Lecture 60

Editing file

Medicine Team

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# Myopathies

## Objectives:

By the end of the lecture the student should be able to:

- ★ Recognize and identify symptoms of myopathic disorders.
- ★ Understand the role of laboratory and radiological investigations in myopathy.
- ★ Discuss clinical and pathological features of selected myopathic disorders.
- ★ Discuss the management of inflammatory myopathies, dystrophic myopathy, malignant hyperthermia and selected drug-induced myopathies (statin and steroid-induced)

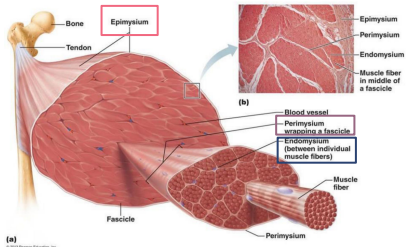
## Color index:

Original text Females slides Males slides
Doctor's notes Textbook Important Golden notes Extra

# Normal Muscle Physiology & Histology

## ◀ Introduction

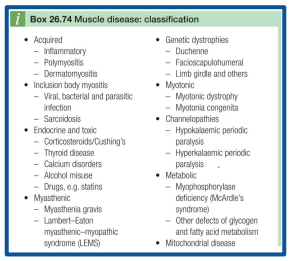
- Myopathies: Myo (muscle) pathos (Suffering)
- A disorder in which there is a primary functional or structural impairment of skeletal muscle




around the muscle is a connective tissue sheath called epimysium, within the muscle we have groups of fascicles surrounded by perimysium, within the fascicles are muscle fibers surrounded by endomysium

| Extra | Muscle Fibers |
|---|---|
| **TYPE 1: Slow twitch, red** | **TYPE 2: Fast twitch, white** |
| ❑ Aerobic<br>❑ Generating force over a more protracted interval.<br>❑ Fatigue slowly<br>❑ More dependent on a steady supply of O2<br>❑ ++++ myoglobin ⟶ redder Contain more lipid and mitochondria than fast-twitch fibers | ❑ Anaerobic<br>❑ Generating large amounts of force quickly .<br>❑ Fatigue easily<br>❑ Contain more glycogen and myofibrillar ATPase<br>❑ Less myoglobin ⟶ white |

## ◀ Classification of myopathies




| Acquired | Hereditary |
|---|---|
| Inflammatory myopathies<br>• **Dermatomyositis**<br>• **Polymyositis**<br>• Inclusion body myositis (IBM)<br>• Immune-mediated necrotizing myopathy | Muscular Dystrophies<br>• Dystrophinopathies<br>  ○ Duchenne<br>  ○ Becker<br>• Limb-girdle muscular dystrophies<br>• Myotonic dystrophies |
| Drug-induced myopathies<br>• **Statin**<br>• Penicillamine<br>• **Steroids**<br>• Chloroquine | Congenital Myopathies |
| Toxic myopathies (Alcohol, Cocaine & Heroin) | Mitochondrial myopathies |
| Endocrine myopathies<br>• Steroid<br>• **Hypothyroidism**<br>• Hypoparathyroidism | Metabolic storage myopathies |
| Infectious myopathies (Parasite, Virus) | Channelopathies |
| Myopathies associated with other systemic illness | Myotonias |

# Approach - 6 Questions



## ◄ Approach

- First goal in approaching patients with a suspected muscle disease is to determine the correct **site** of the lesion:
  - Proximal muscle weakness with preservation of sensation doesn't always equal myopathy. it could be from NMJ, AHC, roots, motor nerves.

**Confirmed site as muscle? then :**

1. Identify whether the myopathy is **caused by:**
   a. defect in the muscle channel
   b. Abnormal muscle structure
   c. dysfunction in muscle metabolism.
2. Determine the **cause** of the myopathy
3. Determine **management**:
   a. Treatable?
   b. Frequency of cardiac/respiratory surveillance? Most of the time you would screen for **cardiac** and **respiratory** function, even with mild myopathy symptoms.
   c. Counselling[1]: exercise? Precautions on rhabdomyolysis[2]

## ◄ Approach - 6 Questions

**6 Questions**

| Q1 | Q2 | Q3 | Q4 | Q5 | Q6 |
|---|---|---|---|---|---|
| Which Negative and/or Positive Symptoms do patients demonstrate? | What is the temporal evolution? | Is there a family history of:<br>- Myopathic disorder?<br>- Cardiac disease? | Are there precipitating factors that trigger episodic weakness or stiffness? | Are there associated systemic symptoms or signs? | What is the distribution of weakness? |

## ◄ Q1: Which Negative and/or Positive Symptoms do patients demonstrate?

**What are the negative/positive symptoms?**

**Negative symptoms:**

- Exercise intolerance
- Fatigue
- Muscle atrophy
- Weakness
- Dysphagia, dysarthria
- SOB

**Positive symptoms[3]:**

- Cramps
- Contractures
- Muscle hypertrophy
- Myalgias
- Myoglobinuria
- Stiffness
- Rippling muscle
- Tremor

1- Specific for rare serious complication of certain type of genetic muscular disorder, ex: pts with RYR1 mutation can have malignant hyperthermia when exposed to volatile anesthetic agents.
2- Any pt with genetic muscular disorder have a risk of developing rhabdomyolysis which is the breakdown of muscles. which can cause renal impairment if not treated with adequate hydration. Educate the pts.
3- fasciculation is a specific form of abnormal muscle movement usually involve Anterior horn cells. A clonus usually means UMN lesion involvement.

# Approach - 6 Questions

## ◀ Symptoms of Myopathies

### I. Fatigue

- Much less useful negative symptom → may be a result of patients' overall health, cardiopulmonary status, level of conditioning, sleeping habits, or emotional state.
- **Define intensity and duration of exercise that provokes fatigue** (They will tell you, after lifting 2kg weights for x times, I feel fatigued.) → metabolic and mitochondrial myopathies.

### II. Exercise intolerance

- Problem with energy utilization.
- Intolerance for short exercise → carbohydrate disorder
- Intolerance for long exercise → lipid disorder

### III. Limb muscle weakness & atrophy

**Proximal muscle weakness** is the **cardinal symptom** of myopathy, most of muscle diseases present with bilateral muscle weakness.

- E.g. difficulty combing hair (due to deltoid weakness), washing hair in shower, climbing stairs (you need to have good proximal thigh muscles), squatting, waddling gait.
- Shoulder girdle → scapular winging (patient will say "i feel something is coming out of my back")
- **Other muscles;**
  - **Eye muscles** → ophthalmoplegia (patient will not be able to move their eyes), ptosis.
  - **Facial weakness** → difficulty closing eyes, whistling, using straw.
  - **Bulbar muscles** → dysphagia, choking, nasal speech due to palatal muscle weakness.
  - **Respiratory muscles** → dyspnea, orthopnea[2], it can lead to death if it's acute.
  - **Cardiomyopathy** → heart failure, arrhythmias

### IV. Myalgias (Muscle pain)

**Myalgias are Vague aches and muscle discomfort that happen with or without exercise.**
**If the neuromuscular examination is normal and laboratory studies (CK) are also normal,** then it is unlikely to be muscle in origin

1) **Episodic** → metabolic myopathies.
2) **Nearly constant** → inflammatory or metabolic myopathies.

1- the most important symptom, distal muscle can be involved but for the sake of teaching you just need to know that if someone has a proximal muscle weakness you should think of muscle disease, not nerve, spinal cord or brain disease.
2- Traditionally you think of cardiac causes e.g. heart failure, but muscle weakness especially diaphragm can cause it (when you lay flat the diaphragm cannot go down by the gravity so it will push on the lung causing almost a constrictive type of lung movement.

# ◀ Symptoms of Myopathies *cont.*

## V. Muscle Cramps

- Specific type of muscle pain.
- Usually localized to a particular muscle region, **typically the calves.**
- EMG: **Rapidly firing** motor unit discharge
- Involuntary contractions of muscle (seconds-minutes).
- It's a common sensation especially if you don't have a good exercise function at baseline.
- Most are benign, not related to an underlying disease process, but they can be a symptoms of muscle disease when they are **persistent, frequent, and happen in exercise.**
- Can occur in MND, chronic neuropathies, etc
- Risk factors: old age, dehydration, prolonged sitting, diuretics (they alter electrolytes), low Mg, hypoT4, DM.
- Other causes: Dehydration, Hyponatremia, Azotemia (renal impairment), Myxedema (hypothyroidism) & disorders of the nerve or motor neuron (ALS"Amyotrophic lateral sclerosis").

## VI. Muscle contractures

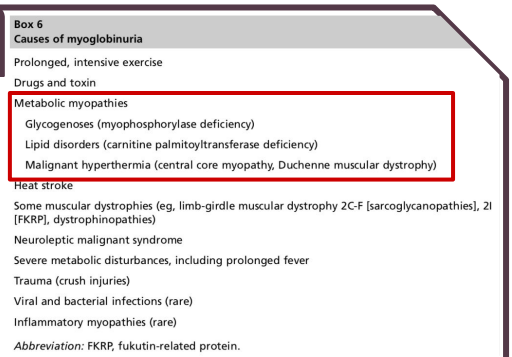
- Uncommon but can superficially resemble a cramp.
- **Typically provoked by exercise** in patients with **glycolytic enzyme defects** (metabolic myopathy)
- **Last longer than cramps** (This is one way to differentiate it from cramps)
- EMG: **silent** (Unlike cramps)
- Do not confuse with fixed contractures of tendons

## VII. Myotonia

- **Impaired relaxation after sustained voluntary contraction**
  - Caused by repetitive depolarization of the muscle fibers or membrane, due to a genetic dysfunction of the channels that move sodium, potassium and sometimes chloride in and out of the cell.
- Eyelids (When they try to open their eyes it will take a long time)
- Hand grip (Opening the hand after making a fist will take much time)
- Myotonia can be tested clinically:
  - Tapping the muscle (percussion myotonia)
  - Voluntary contractions of muscle groups (action myotonia)
- Worsens with cold.
- Improves with repeated exercise.

