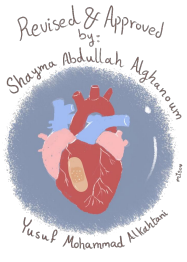
PATHOLOGY TEAM 439

MED439
KING SAUD UNIVERSITY

جامعة الملك سعود
King Saud University
1957



Myopathies & muscular dystrophy

Objectives:

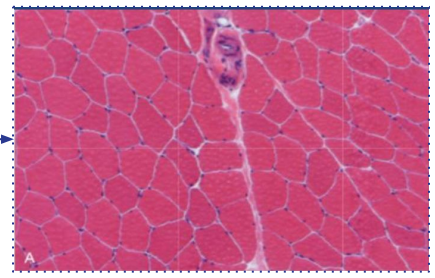
- Understand the structure of the various types of muscle fibers.
- Acquire a basic knowledge of the classification of myopathies and give examples of these disorders.
- Understand the meaning of the term muscular dystrophy and have a basic knowledge of the incidence and clinicopathological manifestations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

Editing File

Index:
Important
NOTES
Extra Information

Skeletal muscle fibers type

-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(the muscle fiber type determined by the nerve supply).

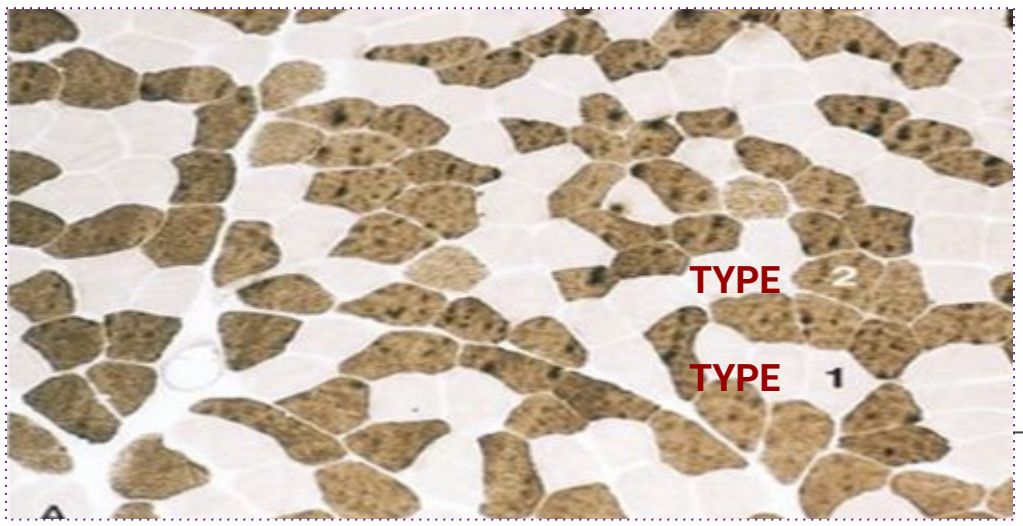
- A single "type I" or "type II" muscle fibre neuron will innervate multiple muscle fibers and these fibers are usually randomly scattered in a "checkerboard pattern" (زي الشطرنج)within a circumscribed area within the larger muscle.

- Since the motor neuron determines fiber type, all muscle fibers of a single unit are of the same type.

Each muscle has differences in the components, some are more type I, and some are more type II

زبدة السلايد:

- each group of muscle fiber supplied by one neuron and this will determine its type either type one or two.
- each neuron supply group of muscle randomly (وهذا السبب الي يعطيه شكل الشطرنج)



المقصود هنا لون الصبغة مب العضلة نفسها .
type 1"white"
type 2"brown"

- cont'

- The different fibers can be identified using specific staining techniques. "ATPase reaction"

FIBER TYPE	TYPE 1	TYPE 2
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 contraction** . (example for long contraction: the contraction during standing)	involved in **rapid phasic** contractions

The two principal pathologic processes seen in skeletal muscle

1. **Denervation atrophy**
   which follows loss of axons

2. **myopathy**
   due to a primary abnormality of the muscle fiber itself
   - is 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

1. Primary disorders of the motor neuron or axon
2. Abnormalities of the neuromuscular junction
3. A wide variety of disorders primarily affecting the skeletal muscle itself **(myopathie)**

★ Skeletal muscle disease can be divided into:

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

Muscular atrophy

A nonspecific response. Characterized by abnormally small myofibers.

