PATHOLOGY TEAM
MED
444

MED444
KING SAUD UNIVERSITY

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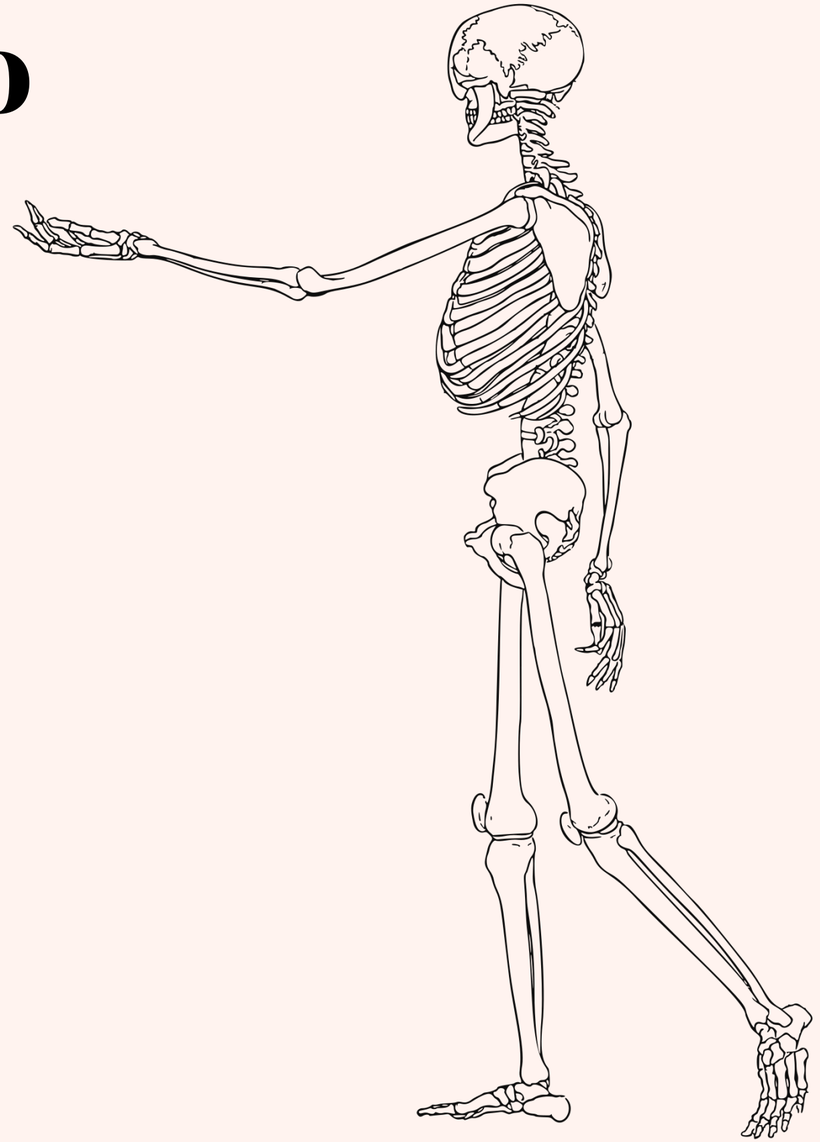
Introduction to myopathies



Editing File

Everything important is marked by red

Special thx to the members

Color index:

Main text (black)

Important (Red)

Dr.Notes (green)

Male slides only (blue)

Female slides only (pink)

Extra info(gray)

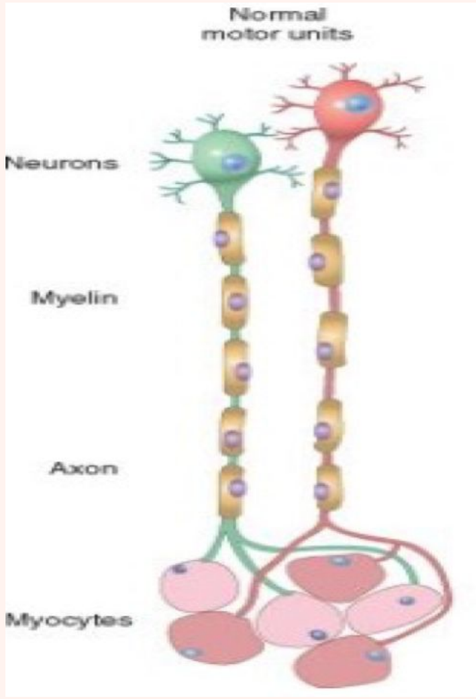
Objectives

- •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.

the principal component of the motor system is the motor unit

the motor unit is composed of:

- one lower motor neuron
- axon
- neuromuscular junction
- the skeletal muscle fibers it innervates



