symptoms

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.

SIGNS AND SYMPTOMS

- Weakness of the eye muscles (ocular myasthenia)
- Drooping of one or both eyelids (ptosis)
- Blurred or double vision (diplopia)
- Changes in facial expressions
- Difficulty swallowing
- Shortness of breath
- Impaired speech (dysarthria)
- Weakness in the arms, hands, fingers, legs, and neck