Muscle trophy: loss or shrinkage of muscle fibers, is not a disease.

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

To identify the etiology of the muscular atrophy we need to know many things such as

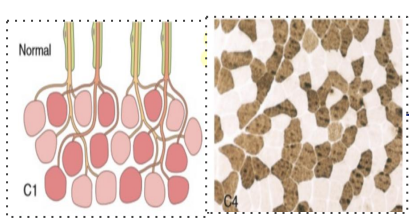
- Fibers distribution in the muscle
- The type of fibers affected by the atrophy
- The morphology of the specific muscle fibers

Causes

- **Simple disuse, affect type II fibers mostly** e.g., prolonged bed rest in the sick, casting of a broken bone
- Exogenous glucocorticoids or endogenous hypercortisolism (proximal weakness), type II fibers will be affected
- Neurogenic atrophy
- Myopathies

Neurogenic atrophy

Characterized by affecting both muscle fiber types and by clustering of myofibers into small groups.

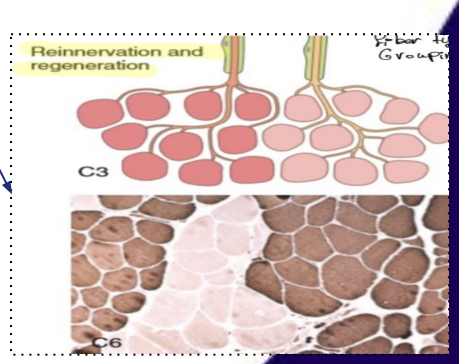


Normal

How does it happen ?

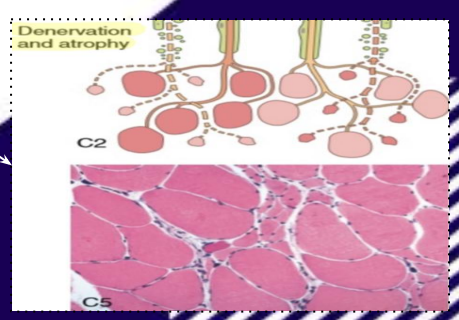
Loss of a single neuron will affect all muscle fibers in a motor unit, so that the atrophy tends to be scattered over the field. لان النيورون يغذي العضلات بشكل عشوائي ومتوزع بينهم

following **re-enervation** (if the muscle fiber was type 1 and then enervated by another motor unit can be changed into type || based on the motor unit), **adjacent intact neurons** send out sprouts,(زي البراعم budding) to engage the neuromuscular junction of the previously denervated 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 (Grow together) groups of fibers are cut off from the trophic stimulation and wither away **(grouped atrophy)** , a hallmark of recurrent neurogenic atrophy (in boys slide)

-injury causing complete atrophy of muscles fibers→Deprived of their normal enervation→skeletal fibers undergo progressive atrophy (girls slide)



Extra explanation in the next slide

EXTRA SLIDE

Extra explanation of muscle atrophy : Type I and type II are intermingled together but in the case of an injury to one of the nerves, what will happen to the muscle? An atrophy will occur. So the muscle fibers which are affected don't have any enervation, the neighboring nerves will re-enervate them..... and they will become enervated of their type(they change their type). This is known is type grouping. Type I and II are no longer intermingled, they instead form small groups. And in case of another injury, the whole group will be atrophied. Which is known is **grouped atrophy**.