Histology of skeletal muscle

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

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

important

Muscle fiber types

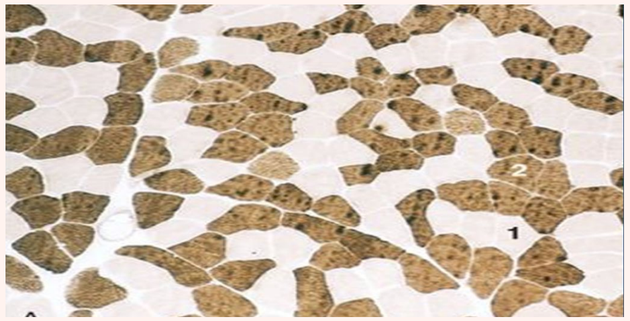
Type one Fibres	Type Two Fibres
• Slow Twitch	• Fast Twitch
• "aerobic" type I are high in myoglobin and oxidative enzymes and have many mitochondria, in keeping with their ability to perform tonic contraction	• are rich in glycolytic enzymes and are involved in rapid phasic contractions
• more dependent on fat catabolism for energy through mitochondrial oxidative phosphorylation	• more dependent on **glycogen** catabolism for energy through glycolysis
• red, refers to this being the dark (red) meat on birds where fiber type grouping in different muscles (e.g., thigh vs. breast meat) is quite pronounced	• **white**

- The fiber types, are determined by the neuron of the motor unit
- The difference fibers can identified using specific staining techniques

• Since the motor neuron determines fiber type, all muscle fibers of a single unit are of the same type.
• The fibers of a single motor unit are distributed across the muscle, giving rise to a checkerboard pattern of alternating fiber types

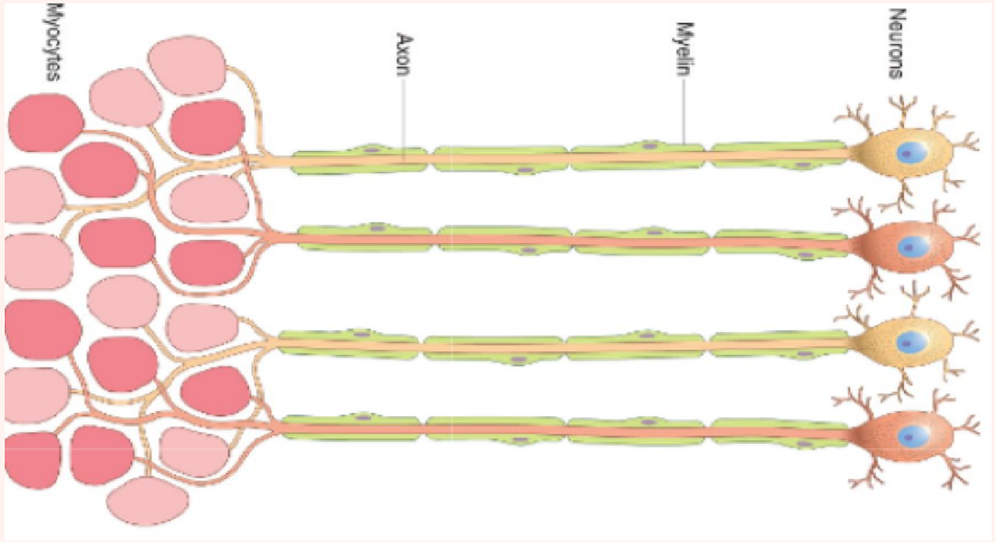
*in female slides only

Muscle fiber types



note from 441

في الوضع الطبيعي تكون عشوائية وجودها بشكل منتظم يدل على المرض



441: myocytes are mixed in an endomysium with different supplies of neutrons

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)

important

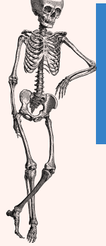
Myopathy

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)

Myopathy

- Myopathy as a term 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



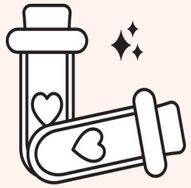
Myopathies

important

skeletal muscle disease

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

important



Muscle Atrophy

- A nonspecific response
- Characterized by abnormally small myofibers

- Muscle fiber atrophy is shared by both neuropathic and myopathic processes. However, certain disorders are associated with particular patterns of atrophy.

- 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

Atrophy is reduction in size of cell, tissue, or organ

Causes

- Simple disuse, type II fibers
- Myopathies
- Exogenous glucocorticoids or endogenous hypercortisolism (proximal weakness) type II fibers
- Neurogenic atrophy

important

MUSCLE ATROPHY (Neurogenic Atrophy)

Deprived of their normal enervation, skeletal fibers undergo progressive atrophy

injury and regeneration of peripheral nerves alters muscle innervation, it will change the distribution of type I and type II myofibers.

