MEDICINE
KING SAUD UNIVERSITY

PATHOLOGY
TEAM 436

Myopathies

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.

- Red : Important
- Green: doctors' notes
- Grey: extra

Revised by
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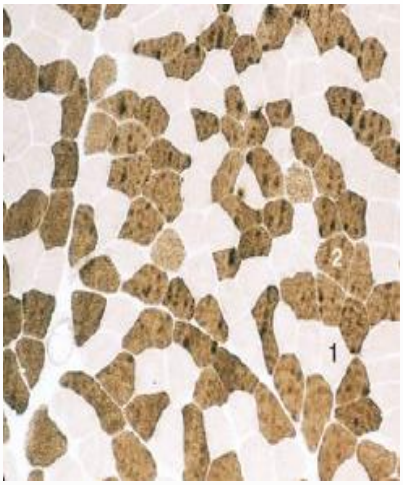
Please check here before viewing the file to know if there any changes or additions.

Skeletal muscle

Fiber type :



- A single "**type I**" or "**type II**" neuron will Innervate (supply or support)multiple muscle fibers

type 1 and type 2 يعني
هم موجودين داخل العضلات وظيفتهم انهم يدعموا و يوصلوا كل شي تحتاجه العضلات

- These fibers are usually randomly scattered in a "checkerboard pattern"

(Neuron لان الشطرنج لونه ابيض واسود فكأن كل لون يمثل نوع معين من اشكالهم كالشطرنج دلالة انهم موزعين بشكل عشوائي)

Within a circumscribed area within the larger muscle .
وايضا هم متوزعين بشكل عشوائي بطريقة مقيدة داخل العضلة

They are mixed and work together inside muscle .

- The different fibers can be identified using **specific Staining techniques (and also it depends on enzyme reaction)**

يعني لما نصبغ الشريحة اللون اللي يطلع على حسب تفاعلات الانزيمات اللي تصير في كل نوع من الfiber

- Depending on the nature of the **nerve fiber** doing the enervation(تغذية) the Associated skeletal muscle develops into
One of two major subpopulations .

fiber	Type 1	Type 2
Color	Red refers to this being the dark (red) meat on birds where fiber type grouping in different muscles	white
Contraction Speed	slow	fast
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)
power	strong	weak
Conduction Velocity	"Slow twitch" (contracting slowly, providing endurance rather than strength)	"Fast twitch" (contracting rapidly, thus providing power rather than endurance)
Example	Thigh (فخذ)meat of the bird	Breast (الصدر) meat of the bird

- Myopathy : as a term may encompasses (تشمل) a Heterogeneous (مختلفة) group of disorders, both

Morphologically (تحت المجهر)and **clinically** (patient presents in different ways).

(و histopathologyيعني هو مجموعة مختلفة من الأمراض يكون الإختلاف تحت الماكروسكوب اختلاف اكلينكي يعني الاعراض اللي يعاني منها المريض مخلتفة من مريض للآخر نظراً لإختلاف الإمراض .

- other definition of Myopathy : it is related to group of skeletal muscle diseases .

- Recognition of these disorders is **important** for Genetic counseling or appropriate treatment Of acquired disease .

Motor unit: * extra just to understand*
Made up of a motor neuronand, a group or a single, skeletal muscle fiberssupplied by that motor neuron's axonal terminals.
➔ Groups of motor units often work together to coordinate the contraction of a single muscle.
➔ All of the motor units within a muscle are considered a motor pool

Diseases that affect skeletal muscle can involve any portion (جزء)of the **motor unit**:

– primary disorders of the motor neuron or axon
(muscle يكون سليم , motor neuron or axon متضرر)

– abnormalities of the neuromuscular junction

Normal state : At the Neuromuscular Junction, the nerve fiber is able to transmit a signal to the muscle fiber by releasing Ach (and other substances), causing muscle contraction .

– a wide variety of disorders **primarily** affecting the Skeletal muscle itself (**myopathies**) .

