Hashemite University
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Medical School Committee

Scientific Team
الفريق العلمي

PATHOLOGY

FINAL LECTURE 1/ Skeletal Muscle

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SKELETAL MUSCLE :

☼ **The motor unit consists of:**
- Motor neuron in CNS (brain or spinal cord)
- Peripheral axon
- Neuromuscular junction
- Skeletal muscle fibers.

☼ **Skeletal muscle fiber are 2 types :**
- Type I "slow twitch"

هي العضلات الحمراء الكبيرة الي بتكون في ال Axil group
- Type II "fast twitch"

هي العضلات البيضاء الصغيرة الي بتكون في الاصابع وجفن العين وفي اي مكان يحتاج الى حركة سريعة

☼ **Diseases that affect skeletal muscle can involve any portion of the motor unit**

☼ **Skeletal muscle diseases can be divided into disorders characterized by;**
(1) Muscle Atrophy (Neurogenic changes or myofiber)
(2) The more common muscular Dystrophies
(3) Myopathies (Selected congenital & toxic)
(4) Disorders of the neuromuscular junction.

☼ 1. MUSCLE ATROPHY ضمور العضلات
- Muscle atrophy is a non-specific response in a variety of muscle disorders. It is characterized by {abnormally small myofibers}

Causes of Atrophy :	**fiber type :**	**characterized by :**
1. Loss of muscle innervation	both fiber types I & II	clustering of myofibers into small groups
2. Simple disuse	type II fibers	prolonged bed rest or immobilization , can cause profound muscle atrophy .
3. Cushing syndrome	type II fibers (typically involving proximal more than distal muscle groups.)	whether exogenous (taken from any source) or endogenous resulting in Glucocorticoids hypercortisolism ,cause muscle atrophy
4. Myopathies	-	cause myofibers atrophy, and the features that suggest a myopathic etiology includes the additional finding of myofiber degeneration & regeneration, or inflammatory infiltrates.

A.Neurogenic Atrophy

☼ Skeletal fibers undergo progressive atrophy if they are deprived of their normal enervation ضمور بسبب فقد اتصالها بالعصب المغذي

☼ It is important to recall that, 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.

اكيد بما انه النيورون الي بغذي مجموعة فايبرز انقطع فالضمور رح يصير بالوحدة الحركية كاملة

● However, following re-enervation, adjacent intact neurons send out sprouts to engage the neuromuscular junction of the previously de-enervated fibers.

Once the new connection is established these fibers assume the type of the innervating neuron. In this manner, whole groups of fibers can eventually fall under the influence of the same neuron & become the same fiber type (fiber type grouping)

في حال رجعنا عملنا لل reenervation التي انقطع عنها التغذية muscle fiber فالنيورونز تبعت العضلات/ الفايبر المجاورة رح تبعت براعم حتى تدعم عملية التغذية

● In that setting, if the relevant enervating neuron now becomes injured, rather large coalescent groups of fibers are cut off from the trophic stimulation & wither away {Shrink} (grouped atrophy), a hallmark of recurrent neurogenic atrophy.

☼ **2. MUSCULAR DYSTROPHIES**

Are inherited heterogeneous group of disorders, often presenting in childhood, characterized by progressive muscle fibers degeneration leading to muscle weakness & wasting.

◙ Histo, in advanced cases, the muscle fibers are replaced by fibrofatty tissue {a histologic feature distinguishes dystrophies from myopathies, which also present with muscle weakness}.

مهم جدا.. ال fibrofatty تحدث فقططططط في ال dystrophies وهاد الي بميزها عن ال myopathies

A.X-Linked Muscular Dystrophy

(Duchenne & Becker Muscular Dystrophy)

DMD is the most severe & the most common form of the two, with an incidence of about 300/per Million live male births.

Pathogenesis:

DMD & BMD are caused by abnormalities in the dystrophin gene located on the short arm of the X chromosome (Xp21).