- Both fiber types
- Clustering of myofibers into small groups

Characterized (hallmark) by fiber type grouping and grouped 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
- 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

important

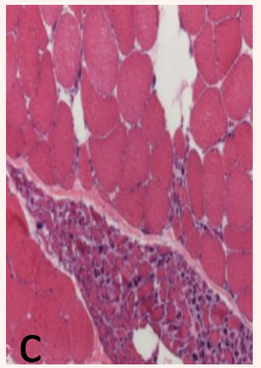
*in female slides only

MUSCLE ATROPHY (Neurogenic Atrophy)

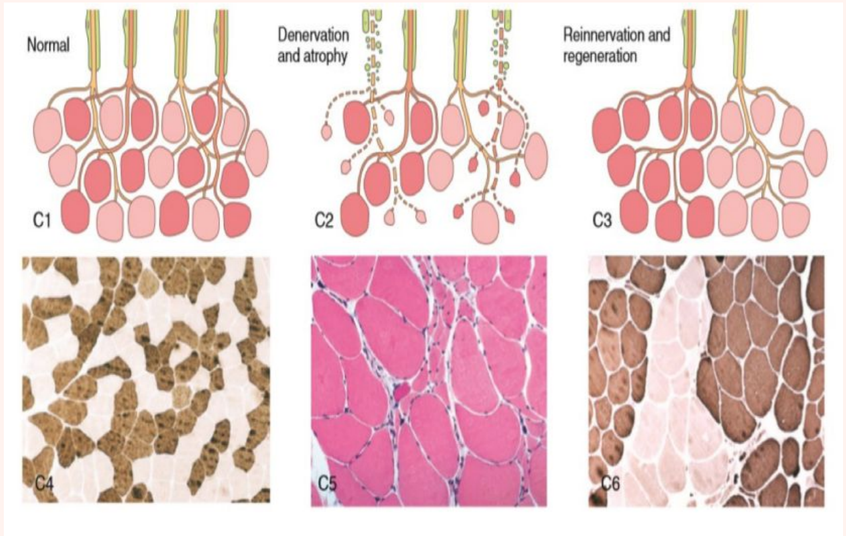
1. Inflammatory infiltrates usually are absent in skeletal muscle disorders caused by abnormal innervation.

2. Prolonged disuse of muscles due to any cause (e.g., prolonged bed rest in the sick, casting of a broken bone) can cause focal or generalized muscle atrophy, which tends to affect type II fibers more than type I fibers.

3. Glucocorticoid exposure, whether exogenous or endogenous (e.g., in Cushing syndrome), also can cause muscle atrophy. Proximal muscles and type II myofibers are affected preferentially by these agents.

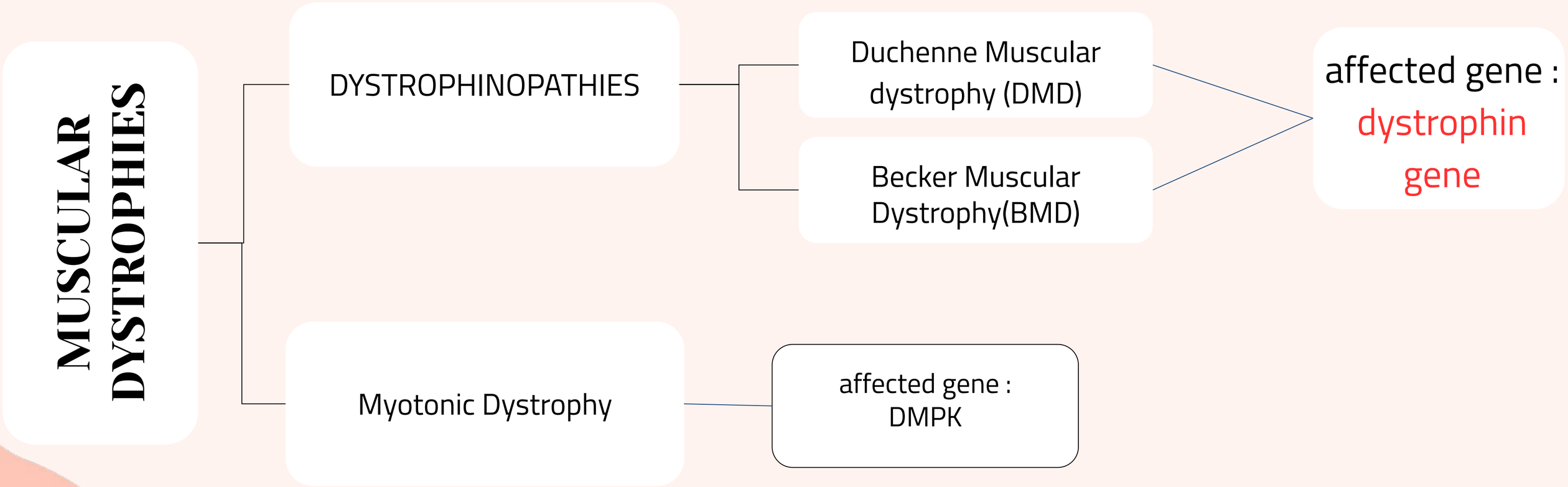


Clusters of both atrophic myofibers (C) (grouped atrophy) and fiber-type grouping (D), patchy areas in which myofibers share the same fiber type, are features of neurogenic remodeling. The ATPase reaction shown in D is one method of distinguishing between fiber types, as type I fibers stain more lightly than type II fibers. Note loss of the “checkerboard” pattern