*Still didn't get it? Well assume that the nerve giving rise to type I is effected. 1) Type I fibers will no longer have enervation since they have no nerve and the nerve of type II will enervate them and convert them into type II. As a result you'll see a grouping of type II.(**fiber type grouping**)
2) In case of another nerve injury, the fiber type grouping which was formed will be atrophied. (group atrophy)

Extra useful information from team 436
-Glucocorticoids are naturally produced steroid hormones, or synthetic compounds, that inhibit the process of inflammation (blocking phospholipase A2).
Cushing's syndrome is a hormone disorder caused by high levels of cortisol in the blood

- Cortisol (hydrocortisone) is a steroid hormone, or glucocorticoid, produced by the adrenal gland. It is released in response to stress and a low level of blood glucocorticoids. Its primary functions are to increase blood sugar through gluconeogenesis; suppress the immune system; and aid in fat, protein and carbohydrate metabolism. It also decreases bone formation. Various synthetic forms of cortisol are used to treat a variety of different diseases

Muscular dystrophy

Muscular dystrophy

Definition

Muscular dystrophy is a heterogeneous (different or broad) group of inherited disorders

Characterization

It is characterized by progressive (meaning continuous) degeneration of muscle fibers, which will lead to muscle weakness and wasting

How is it different from myopathies?

Myopathies and dystrophies result in muscle weakness, but in muscle dystrophy, the muscle fibers will be replace with fibrofatty tissue

Onset

It is often present in childhood

Histological View

Histologically, in advance cases, muscle fibers will be replaced by fibrofatty tissue (which is fibrous and adipose tissue combined)

Muscular dystrophy (like those seen in Duchenne and Becker) is **caused by an abnormality in a gene called dystrophin gene (located on the short arm of the X chromosome -Xp21-) , which will cause an abnormality in a protein called Dystrophin**

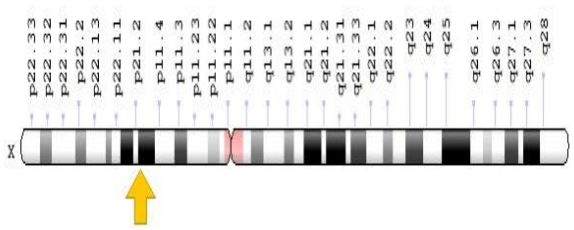
Dystrophin is a large protein (427 kD) that is expressed in a wide variety of tissues, including all types of muscles, brain, and peripheral nerves.

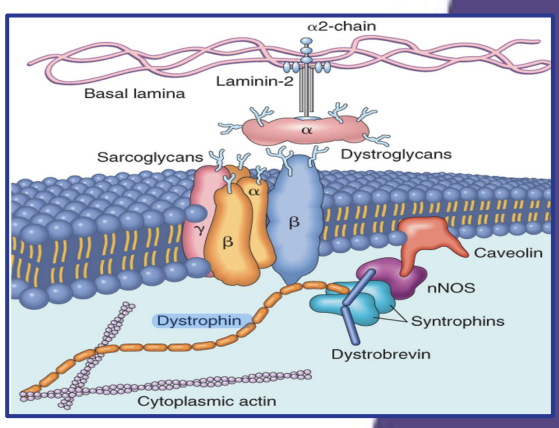
Dystrophin attaches portions of the sarcomere to the cell membrane, **maintaining the structural and functional integrity of skeletal and cardiac myocytes.**

Dystrophin also transfers the contraction force to the connective tissue. This is a proposal as the reason of myocyte degeneration that occur with dystrophin defects, or defects that occur with other proteins that interact with dystrophin

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**

Extra information:
kD stands for kilo dalton, which is a unit of mass
Xp21 is a segment in the short arm of X chromosome





Duchenne (DMD) and Becker (BMD)

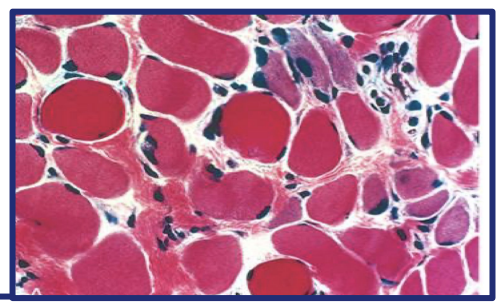
Both are X-Linked Muscular Dystrophies
They are two most common forms of muscular dystrophy
DMD is the most severe and the most common form of muscular dystrophy, with an incidence of about 1 per 3500 live male births
Although the same gene is involved in both BMD and DMD, BMD is less common and much less severe

