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Myopathies and Muscular Dystrophy

Black: Original content
Red: Important
Grey: Explanation,extra notes
Blue: Only in boys' slides
Pink: Only in girls' slide
Green:Dr.Notes

Editing File

Objectives

At the end of this lecture, the students should be able to:

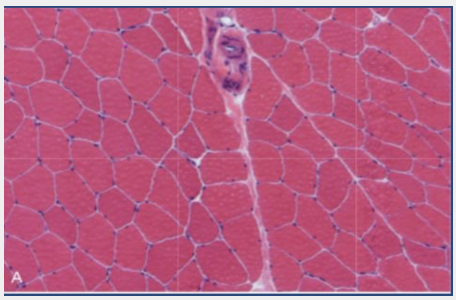
- Understand the structure of the various types of muscle fibers.
- Acquire a basic knowledge of the classification of myopathies and give examples of these disorders.
- Understand the meaning of the term muscular dystrophy and have a basic knowledge of the incidence and clinicopathological manifestations of Duchenne's and Becker's muscular dystrophies.
- Know the pattern of inheritance of myotonic dystrophy and its clinicopathological presentations.

Content

- The definition of motor unit and muscle fiber types.
- Classification of myopathies.
- Muscle atrophy, pathological features and causes.
- Neurogenic myopathy: definition, causes and pattern of nerve injury.
- Duchenne and Becker Muscular Dystrophy: incidence, Clinicopathological characteristics, with special emphasis on the rule of dystrophin protein.
- Myotonic Dystrophy: definition and main Clinicopathological features with special emphasis of inheritance pattern.

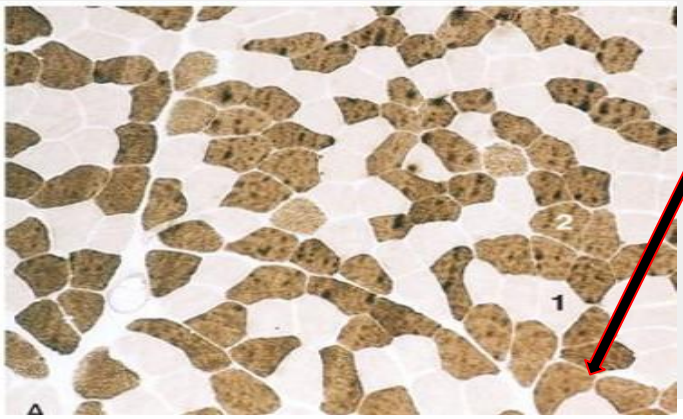
Skeletal muscle Fiber types

Normal skeletal muscle has relatively uniform polygonal myofibers with peripherally placed nuclei that are tightly packed together into fascicles separated by scant connective tissue. A perimysial interfascicular septum containing a blood vessel is present



- Depending on the nature of the nerve fiber doing the enervation, the associated skeletal muscle develops into one of two major subpopulations. (What decide the muscle fiber type is the nerve supply).
- A single "type I" or "type II" muscle fibre will innervate multiple muscle fibers and these fibers are usually randomly scattered in a "checkerboard pattern" within a circumscribed area within the larger muscle.(Each muscle in the skeletal muscle is formed by a checkerboard pattern (زي الشطرنج), and it has two types, type I and type II. Each muscle has differences in the components, some are more type I, and some are more type II
- Since the motor neuron determines fiber type, all muscle fibers of a single unit are of the time type.
- The different fibers can be identified using specific staining techniques “ATPase reaction”

Don’t forget that a motor unit is a **motor neuron**



Cont'

Types	Type I fiber	Type II fiber
Color	Red, noticed on bird's meat where fiber type grouping in different muscles (thigh vs breast meat)	White
Contraction speed	Slow	Fast
Conduction velocity	Slow twitch	Fast twitch
Activity	Aerobic	Anaerobic
Duration	Long	Short
Fatigue	Resistant	Easily fatigued
power	Strong	Weak
Storage of energy	More dependent on fat catabolism for energy through mitochondrial oxidative phosphorylation (aerobic)	More dependent on glycogen catabolism for energy through glycolysis anaerobic
Enzymes	High in myoglobin and oxidative enzymes and have many mitochondria	Rich in glycolytic enzymes
	in keeping with their ability to perform tonic (Healthy) contraction (the long contraction for example : the contraction during standing)	and are involved in rapid phasic contractions

Myopathy

- **Myopathy:** a term that may encompasses a heterogeneous group of disorders, both morphologically and clinically.
- Recognition of these disorders is important for genetic counseling or appropriate treatment of acquired disease.

Myopathies Diseases that affect skeletal muscle can involve any portion of the motor unit:

- Primary disorders of the motor neuron or axon.
- Abnormalities of the neuromuscular junction.
- A wide variety of disorders primarily affecting the skeletal muscle itself (myopathies).