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

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

*The role of dystrophin in 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

*The dystrophin gene spans roughly 2400 kilobases (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.
*Deletions appear to represent a large proportion of the genetic abnormalities.
*Approximately 2/3 of the cases are familial, with the remainder representing new mutations.

Histological feature:
both DMD & BMD show similar changes of marked
*variation in muscle fiber size, caused by concomitant myofiber hypertrophy {evident by sarcoplasmic basophilia, nuclear enlargement, & nucleolar prominence}
*atrophy, with many of the residual muscle fibers show degenerative changes, i.e., fiber splitting & necrosis.
*Connective tissue is increased throughout the muscle بالوضع الطبيعي يكون الكونيكتيف كميته قليلة جداااا
*In the late stages of the disease, extensive fiber loss & adipose tissue infiltration are present in most muscle groups.
*Changes in cardiac muscle in either DMD or BMD includes variable degrees of fiber hypertrophy & interstitial fibrosis.

Clinically :
*DMD becomes clinically evident by age 5, with progressive weakness leading to wheelchair dependence by age 10 to 12 years, & death by the early 20s.
Although the same gene is involved in both BMD & DMD, BMD is less common & much less severe.

*Boys with BMD develop symptoms at a later age than those with DMD. The onset occurs in later childhood or in adolescence, & it is accompanied by a generally slower & more variable rate of progression.
Although cardiac disease is frequently seen in these patients, many have a nearly normal life span

*boys with DMD are normal at birth & early motor milestones are met on time. النقاط مهمين
1. Walking, however, is often delayed
2. Muscle weakness, which begins in the pelvic girdle muscles & then extends to the shoulder girdle.
3. Pseudohypertrophy (enlargement of the calf muscles associated with weakness) is an important clinical finding; the ↑ muscle bulk is caused initially by an↑ in the size of the muscle fibers & then, as the muscle atrophies, by a ↑ in fat & connective tissue.
4. Pathologic changes are also found in the heart, & patients may develop heart failure or arrhythmias.
5. 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 ↓.

*In affected families, females are carriers; they are clinically asymptomatic but often have elevated serum creatine kinase & can show mild histologic abnormalities on muscle biopsy. Female carriers, however, are at risk for developing dilated cardiomyopathy.مهم

Diagnosis :
*Definitive diagnosis is based on the demonstration of abnormal staining for dystrophin in immunohistochemical preparations or by western blot analysis of skeletal muscle مهمم

*Muscle biopsy specimens from individuals with DMD show virtually no dystrophin by either immunohistochemical staining or western blot analysis, explaining the greater severity of their presentation

*In comparison, individuals with BMD show diminished amounts of an abnormal molecular weight dystrophin, reflecting mutations that apparently permit limited synthesis of a defective (but still partially active) protein.

*Death results from **respiratory insufficiency**, **pulmonary infection**, **& HF**.

B.Autosomal Muscular Dystrophies
 Other forms of muscular dystrophy share many features of DMD & BMD but have distinct clinical & pathologic characteristics.
Some of these muscular dystrophies affect specific muscle groups

Diagnosis: is based largely on the clinical pattern of muscle weakness.

● Sixteen (16) autosomal limb girdle muscular dystrophies subtypes have been identified which affect the proximal musculature of the trunk & limbs (similar to the X-linked muscular dystrophies).

● Six inherited as autosomal dominant
● Ten as autosomal recessive disorders; four of which are caused by mutations of the sarcoglycan complex of proteins with other forms being associated with other cytoskeletal proteins or caveolin.

C.Myotonic Dystrophy تقلص لا ارادي مستمر في مجموعة من العضلات
● The cardinal neuromuscular symptom in myotonic dystrophy is Myotonia, a sustained involuntary contraction of a group of muscles;
● Patients often complain of "stiffness تشنج " & have difficulty in releasing their grip, for instance, after a handshake.
● Myotonia can often be elicited by percussion of the thenar eminence.
●The disease often presents in late childhood with gait abnormalities attributable to weakness of foot dorsiflexors; it progresses to weakness of the intrinsic muscles of the hands & wrist extensors; atrophy of facial muscles with ptosis(عدم القدرة على رفع الجفن) ensues.

