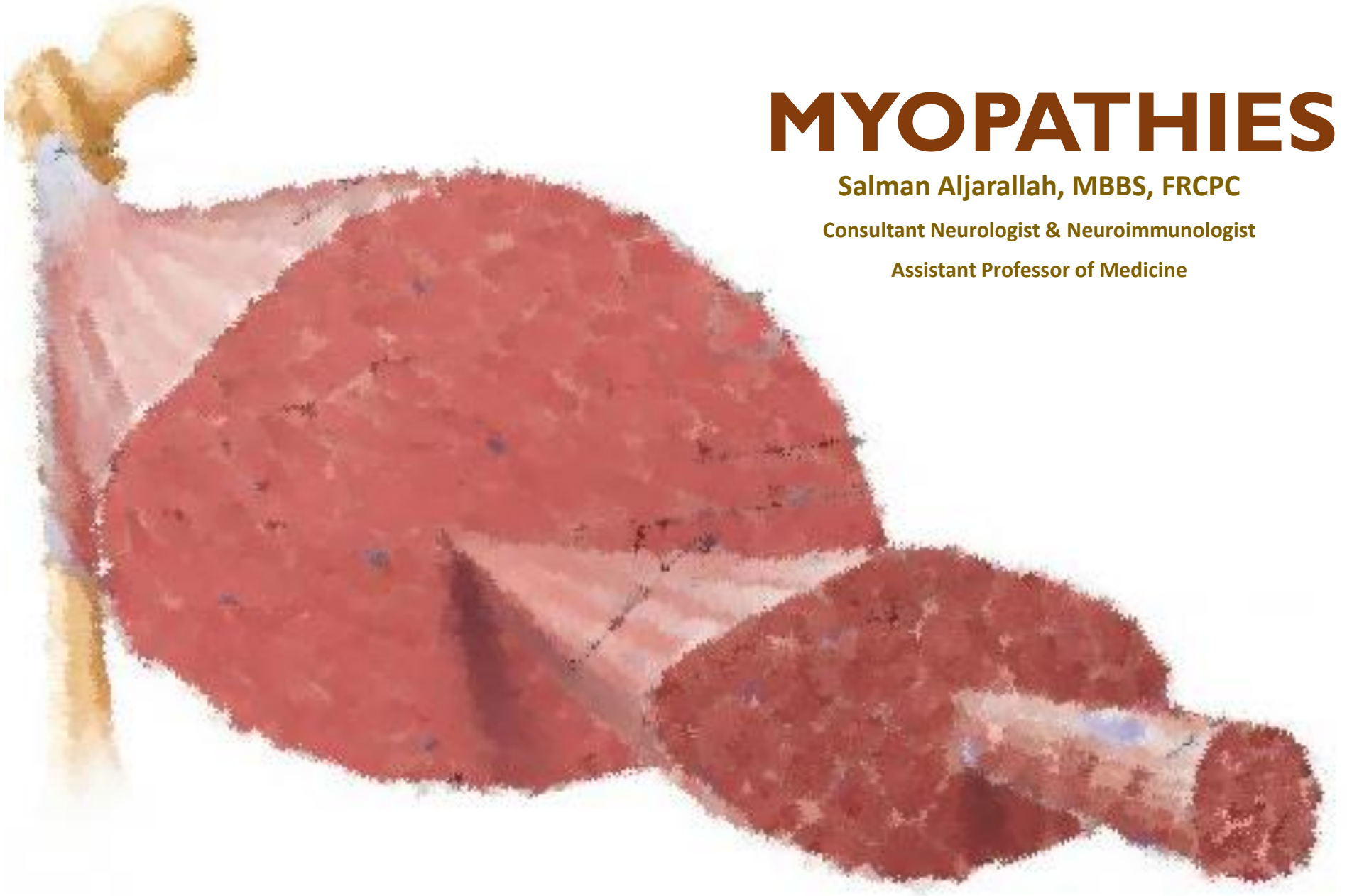


MYOPATHIES

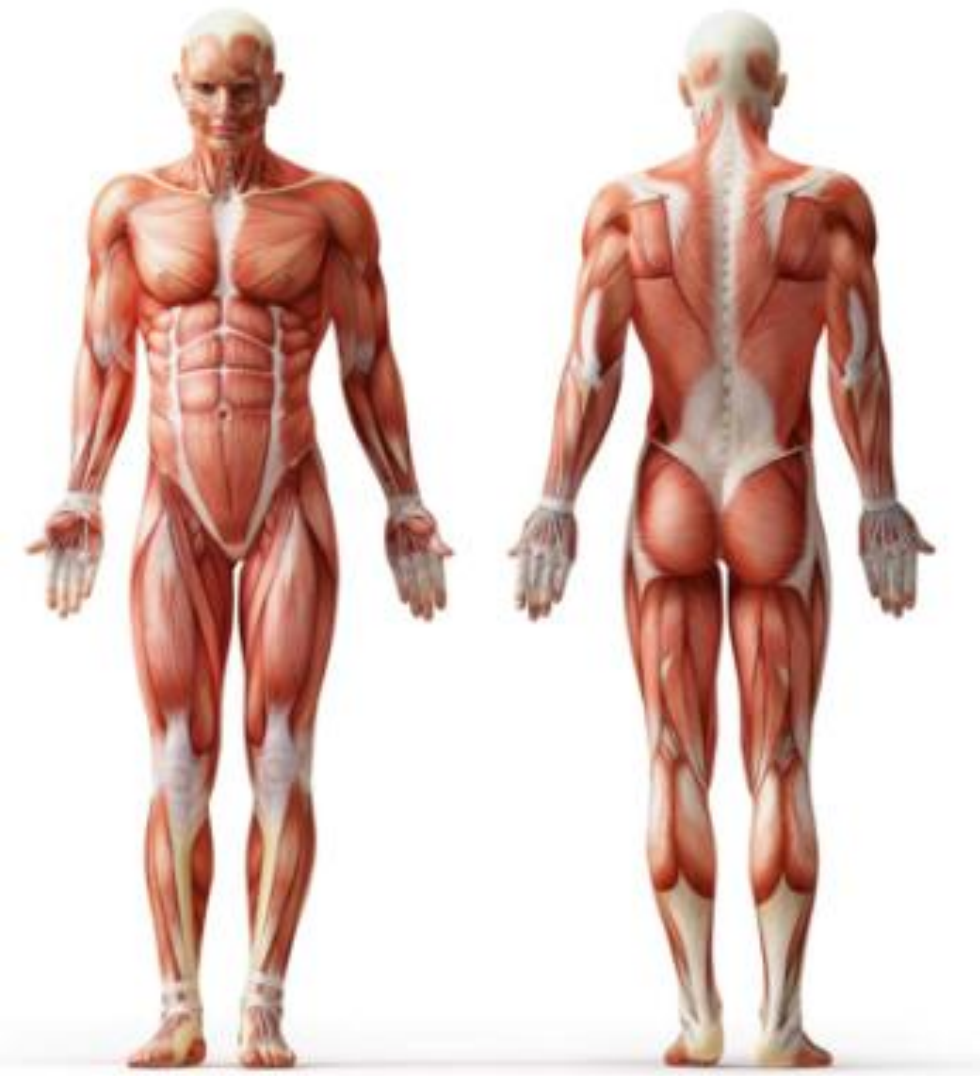
Salman Aljarallah, MBBS, FRCPC

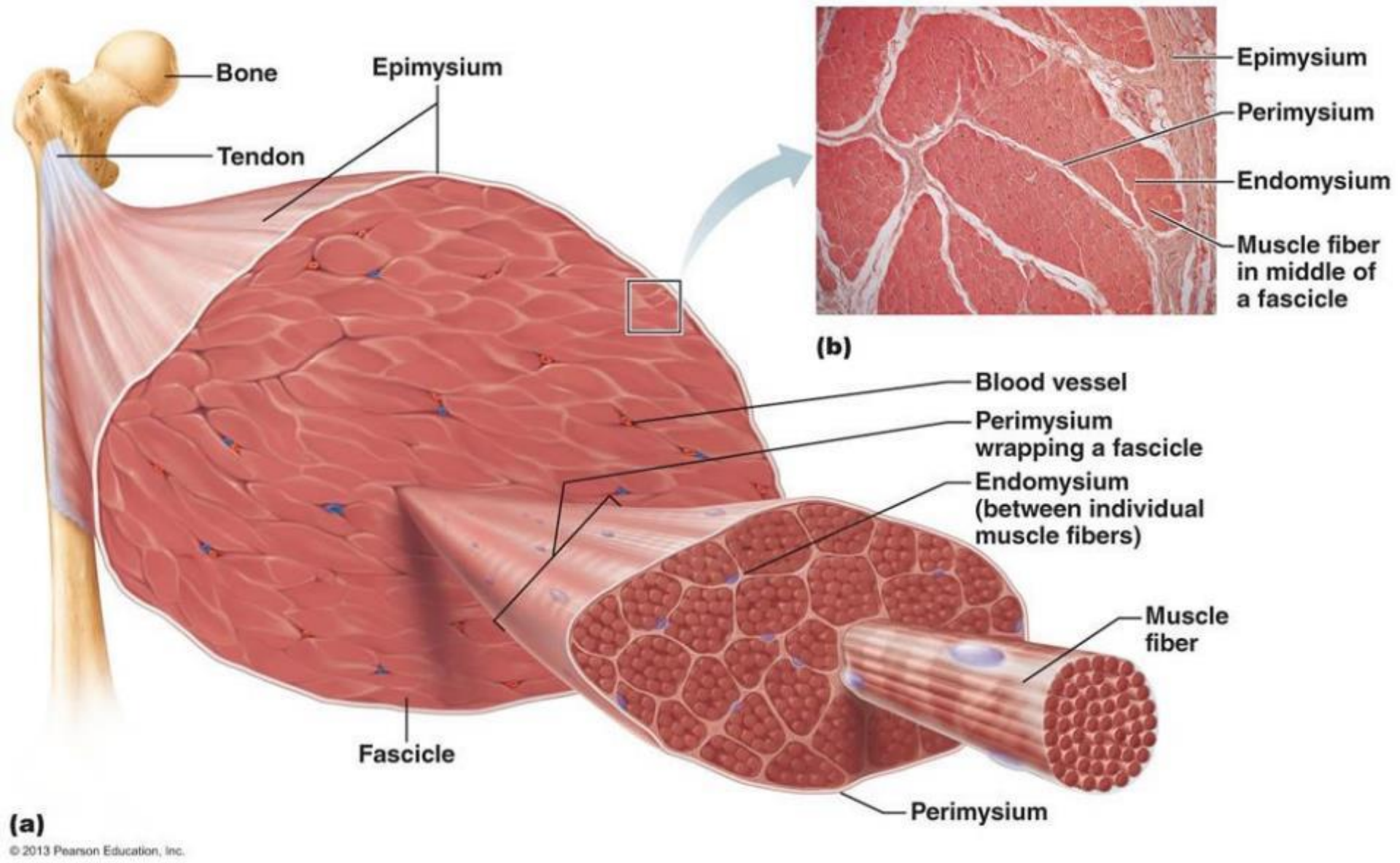
Consultant Neurologist & Neuroimmunologist

Assistant Professor of Medicine

MYOPATHY

- *Myo-* muscle
- *Pathos* - suffering
- A disorder in which there is a primary functional or structural impairment of *skeletal muscle*.




Bone
Tendon
Epimysium
Fascicle
(a)
© 2013 Pearson Education, Inc.
Epimysium
Perimysium
Endomysium
Muscle fiber in middle of a fascicle
(b)
Blood vessel
Perimysium wrapping a fascicle
Endomysium (between individual muscle fibers)