MUSCULAR DYSTROPHY

A heterogeneous group of inherited disorders
– Often presenting in childhood
– Characterized by progressive degeneration of muscle fibers leading to muscle weakness and wasting
– Histologically, in advanced cases muscle fibers are replaced by fibrofatty tissue , This distinguishes dystrophies from myopathies, which also present with muscle weakness



important

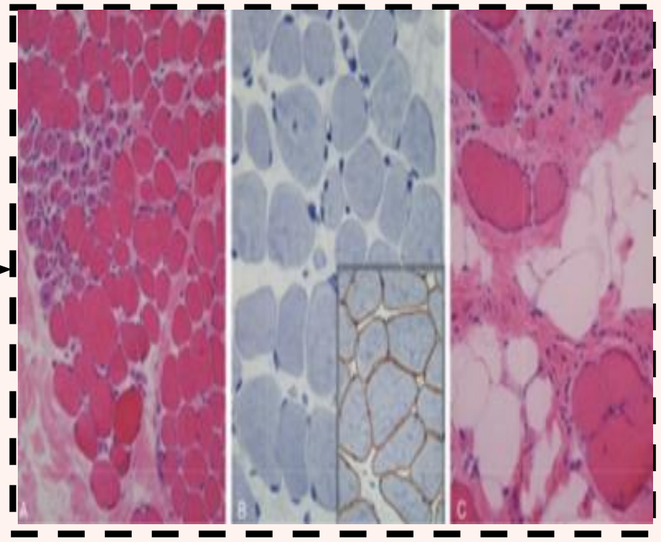
MUSCULAR DYSTROPHY

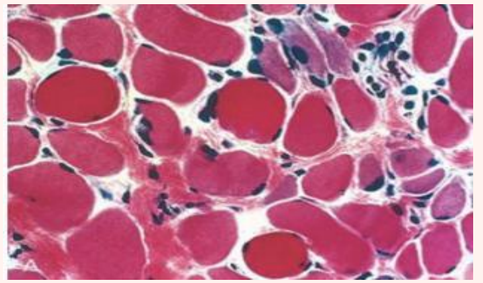
Characteristic	Duchenne Muscular dystrophy (DMD)	Becker Muscular Dystrophy(BMD)
	▪ The two most common forms of muscular dystrophy ▪ X-Linked Muscular Dystrophy	
	▪ is the most severe and the most common form of muscular dystrophy, with an incidence of about 1 per 3500 male births ▪ becomes clinically evident by age of 5, progressive weakness leading to wheelchair dependence by age 10 to 12 years death by the early 20s.	BMD is less common and much less severe
Pathogenesis	▪ Both DMD and BMD are caused by mutations in the dystrophin gene located on the short arm of the X chromosome (Xp21). ▪The role of dystrophin in transferring 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 In the affected families females are carriers; they are clinically asymptomatic but often have elevated serum creatine kinase and show minimal 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 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.

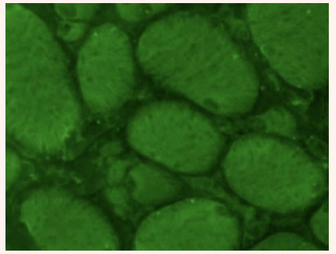
MUSCULAR DYSTROPHIES

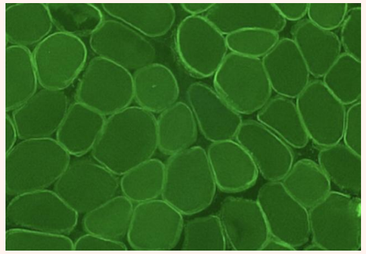
	Duchenne Muscular dystrophy (DMD)	Becker Muscular Dystrophy (BMD)
MORPHOLOGY	The histologic alterations in skeletal muscles affected by DMD and BMD are similar except that the changes are milder in BMD. 1- The hallmarks are ongoing myofiber necrosis(Range of degenerative changes) and regeneration. (including sarcoplasmic basophilia, nuclear enlargement, and nucleolar prominence). 2- Progressive replacement of muscle tissue by fibrosis and fat is the result of degeneration outpacing repair and extensive fiber loss and adipose tissue infiltration 3- **Marked variation in myofiber size** (muscle fiber size (atrophy and hypertrophy)) . 4- Abnormal internally placed nuclei 5- .Connective tissue is increased 6- Abnormal staining for dystrophin Both DMD and BMD also affect cardiac muscles, which show variable degrees of interstitial fibrosis.	

