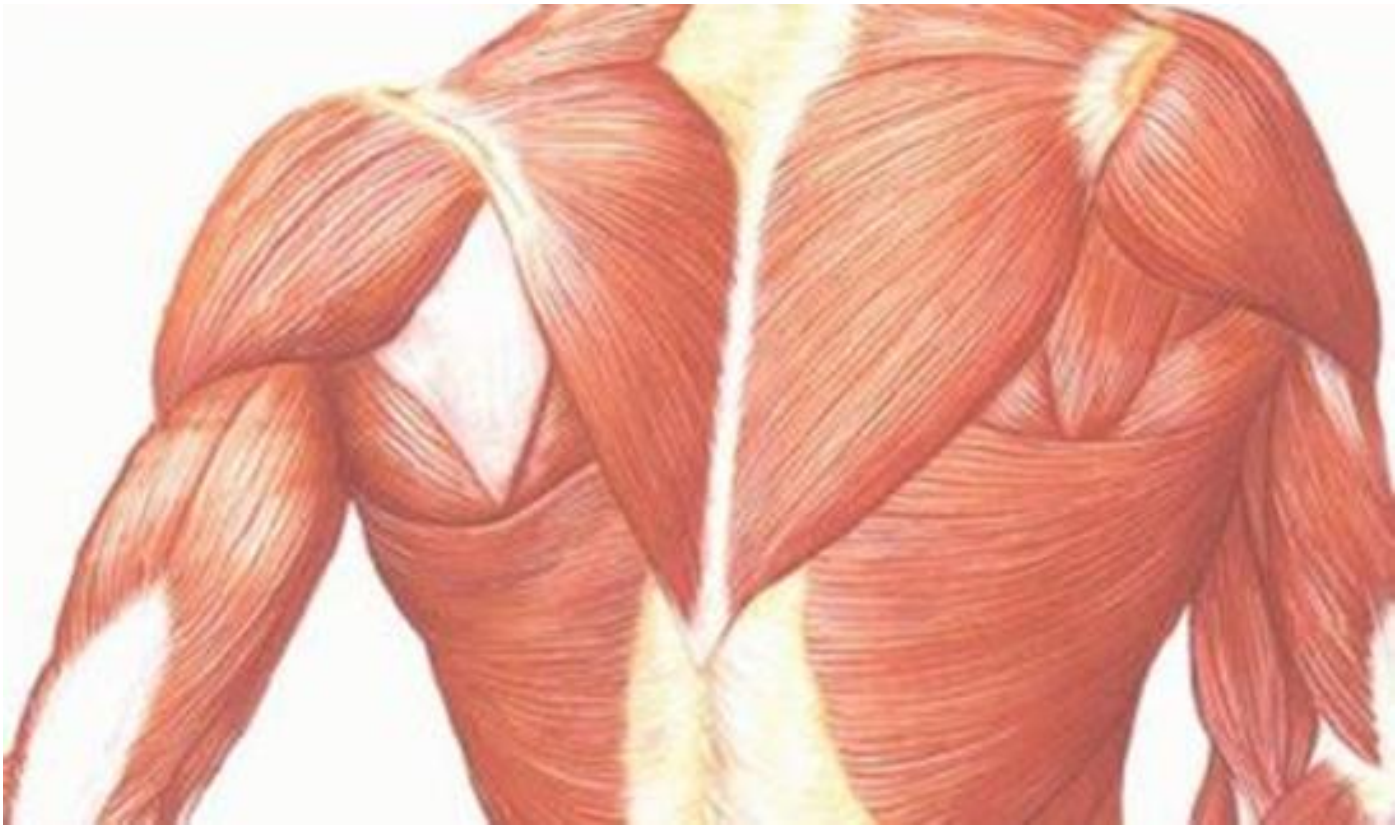
Disorders of Skeletal Muscle

Lecture: 3rd lecture for boys & 1st lecture for girls
Email: pathology433@gmail.com
Date: 17-12-2013



PATHOLOGY
TEAM 433

Objectives:

At the end of this lecture, the students should be able to:

- **Understand the structure of various types of muscle fibers.**
- **Acquire a basic knowledge of the classifications of myopathies and give examples of these disorders.**
- **Understand the meaning of 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.**

Videos to Watch:

- Myopathy ¦ Treatment and Symptoms

http://www.youtube.com/watch?v=a5qMpzUpRj0

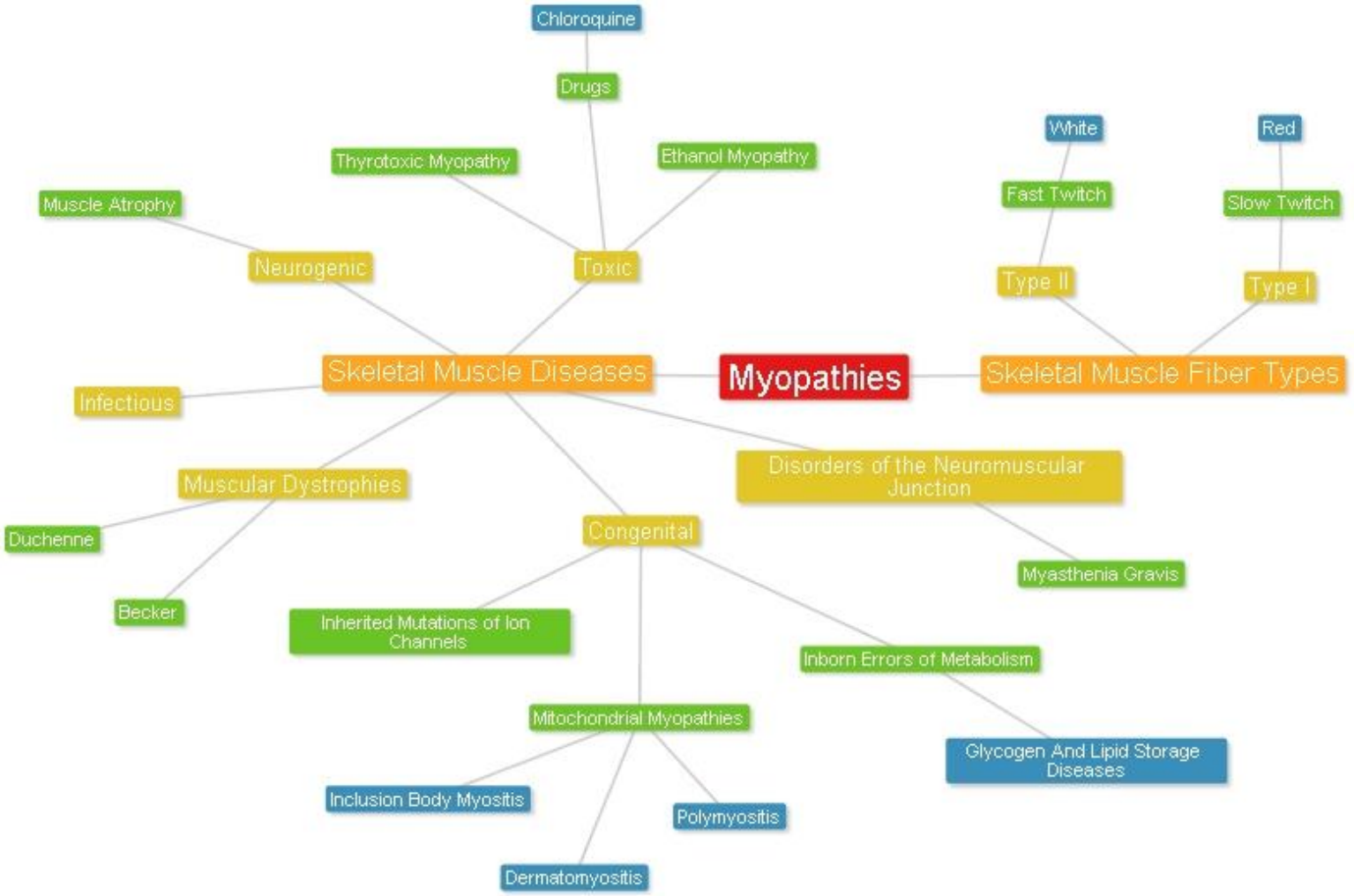
Just the first half is relevant, the rest is about treatment.