(في هذه الحالة العضلات هي المتضرر)

Myopathies

Skeletal muscle **disease** can be divided into: (depend on causes)

- **Neurogenic** (muscle is normal and the axon or neuron are affected)
- **Muscular dystrophies** (we will explain it later)
- **Congenital** (وراثي او خلل في الجينات)

– inherited mutations of ion channels
– inborn errors of metabolism (e.g. glycogen and lipid storage diseases)
– mitochondrial abnormalities

- **Toxic**

– Thyrotoxic myopathy : (hyperthyroidism: increased secretion of thyroid hormone)

بعض الاعراض اللي يشتكي منها المريض (دايما تعبان وكسلان مايقدر يوقف و مايقدر يدخل bathroom(

– Ethanol myopathy

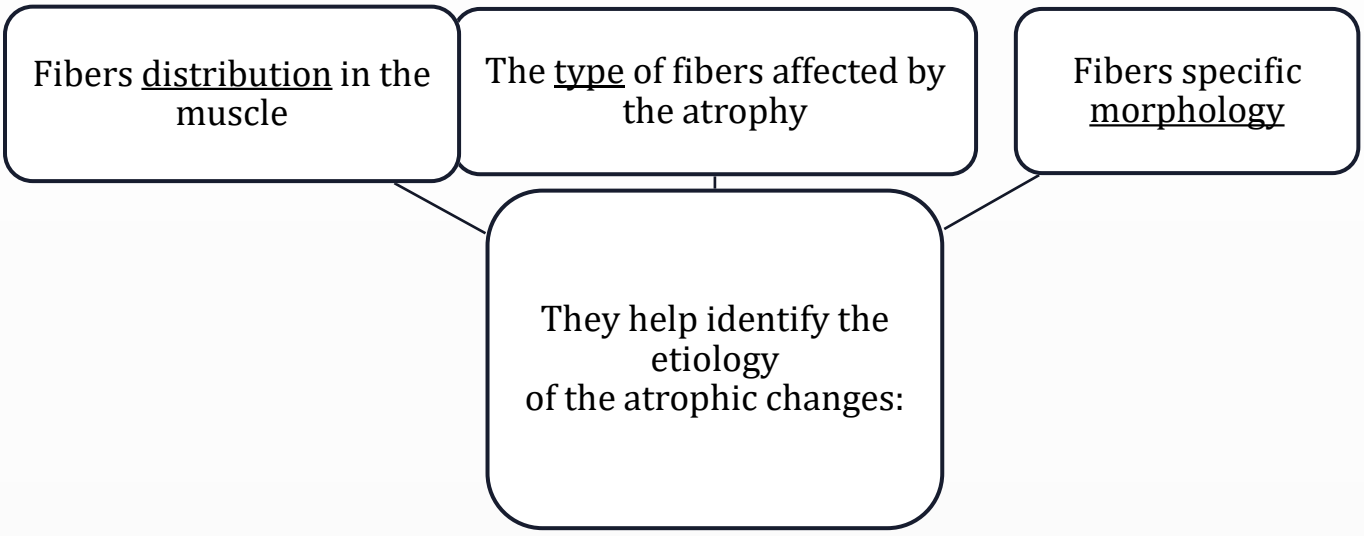
– Chloroquine :is a medication used to prevent and treat malaria and common side effect is muscle problems like (muscle pain or cramp (تشنج) العضلات)

- **Inflammatory myopaties** (under microscope we can see a lot of (lymphocytes) (immune disease)).
- **Infectious** (مُعدي)
- **Disorders of the neuromuscular junction (e.g. myasthenia gravis)**

وهن وضعف في العضلات مثل عضلات جفن العين
The patient can not move or open his eyelid (جفن العين).

MUSCLE ATROPHY

Atrophy: loss or shrinkage of muscle fibers.
A non-specific response, characterized by abnormally small myofibers.



Causes:
–Simple disuse, type II fibers. means when I see fibers of type II I'll know the cause is immobilization.

–Exogenous glucocorticoids or endogenous hypercortisolism (proximal weakness), type II fibers.

–Myopathies.