Duchenne muscular dystrophy.
Histologic images of muscle biopsy specimens from two brothers. A and B, Specimens from a 3-year-old boy.
C, Specimen from his brother, 9 years of age. As seen in A, at a younger age fascicular muscle architecture is maintained, but myofibers show variation in size. Additionally, there is a cluster of basophilic regenerating myofibers (left side) and slight endomysial fibrosis, seen as focal pink-staining connective tissue between myofibers. In B, immunohistochemical staining shows a complete absence of membrane- associated dystrophin, seen as a brown stain in normal muscle (inset).
In C, the biopsy from the older brother illustrates disease progression, which is marked by extensive variation in myofiber size, fatty replacement, and endomysial fibrosis.









important

MUSCULAR DYSTROPHY

Clinical Features

Duchenne Muscular dystrophy (DMD)

Boys with DMD

Normal at birth, and early motor milestones are met on time.

– First symptoms of DMD are clumsiness and an inability to keep up with peers due to muscle weakness.

-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.
- Death results from respiratory insufficiency,pulmonary infection, and cardiac decompensation.

Becker Muscular Dystrophy (BMD)

▪ BMD becomes symptomatic

onset occurs later in childhood or adolescence and progresses at a slower and more variable rate. Many patients live well into adulthood and have a nearly normal life span.

▪ Cardiac involvement can be the dominant clinical feature and may result in death in the absence of significant skeletal muscle weakness.

Deep Focus Question!

Which of the following statements regarding Becker muscular dystrophy (BMD) is TRUE?

A. Dystrophin is absent in Becker muscular dystrophy.

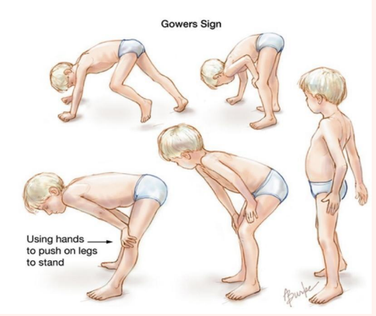
B. There is a higher level of dystrophin in a child with Duchenne muscular dystrophy than one with BMD.

C. Becker muscular dystrophy has an earlier onset than Duchenne muscular dystrophy.

D. A patient with BMD has more dystrophin than a child with Duchenne muscular dystrophy, but less dystrophin than an unaffected individual.

Answer: D

Thank you team 443!



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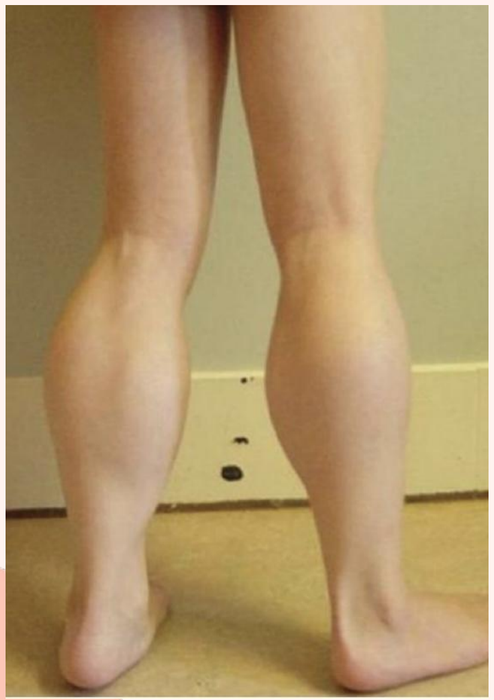
Point :4,5,6,7 from female slides

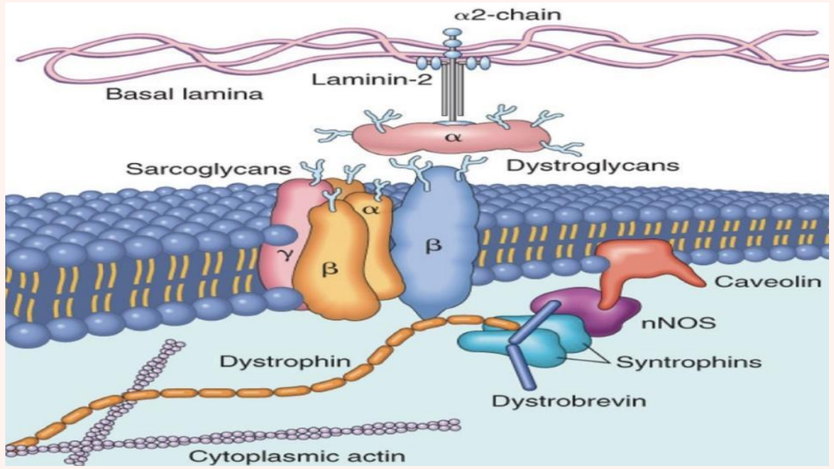
MUSCULAR DYSTROPHIES

This slide is very important

dystrophin gene

- Dystrophin is a very large protein (427 kD) that is expressed in a wide variety of tissues found in skeletal and cardiac muscle, brain, and peripheral nerves.
- Dystrophin attaches portion of the sarcomere to the cell membrane, maintaining the structural and functional integrity of skeletal and cardiac myocyte.
- 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 mutations.
- It is part of the dystrophin-glycoprotein complex . This complex stabilizes the muscle cell during contraction and may be involved in cell signaling through interaction with other proteins.
- Dystrophin-glycoprotein complex defects are thought to make muscle cells vulnerable to transient membrane tears during contraction that lead to calcium influx.
- The result is 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.
- 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, with the remainder representing new mutations.