- Myotonic Dystrophy ¦ Treatment and Symptoms

http://www.youtube.com/watch?v=e5zURmxktjY

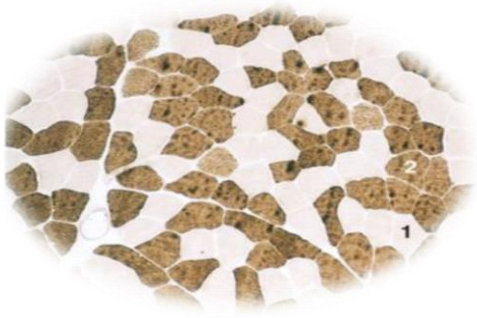
- Myasthenia Gravis ¦ Treatment and Symptoms

http://www.youtube.com/watch?v=Asa8DHsfaoo


Chloroquine
Drugs
Thyrotoxic Myopathy
Ethanol Myopathy
Muscle Atrophy
Neurogenic
Toxic
White
Red
Fast Twitch
Slow Twitch
Type II
Type I
Skeletal Muscle Diseases
Myopathies
Skeletal Muscle Fiber Types
Infectious
Disorders of the Neuromuscular Junction
Muscular Dystrophies
Duchenne
Congenital
Myasthenia Gravis
Becker
Inherited Mutations of Ion Channels
Inborn Errors of Metabolism
Mitochondrial Myopathies
Glycogen And Lipid Storage Diseases
Inclusion Body Myositis
Polymyositis
Dermatomyositis

Skeletal muscle Fiber types:

- Depending on the nature of the nerve fiber doing the enervation, the associated skeletal muscle develops into one of two major subpopulations
- The rule about the color of the muscle relies on the nerve supplying that muscle which means the function of the muscle
- They are normally distributed in Checkerboard pattern.
- Their function depends on:
  1- The protein complex that make up sacromere and dystrophin-glycoprotein complex.
  2- Enzymes.



- A cross section of a normal skeletal muscle shows circles these circles have two different colors depending on the muscle fiber type,
- A normal skeletal muscle looks like chess board, two types in a random fashion.

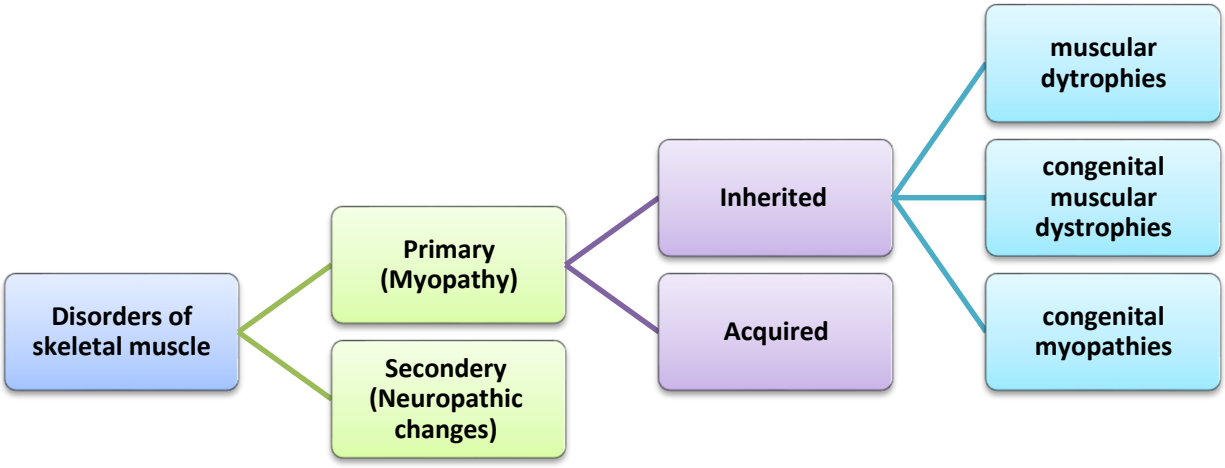
The two major component of skeletal muscle fibers	
Type I	Type II
○ slow twitch & aerobic ○ red, refers to this being the dark (red) meat on birds where fiber type grouping in different muscles (e.g., thigh vs. breast meat, chicken leg, chicken hip, wings and neck) is quite pronounced ○ For example, standing or if the muscle is already strong and lifts weights (aerobic exercise) ○ The routine sustain action	○ fast twitch & anaerobic ○ For example, exercise (تمارين حديد) the process of lifting new weights depends on type 2, the pathway is not oxygenated that's why you feel pain after several exercises (anaerobic exercise). ○ people who lift weights, their biceps will usually have type 2 fibers ○ quick strong action ○ The fast source of energy is glycogen.