Skeletal muscle disease can be divided into:

- **Neurogenic**
- **Muscular dystrophies**
- **Inflammatory myopathies**
- **Infectious**
- **Disorders of the neuromuscular junction**
  - E.g. myasthenia gravis
- **Toxic**
  - Thyrotoxic myopathy
  - Ethanol myopathy
  - Chloroquine
- **Congenital**
  - Inherited mutations of ion channels.
  - Inborn errors of metabolism (e.g. glycogen and lipid storage diseases).
  - mitochondrial abnormalities.

Muscle atrophy

(Decrease in size).

- A non-specific response. (Not for specific disease in general).
- Characterized by abnormally small myofibers.
- The type of fibers affected by the atrophy, their distribution in the muscle, and their specific morphology help identify the etiology of the atrophic changes.

Causes:

- Simple disuse (ex: prolonged bed rest in the sick, type II fibers.
- Exogenous glucocorticoids or endogenous hypercortisolism (proximal weakness), type II fibers.
- Myopathies.
- Neurogenic atrophy

Neurogenic atrophy

Normal checkerboard pattern

Fiber type grouping

Grouped atrophy

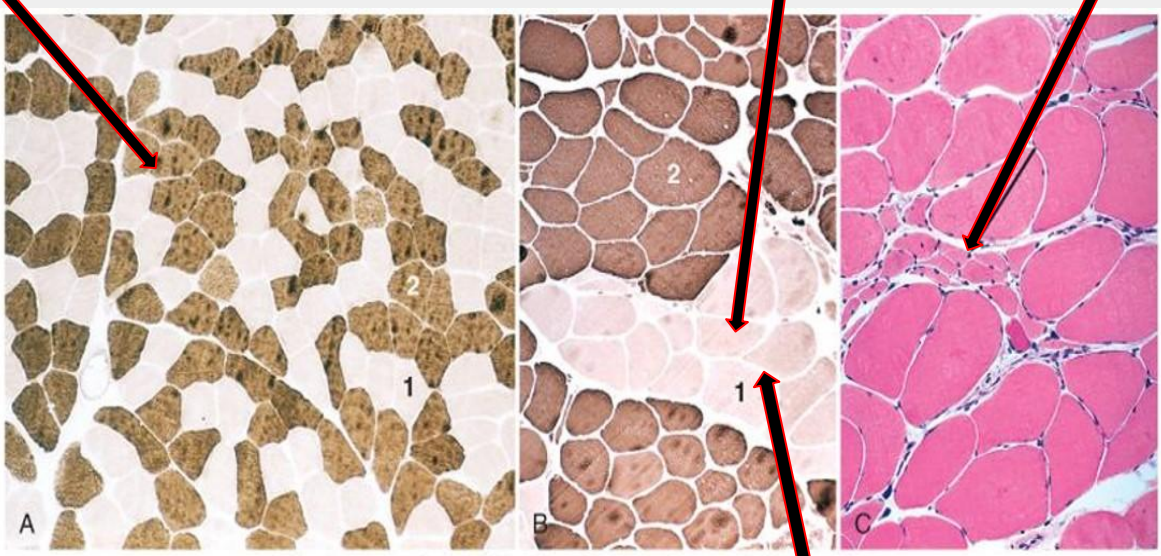


Figure 21-22 **A,** ATPase histochemical staining, at pH 9.4, of normal muscle showing checkerboard distribution of intermingled type 1 (*light*) and type 2 (*dark*) fibers. **B,** in contrast, fibers of either histochemical type are grouped together after reinnervation of muscle. **C,** A cluster of atrophic fibers (group atrophy) in the center (*arrow*).

(Special stain to identify the types (grouping), ATPase reaction).

Neurogenic Atrophy

– Both fiber types.

– Clustering of myofibers into small **groups "grouped atrophy"**

– Deprived (نقص) of their normal enervation, skeletal fibers undergo progressive atrophy.

(One motor unit alters the muscle fibers that are supplied by it have atrophy).

– Loss of a single neuron will affect all muscle fibers in a motor unit, so that the atrophy tends to be scattered over the field (because fibers of one motor unit are scattered over the area, not necessarily next to one another, so when atrophy happens to this specific motor unit, it will result in a scattered atrophy).

With re-enervation, adjacent intact neurons engage the neuromuscular junction of the previously de-enervated fibers → new connection is established → these fibers assume the type of the innervating neuron → whole groups of fibers can eventually fall under the influence of the same neuron, and become the same fiber type (fiber type grouping) .

– In that setting, if the relevant enervating neuron now becomes injured, rather large coalescent groups of fibers are cut off from the trophic stimulation and wither away (**grouped atrophy**), a **hallmark of recurrent neurogenic atrophy**.

Fiber type grouping and grouped atrophy are classic features of neurogenic myopathy (atrophy).

MUSCULAR DYSTROPHY

(Primary in muscles).

•A heterogeneous group of inherited disorders.

– Often presenting in childhood.

– Characterized by progressive degeneration (تحلل مستمر) of muscle fibers leading to muscle weakness and wasting.

– Histologically, in advanced cases muscle fibers are replaced by fibrofatty tissue. (Fibrosis is a major feature in dystrophy, loss of muscle fiber as well)

•This distinguishes dystrophies from myopathies, which also present with muscle weakness.