## VIII. Myoglobinuria

- Excess release of **myoglobin** during periods of excessive muscle breakdown (muscle necrosis) causing **dark urine**
- **Severe episodes:** acute tubular necrosis (ATN) → renal failure, what we fear the most.
- **Isolated episodes** following strenuous unaccustomed exercise: commonly idiopathic
- **What are the common muscle disorders that causes myoglobinuria? Metabolic myopathies**



**Box 6**
**Causes of myoglobinuria**

Prolonged, intensive exercise
Drugs and toxin
Metabolic myopathies
- Glycogenoses (myophosphorylase deficiency)
- Lipid disorders (carnitine palmitoyltransferase deficiency)
- Malignant hyperthermia (central core myopathy, Duchenne muscular dystrophy)

Heat stroke
Some muscular dystrophies (eg, limb-girdle muscular dystrophy 2C-F [sarcoglycanopathies], 2I [FKRP], dystrophinopathies)
Neuroleptic malignant syndrome
Severe metabolic disturbances, including prolonged fever
Trauma (crush injuries)
Viral and bacterial infections (rare)
Inflammatory myopathies (rare)

*Abbreviation:* FKRP, fukutin-related protein.

Also mitochondrial disorder, less common.

# Approach - 6 Questions



## ◀ Q2: What is the temporal evolution?

**Onset**

- **Childhood:** Duchenne. lots of disorders not only Duchenne.
- **Adolescence or later:** FSHD, LGMD
- **Adults:** inflammatory, toxic & also genetic.
- **After 50 yrs:** Inclusion body myositis (IBM)

**Tempo**

- **Episodic with normal strength interictal:** metabolic or Periodic paralysis
- **Acute** or **subacute progression** --> inflammatory myopathies (DM/PM)
- **chronic** slow progression **over years** (most muscular dystrophies)
- **non-progressive weakness** with little change over decades (congenital myopathies).

## ◀ Q3: Is there a family history of a myopathic disorder?

- Use of canes or wheelchairs?
- Skeletal deformities?
- Functional limitations? walking, jumping
- Sudden deaths? due to involvement of cardiac muscle

**Questions:**

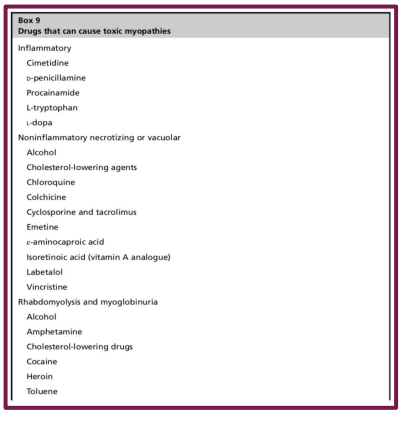
- Pacemakers?
- Early onset cataracts? Myoclonic dystrophy very common to have cataract.
- Deaths/complications from anesthesia? think about malignant hyperthermia-related genes.
- Early onset dementia/Paget's disease of bone?

| Diagnosis of myopathy based on pattern of inheritance | |
|---|---|
| **X-linked** | Becker muscular dystrophy, Duchenne muscular dystrophy, Emery-Dreifuss muscular dystrophy. |
| **Autosomal dominant** | Centre core myopathy, FSH, limb-gridle muscular dystrophy type 1, oculopharyngeal MD, myotonic dystrophy, paramyotonia congenita, periodic paralysis, thomsen disease. |
| **Autosomal recessive** | Becker myotonia, limb-gridle muscular dystrophy type 2, metabolic myopathies. |
| **Maternal transmission** | Mitochondrial myopathies. |

If you get a positive family history; you should have a Pedigree of at least three generations so that you can get an idea about the pattern, is it X-linked, Autosomal dominant, Autosomal recessive or Maternally inherited.

## ◀ Q4: Are there precipitating factors that trigger episodic weakness or stiffness?

- **Fever, Fasting** → carnitine palmitoyltransferase (CPT) deficiency "metabolic myopathy (Lipid-storage myopathies)"
- > carnitine palmitoyltransferase (CPT) deficiency
- **Carbohydrates** followed by rest --> Periodic paralysis
- Toxic
- checkpoint inhibitors, **statin** → Immune mediated



Box 9
Drugs that can cause toxic myopathies

Inflammatory
- Cimetidine
- D-penicillamine
- Procainamide
- L-tryptophan
- L-dopa

Noninflammatory necrotizing or vacuolar
- Alcohol
- Cholesterol-lowering agents
- Chloroquine
- Colchicine
- Cyclosporine and tacrolimus
- Emetine
- ε-aminocaproic acid
- Isoretinoic acid (vitamin A analogue)
- Labetalol
- Vincristine

Rhabdomyolysis and myoglobinuria
- Alcohol
- Amphetamine
- Cholesterol-lowering drugs
- Cocaine
- Heroin
- Toluene

# Approach - 6 Questions

## ◄ Q5: Are there associated systemic symptoms or signs?

| | |
|---|---|
| **Cardiac** | please don't miss on asking about these symptoms<br>• Dystrophinopathy<br>• Myotonic dystrophy 1, Myotonic dystrophy 2<br>• LGMD: emery - dreifuss, sarcoglycanopathies, fukutin |
| **Respiratory** | • Dermatomyositis<br>• Acid maltase (adult pompe)<br>• CNM, nemaline |
| **Fatty liver** | • CPT |
| **Cataracts, frontal balding** | • Myotonic dystrophy |
| **Rash** | • Dermatomyositis |
| **Early contractures** | • laminopathy or Emery – dreifuss muscular dystrophy |
| **Systemic organ disease** | • amyloid, sarcoid, mitochondrial |

## ◄ Q6: What is the distribution of weakness?

### 1- Inspection:

- Exposure
- **periscapular muscle Atrophy → Facioscapulohumeral dystrophy (FSHD)**
- **Asymmetric quadriceps/forearm flexors → Inclusion body myositis**
- **Hypertrophy? → calf in Duchenne**, sarcoglycan, fukutin, sarcoid, amyloid infiltrating the muscles
- Abnormal movements(rippling)/myotonia

### 2- Positions in testing:

- Neck flexors → supine position, you always want to apply resistant.
- Neck extensors → prone position
- Knee extension & hip flexion → seated position
- knee flexion → prone
- Hip abduction → lateral decubitus position.

### 3- Signs:

- **Scapular winging: FSHD**, Pompe (It is a genetic disorder and there's a treatment for it to prevent the progression (enzyme replacement therapy) thus, it's imp to identify it), Laminopathy, calpain & SLONM
- **Waddling gait:** inflammatory or LGMD
- Impaired toe walking (Weakness of calf muscles). "not imp": dysfrelin, ANO-5
- Pointing finger sign: MYH7 "not imp"
- ★ **Anteverted axillary line, protuberant abdomen, facial and scapular weakness: FSHD** " very characteristic"

## ◀ Patterns

**Pattern 1 - Proximal (Shoulder and/or Pelvic) limb girdle:**

- Most common
- Frequent involvement of neck flexor/extensor
- Least specific (the ddx is broad)

**Pattern 2 - Distal Weakness:**

- involves the distal muscles of the upper or lower extremities or both (anterior or posterior compartment muscle groups)
- Usually symmetric.
- Asymmetric posterior compartment : ANO-5, dysferlinopathy
- **Anterior compartment with sparing of quadriceps:** GNE myopathy, it has some occurrences in the middle east, So pay attention to it, because it is one of the rare diseases that have sparing of quadriceps.
- **Finger flexor & quadriceps: IBM**
- Finger extensor: TIA1 (Welander) rare, don't worry about it.
- Rule out neuropathy! localize first then think about aetiology

**Pattern 3 - Proximal Arm/Distal Leg Weakness (Scapuloperoneal):**

- Can be very asymmetric
- **When associated with facial weakness your #1 DDx will be : FSHD (Especially when it is slowly prgressive)**
- Laminopathies (emery dreifuss) frequently associated with cardiac arrhythmias , VCP, calpain.

**Pattern 4 - Distal Arm/Proximal Leg Weakness:**

- Distal forearm muscles (wrist and finger flexors) + proximal leg (quadriceps)
- Facial muscles typically spared
- **Usually Asymmetric:** IBM
- **Symmetric:** IBM, myotonic dystrophies

**Pattern 5 - Ptosis with or Without Ophthalmoparesis:**

- Ocular involvement: ptosis and ophthalmoparesis
- Usually (not always) occurs without diplopia bc it's usually so slow Pt won't develop diplopia, just amblyopia of one eye
- Facial weakness: not uncommon (usually you don't see it)
- Extremity weakness : variable, depending on the diagnosis.
- ★ **Ptosis**, **ophthalmoparesis** without diplopia, and **dysphagia** → Oculopharyngeal muscular dystrophy (OPMD)
- ★ **Ptosis** + **ophthalmoparesis** without prominent pharyngeal Involvement > mitochondrial myopathies.