Note: The rule about the color of the muscle relies on the nerve supplying that muscle which means the function of the muscle

They are normally distributed in Checkerboard pattern.

Their function depends on:

1- **The unique protein complex that make up the sacromere & the dystrophin-glycoprotein complex.**
2- **Enzymes.**



Myopathies:

Myopathies:

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

Note: Biopsy cannot be used for a motor nerve because it will cause paralysis, so biopsy is used for skeletal muscle to determine if it is neurogenic or primary myopathy.

Skeletal Muscle Diseases

Neurogenic	• When the nerve supplying that muscle is damaged.
Muscular dystrophies	• Muscle proteins mutation
Congenital	• Abnormalities in the contraction process of skeletal muscle • *Inherited mutations of ion channels* • *Inborn errors of metabolism* (e.g. glycogen and lipid storage diseases) • *Mitochondrial abnormalities*
Toxic	• *Thyrotoxic myopathy* • *Ethanol myopathy* , can lead to severe myopathy, rhabdomyolysis • *Drugs (e.g Chloroquine for malaria)*
Disorders of the neuromuscular junction	• e.g. Myasthenia Gravis
Infectious	

Myopathies & neuropathic changes are associated with:

1- Altered muscle function & morphology.
2- Disruption of muscle by endomysial fibrosis & fatty replacement.

Myopathic conditions are often associated with:

1- **Segmental necrosis & regeneration of individual muscle fibers.**
2- **Sometimes may have inflammatory infiltrates.**
3- **Intracellular inclusions.**

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 and some are associated with CNS manifestation.**

Congenital Myopathies

- **Heterogenous group of inherited disease that often have a perinatal or early childhood presentation and result in relatively static deficits.**

<table>
<tr><th colspan="2">Inherited Myopathies</th></tr>
<tr><th>(X-linked diseases)</th><th>Channalopathies, Metabolic Myopathies & Mitochondria Myopathies</th></tr>
<tr><td>Dystrophinopathies: Duchenne & Becker Muscular Dystrophy: (DMD & BMD)
<u>Will be explained in the next page</u></td><td rowspan="2">Ion channel myopathies:
- Characterized by myotonia (see the last page).
- Could be characterized by relapsing episodes of hypotonic paralysis associated with abnormal serum potassium levels.
- Caused by: mutations in the gene encoding the skeletal muscle sodium channel protein SCN4A.</td></tr>
<tr><td>Limb-girdle muscular dystrophy.
- Affect the the proximal musculature of the trunk and limbs.
- Some of the responsible mutations affect components of the dystrophin-glycoprotein complex other than dystrophin. Others affect proteins involved in vesicle transport and repair of cell membrane after injury.</td></tr>
<tr><td>Emery-Dreifuss muscular dystrophy. (EMD)
- Rare.
<u>- X-linked form</u>, Caused by mutation in the gene encoding the protein Emerin.
<u>- Autosomal form,</u> caused by mutation in the gene encoding the protein Lamin A/C.
<u>- Clinical Features:</u>
I- Progressive muscle weakness and wasting.
II- Contractures of the elbows and ankles.
III- Cardiac disease.
The cardiac involvement is severe, being associated with cardiomyopathy and arrhythmias that lead to sudden death in up to 40% of patients.</td><td rowspan="2">Myopathies due to inborn errors of metabolism:
- Include disorders of glycogen synthesis and degradation, and abnormalities in lipid handling.