–Neurogenic atrophy. Next slides in details

MUSCLE ATROPHY:

Neurogenic Atrophy

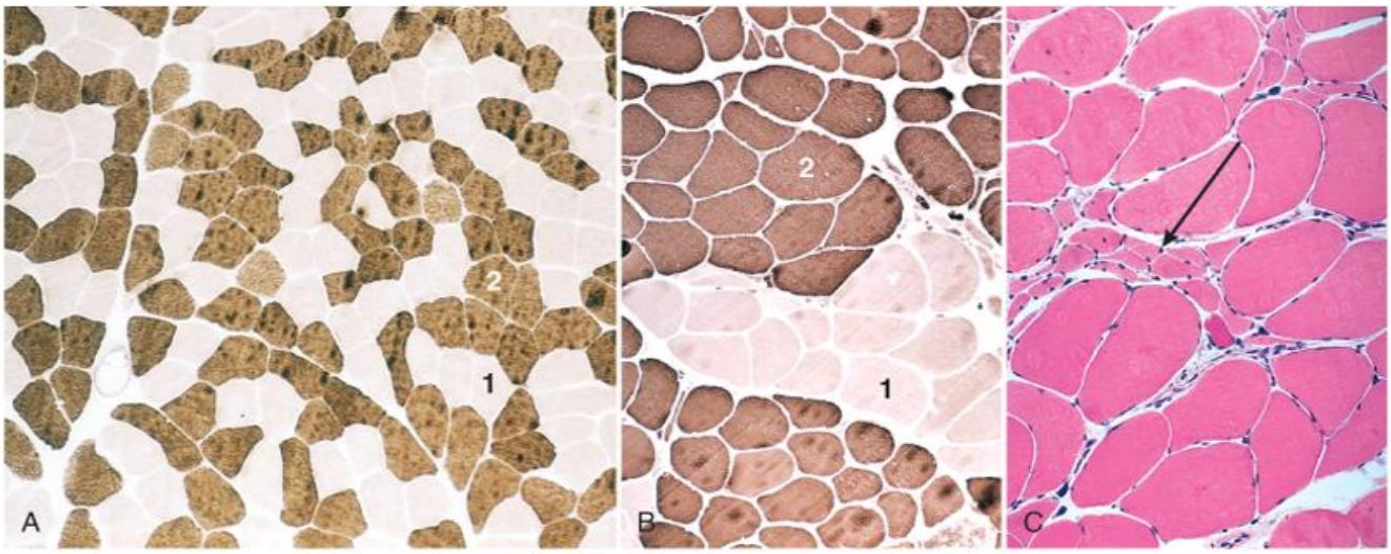


Figure 21-22 **A,** ATPase histochemical staining, at pH 9.4, of normal muscle showing checkerboard distribution of intermingled type 1 (*light*) and type 2 (*dark*) fibers. **B,** in contrast, fibers of either histochemical type are grouped together after reinnervation of muscle. **C,** A cluster of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

Extra explanation of muscle atrophy to understand the next slides:

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 effected don't have any enervation, the neighbouring 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 **group 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.(type grouping)
2) In case of another nerve injury, the type grouping which was formed will be atrophied. (group atrophy)

Picture A shows an intermingled type I and type II fibers
Picture B shows the re-enervating and type grouping
Picture C shows the atrophy of one of the groups (group atrophy)

Neurogenic Atrophy:

–Both fiber types (type I and type II) .

–Clustering of myofibers into small groups.

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

– Loss of a single neuron will affect all muscle fibers in a motor unit, so that the atrophy tends to be scafered over the field.

–With re-enervation, adjacent intact neurons engage the neuromuscular junction of the previously de-enervated fibers ➡ a 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.

Muscular dystrophy

- On of the saddest diseases that effect the male (X-linked disease).
- Often presenting in childhood.
- Heterogeneous group of inherited disease result in progressive muscle injury leading to muscle weakness and wasting which also present with muscle weakness , histologically :(you will see the replacement of the muscle by **fibrofatty tissue**).

(this is the difference between dystrophies and myopathies).

- Duchenne and Becker dystrophy are example of it.

Dystrophin:

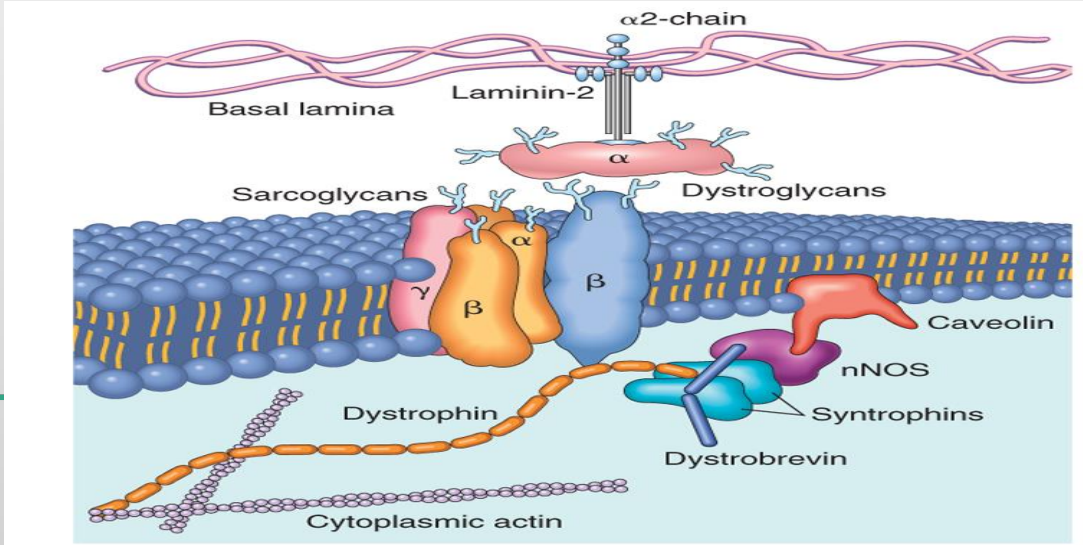
- Dystrophin is a large protein (427 kD) expressed in muscles , brain and peripheral nerves.
- It maintains the structural and functional integrity of skeletal and cardiac myocytes by attaching portion of sarcomere to the cell membrane .

تجي عليهم contraction و بتخلي well function للخلايا الي بتخليهم skeleton هي كانها

- The dystrophin gene found in Xp21 chromosome and span (1% of the total X chromosome) making it one of the largest in human genome.
- Its enormous size is a probable explanation for its vulnerability (قابليته)to mutation .

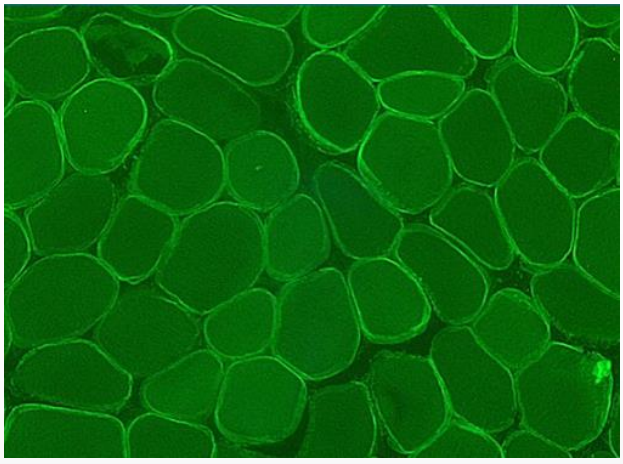
all these muscular dystrophy they are related to dystrophin لازم نعرف انه

- Xp21 : short arm of the chromosome X21

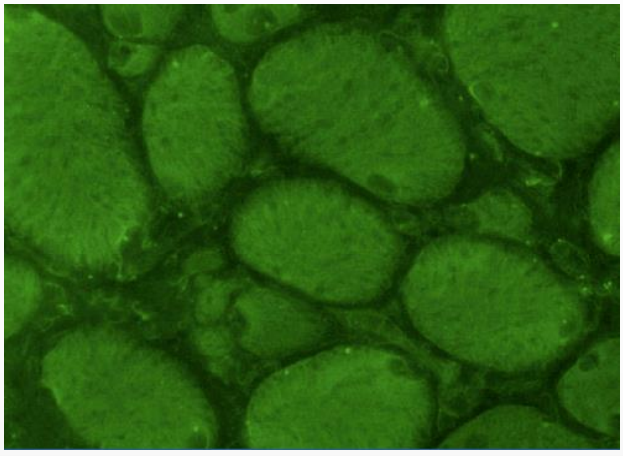


Abnormality in Dystrophin:

- The most common type of mutations is **deletion mutations.** Also it can be frame shift or point mutations .
- approximately two-thirds of the cases are familial (sporadic) with the remainder representing new mutations.
- In effected families, females are carriers: they are clinically asymptomatic but often have elevated serum creartine kinase and show mild histologic abnormalities on muscle biopsy.



