Pathology

Team 435

Lecture (3): 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 Gray: Extra explanation

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Disorders of the skeletal muscles:

Motor unit:

Made up of a **motor neuron** and, a group or a single, **skeletal muscle fibers** supplied 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**.

Skeletal muscles consist of different types of fibers broadly classified as:

- Slow twitch “aerobic” type I fibers.
- Fast twitch “anaerobic” type II fibers.

Thier function depends on:

- The protein complexes that make up the sarcomere and the dystrophin-glycoprotein complex.
- Enzymes that meet the metabolic requirement of the muscle.

Depending on the nature of the nerve fiber doing the enervation, the associated skeletal muscle develops into one of two major subpopulations.

Fiber	Type I	Type II
Color	Red refers to this being the dark (red) meat on birds where fiber type grouping in different muscles (e.g., thigh or breast meat) is quite pronounced.	White
Contraction Speed	Slow	Fast
Conduction Velocity	Slow twitch (contracting slowly, providing endurance rather than strength)	Fast twitch (contracting rapidly, thus providing power rather than endurance)
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)
Normal Distribution	They are normally distributed in checkerboard pattern.	

طريقة لحفظ معلوماته: بما أنه يعتمد على الدهون فنستطيع حفظها كسيناريو، مثلًا: شخص يحب ياكل فرايد تشيكن وغالبًا تكون صدر أو فخذ. فمعناته أكيد تحتوي على دهون ولما نحاول نحرق الدهون ياخذ منا وقت طويل لأن العضلة بطيئة والزيت غالبا يكون أحمر

We must differentiate between **primary muscle diseases (myopathies)** and **secondary neuropathic changes.** Although both are associated with altered muscle function and morphology, each have distinctive features.

Myopathies	Neuropathic changes
- **Primary** muscle diseases. - associated with necrosis and regeneration of **individual** muscle fibers.	- **Secondary** muscle disease. - Caused by disorders that disrupt muscle innervation. - Characterized by fiber type **grouping** and **grouped** atrophy.
Muscle fiber atrophy is **shared** by both neuropathic and myopathic processes.	

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***).

What are Myopathies? It's a skeletal muscle disease.

Myopathy 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.

Skeletal muscle diseases can be divided into:

- Neurogenic: Caused by the nervous system or controlled by it.
- Muscular dystrophies.
- Congenital: (inherited mutations of ion channels, inborn errors of metabolism (e.g. glycogen and lipid storage diseases), mitochondrial abnormalities)
- Toxic: Thyrotoxic myopathy(increased secretion of thyroid hormone), ethanol myopathy and drugs (e.g Chloroquine).
- Infectious.
- Inflammatory myopathies.
- Disorders of the neuromuscular junction (e.g. myasthenia gravis).

We have to know that there are genetic (Inherited) disorders affecting skeletal muscle which include:

- Muscular dystrophies: Inherited diseases that result in progressive muscle injury in patients who usually appear normal at birth.
- Congenital muscular dystrophies: Progressive, early-onset diseases. Some are also associated with CNS[1] manifestations.
- Congenital myopathies:
  A heterogeneous group of inherited diseases that often have a perinatal or early childhood presentation and result in relatively static deficits.

Muscle Atrophy: A nonspecific response, 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.

NOTE: Muscle atrophy is related to high steroid intake.

First remember:
Muscle Atrophy: shrinkage of cell size.
Muscle Dystrophy: Loss of function.

[1] Central nervous system

Causes of Muscle Atrophy:

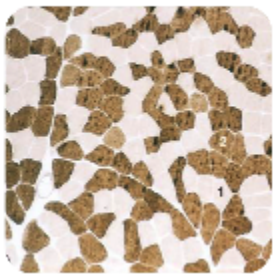
- ❖ Prolonged disuse of muscles:
  - Due to any cause (e.g., prolonged bed rest in the sick, casting of a broken bone).
  - Can cause focal or generalized muscle atrophy, which tends to affect type II fibers more than type I fibers.
- ❖ Glucocorticoid exposure:
  - Whether exogenous or endogenous (e.g. in Cushing Syndrome).
  - Proximal muscles and type II myofibers are affected preferentially by these agents.
- ❖ Myopathies.
- ❖ Neurogenic atrophy:
  - Affects both fiber types. Clustering of myofibers into small **groups**
  - Deprived of their normal innervation, skeletal fibers undergo progressive atrophy.

