Myopathies 341
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Reem Alhammad, MD
Assistant professor of neurology

Pause

- First goal in approaching patients with a suspected muscle disease is to determine the correct *site* of the lesion: NMJ?, AHC?, roots?, motor nerves?

<u>Confirmed site as muscle :</u>

1. Identify whether the myopathy is caused by:
    - defect in the muscle channel
    - Abnormal muscle structure
    - dysfunction in muscle metabolism.
2. Determine the *cause* of the myopathy
3. Determine management:
    - Treatable?
    - Frequency of cardiac/respiratory surveillance?
    - Counselling: exercise? Precautions on rhabdomyolysis

Classification of myopathies

Box 1
Classification of myopathies

Acquired
- Drug-induced myopathies
- Endocrine myopathies
- Inflammatory/immune myopathies
- Myopathies associated with other systemic illness
- Toxic myopathies

Hereditary
- Channelopathies
- Congenital myopathies
- Metabolic myopathies
- Mitochondrial myopathies
- Muscular dystrophies
- Myotonias

History, history, history, history, history, history

6 key questions:

1. Which Negative and/or Positive Symptoms Do Patients Demonstrate?
2. What is the Temporal Evolution?
3. Is There a Family History of a Myopathic Disorder? Cardiac disease?
4. Are There Precipitating Factors That Trigger Episodic Weakness or Stiffness?
5. Are There Associated Systemic Symptoms or Signs?
6. What is the Distribution of Weakness?

What are the negative/positive symptoms?

Box 2
Symptoms associated with myopathies

Negative

- Exercise intolerance
- Fatigue
- Muscle atrophy
- Weakness

Positive

- Cramps
- Contractures
- Muscle hypertrophy
- Myalgias
- Myoglobinuria
- Stiffness

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 ----> metabolic and mitochondrial myopathies.

- Myalgias:
  - episodic → metabolic myopathies
  - nearly constant → inflammatory myopathies

- vague aches and muscle discomfort + normal neuromuscular examination and laboratory studies → unlikely to be muscle in origin

Muscle cramps:

- specific type of muscle pain.
- may last from seconds to minutes
- usually localized to a particular muscle region, typically the calves.
- EMG: rapidly firing motor unit discharges
- typically benign, not related to an underlying disease process
- Other causes:
  - Dehydration
  - Hyponatremia
  - azotemia
  - Myxedema
  - disorders of the nerve or motor neuron (ALS)

Muscle contractures:

- uncommon but can superficially resemble a cramp.
- typically provoked by exercise in patients with glycolytic enzyme defects.
- Last longer than cramps
- EMG: silent
- Do not confuse with fixed contractures of tendons

Myotonia:

- Repetitive depolarization of muscle membrane
- Impaired relaxation after voluntary contraction
- Eyelids, hand grip
- Worsens with cold
- Improves with repeated exercise

Myoglobinuria:

- Excess release of myoglobin during periods of excessive muscle breakdown.
- Severe episodes: ATN → renal failure
- Isolated episodes following strenuous unaccustomed exercise: commonly idiopathic

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.

2.What is the temporal evolution?

Onset:

- Childhood: Duchenne
- Adolescence or later: FSHD, LGMD
- Adults: inflammatory , toxic, also genetic
- After 50 yrs: IBM

2.What is the temporal evolution?

Tempo:

- Episodic with normal strength interictal: metabolic or PP
- 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).

Is There a Family History of a Myopathic Disorder?

Questions :

- use of canes or wheelchairs
- skeletal deformities
- functional limitations
- Sudden deaths
- Pacemakers
- Early onset cataracts
- Deaths/complications from anesthesia
- Early onset dementia/Paget’s disease of bone

Box 8
Diagnosis of myopathy based on pattern of inheritance

X-linked

Becker muscular dystrophy, Duchenne muscular dystrophy, Emery-Dreifuss muscular dystrophy

Autosomal dominant

Central core myopathy, FSH, limb-girdle muscular dystrophy type 1, oculopharyngeal MD, myotonic dystrophy, paramyotonia congenita, periodic paralysis, thomsen disease

Autosomal recessive

Becker myotonia, limb-girdle muscular dystrophy type 2, metabolic myopathies

Maternal transmission

Mitochondrial myopathies

Are There Precipitating Factors That Trigger Episodic Weakness or Stiffness?

- Fever → CPT
- Carbohydrates followed by rest --> PP
- Toxic
- Immune mediated (check point inhibitors, statin)

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

Are There Associated Systemic Symptoms or Signs?