Normal dystrophin



Defect in dystrophin

Duchenne and Becker Muscular Dystrophy

- X-linked muscular dystrophy and the two most common forms of the muscular dystrophy.
- DMD and BMD are caused by abnormalities in dystrophin gene.
- Pathogenesis : Dystrophin support muscle fiber strength, and the absence of it reduces the muscle strength.
- The role of dystrophin is **transferring the force of contraction to connective tissue** has been proposed as the basis for myocyte degeneration that occurs with dystrophin defects, or with changes in other proteins that interact with dystrophin.

Duchenne muscular dystrophy (DMD)

- **severe**
- **Most common .**
- most common . Incidence about 1 per 3500 live male births, lead to rapid muscle degeneration
- become clinically evident by age 5.
- the progressive weakness lead to wheelchair dependence by age 10-12 years.
- death by the early 20s.

Becker muscular dystrophy (BMD)

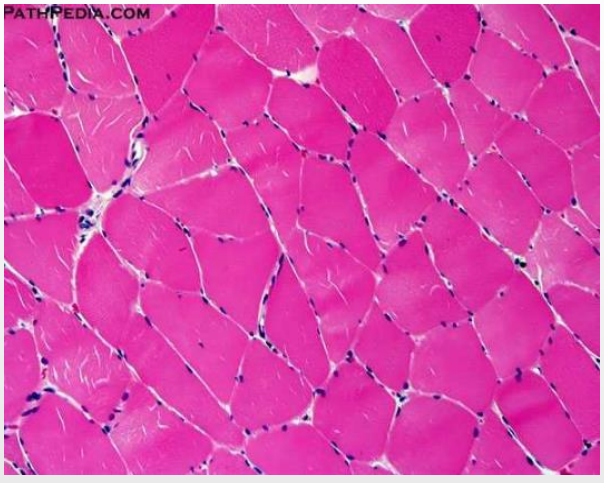
- **Less severe.**
- **Less common.**
- similar to DMD but it takes longer time to develop. slow muscle weakness

A way to remember this (Duchenne is shen , while Becker is Better) 434team

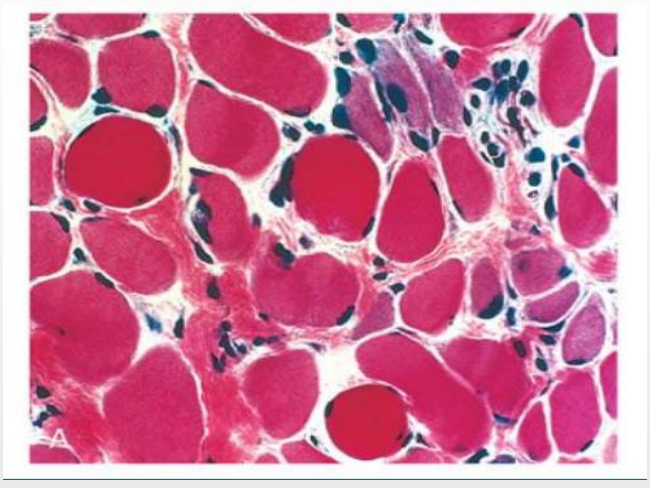
DMD and BMD morphology:

- The histologic features of **both** of them are similar.

- Marked variation in muscle fiber size (atrophy and hypotrophy) .
- Replacement of muscle tissue by fibrosis and fat as a result of degeneration.
- Range of **degenerative changes (fiber necrosis)**
- **Regeneration,** including sarcoplasmic basophilia, nuclear enlargement, and nucleolar prominence
- Connective tissue is increased through out the muscle.
- Extensive fiber loss and adipose tissue infiltration.



Normal skeletal muscle



DMD or BMD

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.

Pathologic changes are also found in the heart , and patient may develop heart failure or arrhythmias.

Cognitive impairment seems to be a component pf disease and it is sever enough in some patient to be considered mental retardation (تخلف عقلي)

Because there is some dystrophin in brain

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 result from : respiratory insufficiency, pulmonary infection, and cardiac decompensation.

Enlargement of the calf muscles associated with weakness, a phenomenon termed pseudohypertroph, 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

Boys with BMD

Develop symptoms at later age than those with DMD.