Dystrophin

•Dystrophin is a large protein (427 kD) that is expressed in a wide variety of tissues, including skeletal and cardiac muscles, brain, and peripheral nerves

•Dystrophin attaches portions of the sarcomere to the cell membrane, maintaining the structural and functional integrity of skeletal and cardiac myocytes

•The dystrophin gene (Xp21) spans (~1% of the total X chromosome), making it one of the largest in the human genome; its enormous size is a probable explanation for its particular vulnerability to mutation.

• **Dystrophin:** a part of the dystrophin-glycoprotein complex (stabilizes the muscle cell during contraction and may be involved in cell signaling through interaction with other proteins).

• **Dystrophin-glycoprotein complex defects**: thought to make muscle cells **vulnerable** to transient membrane tears during contraction that lead to calcium influx.

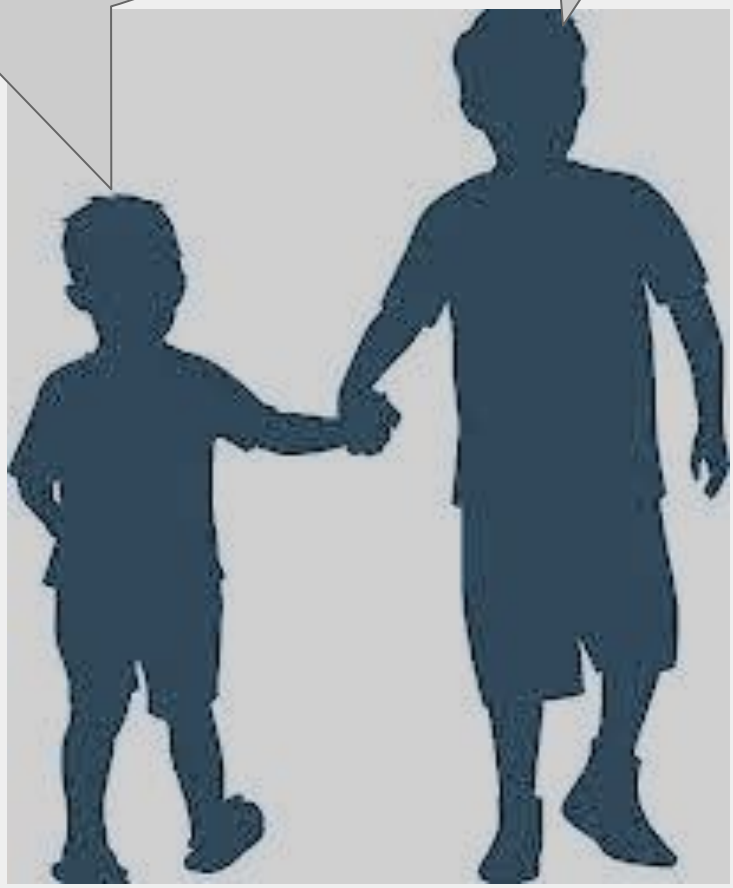
• **Result?** myofiber degeneration that with time outpaces the capacity for repair.

• The dystrophin-glycoprotein complex also is important for **cardiac muscle function**; this explains why cardiomyopathy eventually develops in many patients

Duchenne and Becker Muscular Dystrophy

Hi there my name is Duchenne you can call me (DMD)
I am an X-linked muscle Dystrophy, I am the **most severe** and the **most common** muscular dystrophy you will find me in every 3500 male I appear at the age of 5 and by the age of 10-12 I will make people wheelchair dependent and I am so strong to the point I cause death in the early 20s.

And I am Becker you can call me (BMD) I am (DMD)'s younger brother, we are from the same parents (dystrophin gene) we are caused by mutation but I am not like my brother, I am **less severe** and **less common**



Duchenne and Becker Muscular Dystrophy cont,

•Morphology:

– The histologic features of DMD and BMD are similar except that BMD is milder.

– Marked variation in muscle fiber size (atrophy and hypertrophy)

– Range of **degeneration** and **fiber necrosis** (Hallmark)

– Regeneration,including sarcoplasmic basophilia, nuclear enlargement, and nucleolar prominence(the look of the cell become more basophilic)

- Connective tissue is increased

– Abnormal staining for dystrophin

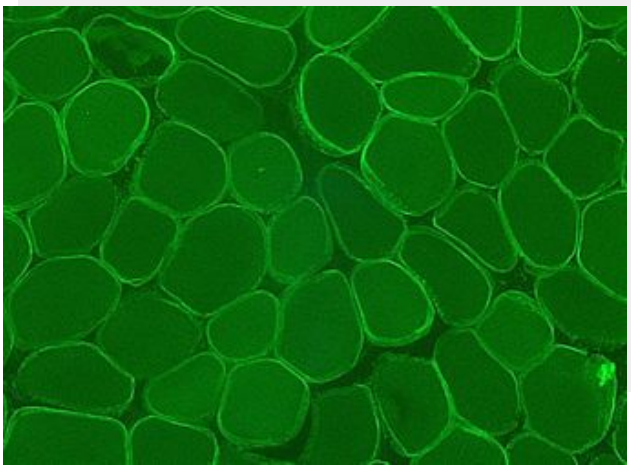
– Extensive fiber loss and adipose tissue infiltration

-abnormal internally placed nuclei.