Deep Focus Question!

Which of the following is characteristic of Duchenne muscular dystrophy?

A. A muscle biopsy will demonstrate the replacement of muscle with adipose tissue.

B. Weakness and hypotonia are typically noted in the first few days or weeks after birth.

C. It is usually caused by poor nutrition or low activity.

D. Patients with Duchenne muscular dystrophy have a near-normal life expectancy.

Thank you team 443!

this slide is very important

Myotonic dystrophy

- Myotonia, the sustained involuntary contraction of a group of muscles, is the cardinal symptom in this disease.
- Patients often complain of “stiffness” and have difficulty in releasing their grip, for instance, after a handshake.
- Myotonia can often be elicited by percussion of the thenar eminence.

Pathogenesis

I. Myotonic dystrophy is a nucleotide repeat expansion disease

II. That is inherited as an **autosomal dominant trait**. More than 95% of patients with myotonic dystrophy have mutations in the gene that encodes the dystrophia myotonica protein kinase **(DMPK).**

III. 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.

IV. Myotonic dystrophy thus falls into the group of disorders associated with trinucleotide repeat expansions.

V. 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

Clinical Course

The disease often presents in late childhood with abnormalities in gait.

weakness of the hand intrinsic muscles and wrist extensors.

Atrophy of muscles of the face and ptosis

Cataracts

Other associated abnormalities include frontal balding, gonadal atrophy, cardiomyopathy, smooth muscle involvement, decreased plasma IgG, and abnormal glucose tolerance.

Dementia has been reported in some cases

Morphology

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

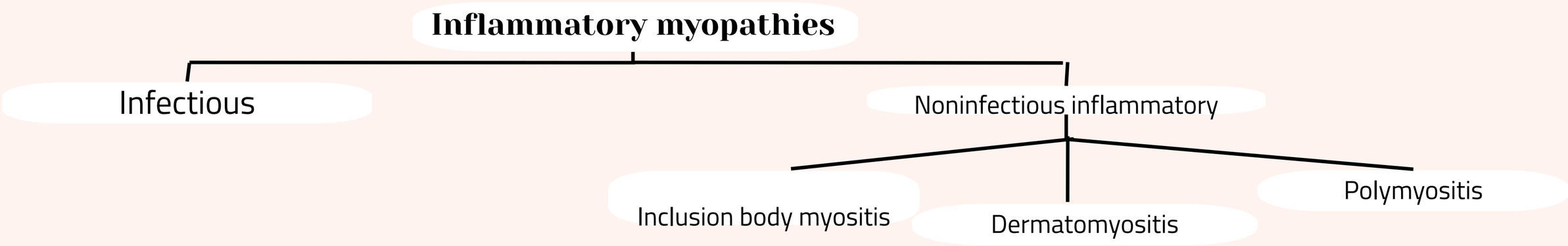
Deep Focus Question! extra not important

Which of the following is true regarding myotonic dystrophy?

A. CTG trinucleotide expansion
B. CGG trinucleotide expansion
C. GAA trinucleotide expansion
D. GAG trinucleotide expansion
E. CAG trinucleotide expansion

Answer: A

Thank you team 443!

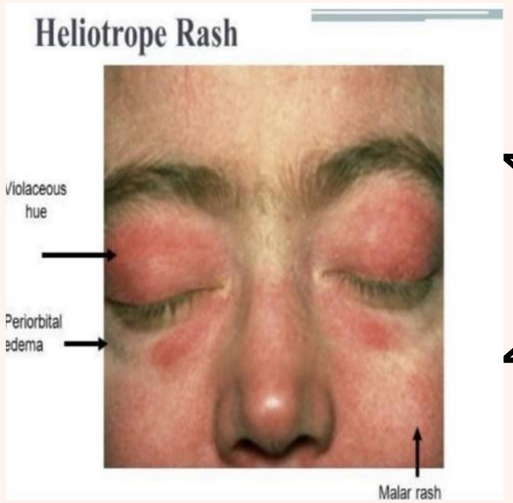


Noninfectious Inflammatory Myopathies

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.