Mitochondrial myopathies:
- Caused by mitochondrial mutations show maternal inheritance.
- Mitochondrial myopathies usually manifest in early adulthood with proximal muscle weakness and sometimes with severe involvement of the ocular musculature.</td></tr>
<tr><td>Fascioscapulohumeral dystrophy.
- Autosomal dominant form of muscular dystrophy that is usually associated with deletions in chromosomal region 4q35.
- <u>Clinical Features:</u>
- Patients become symptomatic by the age of 20 years.
- Weakness in the facial muscles and the shoulder.
- Patients also exhibit weakness in the lower trunk and the dorsiflexors of the foot.
- Most affected persons have a normal life expectancy.</td></tr>
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Dystrophy is a descriptive term, used to describe a muscle if it is fibrotic متليفة, atrophic, and there is necrosis and regeneration of the muscle.
•Most dystrophies تنتج عن تشوهات thus, most of them are present at young age.

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. Because if muscles are damaged they do not get back to normal, regeneration occurs but not effective.
–Histologically, in advanced cases muscle fibers are replaced by fibrofatty tissue (fibrous and fatty tissue)
•This distinguishes dystrophies from myopathies, which also present with muscle weakness

Dystrophinopathies: Duchenne & Becker Muscular Dystrophy: (DMD & BMD)
- The most common of muscular dystrophies.
- The most important diseases manifestations linked to mutation in the Dystrophin gene. (Caused by it)
- Females are carriers with Duchenne and Becker (a mild dystrophy).

Duchenne Muscular Dystrophy	Becker Muscular Dystrophy
1- Incidence of 1 per 3500 live in male births. 2- Follows inexorable fatal course. 3- Become clinically evident by the age of 5. 4- most teenaged-patient are wheelchair-bound. 5- Death occurs at early adulthood. **Clinical features:** - Clumsiness due to muscle weakness. (1st symptom) - Weakness begins in pelvic girdle then shoulder girdle. - Pseudohypertrophy, which is enlargement of the calf muscles due to the replacement of myofibers by adipose tissue & endomysial fibrosis. - Cardiac muscle damage and fibrosis can lead to heart failure and arrhythmias, which may prove fatal. - ↑ Serum keratin Kinase: present at birth, persist through the first decade of life but fall as muscle mass is lost during disease progression. Death results from respiratory insufficiency, pneumonia, and cardiac decompensation.	The Becker type of muscular dystrophy is less common and much less severe. **Clinical Features:** - Becomes symptomatic later in childhood. 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 - Becker may be has normal life expectancy. **Clinical Feature.** - May result in death in the absence of significant skeletal muscle weakness.

Morphology:

- DMD and BMD are morphological similar, except the BMD is milder.
- Progressive replacement of muscle tissue by fibrosis and fat is the result of degeneration outpacing repair. As a result, muscles typically show marked variation in myofiber size and abnormal internally placed nuclei.
- Both affect cardiac muscles, which show variable degrees of myofiber hypertrophy and interstitial fibrosis.
- Abnormal staining for dystrophin.