☼ **3. MYOPATHY**
● Myopathy encompasses both, morphologically & clinically heterogeneous group of disorders, which can be segregated into congenital & acquired toxic forms.
● Recognition of these disorders is important for
(I) genetic counseling
(II) appropriate treatment of acquired disease.

A.Congenital Myopathies:
►Important subcategories include disorders caused by:
1. Ion channel myopathies are a group of familial diseases characterized clinically by
A. myotonia تقلص لا ارادي مستمر
B. relapsing episodes of hypotonic paralysis (associated with variably abnormal serum potassium concentrations), or both. شلل متقطع يحدث على فترات بتميز بارتفاع البوتاسيوم في الدم

These diseases are caused by mutations in genes that encode ion channels. Thus, hyperkalemic periodic paralysis results from mutations in the gene for the skeletal muscle sodium channel protein SCN4A, which regulates sodium entry during contraction.

2. Malignant hyperthermia ارتفاع درجة الحرارة بصورة غير طبيعية
is a rare clinical syndrome characterized by a dramatic hypermetabolic state (tachycardia, tachypnea, muscle spasms, & later hyperpyrexia) triggered by anesthesia, usually involving halogenated inhalational agents & succinylcholine; mutations have been identified in genes encoding calcium channels.

3. Myopathies due to inborn errors of metabolism include disorders of glycogen synthesis & degradation ,& abnormalities in lipid handling (lipid myopathies).

4. Mitochondrial myopathies can involve mutations in either mitochondrial or nuclear DNA that encodes mitochondrial constituents.
*Mitochondrial myopathies typically present in young adulthood with proximal muscle weakness, & sometimes with severe involvement of the ocular musculature (external ophthalmoplegia).

Pathologic findings:
In skeletal muscle are irregular muscle fibers & aggregates of abnormal mitochondria; the latter impart a blotchy red appearance to the muscle fiber on the modified Gomori trichrome stain, hence the term ragged (torn) red fibers

The EM appearance is also often distinctive: there are ↑ numbers of, & abnormalities in, the shape & size of mitochondria, some of which contain paracrystalline parking lot inclusions or alterations in the structure of cristae

B.Toxic Myopathies (can be treated)
1. Thyrotoxic myopathy
can present as either acute or chronic proximal muscle weakness, & can precede the onset of other signs of thyroid dysfunction.
Findings include myofiber necrosis, regeneration, & interstitial lymphocytes.

2. Ethanol myopathy بسبب شرب كميات كبيرة من الكحول وقت قصير
can occur with binge drinking, where there is an acute toxic rhabdomyolysis ذوبان , causing myoglobinuria that can cause renal failure.
Clinically:
The patient may acutely develop pain that is either generalized or confined to a single muscle group.

Histological features:
There is myocyte swelling, necrosis, myophagocytosis and regeneration.

3. Chloroquine
can produce a proximal myopathy, the most prominent finding is myocyte vacuolization progressing to necrosis. يستخدم في علاج الملاريا، ايضا تم استخدامه ضمن علاج كوفيد 19

☼ 4. Diseases of the neuromuscular junction

A. Myasthenia Gravis الضعف الشديد جداً والقاتل في العضلات

● An autoimmune disorder of the neuromuscular junction characterized by muscle weakness, affecting 30 Million persons; it can present at any age & has a predilection for Women (are effected more than men)

● Thymic hyperplasia is found in 65% & a thymoma in 15% of patients.

● Circulating Abs to the skeletal muscle acetylcholine receptors (AChRs) are present in nearly all patients, associated with a ↓ in the number of AChRs. مهمم

●The disease can be transferred to animals with serum from affected patients, demonstrating the causal role of the anti-AChR Abs.