**Box 16**
**Pattern 5: myopathies with ptosis or ophthalmoparesis**

- Ptosis without ophthalmoparesis
  - Congenital myopathies
    - Nemaline myopathy
    - Central core myopathy
  - Desmin (myofibrillar) myopathy
  - Myotonic dystrophy
- Ptosis with ophthalmoparesis
  - Centronuclear myopathy
  - Mitochondrial myopathy
  - Multicore disease
  - Oculopharyngeal muscular dystrophy
  - Oculopharyngodistal myopathy
  - Neuromuscular junction disease (myasthenia gravis, Lambert-Eaton, botulism)

## ◀ Patterns *cont.*

**Pattern 6 - Prominent Neck Extensor Weakness:**

- Severe weakness of the neck extensor muscles → Dropped head syndrome
- or mild that they complain of difficulty stabilizing the neck while running.
- Limb and neck flexor involvement : variable
- Rule out ALS or Myasthenia gravis

**Pattern 7 - Bulbar Weakness:**

- Tongue and pharyngeal weakness
- Acquired: sarcoid, pompe, necrotizing autoimmune myositis (NAM), inflammatory myopathy
- Hereditary: OPMD, myotilin

**Pattern 8 - Episodic Pain, Weakness, and Myoglobinuria:**

- Episodic pain, weakness, +/- myoglobinuria
- May be related to a variety of conditions (non muscle)
- Triggered by exercise à metabolic myopathy likely

**Box 18**
**Pattern 8: myopathies with episodic pain, weakness, and myoglobinuria/rhabdomyolysis**

| |
|---|
| Related to exercise |
| Couch potato syndrome |
| Glycogenoses (McArdle and so forth) |
| Lipid disorders (CPT deficiency) |
| Not related to exercise |
| Central non-neuromuscular causes |
| Neuroleptic malignant syndrome |
| Status epilepticus |
| Drugs/toxins |
| Malignant hyperthermia |
| Polymyositis/dermatomyositis (rarely) |
| Viral/bacterial infections |

*Abbreviation:* CPT, carnitine palmitoyltransferase.

**Pattern 9 - Episodic Weakness Delayed or Unrelated to Exercise:**

- Periodic Paralysis: genetic AD and secondary (thyrotoxicosis)
- Rule out NMJ can present with episodic weakness that exacerbated with exertion or infection

**Pattern 10 - Stiffness and Decreased Ability to Relax:**

- Dystrophic and non-dystrophic myotonia

**Box 20**
**Pattern 10: stiffness/decreased ability to relax**

| |
|---|
| Improves with exercise |
| Myotonia: $Na^{++}$ or $Cl^{-}$ channelopathy |
| Worsens with exercise/cold sensitivity |
| Paramyotonia: $Na^{++}$ channelopathy |
| Brody disease |
| With fixed weakness |
| Myotonic dystrophy (DM 1) |
| Proximal myotonic myopathy (DM 2) |
| Becker disease (AR $Cl^{-}$ channelopathy) |
| Other |
| Malignant hyperthermia |
| Neuromyotonia |
| Rippling muscle |
| Stiff-person syndrome |

*Abbreviation:* AR, autosomal recessive.

An area for your notes or something..

# Summary of Patterns



| | Weakness | | | | Episodic | Trigger | Diagnosis |
|---|---|---|---|---|---|---|---|
| | Proximal | Distal | Asymmetric | Symmetric | | | |
| **Pattern 1:** Limb girdle | + | | | + | | | Most myopathies, hereditary and acquired |
| **Pattern 2*:** Distal | | + | | + | | | Distal myopathies (also neuropathies) |
| **Pattern 3:** ProximaL arm / distal leg scapuloperoneal | **+ Arm** | **+ Leg** | **+ (FSH)** | **+ (Others)** | | | FSH, Emery-Dreifuss, acid maltase, congenital scapuloperoneal |
| **Pattern 4:** Distal arm/proximal leg | **+ Leg** | **+ Arm** | + | | | | IBM Myotonic dystrophy |
| **Pattern 5 :** Ptosis/ Ophthalmoplegia | + | | **+ (MG)** | **+ (Others)** | | | OPD, MG, myotonic dystrophy, mitochondria |
| **Pattern 6*:** Neck, extensor | + | | | + | | | INEM, MG (also ALS) |
| **Pattern 7*:** Bulbar (tongue, pharyngeal) | + | | | + | | | MG, LEMS, OPMD (also ALS) |
| **Pattern 8:** Episodic weakness/Pain/rhabo myolysis + trigger | + | | | + | + | + | McArdle's, CPT, drugs, toxins |
| **Pattern 9:** Episodic weakness Delayed or unrelated to exercise | + | | | + | + | +/- | Primary periodic paralysis Channelopathies: - Na++ - Ca++ - Secondary periodic paralysis |
| **Pattern 10:** Stiffness/ inabilty to relax | | | | | + | +/- | Myotonic dystrophy, channelopathies, rippling muscle (other: stiff-person, neuromyotonia) |

**Abbreviations:** ALS, amyotrophic lateral sclerosis; CPT, carnitine palmityl transferase; FSH, facioscapulohumeral muscular dystrophy; LEMS, lambert-eaton myasthenic syndrome; MG, myasthenia gravis; OPMD, oculopharyngeal muscular dystrophy; PROMM, proximal myotonic myopathy.
*** Overlap pattern with neuropathy/motor neuron disease.**

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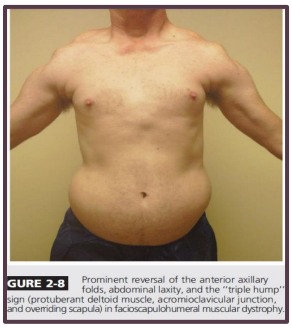
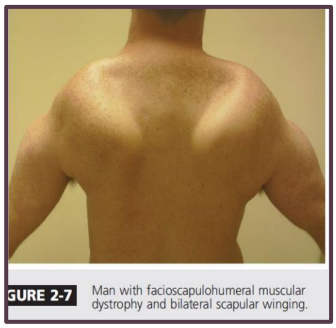
# Physical exam & Labs

## ◀ Physical examination

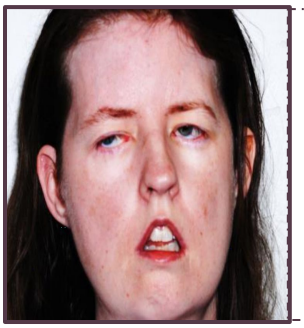
- **General:** wasting, myopathic facies
- **Vital signs:** bradycardia, irregular due to involvement of cardiac muscle.
- **Specific pattern of weakness and atrophy:**
  - limb-girdle "commonest", weakness in the proximal UL and LL.
  - scapuloperoneal (scapular or leg muscles)
  - distal "rare"
  - facioscapulohumeral
  - ocular, etc
- **Gait** examination:
  - Waddling or trendelenburg gait is indicative of proximal muscle weakness (it's not specific for muscle disease).
- **Functional** testing
- **Systemic** examination
- **Cardiac:** heart failure
- **Respiratory:** fibrosis, respiratory distress



GURE 2-8 Prominent reversal of the anterior axillary folds, abdominal laxity, and the "triple hump" sign (protuberant deltoid muscle, acromioclavicular junction, and overriding scapula) in facioscapulohumeral muscular dystrophy.



GURE 2-7 Man with facioscapulohumeral muscular dystrophy and bilateral scapular winging.



**Myopathic facies:**
- flattening of frontalis muscle, ptosis in both eyes, tented mouth (due to weakness of the facial muscles)
- it indicates chronic long standing myopathy

## ◀ Investigations

| | |
|---|---|
| **Muscle Enzymes** | • **Serum Creatinine Kinase** |
| **Other investigations** | • **MRI:** Shows pattern of muscle involvement and features of inflammation, Can't identify the exact etiology<br>• **Muscle biopsy:** Essential for the diagnosis of inflammatory myopathies<br>• **Genetic testing:** for specific syndromes<br>• ELECTROMYOGRAPHY (**EMG**)<br>  ○ Normally we see motor unit potential<br>  ○ Small units with early recruitment<br>  ○ May see and hear myotonic discharges<br>• NERVE CONDUCTION STUDIES (**NCS**) |

| Acute/subacute | chronic |
|---|---|
| CK | CK |
| TSH/PTH | TSH/PTH |
| EMG | EMG |
| HMGCR | Genetic versus muscle biopsy |
| Myositis panel | Acid alpha glucosidase |
| Cardiac and respiratory screen | Cardiac and respiratory screen |
| | ALP |

For acute, you want to rule out the immune disorders. So, do immune myositis panel and HMGCR.