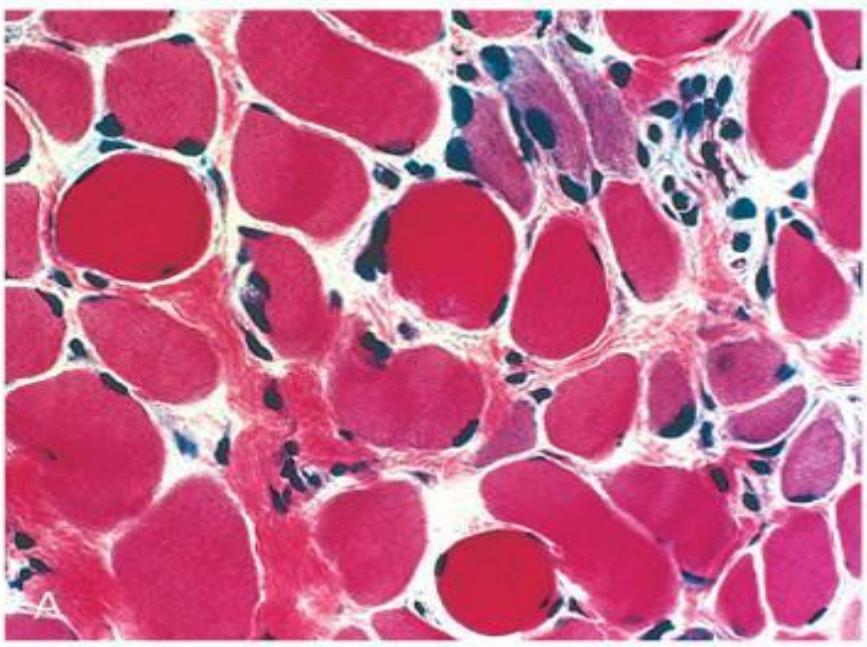
Pathogenesis:

Both DMD & BMD are caused by loss-of-function mutations in the dystrophin gene located on the short arm of the X chromosome (Xp21).

NOTE: Dystrophin is a very large protein found in skeletal and cardiac muscle, brain, and peripheral nerves; it is part of the dystrophin-glycoprotein complex. Dystrophin-glycoprotein complex defects lead to:

1- Disruption of the sarcolemma » Calcium influx.
2- Disruption of intracellular signaling.

Note: The Severity of the disease correlate with the degree of the dystrophin deficiency



The appearance of the muscle where there is atrophy, fibers are not similar some are large others are small. There are basophilic (blue or purple) fibers, and eosinophilic fibers (red or pink) Basophilic means that the muscle fiber is regenerating (trying to develop).

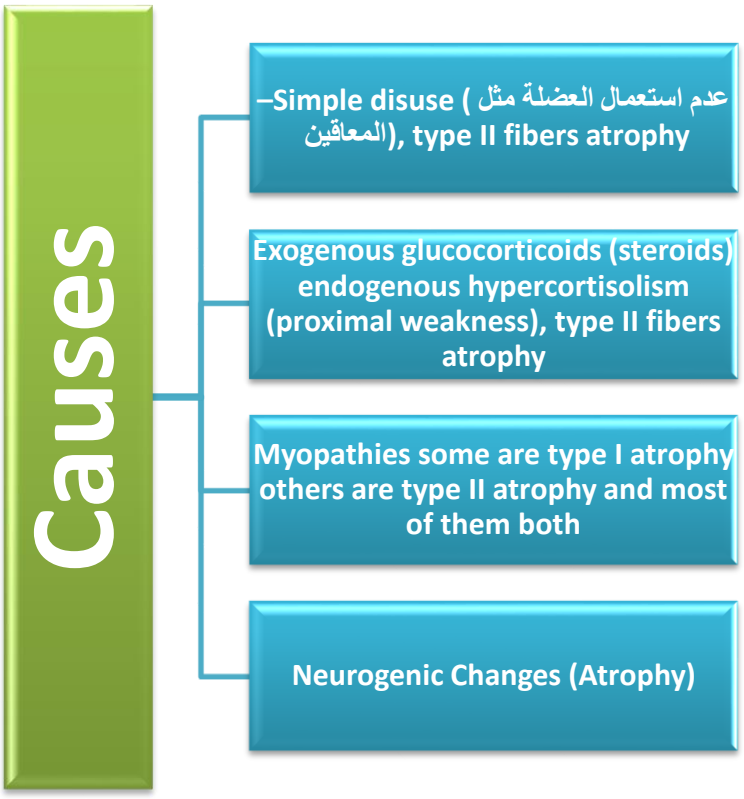
Acquired Myopathy	
Inflammatory Myopathies	**Toxic Myopathies**
Polymyositis: An autoimmune disorder associated with: **1- Increased expression of MHC class I molecules on myofibers.** **2- Predominantly endomysial inflammatory infiltrates containing CD8+ cytotoxic T cells.** **- Patients with polymyositis are often successfully treated with corticosteroids or other immunosuppressive agents.** **Dermatomyositis: The most common inflammatory myopathy in children.** **In adults, it can manifest as a paraneoplastic disorder.** **- Some patients have autoantibodies that are relatively specific for dermatomyositis; these include antibodies against:** **1- Mi-2 (a nuclear helicase).** **2-p155.** **3-p140.** **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, leading some to speculate that this is a degenerative disorder of aging.** **- Typical of chronic inflammatory myopathies.** **- Myopathic changes.** **- The disease follows a chronic, progressive course.** **- Generally does not respond well to immunosuppressive agents.**	**- Intrinsic factors (e.g. thyroxine) & extrinsic factors (e.g. drugs, alcohol) can cause toxic muscle injury.** Thyrotoxic myopathy: - Can cause acute or chronic proximal muscle weakness. - The first indication of thyrotoxicosis. - Histologic findings include myofiber necrosis and regeneration. Ethanol myopathy: - Occurs after drinking too much of alcohol. -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: - Most commonly causes are the drugs of statin family. - The affected muscles show evidence of myopathic injury, usually without an inflammatory component.