Disuse and steroid-induced atrophy primarily affects the type II fibers and causes a random distribution of the atrophic myofibers.

Further explanation: Certain disorders are associated with particular patterns of Atrophy (could be grouped atrophy like in neurogenic changes that affect the body or simply the casting of a broken bone could lead to atrophy of muscles) Which means, Different causes could lead to atrophy.

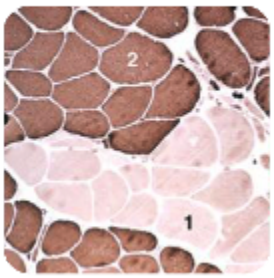
How do neuropathic changes take place?

It starts with a normal checkerboard pattern, normal enervation.
The 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.



Then

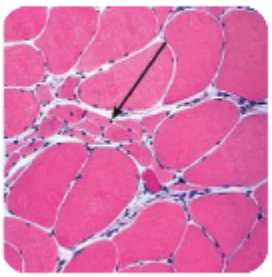
re-enervation takes place, as adjacent intact neurons send out sprouts (budding) to engage the neuromuscular junction of the previously denervated fibers → new connection is established.
These fibers assume the type of the innervating neuron.
After re-enervation:



Then

Type grouping

Whole groups of fibers can eventually fall under the influence of the same neuron, and become the same fiber type.
Grouped Atrophy:



Define:

Type grouping:

When fiber types become independent of one another and become atrophic on their own as they lose their 'checkerboard' appearance.

Group atrophy:

The muscle whose nerve supply was first cut, is mixed or of scattered fibers (types 1&2). However, the enervating nerve (coming in rescue from a nearby muscle) makes the part of muscle it's supplying the SAME fiber type as the nerve's original muscle.

When will grouped atrophy take place?

Results 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

Neuropathy: Disease or dysfunction of one or more peripheral nerves, typically causing numbness or weakness.

Causes could be:

- Nutritional and metabolic.
- Toxic.
- Infections.
- Inflammatory.
- Inherited.
- Vasculopathic.

Pattern of nerve injury:

Most can be subclassified as either axonal or demyelinating. And some disease exhibit both.

	Demyelinating neuropathies	Axonal neuropathies
Description	Characterized by damage to Schwann cells or myelin with relative axonal sparing.	Insults that directly injure the axon.
Result	abnormally slow nerve conduction velocities.	The entire distal portion of the affected axon degenerates.
Morphologically	they show: ➔ Relatively normal density of axons ➔ Features of segmental demyelination and repair.	The morphologic hallmark of axonal neuropathies is a decrease in the density of axons. Regeneration takes place through axonal regrowth and subsequent remyelination of the distal axon.
Recognized by	Presence of axons with abnormally thin myelin sheaths and short internodes.	Axonal degeneration that is associated with secondary myelin loss. Which often referred to as Wallerian Degeneration.
occurs in	Individual myelin internodes[2] randomly; this process is termed segmental demyelination	The axon Secondary myelin loss: Acute axonal injury that results in degeneration of the distal axon and its associated myelin sheath, with atrophy of denervated myofibers.

[2] A space between two nodes

Dystrophinopathies[3]: Duchenne and Becker Muscular Dystrophy

- X-linked Muscular Dystrophy.
- The most common form of muscular dystrophy is DMD.

Duchenne muscular dystrophy (DMD):

Has an incidence of about 1 per 3500 live male births and follows an inexorable fatal course. DMD becomes clinically evident by the age of 5 years; most patients are wheelchair-bound by the time they are teenagers and dead of their disease by early adulthood.

Becker muscular dystrophy (BMD):

This one on the other hand is less common and much less severe, it's considered the "light" version of muscular dystrophy.