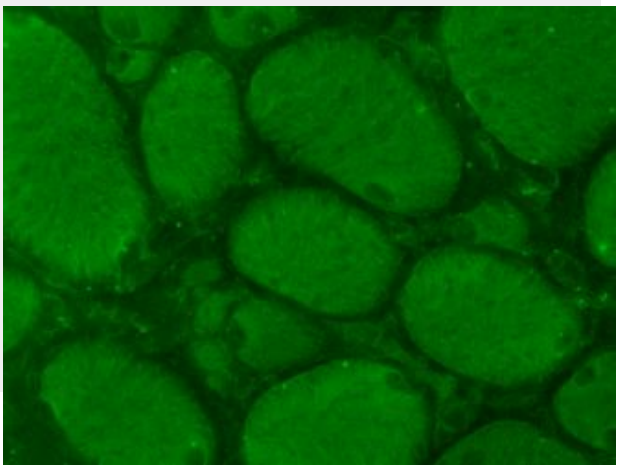
- both DMD and BMD also effect cardiac muscle, Which show variable degrees of interstitial fibrosis.

Pathogenesis

•The role of dystrophin is to transfer the force of contraction to connective tissue has been proposed as the basis for the myocyte degeneration that occurs with dystrophin defects, or with changes in other proteins that interact with dystrophin(the dystrophin work as base for the muscle if there is no base the whole building will fall).



Normal Dystrophin



Abnormal Dystrophin

Pathogenesis con,

•Deletions appear to represent a large proportion of the genetic abnormalities, with frameshift and point mutations accounting for the rest

•Approximately two-thirds of the cases are familial,and the last third is new mutations

•In affected families, females are carriers; they are clinically asymptomatic but often have elevated serum creatine kinase and can show mild histologic abnormalities on muscle biopsy.

• **Female carriers** and **affected males** who survive into adulthood are also at risk for developing dilated cardiomyopathy

• Muscle biopsy specimens from individuals with DMD show **little or no dystrophin** by both **staining and western blot analysis**

• People with BMD, who also have mutations in the dystrophin gene, have diminished amounts of dystrophin, usually of an abnormal molecular weight, reflecting mutations that allow synthesis of an **abnormal protein of smaller size**

