PATHOLOGY TEAM "430"

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Myopathies

The Motor Unit

- *is comprised of:*
  - *a* ***motor neuron*** *in the brain or spinal cord*
  - *its associated peripheral axon*
  - *distal* ***neuromuscular junction***
  - *the* ***skeletal muscle fibers*** *that are innervated*

Skeletal Muscle Fiber Types

There are two types ***"type I" and "type II"*** *neuron will innervate multiple muscle fibers and these fibers are usually randomly scattered in a* ***"checkerboard pattern"***

NOTE:

The normal fibers are arranged in *"checkerboard pattern"*

Also, they are found in "grouping"

Skeletal Muscle Fiber Types

Fiber types	The color	The contraction	The metabolism
Type I	Red	Slow twitch	Fatty acid
Type II	White	Fast twitch	Anaerobic glycolysis Mainly (glycogen)

- Because the TCA and oxidative phosphorylation chain depend on oxygen to continue, high storages of oxygen stored in myoglobin, which is red oxygen bearer, giving the muscle its dominant red color.
- Also because this system goes through a lot of process and cycles it is relatively slower, hence the its name: slow twitch muscles.

Muscle Atrophy

- General term: Atrophy means shrinkage of cell size from loss of its intercellular substance. Atrophy can rise from a number of different reasons, where cells are still alive but functions significantly fall.
- A non-specific response
- Characterized by abnormally small myofibers

Types of muscle atrophy

1- Simple disuse

(e.g., prolonged bed rest, immobilization to allow healing of a bone fracture) can cause profound atrophy.

2- Exogenous glucocorticoids or endogenous hypercortisolism

(e.g., in Cushing syndrome), typically involving proximal muscle groups more than distal ones.

- ***Just to help you understand:***
- ***Glucocorticoids are naturally produced steroid hormones, or synthetic compounds, that inhibit the process of inflammation.***
- ***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.***

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

***Atrophic myofibers** are also found in myopathies*

the finding that suggest a myopathic etiology:

1- *additional morphologic changes like myofiber degeneration and regeneration*
2- *inflammatory infiltrates are features*

Neurogenic Atrophy is one of the types of muscle atrophy

***Def. the loss of the conduction of the neuron to the muscle fibers** and that will lead to*

1- *Atrophy*
2- *Abnormality in grouping (both type I and type II)*

The process of Neurogenic Atrophy (Reading)

However, following re-enervation, adjacent intact neurons send out sprouts to 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.

MYOPATHY

- ***Myopathy as a term may encompasses a heterogeneous group of disorders, both morphologically and clinically***

Types of Myopathies

- ***skeletal muscle disease can be divided into:***
- ***Neurogenic***
- ***Muscular dystrophies***
- ***Congenital***
- ***Toxic***
- ***Infectious***
- ***Disorders of the neuromuscular junction (e.g. myasthenia gravis)***

Congenital Myopathies

1- inherited mutations of ion channels (channelopathies)
2- inborn errors of metabolism
(exemplified by glycogen and lipid storage diseases)
3- mitochondrial abnormalities .

1- Ion channel myopathies

The cause: mutations in genes that encode ion channels.

Example : Hyperkalemic periodic paralysis (cause: mutations in the gene for the skeletal muscle sodium channel protein SCN4A)

***Clinical presentation*: Myotonia, relapsing episodes of hypotonic paralysis (associated with variably abnormal serum potassium concentrations), or both.**

Just to help you understand:

- ***Hypotonia means decreased muscle tone***
- ***Myotonia is a congenital condition that refers to a neuromuscular condition in which the relaxation of a muscle is delayed or slowed. The Condition usually improves after the muscles have warmed-up.***

Def.

myotonia *A sustained involuntary contraction of a group of muscles*

2- Inborn errors of metabolism

Include

- ***glycogen synthesis and degradation***
- ***abnormalities in lipid handling***

***The cause:* abnormalities of the carnitine transport system or deficiencies of the mitochondrial dehydrogenase enzyme systems.**

***Clinical presentation:* significant lipid accumulation within myocytes (lipid myopathies)**

3-Mitochondrial myopathies

The cause: ***Mutations in either mitochondrial or nuclear DNA that encodes mitochondrial constituents.***

It presents :

- ❖ ***in young adulthood***
- ❖ ***with proximal muscle weakness***
- ❖ ***sometimes with severe involvement of the ocular musculature (external ophthalmoplegia)***
- ✓ ***There can be neurologic symptoms, lactic acidosis (decrease in pH value due to increase in lactic acid, becomes more acidic), and cardiomyopathy***