### Serum Creatinine Kinase

- CK is an enzyme composed of muscle (**M**) and brain (**B**) monomers, resulting in **MM**, **MB**, and **BB** isoenzymes
- What we usually look for is MM, also in the lab we can measure total CK (including MM,MB,BB)
- **Elevated CK may be seen with:**
  - Muscle disease (not all muscle diseases cause elevated CK e.g. facioscapulohumeral has normal CK)
  - Nerve, and motor neuron disorders
  - Strenuous exercise
  - intramuscular injections, seizures or muscle trauma

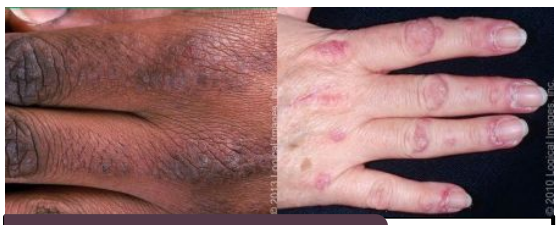
| CK Fold increase | Examples of diagnostic conditions |
|---|---|
| **Normal** | • Facioscapulohumeral muscular dystrophy<br>• Milder limb-girdle muscular dystrophies<br>• Some metabolic myopathies at rest<br>• Rarely dermatomyositis |
| **Mild (<5-10 times the upper limit)** | • Exercise<br>• neurogenic causes<br>• Becker muscular dystrophy<br>• facioscapulohumeral muscular dystrophy<br>• many types of limb-girdle muscular dystrophy<br>• myotonic dystrophy<br>• advanced Duchenne muscular dystrophy<br>• drug-induced<br>• inflammatory myopathies<br>• congenital and metabolic myopathies<br>• congenital myasthenic syndromes |
| **Marked (>20 times the upper limit)** | • Duchenne muscular dystrophy/Becker muscular dystrophy,<br>• some types of limb-girdle muscular dystrophy (eg, types 22, 2D, 2G)<br>• dermatomyositis<br>• immune-mediated necrotizing myopathies<br>• inherited and acquired causes of rhabdomyolysis and myoglobinuria |

# Inflammatory Myopathies

## ◀ Dermatomyositis (DM)

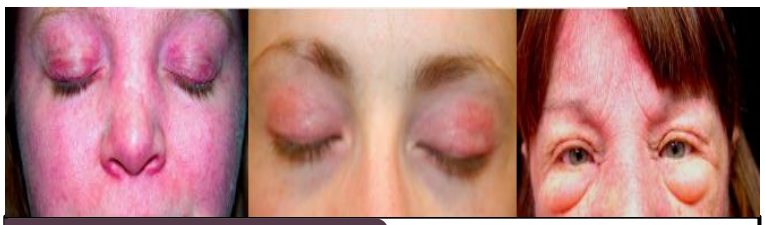
- Idiopathic inflammatory myopathy
- A form of small vessel vasculitis, affects any age (children & adults) with more incident in females (2:1)
- **Proximal muscle weakness more than distal,**
- **Usually affecting the lower limbs (legs) more than the upper limbs (arms)**
- The weakness start acutely (over several weeks) or insidiously (over months)
- Difficulties in swallowing, chewing, and speaking occur in⅓
- DM is primarily distinguished from PM by the characteristic rash.
    - The characteristic cutaneous findings occur in children and adults

### Signs & symptoms:



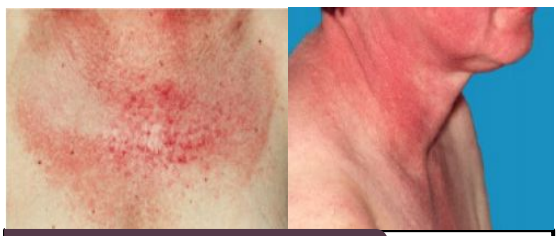
**Gottron's Papule**

**- Pathognomonic for DM**
- Violaceous scaly papules overlying the joints on the dorsal hand.



**Heliotrope Rash**

**- Pathognomonic for DM**
- **Violaceous** eruption on the upper eyelids, sometimes associated with **periorbital edema**



**Shawl sign**

- Erythematous rash covering the upper arms and shoulders or a V-shaped rash affecting sun-exposed surfaces on the upper chest.

**Malignancy**

• **Increased risk of cancer** (up to 40% of adults)
• Breast (mammogram), ovarian, lung, pancreatic, NHL, stomach, colorectal, melanoma, GI.
- PM is also Associated with malignancy, but less than DM.

•can also predate the onset of myositis, particularly in males with DM.

**Eruptions**

**Eruptions on:**
- predominantly on **photo-exposed surfaces**
- along the eyelid margins, with or without periorbital edema
- the dorsal hands, particularly over the knuckles
- the upper outer thighs

**Others**

- Pruritus of skin lesions, sometimes intense enough to disturb sleep
- Erythema of the mid-face
- Changes in the nailfolds of the fingers
- **Scaly scalp or diffuse hair loss**

# Inflammatory Myopathies

## Non-Skeletal Manifestations :

- DM most frequently affects the **skin** and **muscles** but may also affect the
  - **joints;**
  - **Esophagus** causing **Dysphagia** and **delayed gastric emptying**
  - **Lungs** (Respiratory muscle weakness "dyspnea and orthopnea")
  - less commonly, the **heart** (Cardiomyopathy).
- Systemic features of fever, weight loss and fatigue are common
- Periungual nail-fold capillaries are often enlarged and tortuous.
- **Polyarthritis, Raynaud's phenomenon**
- **interstitial lung disease (*antisynthetase syndrome*)**

**Antisynthetase syndrome:**

➔ Some people with PM or DM have **antibodies to tRNA synthetase enzymes**. These people are **more likely to develop:**

- **Pulmonary interstitial fibrosis**
- Raynaud's phenomenon
- arthritis
- Hardening and fissuring of skin over the pulp surface of the fingers (mechanic's hands).

➔ This variant of PM/DM is sometimes called anti-synthetase syndrome and often has a **poor outcome**. Respiratory muscles are affected in PM/DM and this compounds the effects of interstitial fibrosis. Dysphagia is seen in about 50% of patients owing to esophageal muscle involvement.

## ◄ Polymyositis (PM)

- The clinical picture is dominated by inflammation of striated muscle, causing proximal muscle weakness. When the skin is involved, it is called 'dermatomyositis
- Presents mainly in adults (> 20 years), women > men. it can be Acute or insidious (weeks-months).
- The shoulder and pelvic girdle muscles become wasted but are not usually tender
- As the disease progresses, involvement of pharyngeal, laryngeal and respiratory muscles can lead to dysphonia and respiratory failure.
- Can have malaise, Dysphagia, fever, weight loss and anorexia, **NO skin rash.**
- **Extraocular**, **facial** and **distal limb** muscles are spared
- **Associated with malignancy (less than DM)**
- Cardiac myositis (arrhythmia, heart failure)
- Polyarthritis in 45%, positive ANA in 40%

# Inflammatory Myopathies

## ◄ Diagnosis of PM & DM

### Serum Creatine kinase

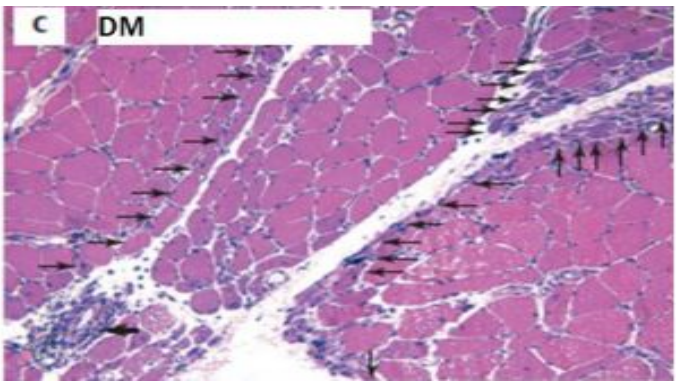
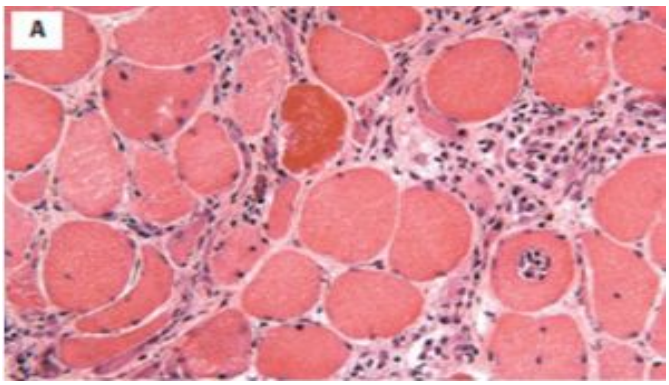
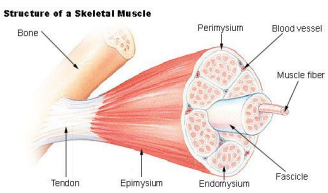
**The best initial test is CPK and aldolase**

- **Serum CK in DM:** Can be elevated or normal
- **Serum CK in PM**: Should always be elevated (x5 folds)

Serum CK is a useful measure of disease activity, although a normal levels does not exclude the diagnosis

### Muscle biopsy & MRI

- **Muscle biopsy is the pivotal investigation (most accurate test)! it is indicated to confirm diagnosis**
  - **MRI should be used to identify areas of abnormal muscle for biopsy.**
- **Muscle MRI:** Edema, inflammation, fibrosis, calcification or fatty replacement of muscle tissue.

| Dermatomyositis | Polymyositis |
|---|---|
|   |   |
| **Antibodies-mediated** | **Cellular-mediated** |
| ➔ **Perifascicular atrophy:**<br>● **Pathognomonic**.<br>● Sublethal myofiber stress and ischemia at the interface of the muscle fascicle and the perimysium.<br><br>➔ **Inflammation:**<br>● Inflammation in **perimysial** blood vessels<br>● CD4+ plasmacytoid dendritic cells.<br>● Complement activation (MAC) and deposition on capillaries. | ➔ Inflammatory cells (**CD8+ T cells**) invading non-necrotic, healthy muscle fibers.<br>➔ Invaded muscle fibers express MHC-1<br>➔ **No perifascicular atrophy.**<br>➔ No immunoglobulin deposition<br>➔ No complement deposition. |
| In DM, Perimysial **and perivascular infiltration of CD4+** cells, and because of that:<br>● We see **skin changes** in DM but not in PM<br>● **Biopsy:**<br>○ Peripheral atrophy<br>○ the center of the muscle is preserved, unlike PM where there is necrosis! |  <br>In PM, **Intrafascicular, Endo**mysial **infiltration of CD8+ T cells**, and because of that:<br>● We **DO NOT** see skin changes in PM<br>● **Biopsy:**<br>○ **Central Necrosis** |

# Inflammatory Myopathies

## ◀ Diagnosis of PM & DM (Cont..)

### Autoantibodies

- **Anti–synthetase antibodies:** commonest **anti-Jo-1** ( associated with dermatomyositis), also anti-PL-7, anti-PL-12, etc.
  - **interstitial lung disease is strongly associated with the presence of antisynthetase (Jo-1) antibodies**
- **Myositis-specific antibodies:** Anti–Mi-2, anti-MDA5 (CADM-140), anti p155/140 or anti-MAS
- **ANA** can be positive

### Others

**↑ Other enzymes**

- Aldolase B
- AST and ALT

**EMG**: Myopathic pattern

Short-duration spiky polyphasic muscle action potentials are seen. Spontaneous fibrillation is occasionally recorded.