* Everything in this slide is from female only

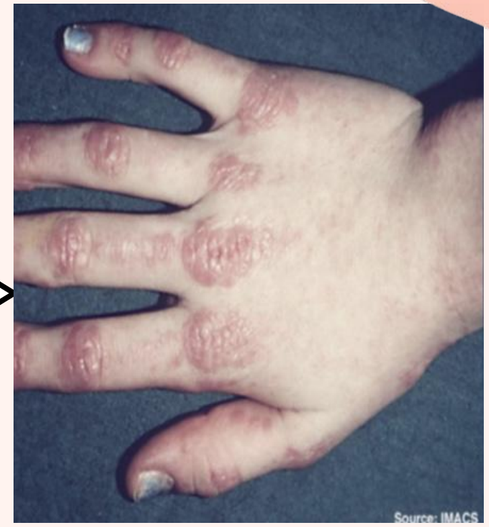
Dermatomyositis



Dysphagia

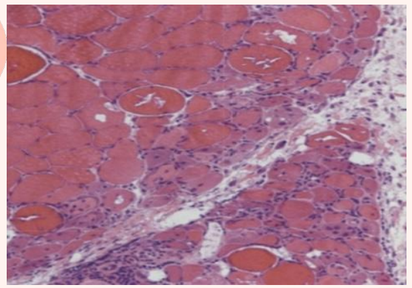
Extramuscular Manifestations, including interstitial lung disease, vasculitis, myocarditis

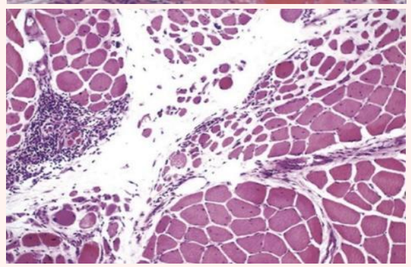
According to several studies, 20% to 25% of adults with dermatomyositis have cancer (paraneoplastic)



morphology

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





what is it?

- 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).
- It typically affects the proximal muscles first. As a result, tasks such as getting up from a chair become increasingly difficult.
- **Muscle weakness** is slow in onset, bilaterally symmetric
- is the most common inflammatory myopathy in children but in adults its considered as paraneoplastic disorder
- it is believed to have an autoimmune basis

Deep Focus Question

What will a muscle biopsy show from a patient suffering from dermatomyositis?
A. Normal findings
B. Intramuscular vacuoles
C. Perimysial and perivascular inflammation
D. Fatty replacement
Answer: C

Thank you team 443!

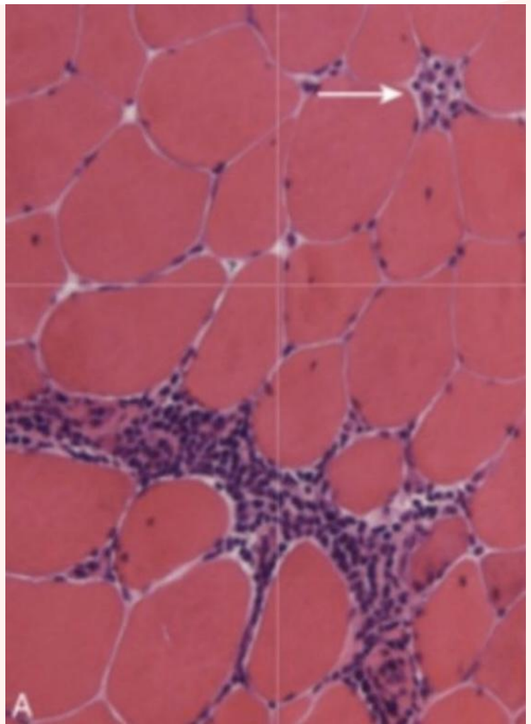
* Everything in this slide is from female only

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 maybe inflammatory involvement of heart, lungs, and blood vessels.
- Serum creatine kinase is elevated.
- an autoimmune disorder associated with increased expression of MHC class I molecules on myofibers and predominantly endomysial inflammatory infiltrates containing CD8+ cytotoxic T cells.

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.



Deep Focus Question!

One major difference between Duchenne's muscular dystrophy (DMD) and polymyositis is that DMD...?

A. has a sudden onset.
B. has elevated CK levels.
C. has an autoimmune basis.
D. is an inherited disorder.

Answer: D

Thank you team 443!

Deep Focus Question!

What would a muscle biopsy from a patient with polymyositis show?