Pathogenesis:
In most cases, the auto-Abs against the AChR lead to
1.loss of functional AChRs at the neuromuscular junction.
2.The link between autoimmunity to AChRs & the thymic abnormalities is unclear. Nevertheless, most patients show improvement after thymectomy.

Clinical Features:
● Typically, weakness is first noticed in the extraocular muscles; drooping eyelids (ptosis) & double vision (diplopia) cause the patient to seek medical attention.
The generalized muscle weakness can fluctuate dramatically, with alterations occurring over the course of days, hours, or even minutes.

(I) Repetitive electrophysiologic stimulation typically elicits diminishing muscle strength
(II) patients show marked improvement after administration of anticholinesterase agents - the latter presumably by ↑ the levels of ACh in the neuromuscular synapse; Both (I & II) maneuvers are diagnostically useful.مهمم

● Sensory & autonomic functions are not affected in myasthenia gravis. مهمم

Respiratory compromise was a major cause of mortality in the past; 95% of patients now survive more than 5 years after diagnosis because of improved treatment
1. anticholinesterase drugs 2. prednisone, 3. plasmapheresis
4. thymic resection 5. ventilatory support.

B. Lambert-Eaton Myasthenic Syndrome
Characteristically develops as a paraneoplastic process, most commonly in the setting of small-cell lung carcinoma of the lung (60% of cases); it can also occur in the absence of malignancy.

Although individuals with Lambert-Eaton syndrome also present with muscle weakness, the syndrome is distinct from myasthenia gravis in several ways:
(1) Anticholinesterase administration does not improve symptoms;
(2) Autonomic function is affected;
(3) Electrophysiologic studies demonstrate that repeated stimulation elicits increasing muscle strength.

بال myasthenia يحدث العكس فالعضلة تضعف اكثر واكثر..

☼ SKELETAL MUSCLE TUMORS

* Almost, all skeletal muscle neoplasms are malignant.
The benign rhabdomyoma is very rare (Cardiac rhabdomyomas are examples of hamartomas.)

Rhabdomyosarcoma
 Rhabdomyosarcoma is the most common soft tissue sarcoma of childhood مهمم & adolescence, usually appearing before age 20.

 Interestingly, they occur most commonly in the head, neck or genitourinary tract, usually at sites where there is little, if any, skeletal muscle as a normal constituent !

The gross appearance:
is variable.
*Some tumors, particularly those arising near the mucosal surfaces of the bladder or vagina (urogenital sinus), can present as soft, gelatinous, grapelike masses, designated sarcoma botryoides
*In other cases they are poorly defined, infiltrating masses.

Sarcoma botryoides (the commonest sub-type of rhabomyosarcoma): urogenital sinus of a neonate.مهم
pink-white tumor arising from the region of the urogenital sinus in a grapelike masses.
The tumor recur & metastasis & having very poor prognosis.

Histologically:
*Rhabdomyosarcoma is subclassified into the embryonal, alveolar, & pleomorphic variants.
*The rhabdomyoblast is the diagnostic cell in all types; it exhibits granular eosinophilic cytoplasm rich in thick & thin filaments. The rhabdomyoblasts may be elongated (also known as tadpole or strap cells) or round & may contain cross-striations visible by light microscopy.
Diagnosis:
is based on the demonstration of skeletal muscle differentiation, either by
(1) Immunohistochemical demonstration of muscle-associated antigens such as desmin, muscle-specific actin & myogene
(2) in the form of sarcomeres under the EM. rarely

Treatment:
● Rhabdomyosarcomas are aggressive cancers treated with a combination of surgery, chemotherapy, & radiation.
Location & the histologic variant of the tumor influence survival; embryonal, pleomorphic, & alveolar variants have progressively worsening prognoses.
The malignancy is curable (?) in almost 2/3 of children, but adults do much more poorly.
علامة الاستفهام بسبب انه ما في حالة شفاء شوهدت على ارض الواقع لكن هيك مكتوب في الكتاب..

كل المطلوب من السلايدات موجود في التلخيص .. الدكتور حذف اول فقرة من سلايد 125 ...