Muscle fiber
Perimysium

Symptoms of Muscle Disease

1. Limb muscle weakness and atrophy :

- *Proximal muscle weakness* is the cardinal symptoms of myopathy
- E.g. difficulty combing hair, washing hair in shower, climbing stairs, squatting, waddling gait
- Shoulder girdle → scapular winging

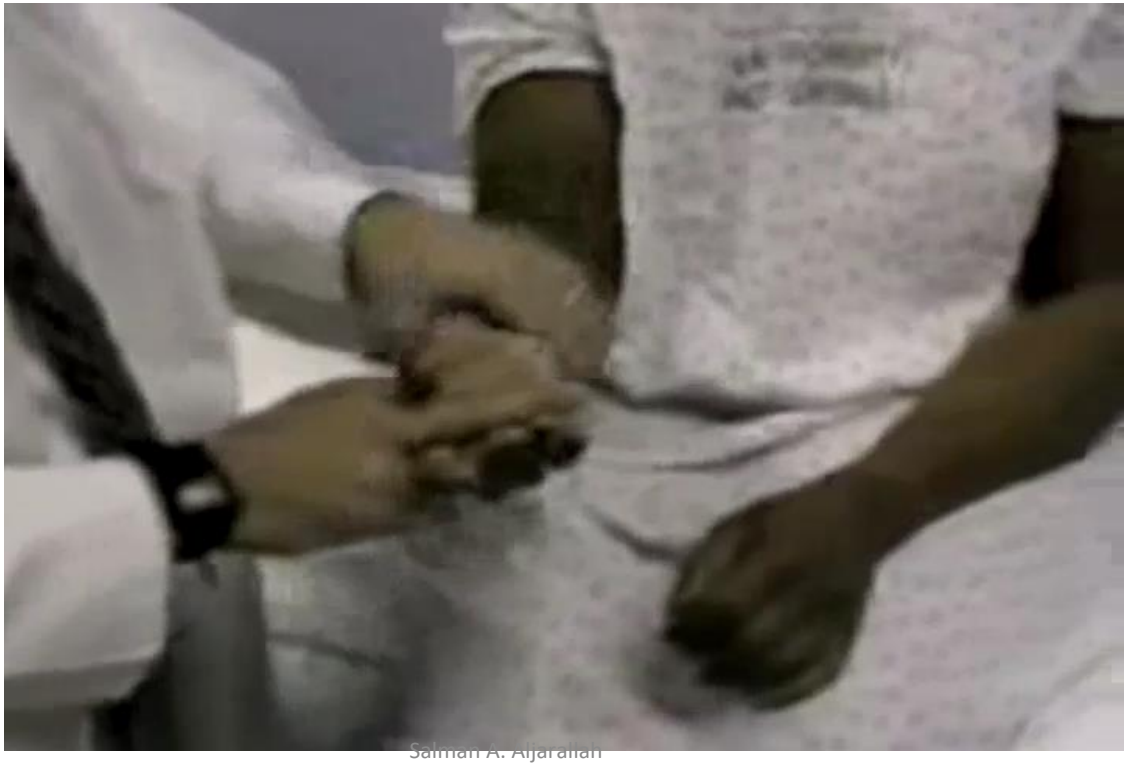
- **Other muscles:**
  - Eye muscles → ophthalmoplegia, ptosis
  - Facial weakness → difficulty closing eyes, whistling, using straw,
  - Bulbar muscles → dysphagia, chocking, nasal speech,
  - Respiratory muscles → dyspnea, orthopnea,
  - Cardiomyopathy → heart failure, arrythmias