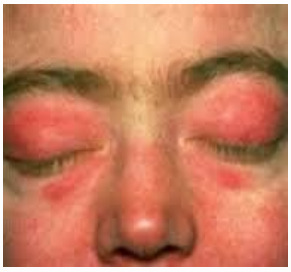
The onset occurs later childhood or in adolescence, and it companied by generally slower and more variable rate of progression

Many have nearly normal life span , although cardiac disease is frequently seen in these patient

Inflammatory Myopathies

(muscle itself disease) , (autoimmune disease)

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



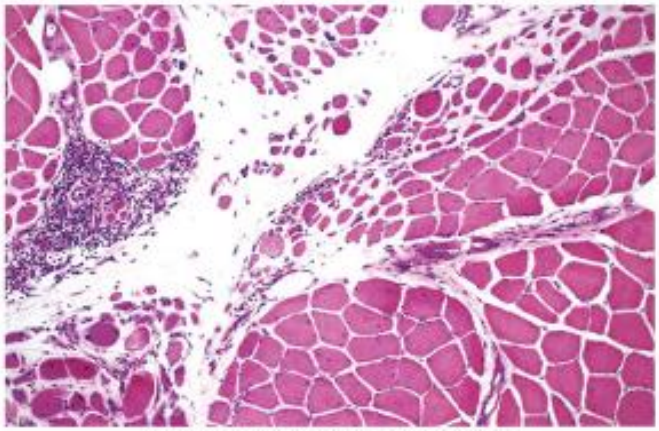
three disorders

Based on the **clinical, morphologic,** and **immunologic features**

- **poly**myositis
  - Multiple muscle are effected by inflammation
- **Dermato**myositis
  - Muscle , derma and skin effected by inflammation
- **Inclusion body** myositis
  - Because we see inclusion body under microscope

From 434

Histologically



- infiltration by lymphocytes.
- degenerating and regenerating muscle fibers.
- The pattern of muscle injury and the location of the inflammatory infiltrates are fairly distinctive for each subtype

The cardinal neuromuscular symptom in myotonic dystrophy is the sustained involuntary contraction of a group of muscles (type of muscular dystrophy)

Characterized by

Myotonia

Clinical features

1- stiffness and difficulty releasing
their grip , Ex : after hand shake .

2- weakness in foot dorsiflexion with weakness of the intrinsic muscles of the hand and wrist extensor.

3- atrophy of facial muscles and ptosis(drooping of the upper eyelid).

4- cardiac arrhythmias.

5- early frontal balding , endrocrinopathies , testicular atrophy and cataracts (a medical condition in which the lens of the eye becomes cloudy)

The mutation

1*Autosomal dominant trait

2*mutation in gene that encodes the dystrophin myotonica kinase DMPK gene

Normally:
This gene contain fewer than 30 repeats of CTG

In affected person :
Several repeats may be present

3*Function of (DMPK) : regulation the production and function of important structure inside muscle cell by interacting with other proteins

5*Location of mutation : the 3' un-translated rejoin in DMPK mRNA

4*Pattern of inheritance: Exhibits the phenomenon anticipation (with each passing generation)

6*Time of incidence : In late childhood

Summery

Classification of skeleton fibers (depending on nerve fiber doing the innervation)

Type I	Type II
Slow twitch	Fast twitch
Dependent on fat	dependent on glycogen
Red meat	White meat

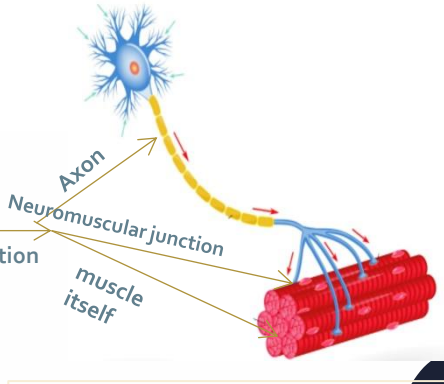
Randomly scattered in a "checkerboard pattern "

Myopathies

Affecting muscles — Morphological features — Clinical features

Common in — Different in

Can involve any portion of motor unite



Classification depends on causes

Neurogenic

Ex : neurogenic atrophy (decrease in size)

Other causes of atrophy rather than neurogenic :
1- Simple disuse (type II)
2-Exogenous glucocorticoid , Or endogenous hypercortisolism (type II)
3- other myopathies

Infectious

Disorders in neuromuscular junction

Ex : Myasthenia gravis

Toxic

Ex :
1-thyrotoxic myopathy .
2- ethanol myopathy.
3- chloroquine .