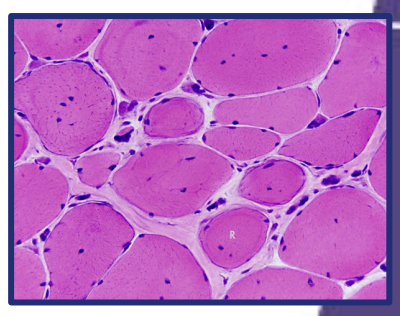
Pathogenesis of Duchenne muscular dystrophy

Becomes clinically evident by age of 5 → **progressive weakness leading to wheelchair dependence by age 10 to 12 years** → **death by the early 20s**

Histology of BMD and DMD

Fibrosis (the bluish dark circles) is present between muscle fibers. This is a feature of muscular dystrophy (both BMD and DMD)





Morphology of BMD and DMD

Marked variation in muscle fiber size (atrophy and hypertrophy), meaning some fibers appear large and other fibers appear small.

Extensive fiber loss and adipose tissue infiltration

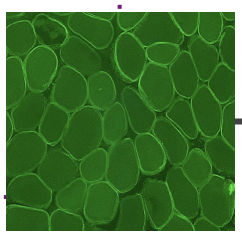
Progressive replacement of muscle tissue by fibrosis and fat (Range of degenerative changes) is the result of degeneration outpacing

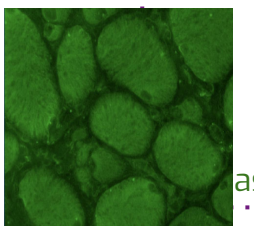
Connective tissue is increased

Regeneration, including sarcoplasmic basophilia (cytoplasm of myocyte appears blue), **nuclear enlargement, and nucleolar prominence** (the nucleolus becomes large)

Abnormal staining for dystrophin in immunofluorescence stain

The patient has white stain
↓
he has dystrophin
↓
he doesn't have muscular dystrophy





No white stain
↓
no dystrophin
↓
as muscular dystrophy

This is a cross section of muscle fibers. The white stain around the fibers is the reaction between the dystrophin and the stain.

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

In affected families, females are carriers; they are clinically asymptomatic but often have elevated serum creatine kinase (enzyme released when the muscles break down), and can show mild histologic abnormalities on muscle biopsy

Pathogenesis

DMD and BMD are caused by abnormalities in the dystrophin gene

For myocyte degeneration that occurs with dystrophin defects, or changes in other proteins that interact with dystrophin, it has been proposed that its basis is that::
dystrophin has a role in transferring the force of contraction to C.T

clinical features of DMD in boys

- 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** (it is an important clinical finding)
  the increase muscle bulk is caused initially by an increase in muscle fibers and then the muscles undergo atrophy, then continues to grow by an increase in fat and C.T.
- 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
- death results from respiratory insufficiency, pulmonary infection, and cardiac decompensation
- **serum creatinine kinase (CK) is elevated** during the first decade of life but returns to normal in the later stages of the disease, as muscle mass decreases
- Gowers sign

BMD

- Boys with BMD develop symptoms at a later age than those with DMD, its onset occurs in later childhood or adolescence. it is accompanied by a generally slower and more variable rate of progression
- Many live a nearly normal lifespan (despite frequency of cardiac disease in these patients.)
- Cardiac involvement can be the dominant clinical feature and may result in death in the absence of significant skeletal muscle weakness.