## ◀ Management of PM & DM

**Steroids (Oral prednisolone is the treatment of choice)**

- high-dose intravenous methylprednisolone may be required in patients with respiratory or pharyngeal weakness
- Some require high dose for long time.
- There is risk of opportunistic infections (PCP), osteoporosis, cataract, weight gait, etc
- Monitor blood glucose, serum potassium levels, BP, and eyes
- One risk of treatment is glucocorticoid-induced myopathy. If the initial response to treatment is poor, further biopsy then shows type II fibre atrophy in glucocorticoid myopathy (compared with fibre necrosis and regeneration in active myositis).

**Steroid-sparing therapy:** Methotrexate, azathioprine, mycophenolate, etc

- Although most patients respond well to glucocorticoids, many need additional immunosuppressive therapy.
- **Methotrexate** and **MMF** are the **first choices** of many but azathioprine and ciclosporin are also used as alternatives
- In clinical practice, rituximab is an option for use with glucocorticoids, to maintain an early glucocorticoid-induced remission.
- Intravenous immunoglobulin (IVIg) may be effective in refractory cases.
- Mepacrine or hydroxychloroquine has been used for skin predominant disease

★ **Screening for underlying malignancy** should be undertaken routinely (full examination, chest X-ray, serum urine and protein electrophoresis, colonoscopy, CT of chest/abdomen/ pelvis, or PET scan; prostate-specific antigen should be included in men, and mammography in women), CA-125 and CA-19-9

- Exclude cardiac and pulmonary involvement (PFTs with diffusion capacity, ECG, esophageal manometry)
- Physical therapy & Occupational therapy
- Evaluate coexisting autoimmune disorders (ANA)
- PM & DM can be part of an overlap syndrome:
  - Associated with another well-defined connective tissue disorder
  - Scleroderma, mixed CTD, Sjögren, SLE, or RA.

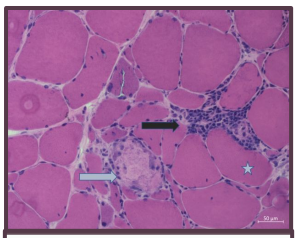
# Inflammatory Myopathies

## ◀ Inclusion Body Myositis (IBM)

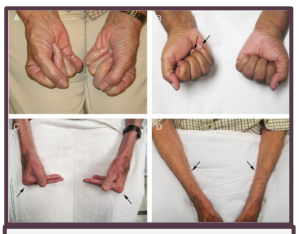
- Common after **age 50,** (prevalence:35-71/1000000 ) with M:F ⟶ 2:1
- It is a slowly progressive **Asymmetric** inflammatory/degenerative myopathy
- ★ **Weakness of mainly distal muscles**
- Unique clinical and pathological features
- **Treatment:**
  - Supportive.
  - Relentless progression, lacks effective therapies

### Clinical presentation

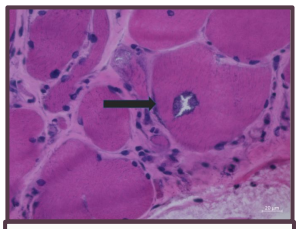
- ★ **Quadriceps muscle weakness (Thigh):** knees lack support ⟶ frequent falling
  - Usually spares rectus femoris muscle
- ★ **+/- long finger Finger flexors:** difficulties gripping, e.g., shopping bags or a briefcase
- **Paraspinal muscles:** Camptocormia or dropped head syndrome
- **Severe Oropharyngeal dysphagia:** 40–86% (upper esophageal sphincter dysfunction)
- **Heart muscle:** usually unaffected.
- **Biceps, foot dorsiflexors**
- **Thigh & finger flexors weakness is a common pattern in IBM!**



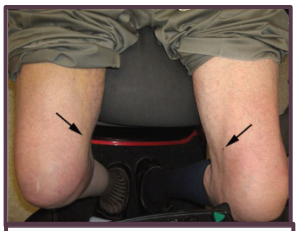
Inflammatory cells invading non-necrotic muscle fibers



Finger flexion



Rimmed vacuoles



Asymmetric atrophy of the quadriceps,

**EMG shows** irritable myopathy.
both **myopathic** and **neuropathic** changes.

**Biopsy suggestive of IBM (most accurate test):**
- **Endomysial inflammation**
- **Rimmed vacuoles**.
- **Inflammatory cells invading non-necrotic muscle fibers.**

**Definitive diagnostic feature** is
- **Filamentous inclusions and vacuoles**

- **Inclusion body myositis is the "oddball of inflammatory myopathies"** for the following reasons:
  - Affects male patients more than female patients
  - Absence of autoantibodies
  - Distal muscle involvement,
  - CK is only slightly elevated or normal; prognosis is poor.
- On **MRI**, the changes are often more **distal** but can be similar to those of polymyositis

# Drug Induced Myopathies



## ◀ Steroid myopathy

### Cause

- Chronic exposure to high-dose oral steroids.
- As short as few weeks of proximal weakness.

### Investigations

- CK: normal.
- EMG: normal or it might show myopathic features.
- Biopsy: type 2 fiber atrophy and lipid accumulation in type 1 fibers.

### Mechanism

- ↓protein synthesis.
- ↑ protein degradation.
- Alterations in carbohydrate metabolism.
- Mitochondrial dysfunction.
- ↓ reduced sarcolemmal excitability

## ◀ Statin Induced Myopathy

Mild statin-associated myalgia or cramps

Myopathic weakness

In most cases, both mild and severe side effects are self-limiting

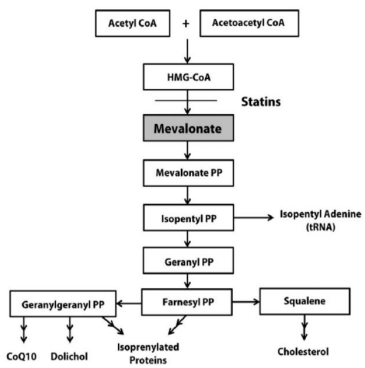
**Statins inhibit HMG-CoA reductase, rate-limiting enzyme of cholesterol biosynthesis. Can cause:**

Severe myotoxicity or rhabdomyolysis, rare

Discontinuation of the statin → resolution of symptom

Rarely, statins can cause an **Immune-Mediated Necrotizing Myopathy with very high CK and antibodies to Anti-HMG CoA-reductase**

### Mechanism (not important)




- ↓Mevalonate → ↓ farnesyl pyrophosphate and geranylgeranyl pyrophosphate → ↓ protein prenylation
- Reduced prenylation of proteins causes:
  1. impaired ubiquinone synthesis → mitochondrial dysfunction.
  2. Impairment GTPases that promote cell survival →cell death.
  3. Impairment of the process of Nglycosylation → defective proteins → muscle cells damage.

## ❖ Risk factors

- Older Age
- Obesity
- Type & Dose of statin: fluvastatin and pravastatin are worse than rosuvastatin
  - ➔ Preexisting liver disease → reduce metabolism of statin
  - ➔ Liver enzyme inhibitors → increase levels of statins
- Hypothyroidism
- Genetic susceptibility: SLCO1B1 gene.