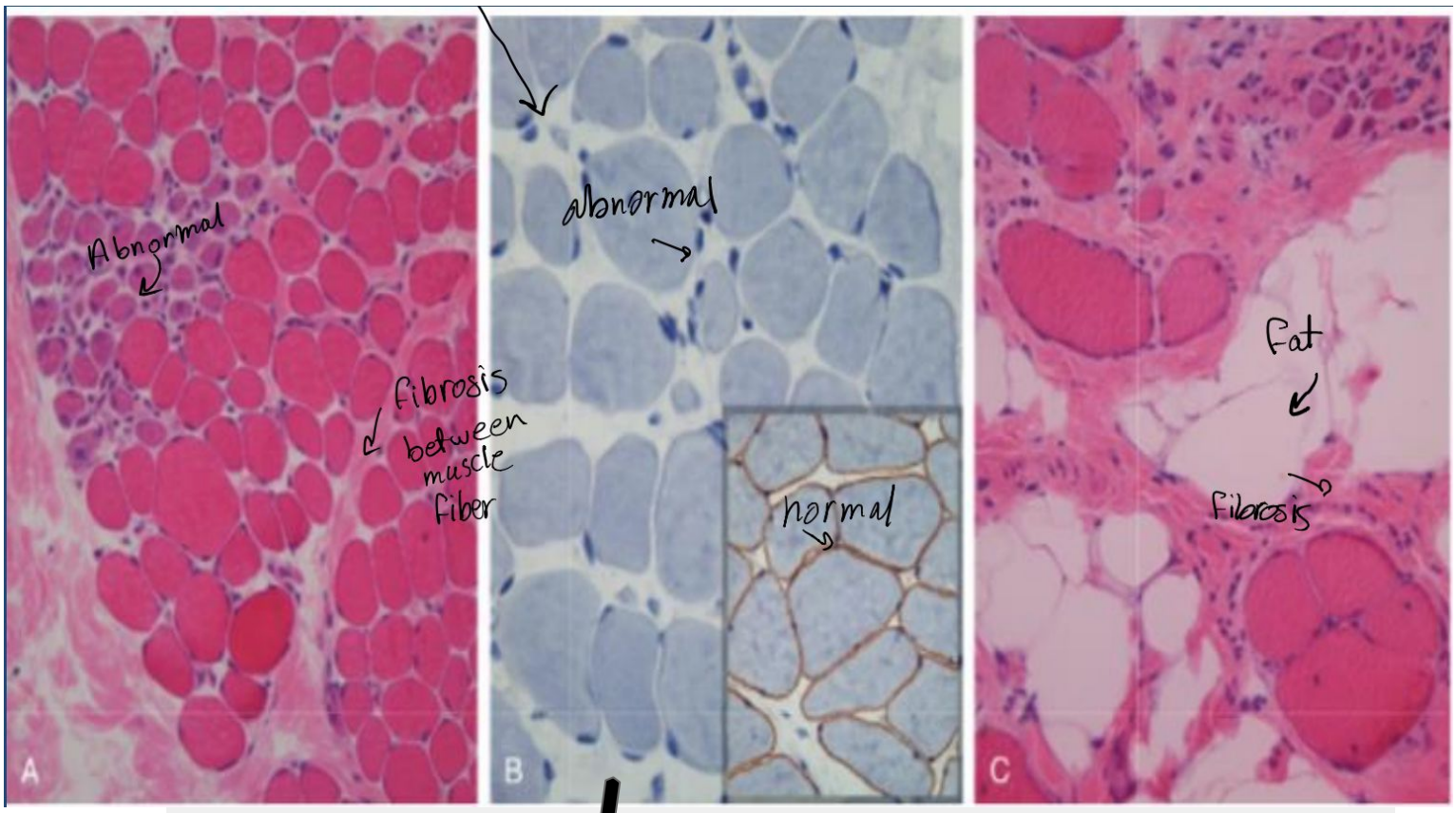
Morphology

Found in girls slides.

The histologic alterations in skeletal muscles affected by DMD and BMD are similar except that the changes are milder in BMD

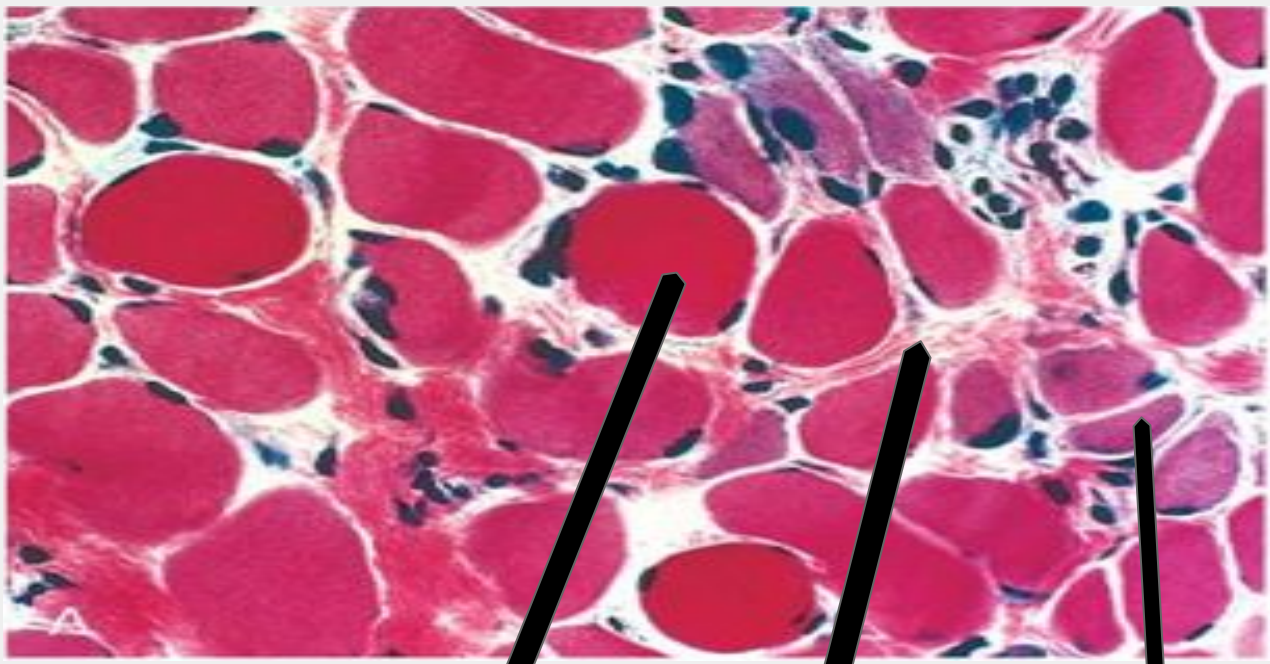
- The **hallmarks** are ongoing myofiber necrosis and regeneration.
- Progressive replacement of muscle tissue by fibrosis and fat is the result of degeneration outpacing repair.
- marked variation in myofiber size and
- abnormal internally placed nuclei.