Myotonic Dystrophy

myotonia, the sustained involuntary contraction of a group of muscles, is the cardinal 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

there are mutations in the genes that code **DMPK** (dystrophia myotonica protein kinase)

there are fewer than 30 repetition in the CTG sequence in normal people, while in affected people several thousand may be present

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

it exhibits the phenomenon of anticipation (mentioned in human genetics in foundation block)

Morphology

skeletal muscle may show fiber size variation

increase in the number of internal nuclei

another well-recognized abnormality is **ring fiber**

clinical course

often presents in late childhood with abnormalities in gait

weakness of intrinsic muscles of hand 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

inflammatory myopathies

- infectious
- non-infectious

inflammatory myopathies

- inflammatory myopathies make up a heterogenous group of rare disorders characterized by immune-mediated muscle injury and inflammation
- Based on the the clinical, morphologic and immunologic feature, they are three disorders:
  - polymyositis
  - dermatomyositis
  - inclusion body myositis

Dermatomyositis

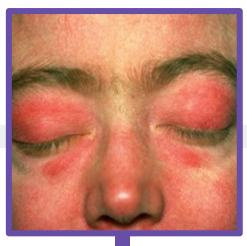
Inflammatory disorder of the skin as well as skeletal muscle

1-slow onset, bilaterally symmetric.

2- it typically affects the proximal muscle first.(tasks such as getting up from a chair becomes increasingly difficult.)

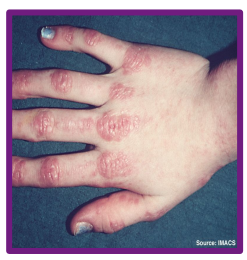
3-Dysphagia (swallowing difficulty).

Skin rash



Muscle weakness

extramuscular manifestations,

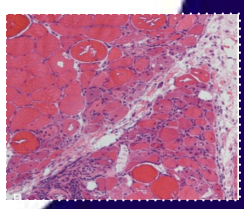


may accompany or precede the onset of muscle disease. The classic rash takes the form a **discoloration of the upper eyelids associated with periorbital edema (Heliotrope** Rash), scaling erythematous eruption over the knuckles (gottron's lesions).

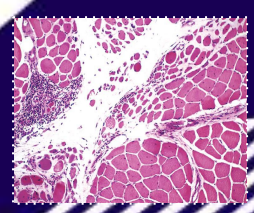
1-interstitial lung disease
2-vasculitis
3-myocarditis may be present in some cases.
-according to several studies, 20-25% of adults with this disease have cancer (paraneoplastic)

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 intramuscular capillary reduction

polymyositis

characteristic

symmetric proximal muscle involvement, similar to that seen in dermatomyositis.

difference with dermatomyositis

lack of cutaneous involvement and its occurrence mainly in adults

similarity to dermatomyositis

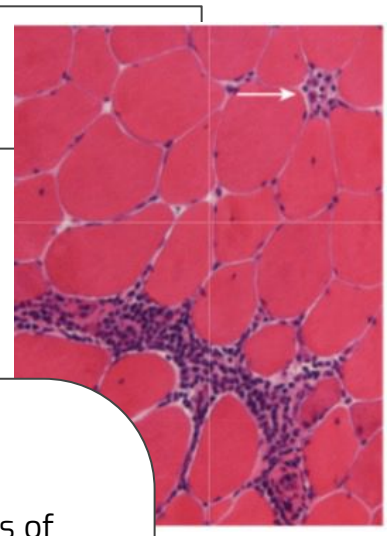
there may be inflammatory involvement of heart, lungs, and blood vessels

Morphology

Lymphocytes surround and invade healthy muscle fibers

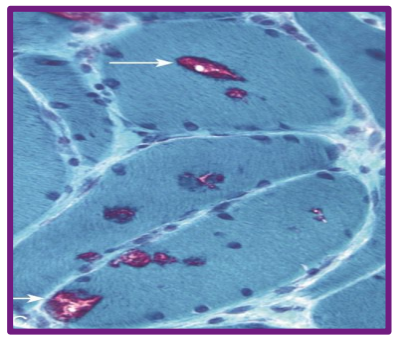
both necrotic and regenerating muscle fibers are scattered throughout the fascicle, without the perifascicular atrophy seen in dermatomyositis

there is no evidence of vascular injury in polymyositis



Inclusion body myositis

- The most common inflammatory myopathy in patients older than 60 yrs of age
- The morphologic hallmark of inclusion body: presence of rimmed vacuoles, they contain aggregates of the same protein 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 course of the disease is chronic and progressive, generally does not respond well to immunosuppressive agents.



inclusion body myositis, showing myofibers containing rimmed vacuoles (arrows). modified gomori trichrome stain

summary

- The structure of the various types of muscle fibers.