# Muscular Dystrophies

- ➔ Inherited myopathies caused by mutation in genes that are important in maintaining the structure of muscle fibers
- ➔ **Progressive degeneration of the muscles with connective tissue or fat replacing muscle fibers. Variable age at onset**
- ➔ Systemic involvement
- ➔ **Screening for an associated cardiac abnormality (cardiomyopathy or dysrhythmia) is important.**

| Classification of MUSCULAR DYSTROPHIES (MD) | |
|---|---|
| **Dystrophinopathies**<br>• Duchenne muscular dystrophy<br>• Beker muscular dystrophy | Myotonic dystrophy (MD)<br>Barths syndrome |
| Limb girdle muscular dystrophies (LGMD) | Facioscapulohumeral MD (FSHD) |
| Oculopharyngeal MD (OPMD) | Emery-Dreifuss muscular dystrophy |

# Dystrophinopathies: DMD & BMD

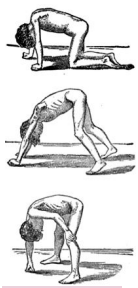
- **They are x-linked recessive disorders** (manifest in males). **Duchenne** (**early** age) and **becker** (**late** age).
- **Mutation** in the **dystrophin gene (Xp21)** → **absent** (in duchenne) or **reduced** (in becker) Dystrophin protein → loss of mechanical reinforcement to the sarcolemma and instability of the glycoprotein complex → Degeneration of muscle fibers.
- **Duchenne is the Most common dystrophy**

## ◀ Duchenne Muscular Dystrophy (DMD)

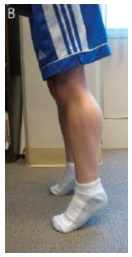
### Features:

- **Symmetrical progressive (Proximal > distal) muscle weakness** (**Legs** & **Arms**)
- **Course:** Onset age **2 to 5 yrs**, There is reduction in the motor function by 2 to 3 years with a steady decline in strength after 6 to 11 years.
  - ➢ Can't **jump** or **climb** at **5-6** years
  - ➢ **Wheelchair** at **10** (13) years of age
- **Gower's sign:** Standing up with the aid of hands pushing on knees (because the weakness in the proximal lower extremity muscles makes it difficult to arise without support.)
- **Loss of ambulation** at age 9-13 years. Later resolved with: Steroid treatment. (Prednisone)
  - ➢ Weak knee extensors → **toe walking.**
- **Muscle hypertrophy: Especially calf**. It starts with true muscle hypertrophy at first, followed by pseudo- hypertrophy as **fat & CT replaces muscle**, muscles are degenerated and replaced
  - ➢ It may be generalize and increases with age.
- There is **Sparing** of the **cranial muscles** !
- Death: 15-30(25) years.

**Typical presentation:** A boy who noticed to have difficulty running and rising to his feet; he uses his hands to climb up his legs (Gowers' sign}. There is initially a proximal limb weakness with calf pseudohypertrophy. The myocardium is affected. Severe disability is typical by the age of 10



Gower's sign



### Complications:

- ★ **Dilated cardiomyopathy:** common after age 15
- Respiratory failure
- Malignant Hyperthermia like reactions with **rhabdomyolysis**
- Kypho-Scoliosis because of the weakness
- Exaggerated lumbar lordosis
- Cognitive impairment, Mental retardation, learning disabilities,
- Contractures

# Dystrophinopathies: DMD & BMD

## ◀ Duchenne Muscular Dystrophy (DMD) (Cont..)

### Investigations:

- **CK:** very high, usual is 100 X ULN **(Initial test)**
- **Muscle biopsy:** variation in muscle fibre size, necrosis, regeneration and replacement by fat. on immunochemical staining, **absent dystrophin staining**.
- **Genetic testing** is **gold standard**: Detect dystrophin gene mutation

### Management: Glucocorticoids !

1. Steroids slow the progression of the disease.
2. Patient usually die at the age of 15 but they can live up to the age of 30 years with steroids.
3. Stabilizes sarcolemma
4. Increases strength, muscle, and pulmonary functions
5. Anabolic action in contrast to its catabolic action on normal skeletal muscle in unaffected people.
6. **Reduces cardiomyopathy and lowers mortality**

### Other Management:

1. Screening and treatment of cardiac, respiratory, gastrointestinal, and orthopedic complications.
2. Screening for osteoporosis
3. Physical therapy, occupational therapy and bracing
4. Avoidance of anesthesia and sedation if possible

## ◀ BECKER Muscular Dystrophy (BMD)

| | |
|---|---|
| 01 | Midler form, Older age at onset, Muscle weakness starts from > 7 yrs. |
| 02 | **Proximal > Distal**; Symmetric; Legs & Arms. Maybe especially prominent in quadriceps or hamstrings. |
| 03 | The severity & onset age **correlate with muscle dystrophin levels.** |
| 04 | **Slowly progressive**. "Becker is Better." **Loss of ambulation** usually in the 4th decade. Failure to walk 16 - 80 years. |
| 05 | they usually have myalgias and **Muscle hypertrophy:** Especially calf. Calf pain on exercise. Cardiomyopathy may occur before weakness. |

### ❖ Investigations:

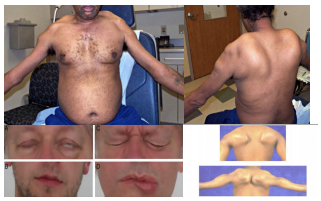
- **High CK:** 2000 to 20,000
- **Muscle biopsy:** decreased staining patterns rather than complete absence of dystrophin ( **Partial loss** of dystrophin staining )
- **Genetic testing** is gold standard.

| | Clinical Phenotype | | | Gene Information | | |
|---|---|---|---|---|---|---|
| Condition | Typical Onset | Progression | Creatine Kinase Level | Allelism | Gene | Protein |
| Duchenne muscular dystrophy | Early childhood | Slow to moderate | 100-200X | Becker muscular dystrophy | *DMD* | Dystrophin |
| Becker muscular dystrophy | Late childhood | Slow | 10-15X | Duchenne muscular dystrophy | *DMD* | Dystrophin |

# Muscular Dystrophies

## ★ Facioscapulohumeral dystrophy

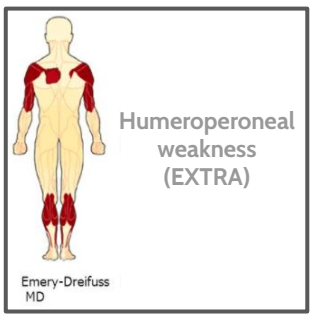
- The 3rd most common dystrophy in adult (**Autosomal dominant**).
- **Manifestations are Asymmetrical**
  - **Face:** Initial manifestation, 95% you will detect it at the age of 30 with examination
  - **Eyes:** Often early in disease course
  - **Lid closure:** Incomplete
  - **Sleeping:** With eyes partially open
  - **Shoulder:** Pain in shoulder girdle, scapular winging, triple humb
  - **Ear:** deafness
  - **Bulbar** dysfunction: eg. inability to use straws, blowing a balloon
  - Using straws - blowing up balloons
  - **Protuberant abdomen**



- **Screen for:**
  - **Hearing loss**
  - **Retinal vascular disease**
- **No screening** for cardiac needed unless symptomatic
  - Cardiorespiratory involvement rare

## ◄ Emery – dreifuss muscular dystrophy

- **Autosomal dominant or recessive** With more than 7 subtypes with various genes.
- **Age:** Neonatal hypotonia to 3rd decade; Mean in teens.
- **Function:** Difficulty walking or climbing stairs.
- **Weakness: Humeroperoneal**
  - Bilateral
  - Symmetrical
  - Arms: Biceps & triceps; **Deltoids spared.**
  - Scapular winging
  - Legs: Involved later on.
  - Face: Mild weakness or normal

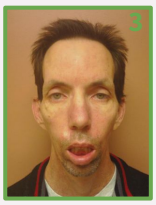



★ **Contractures occurs before weakness and it is often more limiting to function than weakness.**
  - **in elbow, achilles tendon**
  - **Spine:**
    - Posterior neck (extension)
    - Lower back: Usually later onset, but may present with rigid spine syndrome.
- **Testing:**
  - CK, EMG
  - **Cardiac screening for arrhythmia and cardiomyopathy**
    - **A lot of doctors would put them on prophylactic pacemakers, even** if they don't have anything. because cardiac involvement may **lead to death**

# Muscular Dystrophies

## Myotonic Dystrophy

- The **most prevalent** inherited neuromuscular disease in **adults** (**Autosomal dominant**).
- **Tandem repeats[1] at DMPK gene[2] (Anticipation phenomenon)**
  - Every generation will have earlier onset
- **Characterized by progressive symmetrical muscle wasting and weakness**
  - Weakness is usually **proximal**, except in **myotonic dystrophy type 1**, when it is **distal**.
- **Prolonged** muscle contractions (**myotonia**) and are not able to relax certain muscles after use (percussion and grip myotonia).
- **difficulty releasing hand grip on a doorknob or handle.**
- Slurred speech or temporary locking of their jaw
- **Frontal balding,**
- **Cardiorespiratory weakness:**
  - arrhythmias, heart failure, sudden death, conduction defects & orthopnea
- **Endocrine:** NIDDM, hypothyroidism, male hypogonadism
- **GIT:** dysmotility (and aspiration), constipation and diarrhea
- **Others:** Cataracts, cognitive impairment & Low IQ



### ❖ LABS

- CK: Usually elevated
- **EMG:** myopathic plus **myotonic** discharges.
- ECG, echo: to look for arrhythmias
- Genetic testing (confirmatory test): type 1 and type 2.

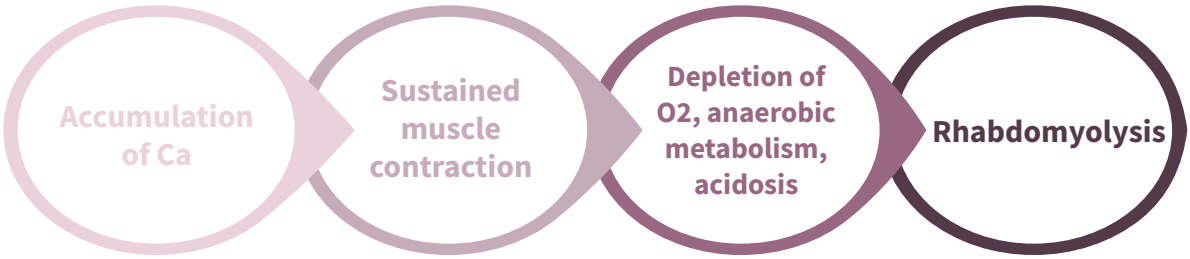
| Type of myotonic dystrophy | Genetics Autosomal dominant | Muscles affected | Other features |
|---|---|---|---|
| **Type 1** (Age: Any) | Expanded triplet repeat chromosome 19q | • Face (including ptosis)<br>• sternomastoids<br>• **Distal limb**<br>• Generalised later | • **Myotonia**<br>• Cognitive impairment<br>• **Cardiac conduction abnormalities**<br>• Lens opacities<br>• **Frontal balding**<br>• **Hypogonadism** |
| **Type 2** (Age: 8-50 yrs) | Quadruplet repeat expansion in Zn finger protein 9 gene chromosome 3q | • **Proximal**, especially thigh<br>• Sometimes muscle hypertrophy | • As for DM1 but cognition not affected<br>• Muscle pain |

1- when you have a mutation in the gene that causes excessive transcription of that gene, so instead of having on copy you will have multiple copies, and each generation you will have more and more copies leading to "Anticipation", the fathers will have the phenotype and the sons will have even worse phenotype and so on…
2- important for stabilizing muscle membrane.
3- features of myopathic facies with ptosis, frontal balding, wasting of the temporalis muscle & other muscles of mastication, bilateral facial muscle weakness and tented mouth.