Both DMD and BMD also affect cardiac muscles, which show variable degrees of interstitial fibrosis



immunoHistochemical staining

Girls slide



Muscle fibers

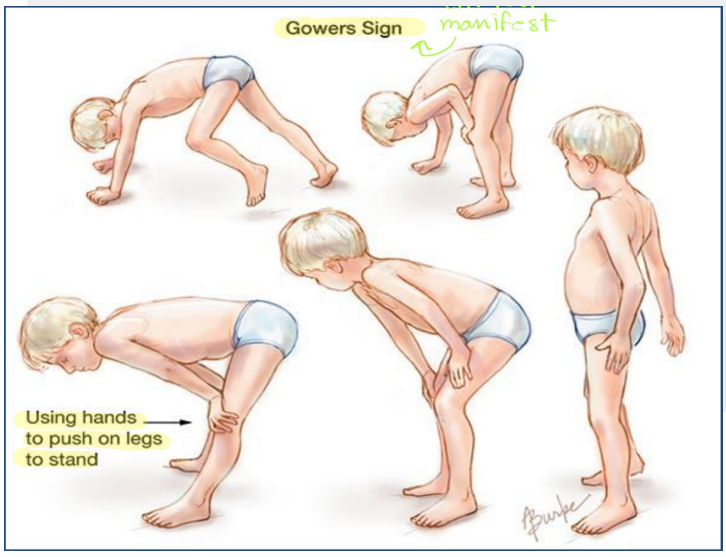
Fibrosis

Atrophic fiber

Clinical Features

•Boys with DMD:

- Normal at birth, and early motor milestones are met on time
- Walking is often delayed.
- Weakness begins in the pelvic girdle muscles and then extends to the shoulder girdle.
- Enlargement of the calf muscles associated with weakness, a phenomenon termed *pseudohypertrophy*,is an important clinical finding.
- The increased muscle bulk is caused initially by an increase in the size of the muscle fibers and then, as the muscle atrophies, by an increase in fat and connective tissue.
- Pathologic changes are also found in the heart, and patients may develop heart failure or arrhythmias.
- Cognitive impairment seems to be a component of the disease and is severe enough in some patients to be considered mental retardation.
- Serum **creatine kinase is elevated** during the first decade of life but returns to normal in the later stages of the disease, as muscle mass decreases (then it disappear).
- Death results from respiratory insufficiency, pulmonary infection, and cardiac decompensation.



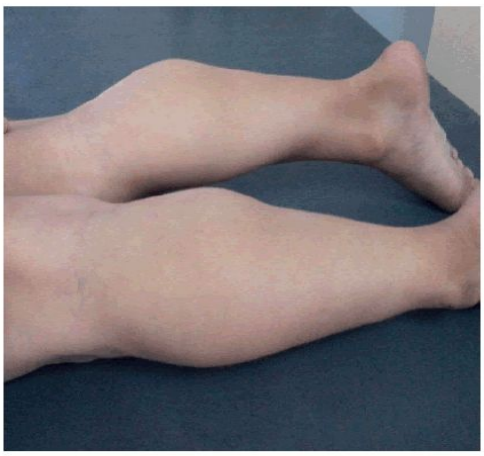


Figure 2: Patient with DMD enlarged calf muscles

This slide is IMPORTANT

BMD

•Boys with BMD develop symptoms at a later age than those with DMD. The onset occurs in later childhood or in adolescence, and it is accompanied by a generally slower and more variable rate of progression

•Although cardiac disease is frequently seen in these patients, many have a nearly **normal life span** but it may result in death in the absence of significant skeletal muscle weakness.

Inflammatory Myopathies

1-Infectious 2-Noninfectious inflammatory

(We are going to talk about the second type only)

•Inflammatory myopathies make up a heterogeneous group of rare disorders characterized by **immune-mediated** muscle injury and inflammation

•Based on the clinical, morphologic, and immunologic features, three disorders:

–*Polymyositis*

–*Dermatomyositis*

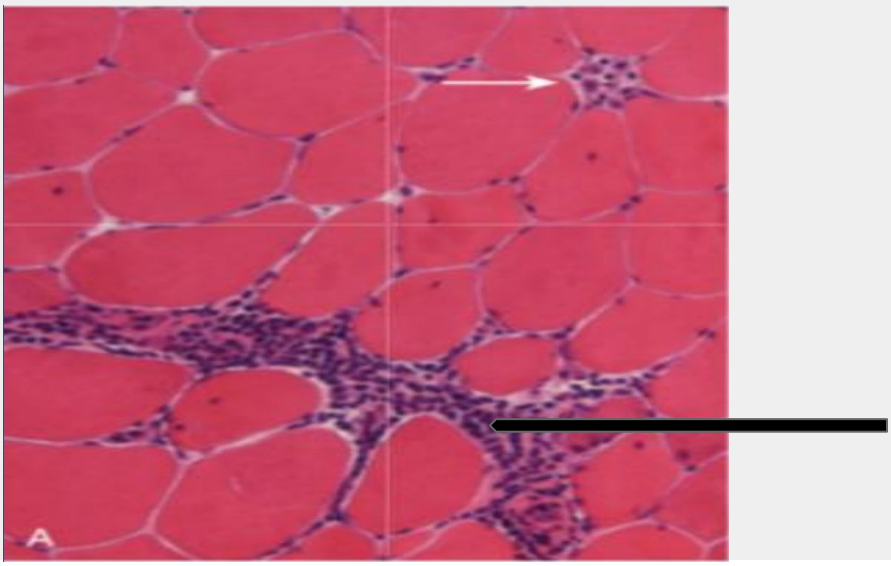
–*Inclusion body myositis*

Polymyositis.