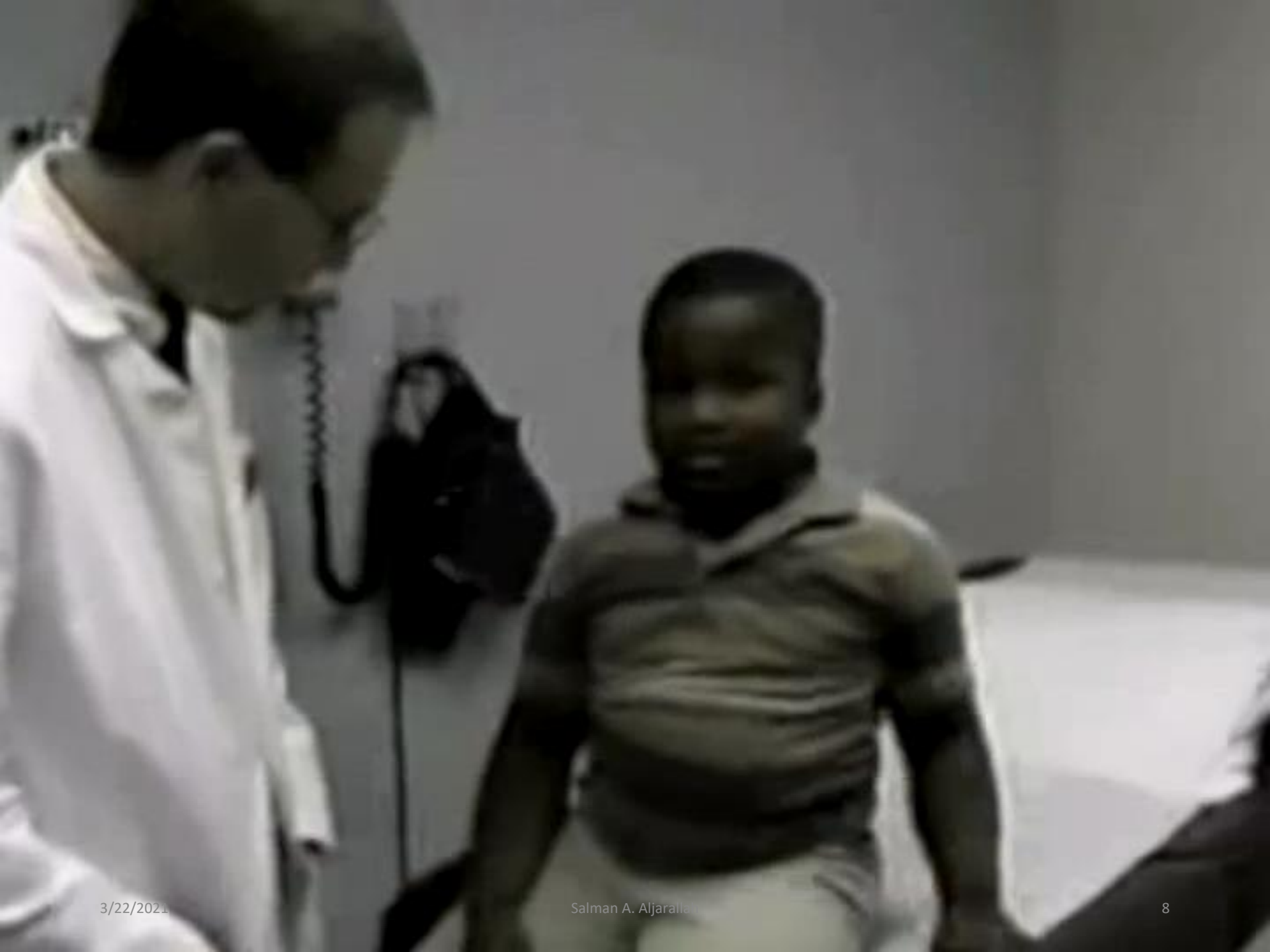
Symptoms of Muscle Disease

Exercise intolerance	• Problem with energy utilization. • Intolerance for short exercise → carbohydrate disorder • Intolerance for long exercise → lipid disorder
Cramps:	• Involuntary contractions of muscle (seconds-minutes). • Most are benign (typically calves). • Can occur in MND, chronic neuropathies, etc • Risk factors: old age, dehydration, prolonged sitting, diuretics, low Mg, hypoT4, DM
Myalgia	• Muscle pain
Dark urine	• Indicates myoglobinuria
Myotonia	• Impaired relaxation after sustained voluntary contraction.

Myotonia

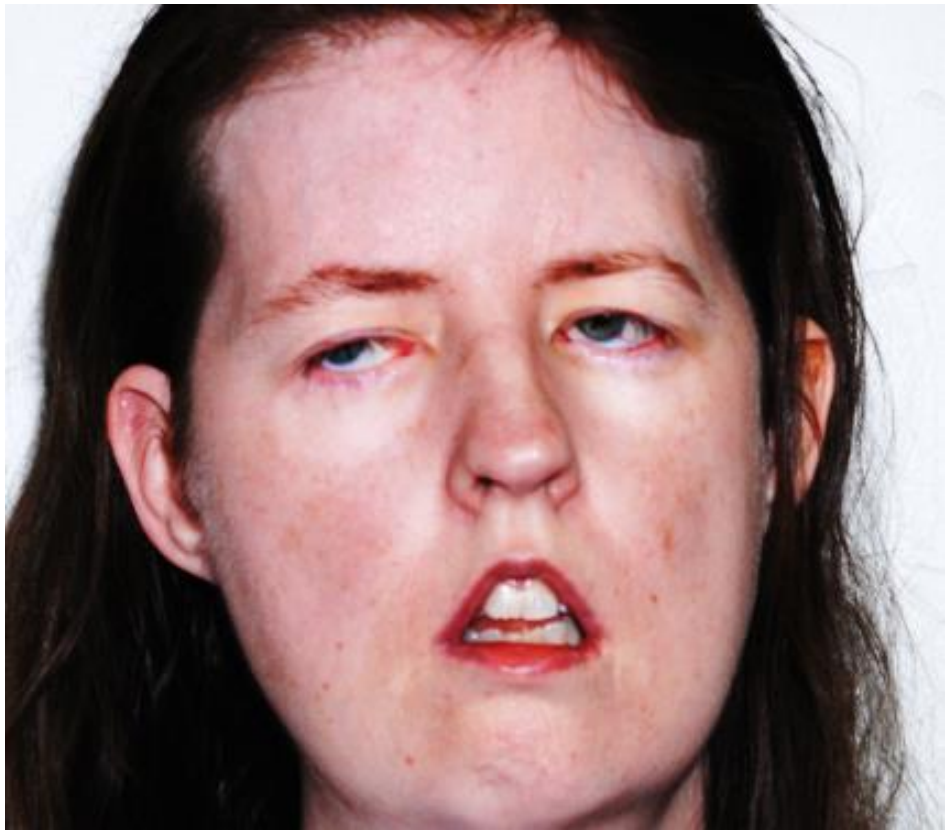
- Caused by repetitive depolarization of the muscle fibers
- Myotonia can be tested clinically :
  - Tapping the muscle (percussion myotonia)
  - Voluntary contractions of muscle groups (action myotonia)

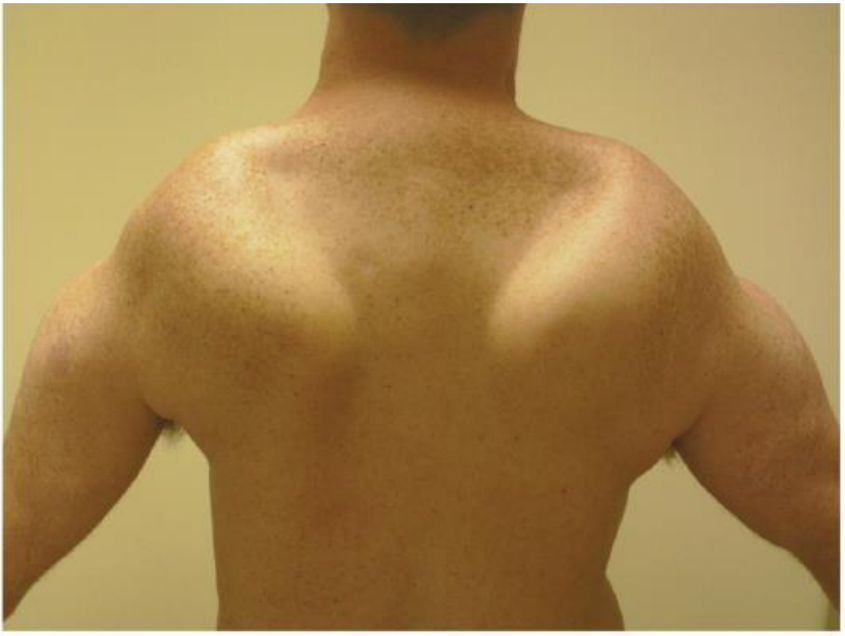




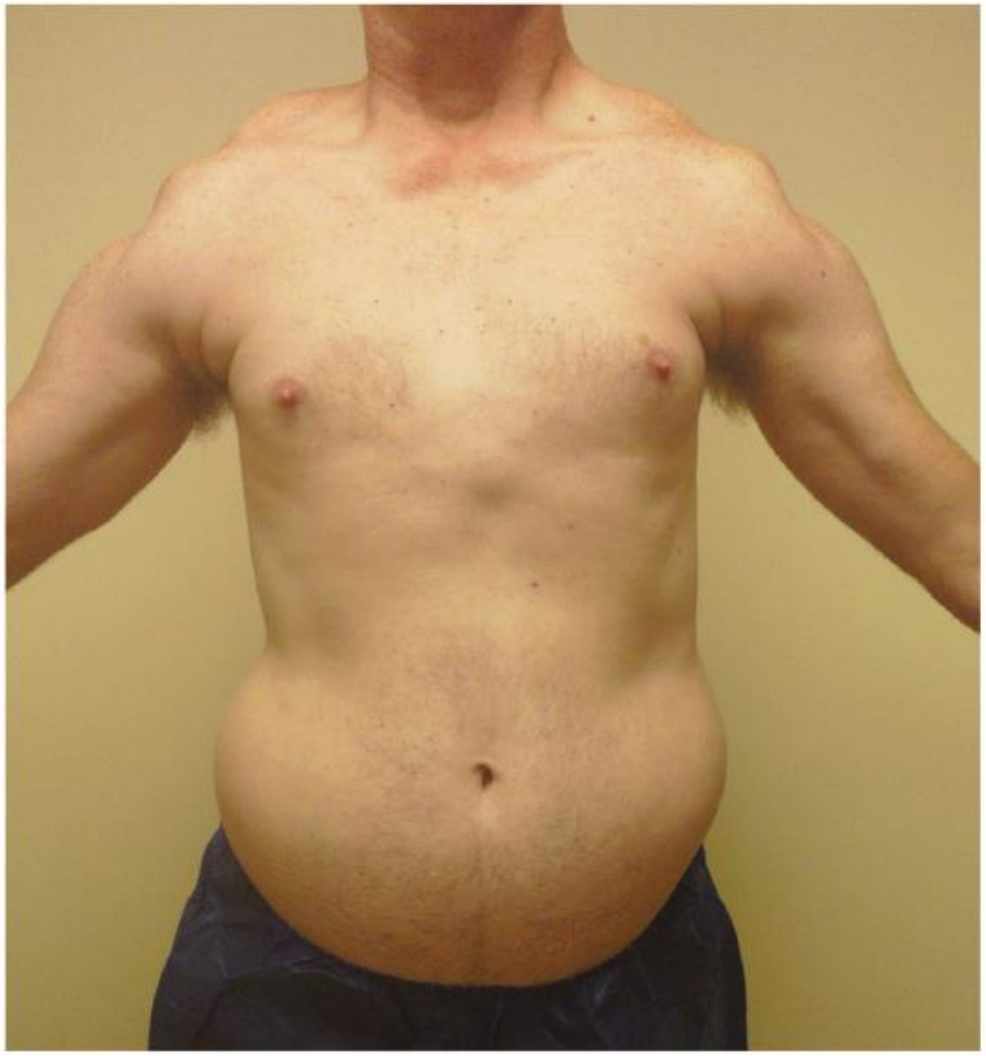
Examination

- General: wasting, myopathic facies, respiratory distress
- V/S: bradycardia, irregular
- Specific pattern of muscle weakness and atrophy:
  - Llimb-girdle
  - Scapulocperoneal
  - Distal
  - Facioscapulohumeral
  - Ocular, etc
- Gait examination
- Functional testing
- Systemic examination Cardiac: heart failure
- Respiratory: fibrosis





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



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.