Morphology:

- ➔ The histologic features of DMD and BMD are similar except changes are milder in BMD.
- ➔ Progressive replacement of muscle tissue by fibrosis and fat as a result of degeneration outpacing repair.
- ➔ Marked variation in muscle fiber size, and abnormal internally placed nuclei.
- ➔ Both BMD and DMD affect cardiac muscles **(this shows variable degrees of myofiber hypertrophy and interstitial fibrosis)**
- ➔ Hallmarks are: Myofiber necrosis and repair.

Pathogenesis:

- ➢ Both DMD and BMD are caused by loss-of-function mutations in the dystrophin gene located on the short arm X chromosome (Xp21).
- ➢ Dystrophin is a very large protein[4] found in skeletal and cardiac muscles, brain and peripheral nerves.
  - ➔ It is part of the dystrophin – glycogen complex. This complex stabilizes the muscle cell during contraction and may be involved in cell signaling through interaction with other protein.
  - ➔ The dystrophin gene (Xp21) spans (about 1% of the X chromosome), making it one of the largest human genes. (its size is a probable explanation for its particular vulnerability to mutations).
- ➢ The most common type of mutations is deletion mutations.

[3] Mutation in a single gene.
[4] (427 kD in molecular weight)

Clinical features:

Duchenne muscular dystrophy (DMD):

- Muscle weakness begins in the pelvic girdle and next involves the shoulder girdle.
- Enlargement of the calf muscles, termed pseudohypertrophy, is an important early physical finding.
- The increased muscle bulk initially stems from myofiber hypertrophy, but as myofibers progressively degenerate, an increasing part of the muscle is replaced by adipose tissue and endomysial fibrosis.
- High serum creatine kinase levels are present at birth and persist through the first decade of life but fall as muscle mass is lost during disease progression.
- Death results from:
  - Respiratory insufficiency.
  - Cardiac decompensation.
  - Pneumonia.
- Cardiac muscle damage and fibrosis can lead to heart failure and arrhythmias, which may prove fatal.
- No structural abnormalities in the central nervous system have been described.
- cognitive impairment is also sometimes seen and may be severe enough to manifest as mental retardation.

Becker muscular dystrophy (BMD):

- Becomes symptomatic 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

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What is a creatine kinase lab test?

Creatine kinase (CK) is an enzyme produced by the muscles. There are three types of CK produced by major muscle groups:

- **The brain.**
- **The heart.**
- **The skeletal muscle tissue.**

When muscle cells are injured or diseased, enzymes leak out of the cells and enter the bloodstream. Normally, very little CK is found circulating in the blood. Determining which type of CK level is high helps doctors determine which muscle has been damaged. Abnormal levels of this enzyme can provide early warning of a muscular disease, such as:

- **Evidence of a heart attack (Myocardial infarction).**
- **Acute renal failure.**
- **DMD**

CK levels are also higher in women who carry the X-linked gene for Duchenne muscular dystrophy.

Approximately two-thirds of the cases are familial, with the remainder representing new mutation (sporadic). 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.

Note: The doctor pointed out a common confusion with dystrophin, please remember that it is PRESENT in normal individuals and becomes abnormally mutated once affected.

Pathogenesis:

The role of dystrophin is 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.

Acquired Diseases of skeletal muscles

An acquired disorder is a medical condition which develops post-fetally, in contrast with a congenital disorder, which is present at birth.

Toxic Myopathies

A number of insults can cause toxic muscle injury, including intrinsic factors (e.g. thyroxine) and extrinsic factors (e.g., acute alcohol intoxication, various drugs).

Inflammatory Myopathies

The inflammatory myopathies are a group of diseases, with no known cause, that involve chronic muscle inflammation accompanied by muscle weakness.

Toxic Myopathies

Thyrotoxic myopathy:

May take the form of either acute or chronic proximal muscle weakness.

Can be the first indication of thyrotoxicosis. Histologic findings include myofiber necrosis and regeneration.

Ethanol myopathy:

Occurs after an episode of binge drinking.

The degree of rhabdomyolysis may be severe, sometimes leading to acute renal failure.

Patients usually complain of acute muscle pain, which may be generalized or confined to a single muscle group. Microscopically:

there is myocyte swelling, necrosis, and regeneration.