- This inflammatory myopathy is characterized by symmetric proximal muscle involvement, similar to that seen in dermatomyositis.
- It differs from dermatomyositis by the lack of cutaneous involvement and its occurrence mainly in adults.
- Similar to dermatomyositis, there may be inflammatory involvement of heart, lungs, and blood vessels.

Morphology.

- lymphocytes surround and invade healthy muscle fibers.
- Both necrotic and regenerating muscle fibers are scattered throughout the fascicle, without the perifascicular atrophy seen in dermatomyositis.
- There is no evidence of vascular injury in polymyositis.



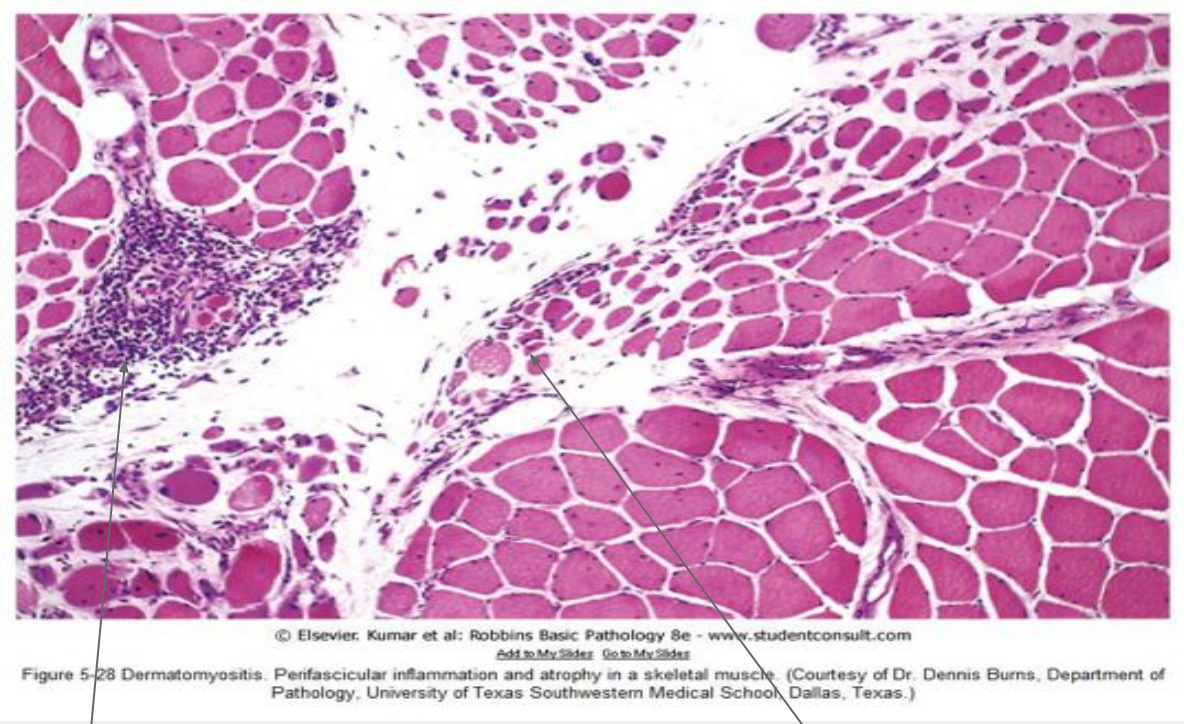
Dermatomyositis

- inflammatory disorder of the skin as well as skeletal muscle.
- skin rash that may accompany or precede the onset of muscle disease. The classic rash takes the form of a discoloration of the upper eyelids associated with periorbital edema scaling erythematous eruption over the knuckles(Gottron's lesions).
- Muscle weakness is slow in onset, bilaterally symmetric It typically affects the proximal muscles first. As a result, tasks such as getting up from a chair become increasingly difficult.
- Dysphagia
- Extramuscular manifestations, including interstitial lung disease, vasculitis, and myocarditis, may be present in some cases
- According to several studies, 20% to 25% of adults with dermatomyositis have cancer (paraneoplastic) (we need to exclude cancer)

Morphology

- Mononuclear inflammatory infiltrate (lymphocytes,monocytes) located predominantly around small blood vessels.
- Groups of atrophic fibers are particularly prominent at the periphery of fascicles. This "perifascicular atrophy(the main morphology) is sufficient for diagnosis, even if the inflammation is mild or absent.
- marked reduction in the intramuscular capillaries

Dermatomyositis



Inflammatory cells neutrophils

Peripheral atrophy

And this is how the disease going to look like and the pattern will look like the flower on the right

This slide was the homework for for male students.