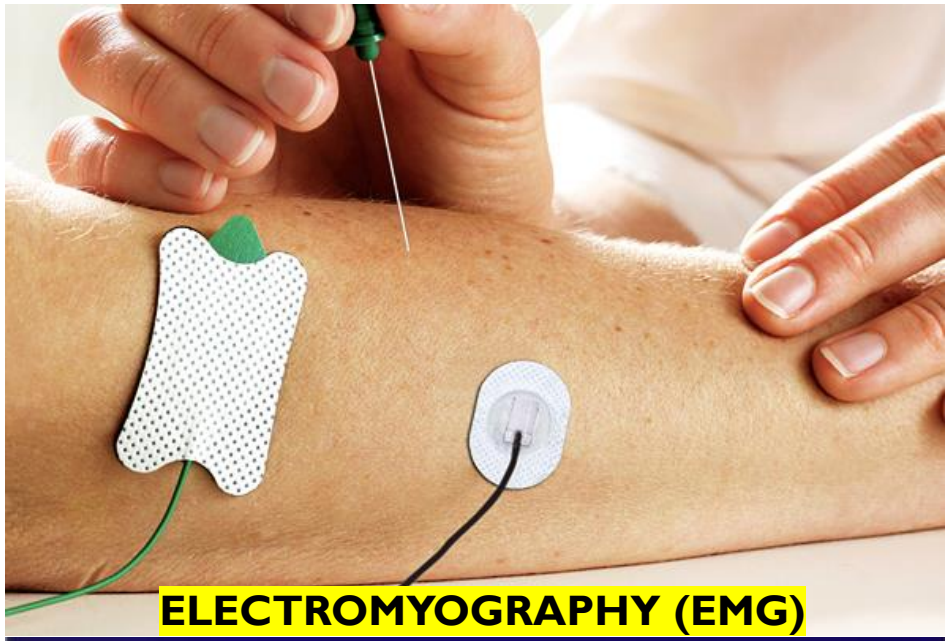
Lab Investigations

- CK enzyme:
  - MM, MB, and BB isoenzymes
  - Muscle (M) monomers
  - Brain (B) monomers
- Elevated in:
  - Muscle diseases
  - Also, nerve, and MND.
  - Strenuous exercise, seizure, IM injections, or muscle trauma

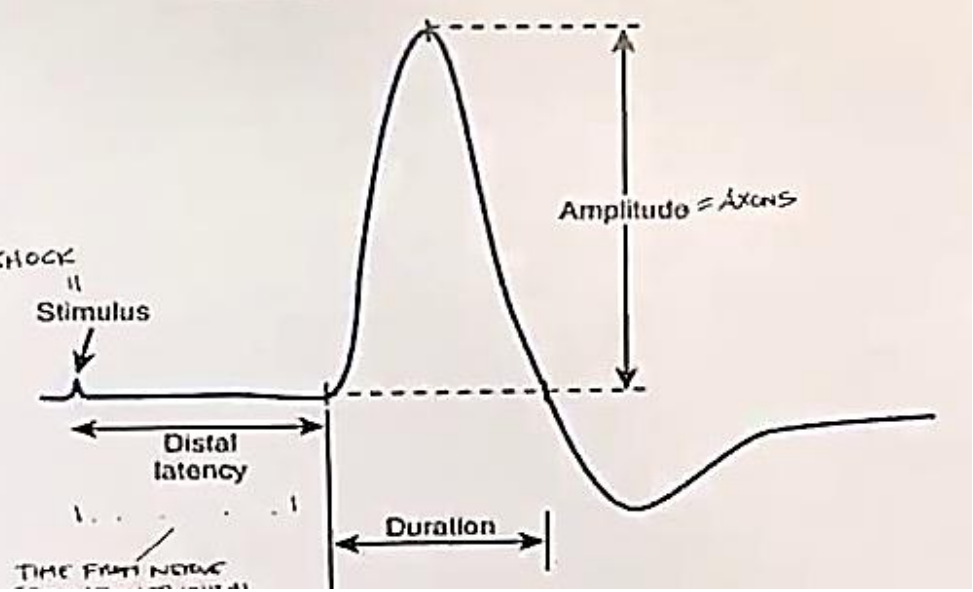
TABLE 2-3 Serum Creatine Kinase Levels

Creatine Kinase Fold Increase	Examples of Diagnostic Considerations
Normal	Facioscapulohumeral muscular dystrophy, milder limb-girdle muscular dystrophies, some metabolic myopathies at rest, rarely dermatomyositis
Mild (<5–10 times the upper limit of normal)	Exercise, neurogenic causes, Becker muscular dystrophy, facioscapulohumeral muscular dystrophy, many types of limb-girdle muscular dystrophy, myotonic dystrophy, advanced Duchenne muscular dystrophy, drug-induced, inflammatory myopathies, congenital and metabolic myopathies, congenital myasthenic syndromes
Marked (>20 times the upper limit of normal)	Duchenne muscular dystrophy/Becker muscular dystrophy, some types of limb-girdle muscular dystrophy (eg, types 2B, 2D, 2G) dermatomyositis, immune-mediated necrotizing myopathies, inherited and acquired causes of rhabdomyolysis and myoglobinuria

NERVE CONDUCTION STUDIES (NCS)



ELECTROMYOGRAPHY (EMG)