# Malignant Hyperthermia (MH)

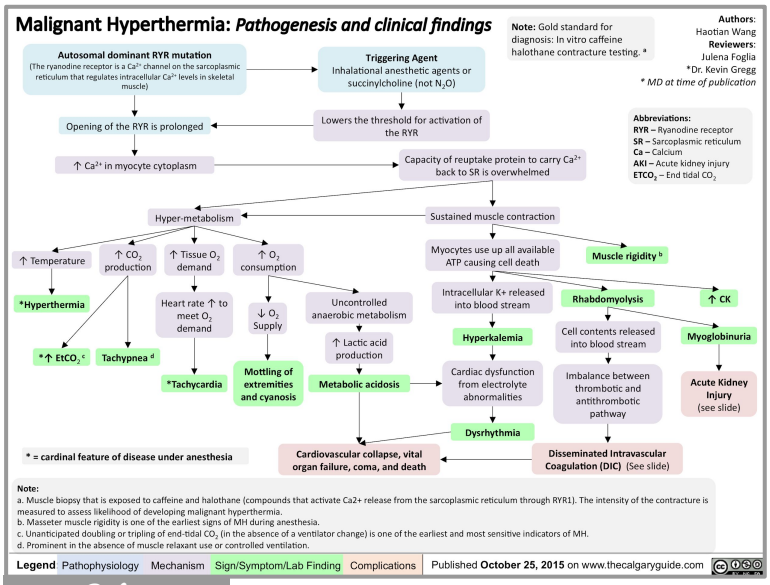


- Uncontrollable contraction of skeletal muscle that leads to a life-threatening hypercatabolic state and increase in body temperature
- Genetic mutations → calcium accumulation
  - due to a genetic defect in the sarcoplasmic reticulum calcium release channel of the muscle ryanodine receptor, RyR1.
- **Triggered:**
  - Anesthetics
  - Depolarizing neuromuscular blocking agents
- **CAN BE FATAL! (most common cause of death during general anaesthetic)**




## Clinical features

- Tachypnea, tachycardia
- **Rigidity**
- Acidosis
- **Hyperkalemia**
- **Rhabdomyolysis**
- **High CK**
- **Hyperthermia.**




Extra

## ◀ Treatment

- **Remove** anesthetic agent.
- Core **cooling**
- **Dantrolene sodium:** An inhibitor of calcium release from the sarcoplasmic reticulum.

# Rhabdomyolysis

## Definition

- Acute Syndrome of **muscle necrosis** due to extensive **injury** of skeletal muscle with **release of intracellular** muscle materials into the **circulation**.

## ◀ Causes

| | | | |
|---|---|---|---|
| **Most common causes** | • **Exercise**<br>• **Drugs**<br>• **Alcohol** | **Common etiologies** | • **Metabolic myopathy:**<br>  ○ Glycogen, lipid, mitochondrial<br>• Statins<br>• Muscular dystrophy: baseline ck high<br>• Malignant hyperthermia ! |
| **More likely hereditary etiology:** | • Rhabdomyolysis on minimal exertion or fasting<br>• Family history<br>• Multiple episodes | | |

## ◀ Presentation & Complications

### Clinical features

- Muscle Pain, Swelling
- Muscle Weakness (Proximal > Distal)
- **Cola or tea color "dark" urine (Myoglobinuria)**
- **Elevated blood and urine myoglobin**
- Fever, **leukocytosis**
- Markedly **elevated CK** (1500 to >100,000) usually >30000
- Might be asymptomatic

### Complications

- ↑ **K+** → **arrhythmia** → **death**
- Myoglobin can block the tubules in the kidney causing **Acute kidney injury.**
- ↑PO4. ↓Ca. ↑Uric acid
- Metabolic acidosis due to kidney injury.
- Compartment syndrome
  - if the muscle is severely damaged it will be swollen and this will lead to compartment syndrome causing ischemia to the muscle.

## ◀ Management

★ **IV hydration** to **avoid** acute tubular necrosis (**ATN**) and **renal failure** !!!

- Correct electrolyte
- Monitoring for potassium complications
- Other treatment according to underlying etiology.

# Summary

| | |
|---|---|
| **Inflammatory Myopathies** | **Polymyositis (PM):** inflammatory myopathy affecting the proximal skeletal muscles<br>**Dermatomyositis (DM):** inflammatory myopathy that presents similarly to polymyositis, with the addition of skin involvement<br>**Inclusion body myositis (IBM):**<br>• **Skin features (Specific for DM):** Gottron papules, heliotrope rash, and the shawl sign<br>• **Malignancies are associated with DM > PM**<br>• Patients with IM typically complain of **muscle weakness** with difficulties reaching overhead, **climbing the stairs**, and/or **standing up**. Advanced disease may present with **dysphagia** and **aspiration** because of oropharyngeal muscle involvement, or even **respiratory failure** if breathing muscles are affected.<br>• **DM** is primarily **distinguished** from **PM** by the **characteristic rash.**<br>• **The best initial test is CPK and aldolase**<br>• **Muscle biopsy is the pivotal investigation (most accurate test)!**<br>  ○ **DM:** Perifascicular atrophy<br>  ○ **PM:** No Perifascicular atrophy<br>• **interstitial lung disease is strongly associated with the presence of antisynthetase (Jo-1) antibodies**<br>• **Management: Steroids & screen for underlying malignancies** |
| **Inclusion body myositis** | **Inclusion body myositis (IBM):** inflammatory myopathy affecting both the proximal and distal skeletal muscles (mainly Distal). Common after **age 50**<br>• **Quadriceps muscle weakness (Thigh):** knees lack support → frequent falling<br>  ○ Usually spares rectus femoris muscle<br>• **+/- long finger Finger flexors:** difficulties gripping, e.g., shopping bags or a briefcase<br>• **Severe Oropharyngeal dysphagia**<br>• **Biopsy (most accurate test):** Inflammatory cells invading non-necrotic muscle fibers, Rimmed vacuoles.<br>• Relentless progression, lacks effective therapies |
| **Drug Induced Myopathies** | • **Steroid myopathy:** due to chronic exposure to steroids<br>  ○ Biopsy: type 2 fiber atrophy and lipid accumulation in type 1 fibers.<br>• **Statin Induced Myopathy:** Statins inhibit HMG-CoA reductase, rate-limiting enzyme of cholesterol biosynthesis. Can cause:<br>  ○ Discontinuation of the statin → resolution of symptom |
| **Dystrophinopathies** | • **They are x-linked recessive disorders** (manifest in males). **Duchenne** (**early** age) and **becker** (**late** age).<br>• **Mutation** in the **dystrophin gene (Xp21)** → **absent** (in duchenne) or **reduced** (in becker) Dystrophin<br>**DMD:**<br>• **Symmetrical progressive (Proximal > distal) muscle weakness** (**Legs** & **Arms**)<br>• **Course:** Onset age **2 to 5 yrs**, **Wheelchair** at **10/**<br>• **Gower's sign, Loss of ambulation** at age 9-13 years, **Muscle hypertrophy: Especially calf**<br>• **Dilated cardiomyopathy:** common after age 15 (usually the cause of death)<br>**Becker:**<br>• Older age at onset, Muscle weakness starts from > 7 yrs. Slowly progressive. "Becker is Better." Loss of ambulation usually in the 4th decade<br>Investigations & Management:<br>• Muscle biopsy: **absent dystrophin staining** (DMD). **Partial loss** of dystrophin staining (BMD) |