Muscle Atrophy:

A non-specific response (less organelles, degeneration means it is a live cell not dead)

- **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**
- **Atrophy: shrinkage of an organ because of a decreased cell size**
- **Histologically, in advanced cases muscle fibers are replaced by fibrofatty tissue.**

It is shared by both myopathic processes and neuropathic changes (atrophy).



1- Neuropathic changes (Atrophy): (MOST SEVERE)

-Are characterized by fiber type grouping and grouped atrophy.

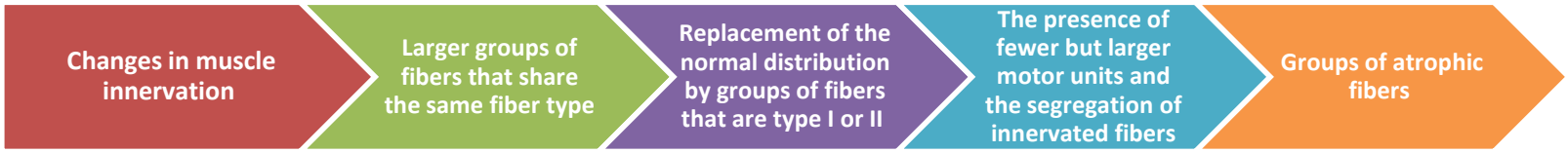
-Mechanism:

2 - Prolonged disuse of muscles:

e.g., prolonged bed rest in the sick, casting of a broken bone) can cause local 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.



Note for neuropathic changes (Atrophy): The fiber type of myofibers is not an inherent feature, but is dictated by the innervating motor neuron. Thus, if injury and regeneration of peripheral nerves alters muscle innervation, it will change the distribution of type I and type II myofibers.