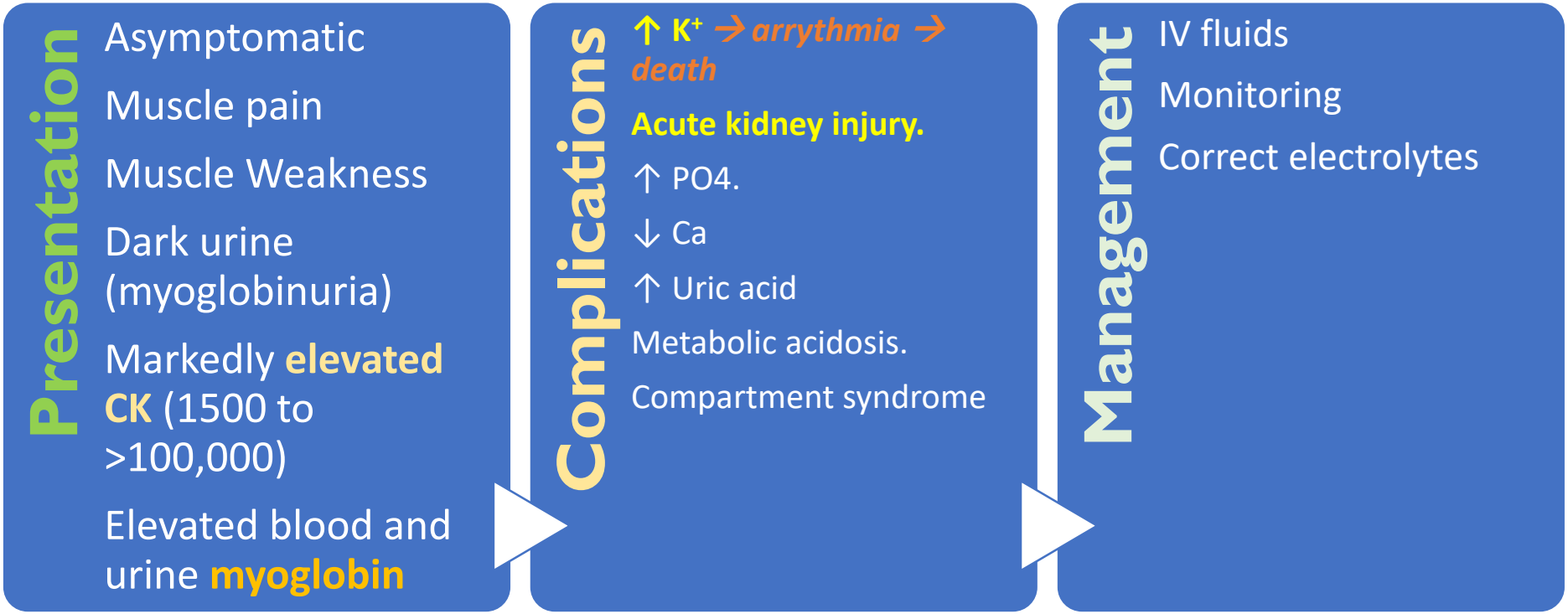


INVESTIGATIONS

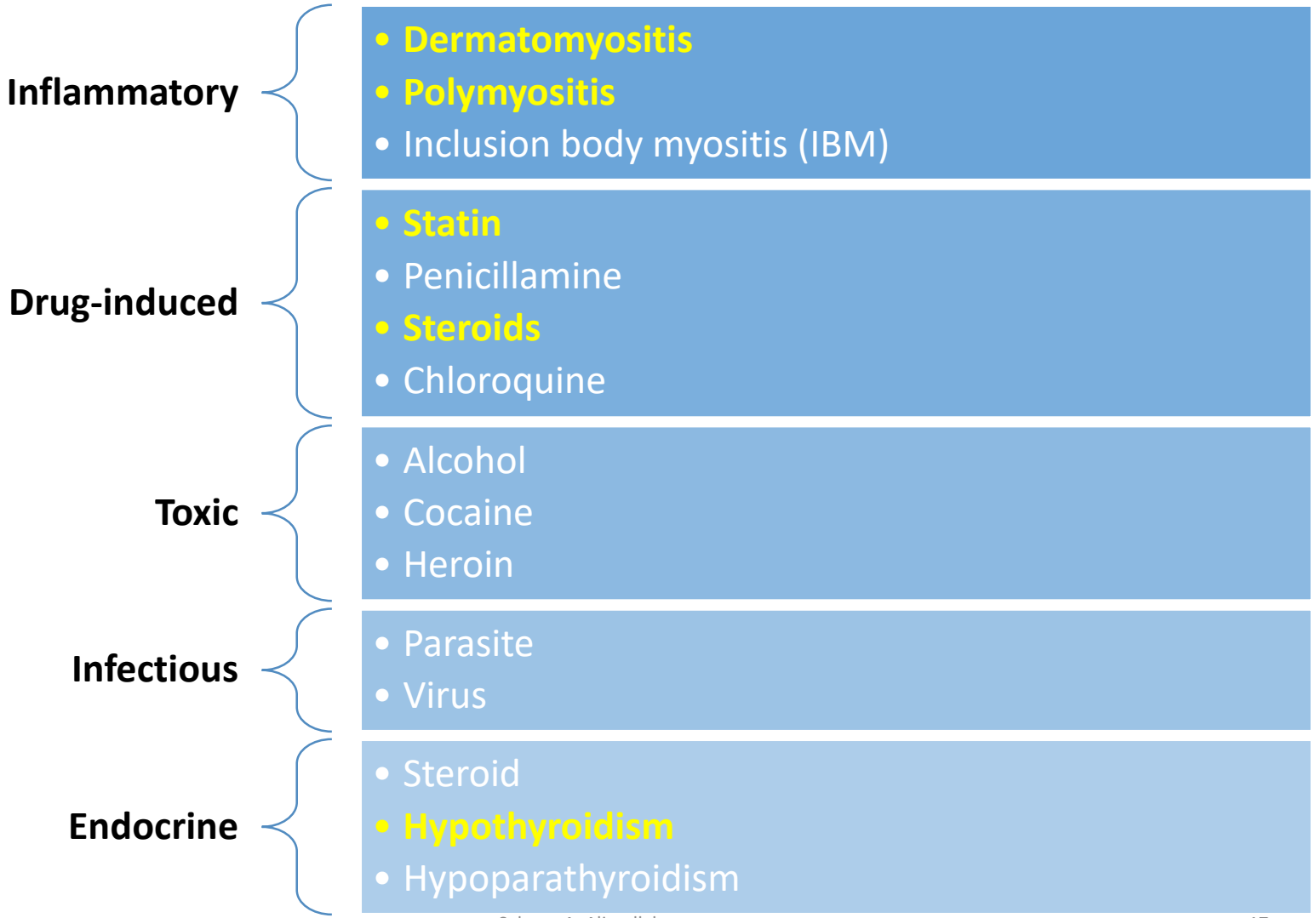
- MRI:
  - Shows pattern of muscle involvement and features of inflammation
  - Can't identify the exact etiology
- Muscle biopsy:
  - Essential for the diagnosis of inflammatory myopathies
- Genetic testing: for specific syndromes

Rhabdomyolysis

- Syndrome of muscle necrosis with release of intracellular muscle materials into the circulation.



CLASSIFICATION OF MUSCLE DISORDERS



INFLAMMATORY MYOPATHIES

Dermatomyositis

Polymyositis

Inclusion body myositis

Immune-mediated necrotizing myopathy

POLYMYOSITIS (PM) AND DERMATOMYOSITIS (DM)

- Female to male ratio of 2:1
- DM children and adults
- PM mainly adults
- Can be part of an **overlap syndrome**:
  - Associated with another well-defined connective tissue disorder
  - Scleroderma, mixed CTD, Sjögren, SLE, or RA.
- Malignancy:
  - Increased risk of cancer (up to 40% of adults with).
  - Breast, ovarian, lung, pancreatic, NHL, stomach, colorectal or melanoma

DERMATOMYOSITIS (DM)

- A form of small vessel vasculitis.
- Weakness: acutely (over several weeks) or insidiously (over months)
- Proximal > distal
- Legs > arms.
- Difficulties swallowing, chewing, and speaking occur (1/3).

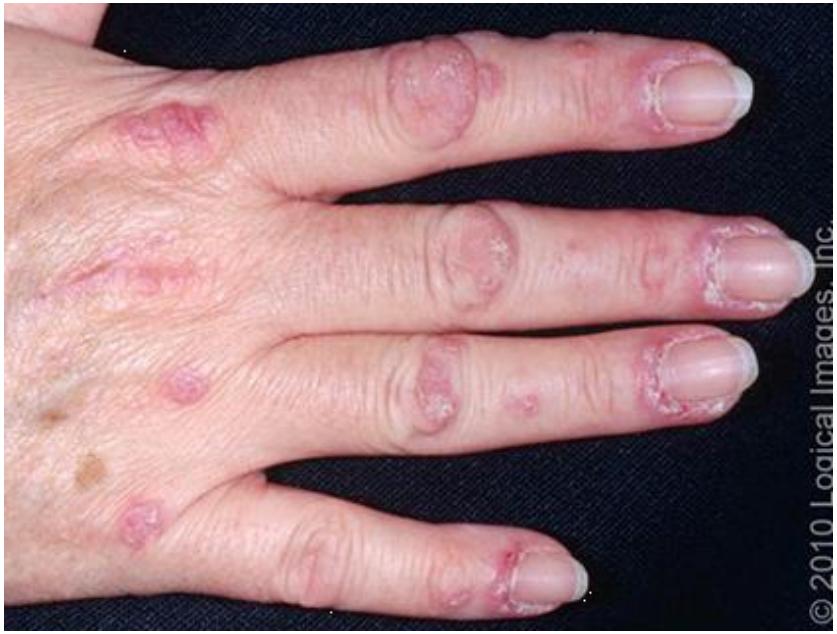
DERMATOMYOSITIS

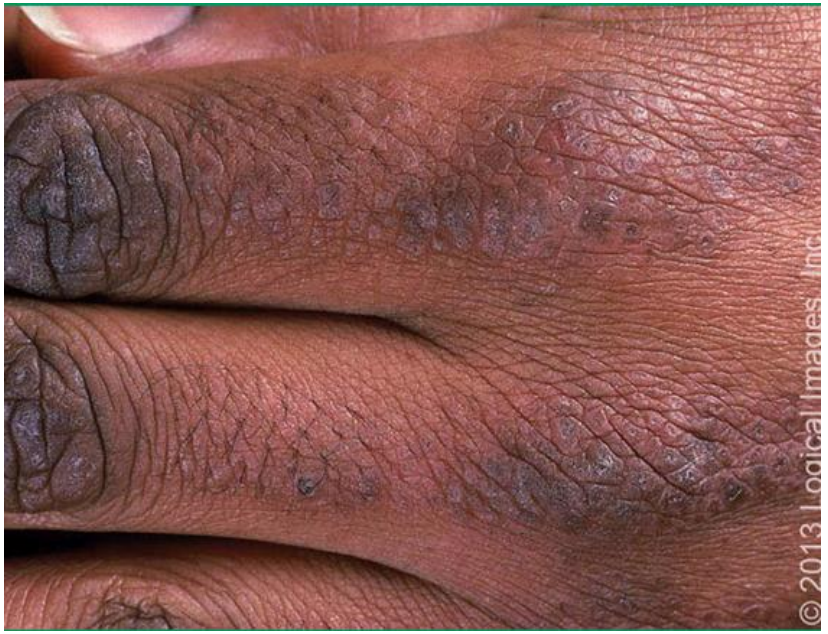
- Non-Skeletal Manifestations :
  - Cardiomyopathy.
  - Dysphagia and delayed gastric emptying.
  - Respiratory muscle weakness.
- Autoimmunity:
  - Interstitial lung disease (usually anti-Jo-1), Raynaud's or polyarthritis
  - ANA
  - Anti–synthetase antibodies (**anti-Jo-1,** also anti-PL-7, anti-PL-12, etc).
  - Myositis-specific antibodies: *Anti–Mi-2, anti-MDA5 (CADM-140), anti p155/140 or anti-MAS*