Congenital

Ex :
1- inherited mutation of ion channels .
2- inborn errors of metabolism .
3- mitochondrial abnormalities .

Inflammatory myopathies

Characterized by immune-mediated muscle injury and inflammation

Ex :
1-polymytosis.
2- dermatomytosis.
3- inclusion body mytosis .

Dystrophy

Degeneration of muscles fiber leading to weakness

Due to

Replacement by fibrofatty tissue

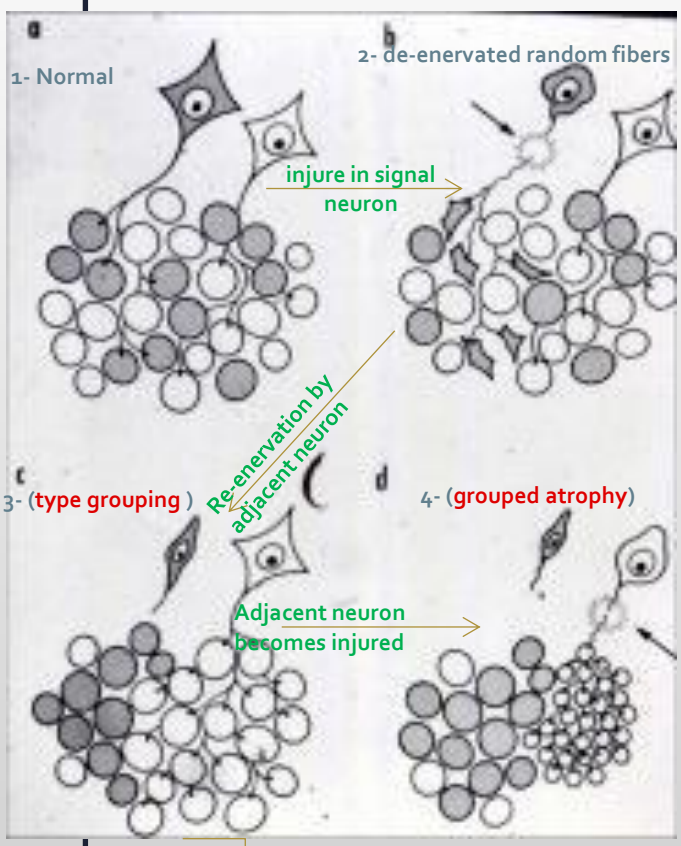
Because of

Mutation in (Xp21) which is responsible for production of dystrophin which maintains structure and function of myocytes

Ex :
1-Mytonia : a type of muscular dystrophy characterized by sustained involuntary.
2-BMD .
3- DMD.

Types

BMD	DMD
Morphology : 1- atrophy and hyper trophy 2- fiber necrosis 3- connective tissue is increased 4- abnormal staining for dystrophin.	
Less common Less sever Normal life span	More common More sever With high mortality
Clinical feature : Cardiac diseases	Clinical features : 1- begins with pelvic girdle then extends to shoulder girdle 2- pseudohypertrophy 3- heart failure or arrhythmias 4- cognitive impairment 5- ↑ serum creatine kinase 6- pulmonary infection 7- cardiac decompensation



Both fibers types

MCQ

1- skeletal muscles which depend on fat catabolism:

A) Type II

B) Type I

C) Both type I and type II

2- loss or shrinkage of muscle fiber is known as:

A) Dystrophy

B) Atrophy

C) Hypertrophy

3- which type of fiber is affected in neurogenic atrophy?

A) Type I

B) Type II

C) Both

4- the most common type of mutation in dystrophin gene is:

A) Nondisjunction

B) Deletion

C) Translocation

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

A) True

B) False

6) Myotonia is:

A) Autosomal recessive disease

B) Autosomal dominant disease

C) X- linked disease

7) What is the gene affected in myotonia ?

1)B
2)B
3) C
4)B
5)B
6) B
7) DMPK gene

Good Luck

Team leaders:

Ashwaq Almajed – Fahad Alzahrani

Team members

Girls:

Nehal Beyari
Ghadah Almuhana
Atheer Alrsheed
Muneerah Alzayed
Raneem Alghamdi

Boys

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