Drug myopathy:

Can be produced by a variety of agents.

Clinical features:

The affected muscles show evidence of myopathic injury, usually without an inflammatory component.

Inflammatory Myopathies

Polymyositis, dermatomyositis, and inclusion body myositis are the most important primary inflammatory myopathies.

Polymyositis: is an autoimmune disorder

Clinical Features:

- Increased expression of MHC class I molecules on myofibers

-predominantly endomysial inflammatory infiltrates containing CD8+ cytotoxic T cells.

Dermatomyositis:

is the most common inflammatory myopathy in children, in whom it appears as an isolated entity. In adults, it can manifest as a Para-neoplastic disorder.

Inclusion body myositis:

the most common inflammatory myopathy in patients older than 60 years of age. It is lumped in with other forms of myositis.

The morphologic hallmark of inclusion body myositis is the presence of rimmed vacuoles

Other x-linked and autosomal muscular dystrophies:

Muscular Dystrophy	Description and Symptoms	How does it affect people?
Myotonic dystrophy (Inherited as an autosomal dominant trait)	**Description:** Involuntary contraction of group of muscles (the most important symptom) Mutation in the gene that encodes for dystrophia myotonica protein kinase{DMPK}. **Symptoms:** - Stiffness and difficulty in releasing the grip after a hand shaking. - Anticipation happens : the disease gets worse by new generations. E.g.: if my mother gets diabetes at age of 40 and was mild , I will get it by 35 and it will be severe.	- Normally, we have less than 30 repeats of the sequence CTG {nitrogenous bases : cytosine, thymine, guanine}. - In affected people they have several thousand repeats {trinucleotide repeat expansion }. - It's accompanied with Myotonia which is Inability to relax voluntary muscle after vigorous effort. **Consequences and symptoms:** Manifests in late childhood with gait abnormalities (abnormal walking) due to weakness of foot dorsiflexors , cataracts , early frontal balding , testicular and facial muscle atrophy , ptosis {eyelids falling down} , cardiac arrhythmias.
Limb-girdle muscular dystrophy (Inherited as either autosomal dominant or autosomal recessive)	Affects proximal musculature of trunk and limbs.	- The genetic basis are heterogeneous **The mutations affect:** - Dystrophin-glycoprotein complex other than dystrophin. - Proteins involved in vesicle transport and repair of cell membrane after injury (caveolin-3 and dysferlin)
emery-dreifuss muscular dystrophy (X-linked or autosomal dominant form)	**Description:** A structural protein in nucleus gets affected by mutations. **Symptoms:** - Muscle weakness and wasting. - Contractures of the elbows and ankles, and cardiac disease. - If the cardiac involvement is severe, it might lead to death..	**It's rare but has 2 types :** - The x-linked form : mutation in gene encoding for protein emerin. - The autosomal dominant form : Mutation in gene encoding for lamin A/C (a Protein). It is hypothesized that defects in these proteins compromise the structural integrity of the nucleus in cells that are subjected to repetitive mechanical stress {e.g.cardiac and skeletal muscle}.
Facioscapulohumeral dystrophy. (Inherited as an autosomal dominant form)	- Patients become symptomatic by the age of 20 years, with weakness in the facial muscles, the shoulder, the lower trunk and the dorsi-flexors of the foot.	- There is a deletion in chromosomal region (4q35) - Most affected people have a normal life expectancy.

Mitochondrial Myopathies:

It can stem from mutations in either the mitochondrial or nuclear genomes; because some mitochondrial enzymes are encoded in nuclear DNA.

Clinical Features (Mitochondrial myopathies typically present:):

- Manifestation in early adulthood. - Proximal muscle weakness.
- Sometimes with severe involvement of the ocular musculature (external ophthalmoplegia).
- There can also be neurologic signs and symptoms, lactic acidosis, and cardiomyopathy.

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قال صلى الله عليه وسلم: من سلك طريقاً يلتمس فيه علماً سهل الله له به طريقاً إلى الجنة.

دعواتنا لكم بالتوفيق.