– ***Just to help you understand: Proximal muscle weakness: Symmetric weakness of the large muscles closest to the trunk of the body. Initially, hips, thighs and shoulders are commonly affected. Shoulder and pelvic girdle muscles are most severely affected. The weakness may make it difficult to lift heavy objects, climb stairs, or lift your arm to comb hair or put on a coat. The weakness can progress to the point that it is difficult to rise from a chair. If your neck muscles are involved, which is the case for about half of patients, it may be difficult to lift your head when lying down.***

The findings in skeletal muscle are:

- ✓ ***irregular muscle fibers***
- ✓ ***aggregates of abnormal mitochondria***
- ✓ ***the latter impart a blotchy (an irregular patch or unsightly mark on a surface) red appearance to the muscle fiber on the modified Gomori trichrome stain (stain used for histological preparation***

of slides) " Ragged red fibers " Ragged means: (rough, imperfect, or faulty

Under the electron microscopic:

Some of them contain paracrystalline parking lot inclusions or alterations in the structure of cristae of mitochondria.

Toxic Myopathies

Include disorders caused by intrinsic exposures (e.g. thyroxine) versus extrinsic exposures (e.g., alcohol, therapeutic drugs)

	Thyrotoxic myopathy	*Ethanol myopathy "binge drinking"*	*Chloroquine*
Site of myopathy	*acute or chronic proximal muscle weakness*	*Acute toxic rhabdomyolysis with accompanying myoglobinuria that can cause renal failure*	*proximal myopathy*
The finding	*myofiber necrosis, regeneration, and interstitial lymphocytes*	*myocyte swelling and necrosis, myophagocytosis, and regeneration*	*myocyte vacuolization, and with progression, myocyte necrosis*

- **Just to help you understand: Chloroquine is used to treat and to prevent malaria. it is also used to treat infections caused by amoebae.**

DISEASES OF THE NEUROMUSCULAR JUNCTION

Myasthenia Gravis

Def. ***An autoimmune disorder of the neuromuscular junction characterized by muscle weakness***

- ***3 in 100,000 person***
- ***Any age and has a predilection for women***
- ***Thymic hyperplasia is found in 65% and a thymoma in 15% of patients***

The cause: ***the autoantibodies against the Ach receptors lead to loss of functional Ach receptors at the neuromuscular junction.***

Clinical presentation:

- ***weakness is first noticed in the extraocular muscles***
- ***Repetitive electrophysiologic stimulation typically elicits diminishing muscle strength***

Treatment: ***anticholinesterase agents "Neostigamine"***

Inflammatory Myopathies

It is characterized by immune-mediated muscle injury and inflammation

Three disorders:

- ❖ *Polymyositis*
- ❖ *Dermatomyositis*
- ❖ *Inclusion body myositis*

	Polymyositis	Inclusion body	Dermatomyositis
Type Of immunity	mediated by cellular immunity (cytotoxic T cells)	mediated by cellular immunity (cytotoxic T cells)	Humeral immunity (antibody-mediated)
The site	Proximal muscles	Distal muscles	Proximal muscles

- ✓ *The diagnosis feature of myopathies injury (e.g., increased blood levels of creatine kinase)*

Additional info. About Dermatomyositis

- ✓ *Women with dermatomyositis may develop visceral cancers (of the lung, ovary, stomach)*

Histologically:

- ✓ *infiltration by lymphocytes*
- ✓ *degenerating and regenerating muscle fibers*

Clinical presentation:

- ✓ *symmetric muscle weakness*

- ✓ ***it may be associated with rash (classically described as a lilac or heliotrope discoloration) affects the upper eyelids and causes periorbital edema.***

Homework

- ***What does the mitochondrial genome (mtDNA) encode?***

  Twenty-four of the genes specify RNA molecules involved in protein synthesis while the remaining 13 encode proteins required for the biochemical reactions that make up respiration. A number of rare diseases are caused by mutations in mitochondrial DNA, and the tissues primarily affected are those that most rely on respiration, i.e. the brain and nervous system, muscles, and the kidneys and liver.

  Mitochondrial diseases include Leber's hereditary optic neuropathy, in which there is loss of vision often combined with cardiac arrhythmia, and Kearns-Sayre syndrome, which involves paralysis of the eye muscles, dementia and seizures.

- ***Why the Diseases that involve mtDNA show maternal inheritance?***
  all mitochondrial diseases are maternally inherited, i.e. passed exclusively from mothers to their children.

This is because all the mitochondria in the developing human embryo come from the egg. There are no mitochondria in the sperm head, which carries the paternal half of the nuclear genome.

Source: Robbins basic pathology, 8th edition