A. Lymphocytic infiltration
B. Absence of dystrophin protein
C. Neutrophilic infiltration
D. Normal-appearing muscle tissue

Answer: A

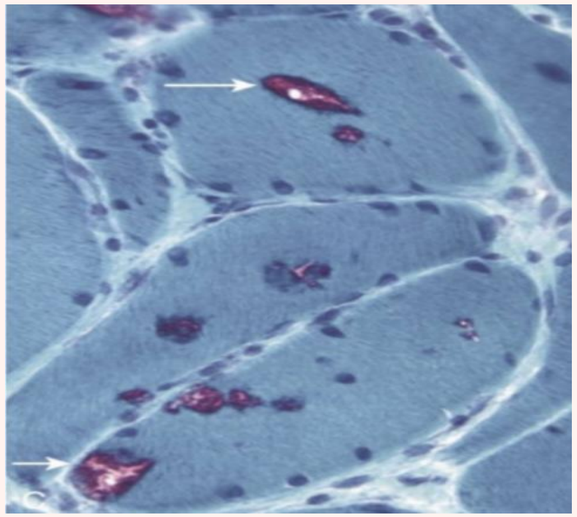
* Everything in this slide is from female only

Inclusion body myositis

- the most common inflammatory myopathy in patients older than 60 years of age.
- The morphologic hallmark of inclusion body myositis is the presence of rimmed vacuoles that contain aggregates of the same proteins that accumulate in the brains of patients with neurodegenerative diseases—hyperphosphorylated tau, amyloid derived from β-amyloid precursor protein, and TDP-43 —leading some to speculate that this is a degenerative disorder of aging.
- Other features typical of chronic inflammatory myopathies, including myopathic changes, mononuclear cell infiltrates, endomysial fibrosis, and fatty replacement, also are evident.
- The disease follows a chronic, progressive course and generally does not respond well to immunosuppressive agents.

morphology

Inclusion body myositis, showing myofibers containing rimmed vacuoles (arrows). Modified Gomori trichrome stain.



Deep Focus Question!

What will a muscle biopsy show in a patient suffering from inclusion body myositis?

A. Normal findings

B. Perimysial and perivascular inflammation

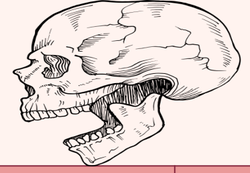
C. Fatty replacement

D. Vacuoles within muscle fibers

Answer: D

Thank you team 443!

Keywords



Word (disease)	The word that leads to the disease (symptoms, features or a word)
Muscle atrophy (Neurogenic atrophy)	fiber type grouping and grouped atrophy
Duchenne muscular dystrophy	Little or no dystrophin gene
Becker muscular dystrophy	Abnormal dystrophin of small size (Abnormal molecular weight)
Becker + duchenne	are ongoing myofiber necrosis + creatine kinase serum are elevated Both have mutations in dystrophin gene located in X chromosome 21 short arm (Xp-21) + X linked disorder
Dystrophin	skeletal and cardiac muscle, brain, and peripheral nerves.+ Stabilizes the muscle cell during contraction
Myotonic dystrophy	Mutations in DMPK (dystrophia myotonica protein kinase) + autosomal dominant trait

Word (disease)	The word that leads to the disease (symptoms, features or a word)
Dermatomyositis	Mononuclear inflammatory infiltration + perifascicular atrophy
Polymyositis	Creatine serum are elevated but lymphocytes are present with no perifascicular atrophy
Inclusion body myositis	presence of rimmed vacuoles that contain aggregates of the same proteins that accumulate in the brains of patients with neurodegenerative diseases
Noninfectious Inflammatory Myopathies	**a discoloration of the upper eyelids associated with periorbital edema,gottron's lesions**

MCQs

Q1–The most common type of mutation in dystrophin gene is?						
A– Nondisjunction		B–deletion		C– translocation		D– addition
Q2–Which one of the following is can cause muscle atrophy ?						
A– Fiber type 1		B–Myopathies		C– A+B		D– Other
Q3–Myotonia is considered as?						
A– Autosomal dominant Disease		B– Acquired disease		C– Autosomal recessive		D–X linked disease

1-B 2-B 3-A

Cases

Q1-A 48-year old male was referred because of worsening exercise intolerance of more than 1-year duration. On physical examination, he had reduced muscle and motor strength in both extremities with no muscle pain or decreased joint mobility. A deltoid muscle biopsy was obtained. Immunohistochemical stain for dystrophin showed reduced staining to about 25-30% of muscle fibers.

A- Polymyositis		B-Becker muscular dystrophy		C- Myasthenia gravis		D- Duchenne muscular dystrophy

Q2-A 3-year-old boy is having difficulty running, jumping, and walking up steps. Physical examination reveals pseudohypertrophy of the calf and a waddling gait. Serum creatine kinase (CK) concentrations are markedly elevated. What is the most likely diagnosis?

A- duchenne muscular dystrophy		B- becker muscular dystrophy		C- Polymyositis		D- Dermatomyositis

Q3-3-year-old girl presents with progressive generalized weakness. Her mother notices that when she stands up, she uses her arms to push up her body and has a hard time when walking. She also mentions the child has gotten "thinner." On physical examination, you notice some muscle wasting and pseudohypertrophy of calves.
Which of the following is not consistent with the diagnosis of Duchenne muscular dystrophy?

A- Age of onset		B- muscle wasting		C- Female sex		D- Abnormal gait

1-B , 2-A 3-C

Pathology Team

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