DERMATOMYOSITIS (DM)

Gottron's Papules

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

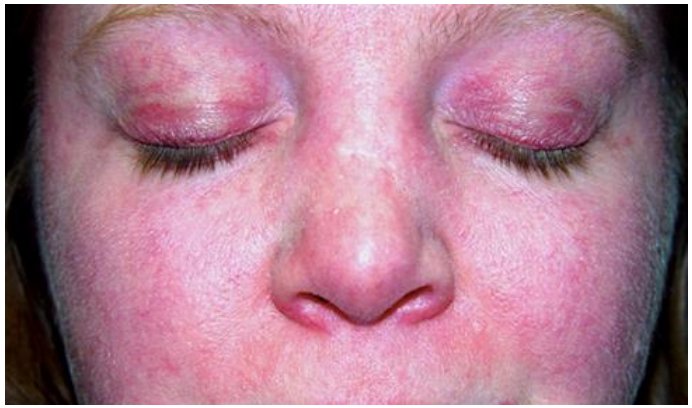


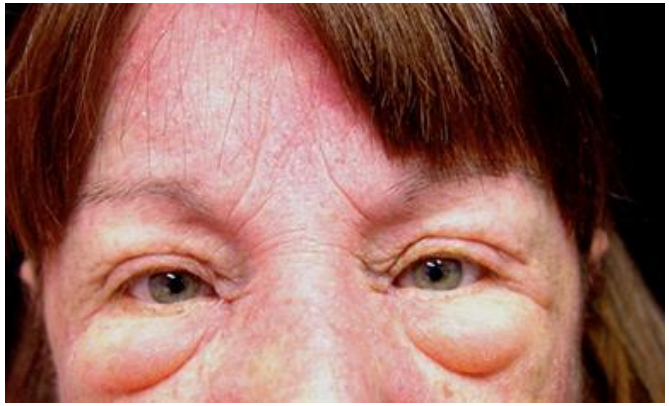


DERMATOMYOSITIS (DM)

Helitrope Rash

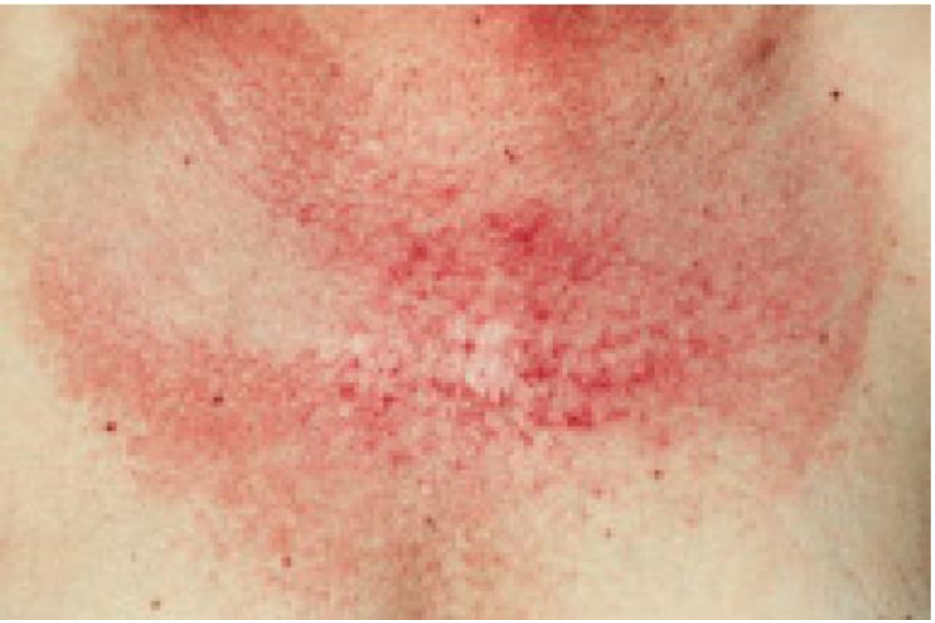
- Pathognomonic for dermatomyositis
- Violaceous eruption on the upper eyelids, sometimes associated with periorbital edema

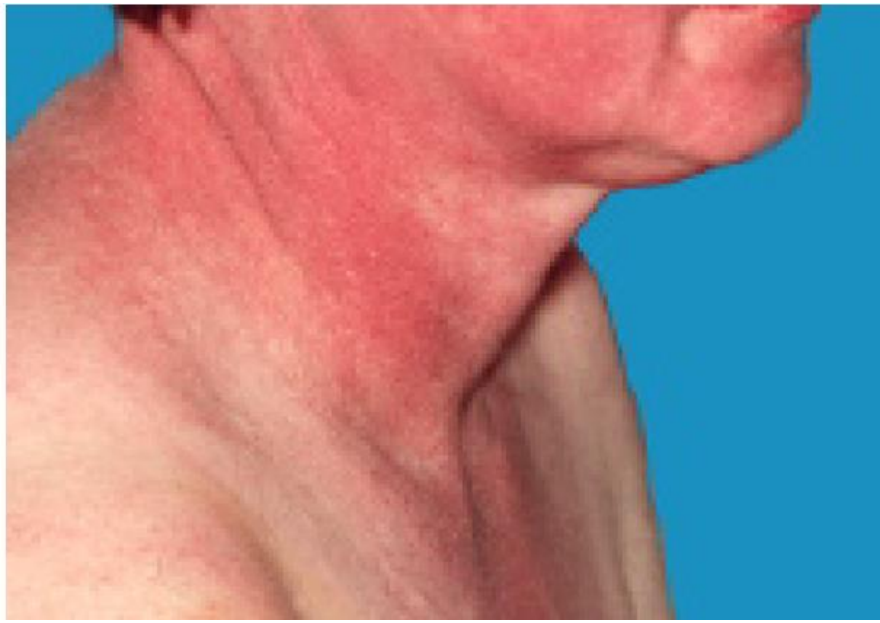




DERMATOMYOSITIS (DM)

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

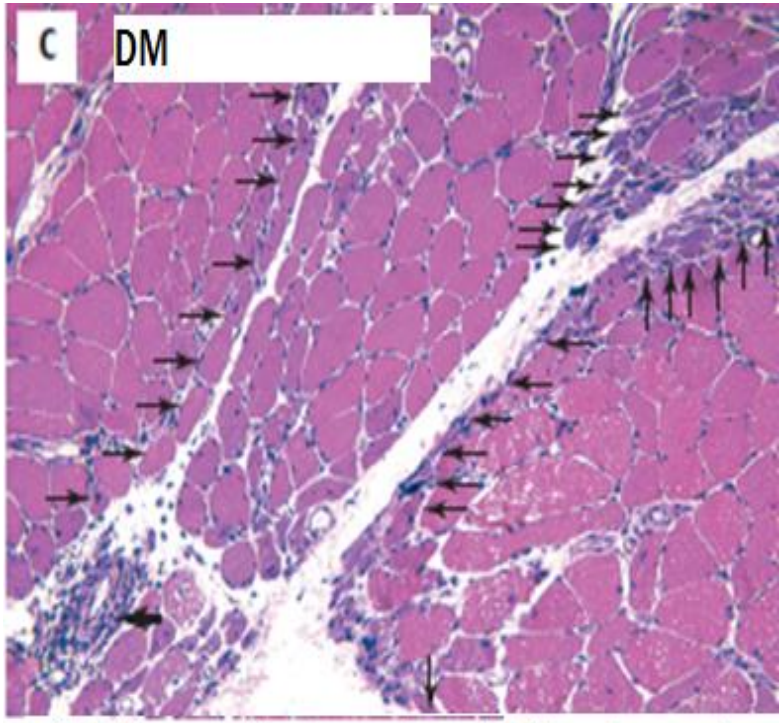




DERMATOMYOSITIS

Pathology

- Inflammation:
  - Perivascular in blood vessels in the perimysium
  - CD4+ plasmacytoid dendritic cells.
  - Complement activation (MAC) and deposition on capillaries.
- Perifascicular atrophy:
  - Pathognomonic.
  - Sublethal myofiber stress and ischemia at the interface of the muscle fascicle and the perimysium.