Type 1 is: Red, slow twitch and contraction with long duration and high power, aerobic activity, resistant to fatigue, depends on fat catabolism, tonic contraction and is high in myoglobin and oxidative enzymes.

Type 2 is: White, fast twitch and contraction with short duration and low power, anaerobic activity, fatigable, depends on glycogen catabolism, rapid phasic contractions and is rich in glycolytic enzymes

- The classification of myopathies and examples of these disorders.

Hereditary (muscular dystrophies, congenital myopathies, myotonias and channelopathies, metabolic myopathies and mitochondrial myopathies.

Acquired (inflammatory myopathies, endocrine myopathies, drug induced/ toxic myopathies, myopathies associated with systemic illness)

- Muscular dystrophy and the incidence and clinicopathological manifestations of Duchenne's and Becker's muscular dystrophies.

Muscular dystrophy is a heterogeneous (different or broad) group of inherited disorders

REST IS IN SLIDE 8 AND 9

- The pattern of inheritance of myotonic dystrophy and its clinicopathological presentations.

SLIDE 7

Doctors homework:

1- Define Myotonia?

is disorder characterized by sustained contraction of involuntary muscles

2- What is the inheritance and the mutation pattern that characterize myotonic dystrophy?

mutation in gene the encodes the dystrophia myotonia protein kinase (DMPK) which is the repeated sequence of CTG and in the normal person it's (fewer than 30) while the severe affected person (several thousands). It falls into several disorders associated with Trinucleotide repeat expansion + exhibit the anticipation

3-What is the clinical presentation of myotonic dystrophy?

abnormal gait , weakness of intrinsic muscles of the arm and the extensors + atrophy of ptosis and the face + cataract + dementia in some cases

Quiz

1- Duchenne muscular dystrophy is mutation in which of the following?			
a- Actin	b- Myosin	c- Dystrophin	d- Hemoglobin
2- Patients with Duchenne muscle are usually associated with elevated			
a- Troponin	b- Creatine Kinase	c- AL amyloid	d- ALT
3- Skeletal muscle disease can be divided into?			
a- Toxic	b-congenital	c- infectious	d- all
4-:40-year-old man presents with muscle weakness. He cannot open his hand for a handshake and cannot extend his arm after flexing it. On physical examination, he has marked atrophy of leg and arm muscles, ptosis, and a fixed facial expression. There is testicular atrophy. Laboratory studies demonstrate mild diabetes. A muscle biopsy reveals atrophy of type I fibers, hypertrophy of type II fibers, and numerous fibers with centrally located nuclei. Which of the following is the most likely diagnosis?			
a- Dermatomyositis	b- Duchenne Muscular dystrophy	c- Limb-girdle muscular dystrophy	d- Myotonic Dystrophy
5-year-old boy is brought to the physician by his parents because he falls a lot, cannot jump, and tires easily. Physical examination reveals weakness in the pelvic and shoulder girdles and enlargement of the child's calf muscles. The serum level of creatine kinase is elevated. A biopsy of calf muscle reveals marked variation in size and shape of muscle fibers. There are foci of muscle fiber necrosis, myophagocytosis, regenerating fibers, and fibrosis. Which of the following is the most likely cause of death expected in this patient?			
a- Dissecting aortic aneurysm	b- Disseminated intravascular coagulation	c- Pulmonary Embolism	d- DMD
6-Type ONE fibers high in ?			
a-myoglobin	b-oxidative enzyme	c-glycolytic enzyme	d-a and b
7-All muscle fibers of a single unit are?			
a-different types	b-the same type	c- similar types	d- b and c

- SAQ

1.The two principal pathologic processes seen in skeletal muscle are?

denervation atrophy and myopathy.

2.what are the clinical features of DMD ?

1- C
2- B
3-D
4-D
5-D
6-D
7-B

Team Leaders

-Rania Almutiri
- Hadi AlHemsi

Team members

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