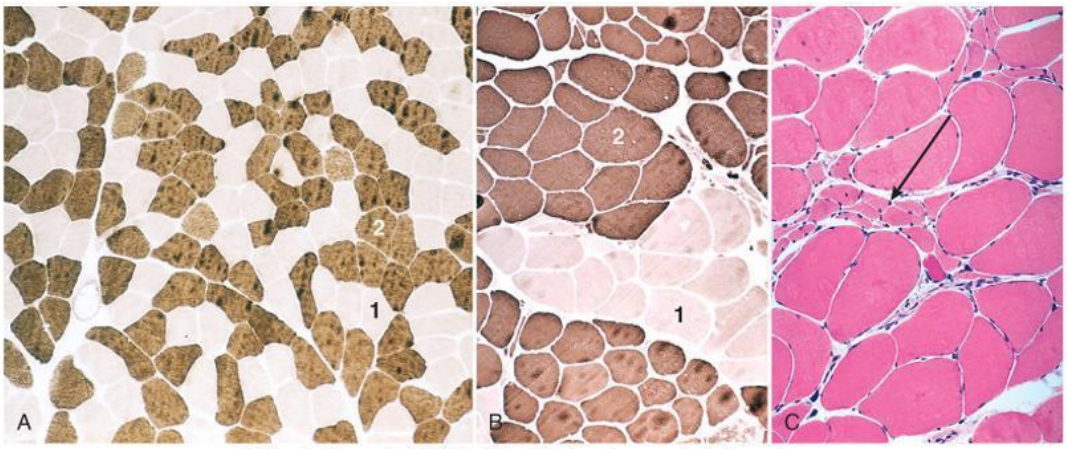


Figure 21-22 **A,** ATPase histochemical staining, at pH 9.4, of normal muscle showing checkerboard distribution of intermingled type 1 (*light*) and type 2 (*dark*) fibers. **B,** in contrast, fibers of either histochemical type are grouped together after reinnervation of muscle. **C,** A cluster of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

ATPase stain is used to distinguish between type I and type II

Homework:

- **Define Myotonia?**

The sustained involuntary contraction of a group of muscles is the cardinal neuromuscular symptom in myotonic dystrophy. Patients often complain of stiffness and difficulty releasing their grip, for instance, after a handshake.

- **What are the inheritance and the mutation pattern that characterize myotonic dystrophy?**

Myotonic dystrophy is inherited as an autosomal dominate trait. More than 95% of patients with myotonic dystrophy have mutation in the gene that encodes the dystrophia myotonic a protein kinase (DMPK). In normal subjects this gene contains fewer than 30 repeats of the sequence CTG, whereas in severely affected person, several thousand repeats maybe present. Myotonic dystrophy thus falls into the group of disorders associated with trinucleotide repeat expansions.

- **What is the clinical presentation of myotonic dystrophy?**

The disease often manifests in late childhood with gait abnormalities due to weakness of foot dorsi flexors, with subsequent progression to weakness of the intrinsic muscles of the hands and wrist extensors, atrophy of the facial muscles, and ptosis. Other tissues may also be affected presenting as cardiac arrhythmias, cataracts, early frontal balding, endocrinopathies, and testicular atrophy.

MCQ'S:

1) 5 years old boy displays muscular weakness. He is unable to play with the other children. Quickly becoming tired and unable to keep up. The serum creatine kinase level is elevated. A muscle biopsy is performed, and it has the appearance shown her at low magnification. Which of the following laboratory test finding would be most appropriate to determine the diagnosis?

A. **Serum Acetylcholinesterase Antibodytiter**
B. **Immunuohistochemical Staining for Dystrophin**
C. **Eosinophil Count in Blood**
D. **Presence of Oligoclonal Bands of Immunoglobulin In Cerebrospinal Fluid**

Important Note:
Inherited muscle dystrophy x-linked muscle dystrophy

2) A 35-year- old man has experienced increasing weakness of pelvic and shoulder girdle muscles over several years time. A western blot analysis of affected muscles showed reduced amounts of dystrophin with an abnormal molecular weight.

A. **Amyotrphic Lateral Sclerosis**
B. **Becker Muscular Dystrophy**
C. **Dermatomysitis**
D. **Duchenne Muscular Dystrophy**

Answers:
1. B
2. B

3) A 56- year-old female has had increasing generalized muscle weakness for the past 2 months. On physical examination: She has 3/5 motor strength in both upper and lower extremities. She is afebrile but has a blood pressure of 155/90 mm hg. A gastrocnemius muscle biopsy is performed and histochemical staining of the biopsy shows type 2 muscle fiber atrophy . Which of the following conditions is the most likely to have?

A. Cushing Syndrome

B. Mcardle Disease

C. Duchenne Muscular Dystrophy

D. Myasthenia Gravis

4) A 44-year- male, who has worsening congestive heart failure for the past year. Has muscular weakness involving upper arms and legs .A deltoid muscle biopsy is performed, and the immunuohistochemical staining pattern with antibody to dystrophin is shown here (A, normal: B, patient). Which of the following conditions does he most likely have?

A. Werding – Hoffmann Disease

B. Polymyositis

C. Becker Muscular Dystrophy

D. Myasthenia Gravis

Note: The biopsy shows reduced amount of dystrophin suggesting becker muscle

Answers:
3. A
4. C