1. Inflammation in perimysial blood vessels
2. Perifascicular atrophy

POLYMYOSITIS (PM)

- Acute or insidious (weeks-months).
- Mild pain and muscle tenderness.
- Can have malaise, fever, and anorexia.
- Dysphagia
- Extraocular and facial muscles spared.
- Associated with malignancy (less than DM)
- Cardiac myositis (arrythmia, heart failure)
- Polyarthritis in 45%, positive ANA in 40%

DIAGNOSIS of PM & DM

- **Blood tests:**
  - In PM, **CK** should always be **elevated** (>fivefold),
  - In DM, **CK** can be elevated or normal.
  - Elevated levels of other enzymes such aldolase, AST, and ALT
  - Autoantibodies: ANA, anti-Jo1, anti SRP, anti-Mi-2
  - Overlap antibodies: anti-PM/Scl, anti-Ro, anti-La, anti-U1 snRNP (SLE, systemic scleroderma, RA or mixed CTD), anti-U2 snRNP (scleroderma)
- **EMG**: myopathic pattern
- **Muscle MRI**: edema, inflammation, fibrosis, calcification or fatty replacement of muscle tissue.
- **Muscle biopsy** is indicated to confirm diagnosis.

MANAGEMENT of PM & DM

- Corticosteroids:
  - Some require high dose for long time.
  - Risk of opportunistic infections (PCP), osteoporosis, cataract, weight gait, etc
  - Monitor blood glucose, serum potassium levels, BP, and eyes
- Steroid-sparing therapy:
  - Methotrexate, azathioprine, mycophenonlate, etc
- Cancer screening.
- Evaluate coexisting autoimmune disorders , ANA,
- Exclude cardiac and pulmonary involvement
- Physical therapy
- Occupational therapy

STATIN-INDUCED MYOPATHY

- Statins inhibit HMG-CoA reductase, rate-limiting enzyme of cholesterol biosynthesis.
- Can cause
  - Mild statin-associated myalgia or cramps
  - Myopathic weakness.
  - Severe myotoxicity or rhabdomyolysis, rare
  - Rarely, statins can cause an ***Immune-Mediated Necrotizing Myopathy*** *with* ***very high CK*** *and* ***antibodies to*** **Anti-HMG CoA-reductase**
- Discontinuation of the statin → resolution of symptoms in most cases

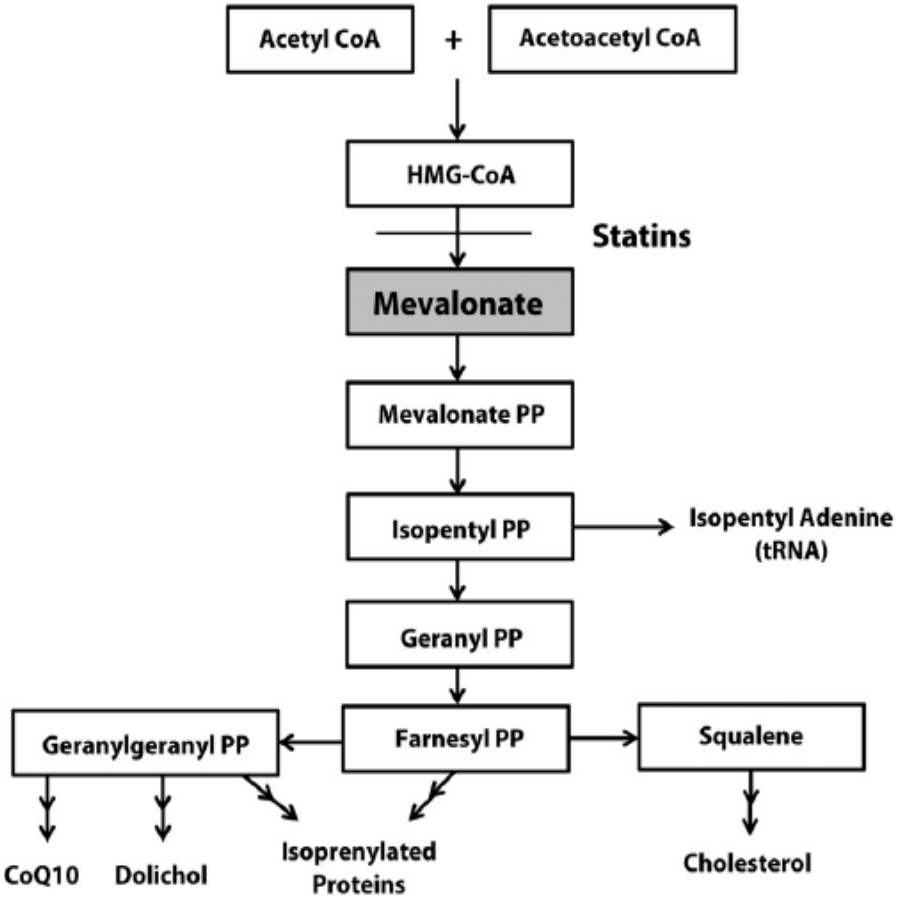
STATIN-INDUCED MYOPATHY

- Risk factors
  1. Older age
  2. Hypothyroidism
  3. Obesity
  4. Type of statin: fluvastatin and pravastatin are worse than rosuvastatin
  5. Dose of statin.
  6. Preexisting liver disease → reduce metabolism of statin
  7. Liver enzyme inhibitors → increase levels of statins
  8. Genetic susceptibility: SLCO1B1 gene.

STATIN-INDUCED MYOPATHY

- Mechanism
  - ↓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 N-glycosylation → defective proteins → muscle cells damage.



STEROID-INDUCED MYOPATHY

- ***Chronic*** exposure to ***high-dose*** oral steroids .
- As short as few weeks of proximal weakness.
- **CK**: normal.
- **EMG**: normal or myopathic.
- Biopsy: *type 2 fiber atrophy and lipid accum type 1 fibers.*
- ?mechanism.
  - ↓*protein synthesis.*
  - ↑ *protein degradation.*
  - *Alterations in carbohydrate metabolism.*
  - *Mitochondrial dysfunction.*
  - ↓ *reduced sarcolemmal excitability*

HEREDITARY MUSCLE DISORDERS

Muscular Dystrophies

- **Dystrophinopathies**
  - Duchenne
  - Becker
- Limb-girdle muscular dystrophies
- **Myotonic dystrophies**

Congenital Myopathies

Channelopathies

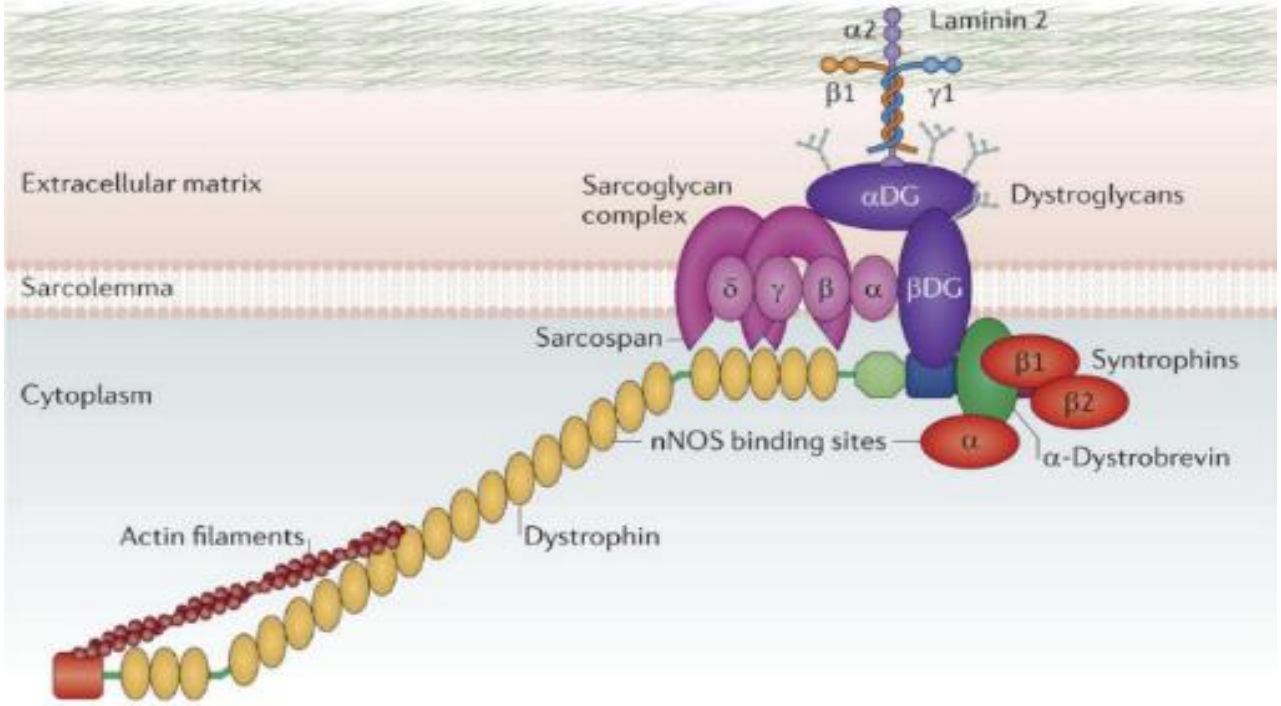
Mitochondrial myopathies

Metabolic storage myopathies

MUSCULAR DYSTROPHIES (MD)