Myotonic dystrophy

- Myotonia, the sustained involuntary contraction of a group of muscles, is the cardinal neuromuscular symptom in myotonic dystrophy
- Patients often complain of stiffness and difficulty in relaxing their grip, for example, after a handshake
- It is is inherited as an autosomal dominant (page 843 robbins))
- Myotonic dystrophy is a nucleotide repeat expansion disease
- Myotonia can often be elicited by percussion of the thenar eminence

Pathogenesis

- Mutations in the gene that encodes the dystrophia myotonica protein kinase (DMPK).
- In normal subjects, this gene contains fewer than 30 repeats of the sequence CTG, whereas in severely affected persons, several thousand repeats may be present.
- Myotonic dystrophy exhibits the phenomenon of anticipation, characterized by worsening of the disease manifestations with each passing generation due to further trinucleotide repeat expansion
- Myotonic dystrophy thus falls into the group of disorders associated with trinucleotide repeat expansions

This slide was the homework for for male students.

Morphology

- Skeletal muscle may show variation in fiber size.
- Increase in the number of internal nuclei.
- Another well-recognized abnormality is the ring fiber

Clinical Features of Myotonic dystrophy

- ❏ Myotonic dystrophy often manifests in late childhood with gait abnormalities due to weakness of foot dorsi exors, with subsequent progression to weakness of the intrinsic muscles of the hands and wrist extensors,
- ❏ atrophy of the facial muscles, and ptosis.
- ❏ Involvement of other organ systems results in potentially fatal cardiac arrhythmias, cataracts, early frontal balding, endocrinopathies, and testicular atrophy.
- ❏ Dementia has been reported in some cases

Summary

	Etiology	Pathogenesis	Clinical features
Neurogenic atrophy	Genetic disease affects the motor neuron • Involve both fibers types (1,2). •Clustering of myofiber into small groups .	**1.** Loss of single neuron **2.** Re-enervation **3.** Grouped atrophy	
Myasthenia gravis	Genetic disorder affect the neuromuscular junction Caused by autoantibodies that block the function of post synaptic Ach receptors which results in degradation & depletion of receptors.	autoimmune attack. occurs when autoantibodies form against the nicotinic acetylcholine postsynaptic receptors at the neuromuscular junction of skeletal muscles	**1.** Ptosis or diplopia due to weakness in the 4 5 extraocular muscles. **2.** Repetitive use of muscles make the weakness mor severe. **3.** More commonly seen in women. **4. Effective treatment**:cholinesterase inhibitory drugs, immunosupperssion
Muscular dystrophies	• Genetic disorder in muscle itself. • Degenerative disorder characterized by muscle wasting & replacement of skeletal muscle by adipose tissue. • Due to mutations of dystrophin gene.	Duchenne muscular dystrophy (DMD) : deletion of dystrophin. • Becker muscular dystrophy (BMD) : mutated dystrophin protein of smaller size. • Present in childhood.	DMD : **1.** Proximal muscle weakness at 1 year of age, progress to involve distal muscles. **2.** Death results from cardiac or respiratory failure, myocardium is commonly involved. BMD: **1.** Results in milder disease **2.** Cardiac involvement can be the dominant..
Myotonic dystrophy	Genetic **Sustained involuntary contraction** of a group of muscles, is the cardinal symptom in this disease.	• Mutations in the gene that encodes the dystrophia myotonica protein kinase(**DMPK**). • Present in late childhood.	**1.** Stiffness & difficulty in releasing the grip. **2.** Weakness of the hand intrinsic muscles & wrist extensor. **3.** Atrophy of muscles of the face and ptosis. **4.** Cataracts & Dementia.
polymyositis	Acquired Uncommon inflammatory disease	• Affect and seen mainly in adults.	**1.** Symmetrical proximal muscles weakness. **2.** Lack of cutaneous involvement. **3**. Inflammatory involvement of heart, lungs and blood vessels. From teamwork 437
dermatomyositis	Acquired. **Unknown etiology** Inflammatory disorder of the skin and skeletal muscles.		**1.** Skin rash. **2.** Muscle weakness. **3**. Dysphagia. **4.** Extramuscular manifestations. **5**. Cancer (paraneoplastic).

MCQs

1) The dystrophin gene is located on and it spans through

A) (Xp21) spans (~1% of the total Y chromosome)
B) (Xp21) spans (~0.1% of the total X chromosome)
C) (Xq21) spans (~1% of the total X chromosome)
D) (Xp21) spans (~1% of the total X chromosome)

2) The most genetic abnormalities are

A) frameshift
B) point mutations
C) Deletions

3) Myotonic dystrophy is

A) It is autosomal dominant
B) It is is autosomal recessive
C) X-linked
D) Y-liked

4) One of the following is not one of the morphology of DMD and BMD

A) Connective tissue is increased
B) nuclear disappearance, and nucleolar prominence
C) C) Abnormal staining for dystrophin
D) D) Extensive fiber loss and adipose tissue infiltration

5- BMD is more severe and more common than DMD.

A) True
B) False

6- Which type of fiber is affected in neurogenic atrophy?

A) Type I
B) Type II
C) Both

1)D 2)C 3)A 4)B 5)B 6)C

Team leaders

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