# Summary

| | |
|---|---|
| **Facioscapulohumeral dystrophy** | • **Manifestations are Asymmetrical**<br>  ○ **Face:** Initial manifestation, 95% you will detect it at the age of 30 with examination<br>  ○ **Eyes:** Often early in disease course<br>  ○ **Lid closure:** Incomplete<br>  ○ **Sleeping:** With eyes open<br>  ○ **Shoulder:** Pain in shoulder girdle, scapular winging, triple humb<br>  ○ **Ear:** deafness<br>• **Screen for:**<br>  ○ **Hearing loss**<br>  ○ **Retinal vascular disease**<br>• **No screening** for cardiac needed unless symptomatic |
| **Emery – dreifuss muscular dystrophy** | • **Weakness: Humeroperoneal**<br>  ○ Bilateral, Symmetrical<br>  ○ Arms: Biceps & triceps; Deltoids spared.<br>  ○ Scapular winging<br>  ○ Legs: Late<br>  ○ Face: Mild weakness or normal<br>★ **Contractures occurs before weakness and it is often more limiting to function than weakness.**<br>  ○ **in elbow, achilles tendon**<br>  ○ **Spine:**<br>  ■ Posterior neck (extension), Lower back: Usually later onset, but may present with rigid spine syndrome.<br>• **Testing:**<br>  ○ CK, EMG, **Cardiac screening for arrhythmia and cardiomyopathy (leads to sudden death)** |
| **Myotonic Dystrophy** | • The **most prevalent** inherited neuromuscular disease in **adults** (**Autosomal dominant**).<br>• **Tandem repeats at DMPK gene (Anticipation phenomenon)**<br>• **difficulty releasing hand grip on a doorknob or handle.**<br>• **Frontal balding, Cardiorespiratory weakness**<br>• **EMG:** myopathic plus **myotonic** discharges. Genetic testing (confirmatory test) |
| **Malignant Hyperthermia** | • **Triggered:** Anesthetics, Depolarizing neuromuscular blocking agents<br>• **Clinical features:** Tachypnea, tachycardia, Rigidity, Acidosis ,Hyperkalemia Rhabdomyolysis, High CK, Hyperthermia.<br>• **Treatment:** Remove anesthetic agent, Dantrolene sodium |
| **Rhabdomyolysis** | • Acute Syndrome of **muscle necrosis** due to extensive **injury** of skeletal muscle with **release of intracellular** muscle materials into the **circulation**.<br>• **What is the commonest muscle disorder that causes myoglobinuria? Metabolic myopathies**<br>• **Clinical features:**<br>  ○ **Cola or tea color "dark" urine (Myoglobinuria)**<br>  ○ **Elevated blood and urine myoglobin**<br>  ○ Fever, **leukocytosis**<br>  ○ Markedly **elevated CK**<br>• **Complications: ↑ K+ → arrhythmia → death**<br>• **Management: IV hydration** to **avoid** acute tubular necrosis (**ATN**) and **renal failure** !!! |

**click here for patterns summary**

# Lecture Quiz

**Q1: A 60-year-old woman presents to her GP with a two-month history of lethargy and weakness. She mentions that she is finding it increasingly difficult to climb the stairs and do the housework. On examination, there is wasting and weakness of the proximal muscles in the upper and lower limbs. What is the most likely diagnosis?**

A- Dermatomyositis
B- Polymyositis
C- Polymyalgia rheumatica
D- Kawasaki's disease

**Q2: A 45-year-old woman presents to her physician with a 6-week history of gradually increasing limb weakness. She first noticed difficulty climbing stairs, then problems rising from a chair, and, finally, lifting her arms above shoulder level. Aside from some difficulty swallowing, she has no ocular, bulbar, or sphincter problems and no sensory complaints. Family history is negative for neurological disease. Examination reveals significant proximal limb and neck muscle weakness with minimal atrophy, normal sensory findings, and normal deep tendon reflexes. Affected muscles are slightly tender; there is no skin rash. What is the likely pathogenesis of her condition?**

A- B- and T-cell mediated attack against muscle autoantigens
B- Anterior horn cell degeneration in the spinal cord
C- Antibodies to the acetylcholine receptor at the neuromuscular junction
D- Abnormal trinucleotide repeat in the DMPK gene

**Q3: A 4-year-old boy is brought to the emergency department for a right ankle injury sustained during a fall earlier that morning. His parents report that he is 'clumsy' when he runs and has fallen multiple times in the last year. He has reached most of his developmental milestones but did not walk until the age of 17 months. He is an only child and was adopted at age 1. He appears tearful and in mild distress. His temperature is 37.2°C (98.9°F), pulse is 72/min, respirations are 17/min, and blood pressure is 80/50 mm Hg. His right ankle is mildly swollen with no tenderness over the medial or lateral malleolus; range of motion is full with mild pain. He has marked enlargement of both calves. Patellar and Achilles reflexes are 1+ bilaterally. Strength is 4/5 in the deltoids, knee flexors/extensors, and 5/5 in the biceps and triceps. Babinski sign is absent. When standing up from a lying position, the patient crawls onto his knees and slowly walks himself up with his hands. Which of the following is the most likely underlying mechanism of this patient's condition?**

A- SMN1 gene defect
B- Loss of the ATM protein
C- Myotonin protein kinase defect
D- Absence of dystrophin protein

**Q4: A 35-year-old woman comes to the physician for the evaluation of fatigue over the past 6 months. During this period, she has also had fever, joint pain, and a recurrent skin rash on her face. She has smoked one pack of cigarettes daily for the past 15 years. Her temperature is 38.5°C (101.3°F), pulse is 90/min, and blood pressure is 130/80 mm Hg. Physical examination shows a facial rash that spares the nasolabial folds and several oral ulcers. Joints of the upper and lower extremities are tender with no reddening or swelling. Laboratory studies show anti-dsDNA antibodies. The patient is diagnosed with systemic lupus erythematosus and treatment of choice is initiated. Eight months later, the patient has weakness in her shoulders and hips. Examination shows slight weakness of the proximal muscles. Deep tendon reflexes are 2+ bilaterally. Laboratory studies show normal erythrocyte sedimentation rate and creatine kinase. Which of the following is the most likely underlying cause of this patient's symptoms?**

A- Autoantibodies against postsynaptic acetylcholine receptors
B- Dystrophin gene mutation
C- Adverse effect of medication
D- Autoantibodies against myelin

**Q5: A 3-year-old boy is brought to the physician by his parents because of a 6-month history of worsening mobility issues. During this period, his parents noticed that he had occasional falls and increasing difficulties climbing stairs and running. The boy had a normal development up until then; he was able to walk by the age of 15 months. There is no personal or family history of serious illness. He is at the 10th percentile for height and 25th percentile for weight. Vital signs are within normal limits. Musculoskeletal examination shows enlarged calf muscles bilaterally. Deep tendon reflexes are 1+ on the lower extremities and 2+ on the upper extremities. He has a waddling gait and when asked to get up from the floor, he supports himself with his hands on his legs to get to an upright position. Which of the following is the most appropriate initial step in diagnosis?**

A- Serum creatine kinase concentration
B- Muscle biopsy
C- Genetic analysis
D- Electromyography

Answers: Q1:B | Q2:A | Q3:D | Q4:C | Q5:A

Answers Explanation File!

# Lecture Quiz

**Q6: A 20-year-old woman is brought to the emergency department because of severe muscle soreness, nausea, and darkened urine for 2 days. The patient is on the college track team and has been training intensively for an upcoming event. One month ago, she had a urinary tract infection and was treated with nitrofurantoin. She appears healthy. Her temperature is 37°C (98.6° F), pulse is 64/min, and blood pressure is 110/70 mm Hg. Cardiopulmonary examination shows no abnormalities. The abdomen is soft and non-tender. There is diffuse muscle tenderness over the arms, legs, and back. Laboratory studies show:**

| | |
|---|---|
| Hemoglobin | 12.8 g/dL |
| Leukocyte count | 7,000/mm3 |
| Platelet count | 265,000/mm3 |
| **Serum** | |
| Creatine kinase | 22,000 U/L |
| Lactate dehydrogenase | 380 U/L |
| **Urine** | |
| Blood | 3+ |
| Protein | 1+ |
| RBC | negative |
| WBC | 1–2/hpf |

**This patient is at increased risk for which of the following complications?**

A- Metabolic alkalosis
B- Acute kidney injury
C- Myocarditis
D- Hemolytic anemia

**Q7: A 4-year-old boy is brought to the pediatrician for evaluation of frequent falls. His mother says that for the past 6 months he seems to be moving more slowly than usual, and he can't run as quickly and can't climb stairs. The boy was born at 39 weeks' gestation via normal spontaneous vaginal delivery with no complications. He has been otherwise healthy and achieved all of his appropriate motor and speech milestones. Family history is significant for a maternal uncle who died at age 20 years from respiratory failure. On physical examination the patient has hyperlordosis of the spine. His calves are very prominent bilaterally. When asked to lie on his back and stand up, he first rolls over onto his stomach and then uses his hands to climb up his legs until he is standing. He has 3/5 strength in his shoulders and thighs bilaterally, but 5/5 strength in his hands, calves, and feet. The rest of the neurologic examination is unremarkable. Serum creatine kinase level is 1500 U/L. How was this boy's disorder most likely inherited?**

A- Autosomal dominant
B- Autosomal recessive
C- Mitochondrial
D- X-linked recessive

**Q8: A 50-year-old man complains of weakness. His symptoms began as difficulty with buttoning his shirt and using keys to open doors about 2 years ago. He was treated empirically with nonsteroidal anti-inflammatory medications for arthritis, but responded only minimally. His symptoms have slowly progressed to the point where he has weakness in both hands and feet. He avoids going outside because of frequent falls. On examination, he has weakness and atrophy of the foot extensor and finger flexors. Proximal muscle strength is normal. Reflexes are normal, and sensation is intact. He is able to rise out of a chair, but the Romberg test is not able to be performed due to weakness once standing. Cranial nerves are intact. Serum creatine kinase is 600 U/L. Complete blood count, differential, electrolytes, and thyroid-stimulating hormone (TSH) are normal. Based on the clinical presentation, what is the most likely diagnosis?**

A- Dermatomyositis
B- Eosinophilic myofasciitis
C- Inclusion body myositis
D- Polymyositis

Answers: Q6:B | Q7:D | Q8:C

Answers Explanation File!

# THANKS!!

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Send us your feedback:
We are all ears!