MUSCULAR DYSTROPHIES (MD)

- Inherited myopathies
- Caused by mutation in genes important in maintaining the **structure** of muscle fibers
- Progressive degeneration of the muscles with connective tissue replacing muscle fibers
- Variable age at onset
- Systemic involvement



MUSCULAR DYSTROPHIES (MD)

Dystrophinopathies

- Duchenne muscular dystrophy (DMD)
- Beker muscular dystrophy

Myotonic dystrophy (MD)

Limb girdle muscular dystrophies (LGMD)

Facioscapulohumeral MD (FSHD)

Oculopharyngeal MD (OPMD)

Emery-Dreifuss muscular dystrophy

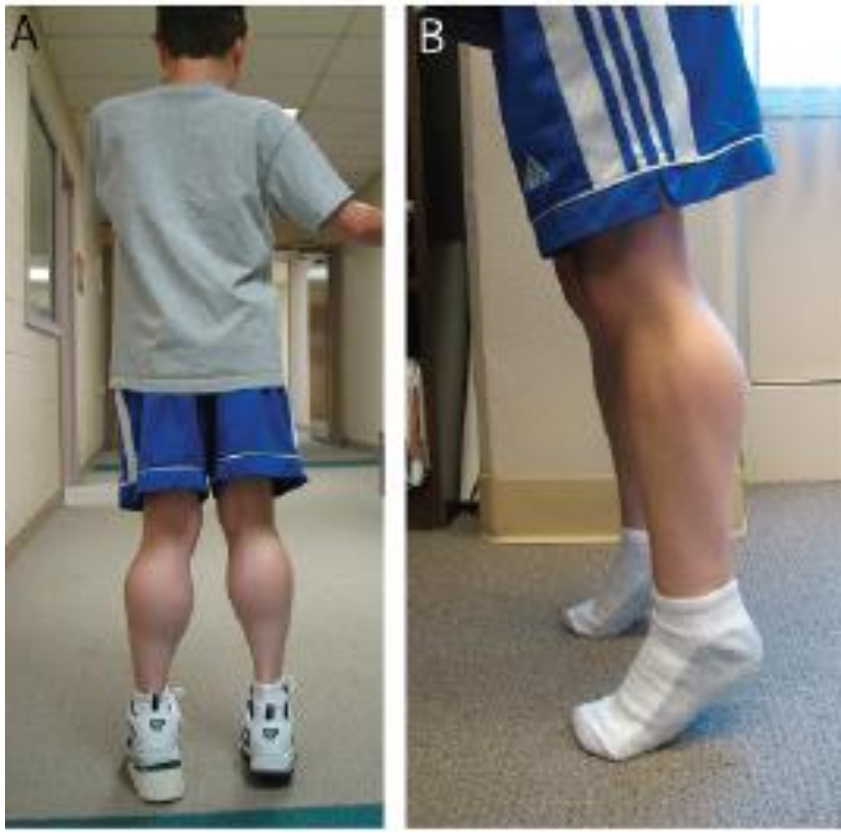
Barths syndrome

DYSTROPHINOPATHIES

- X linked recessive disorders (manifest in males)
- Duchenne & Becker (DMD, BMD)
- Mutation in the **dystrophin gene** → absent or reduced Dystrophin protein → loss of mechanical reinforcement to the sarcolemma and instability of the glycoprotein complex → degeneration of muscle fibers

DUCHENNE MD (DMD)

- Boys.
- Absence of dystrophin
- Progressive weakness proximal UE and LE
- Onset 2-5 years, 5-6 y can't jump or climb then wheelchair 10 years of age
- Death at 15-30 years.
- Sparing of the cranial muscles
- Weak knee extensors → toe walking.
- Gower's sign
- Pseudo-hypertrophy of the calves
- Complications: contractures, kypho-scoliosis, exaggerated lumbar lordosis



DMD

- **Management**:
  - **Glucocorticoids**:
    - Stabilizes sarcolemma
    - Increases strength, muscle, and pulmonary functions
    - Reduces cardiomyopathy and lowers mortality
    - Anabolic action in contrast to its catabolic action on normal skeletal muscle in unaffected people.
  - Physical therapy, occupational therapy and bracing
  - Cardiac, respiratory, GI, and orthopedic complications.
  - Osteoporosis screening
  - Avoidance of anesthesia and sedation if possible

BECKER MUSCULAR DYSTROPHY

- Older age at onset
- Less severe symptoms
- Loss of ambulation is usually in the 4th decade
- Muscle biopsy shows reduced dystrophin

	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 (MD)

Dystrophinopathies

- Duchenne muscular dystrophy (DMD)
- Beker muscular dystrophy

Myotonic dystrophy (MD)

Limb girdle muscular dystrophies (LGMD)

Facioscapulohumeral MD (FSHD)

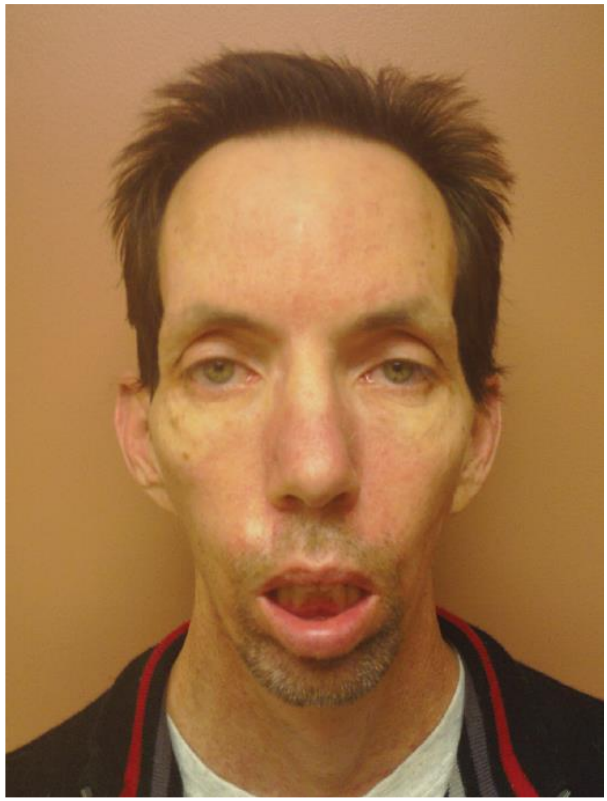
Oculopharyngeal MD (OPMD)

Emery-Dreifuss muscular dystrophy

Barths syndrome

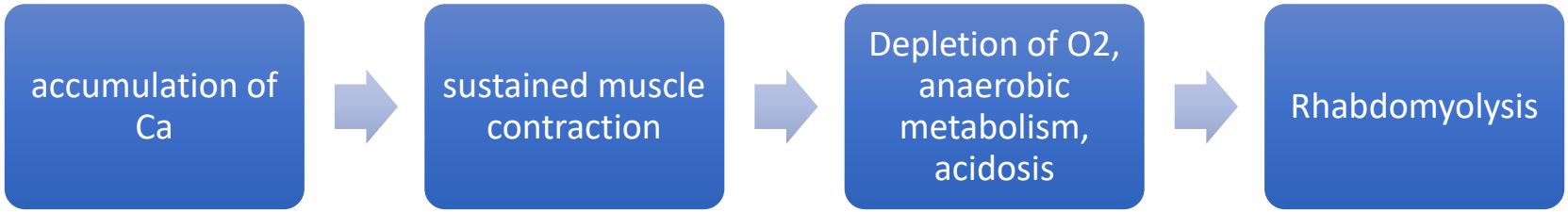
MYOTONIC DYSTROPHY (MD)

- The most prevalent inherited neuromuscular disease in adults
- Autosomal dominant
- Tandem repeats at DMPK gene (Anticipation phenomenon)
- Myotonia
- Cardiac: arrythmias, heart failure, sudden death
- Respiratory weakness: orthopnea,
- GIT dysmotility, constipation and diarrhea
- Cataract
- Endocrine abnormalities: NIDDM, hypoT4, male hypogonadism
- Low IQ



MALIGNANT HYPERTHERMIA (MH)

- Hypermetabolic reaction.
- Triggered: anesthetics and depolarizing neuromuscular blockers.
- Tachypnea, tachycardia, **rigidity**, acidosis, hyperkalemia, rhabdomyolysis, **high CK**, and **hyperthermia**.
- Genetic mutations → calcium accumulation
- Can be fatal
- Treatment:
  - **Remove** anesthetic agent.
  - Core **cooling**
  - **Dantrolene sodium**, reduces calcium release from the sarcoplasmic reticulum.



Conclusion

- Thank you