Cardiac:

- Dystrophinopathy
- DM1, DM2
- LGMD: emery - dreifuss, sarcoglycanopathies, fukutin

Respiratory:

- DM
- Acid maltase (adult pompe)
- CNM, nemaline

Are There Associated Systemic Symptoms or Signs?

- Fatty liver: CPT
- Cataracts, frontal balding: DM
- Rash: dermatomyositis
- Early contractures: laminopathy
- Systemic organ disease: amyloid, sarcoid, mitochondrial

What is the Distribution of Weakness?

- Exposure
- Atrophy? → periscapular in FSHD, asymmetric quadriceps/forearm flexors in IBM
- Hypertrophy? → calf in dystrophin, sarcoglycan, fukutin, sarcoid, amyloid
- Abnormal movements(rippling)/myotonia

What is the Distribution of Weakness?

Positions in testing:

- Neck flexors : supine position
- neck extensors : prone position
- Knee extension and hip flexion : tested in seated position
- knee flexion : tested prone
- hip abduction : tested in the lateral decubitus position.

What is the Distribution of Weakness?

Scapular winging:

- FSHD
- Pompe
- Laminopathy
- calpain
- SLONM

What is the Distribution of Weakness?

Signs:

Waddling gait → inflammatory or LGMD

Impaired toe walking → dysfrelin, ANO-5

Pointing finger sign →MYH7

Anteverted axillary line, protuberant abdomen, facial and scapular weakness → FSHD

Patterns

Pattern 1:Proximal limb girdle:

- Most common
- Frequent involvement of neck flexor/extensor
- Least specific

Patterns

Pattern 2: Distal Weakness

- involves the distal muscles of the upper or lower extremities (anterior or posterior compartment muscle groups)
- Usually symmetric.
- Assymmetric posterior compartment : ANO-5, dysferlinopathy
- Anterior compartment with sparing of quadriceps: GNE
- Finger flexor: IBM
- Finger extensor: TIA1 (Welander)
- Rule out neuropathy!!!!

Patterns

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

- can be very *asymmetric*
- When associated with facial weakness : FSHD
- Laminopathies (emery dreifuss) frequently associated with cardiac arrhythmias , VCP, calpain

Patterns

Pattern 4: Distal Arm/Proximal Leg Weakness

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

Patterns

Pattern 5: Ptosis with or Without Ophthalmoparesis

- ocular involvement :ptosis and ophthalmoparesis
- usually (not always), occurs *without* diplopia
- Facial weakness: not uncommon
- extremity weakness : variable, depending on the diagnosis.
- Ptosis, ophthalmoparesis without diplopia, and dysphagia →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)

Pattern 6: Prominent Neck Extensor Weakness

- severe weakness of the neck extensor muscles
- *dropped head syndrome*
- Limb and neck flexor involvement : variable
- Rule out ALS or MG

Patterns

Pattern 7: Bulbar Weakness

- tongue and pharyngeal weakness
- Acquired: sarcoid, pompe, NAM, inflammatory
- Hereditary: OPMD, myotilin

Patterns

Pattern 8: Episodic Pain, Weakness, and Myoglobinuria

- episodic pain, weakness, +/- myoglobinuria
- may be related to a variety of conditions (non muscle)
- *Triggered by exercise* → 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.

Patterns

Pattern 9: Episodic Weakness Delayed or Unrelated to Exercise

- PP: genetic AD and secondary (thyrotoxicosis)
- Rule out NMJ

Patterns

Pattern 10: Stiffness and Decreased Ability to Relax

- Dystrophic and non-dystrophic myotonias

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

workup

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

EMG:

- Small units with early recruitment
- May see and hear myotonic discharges

Acquired

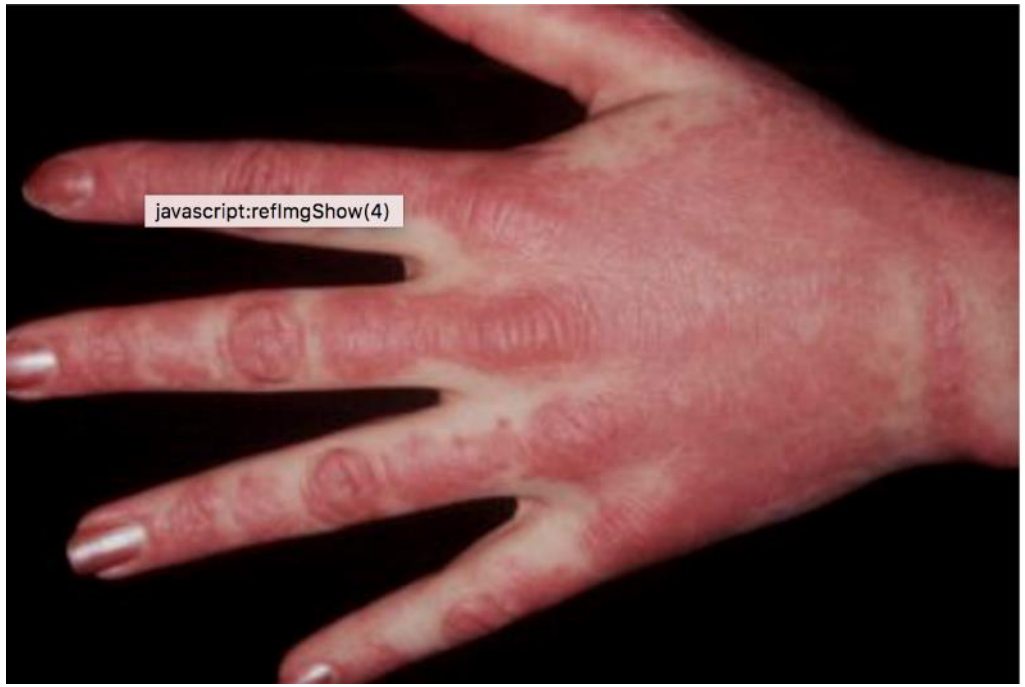
Dermatomyositis

- idiopathic inflammatory myopathy
- characteristic cutaneous findings that occur in children and adults
- systemic disorder most frequently affects the skin and muscles but may also affect the joints; the esophagus; the lungs; and, less commonly, the heart.

Acquired,cont.

Dermatomyositis

- Eruption predominantly on photo-exposed surfaces
- Pruritus of skin lesions, sometimes intense enough to disturb sleep
- Erythema of the mid-face
- Eruption along the eyelid margins, with or without periorbital edema
- Eruption on the dorsal hands, particularly over the knuckles
- Changes in the nailfolds of the fingers
- Eruption of the upper outer thighs
- Scaly scalp or diffuse hair loss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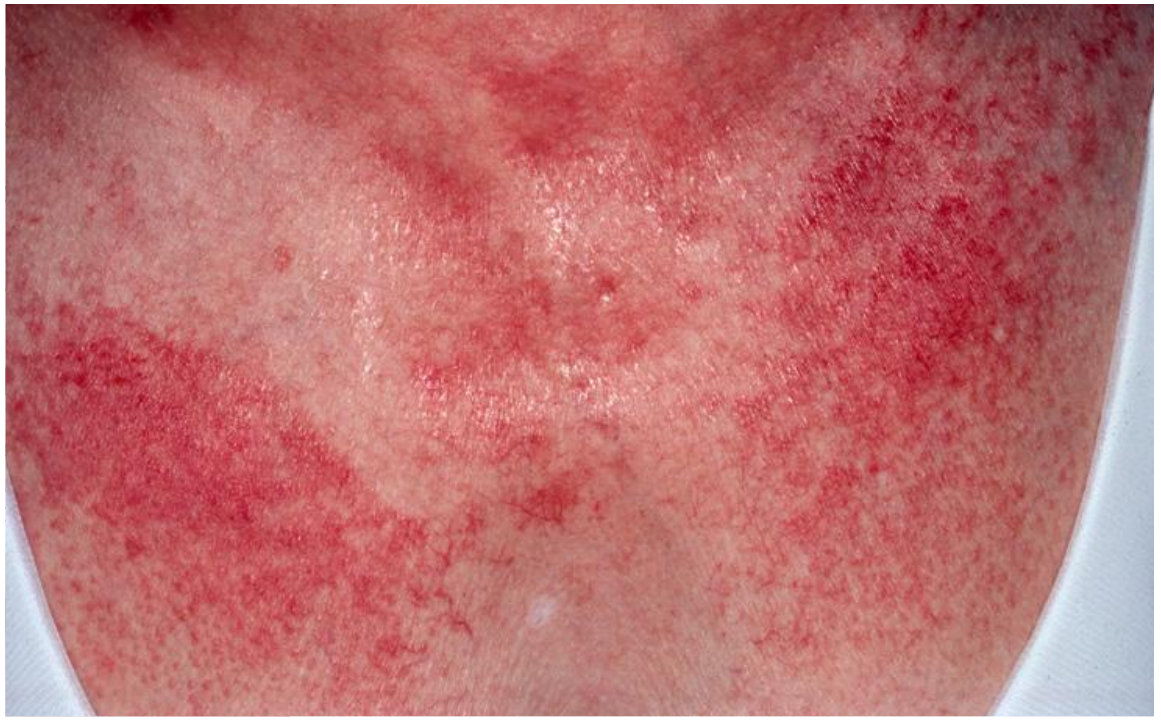
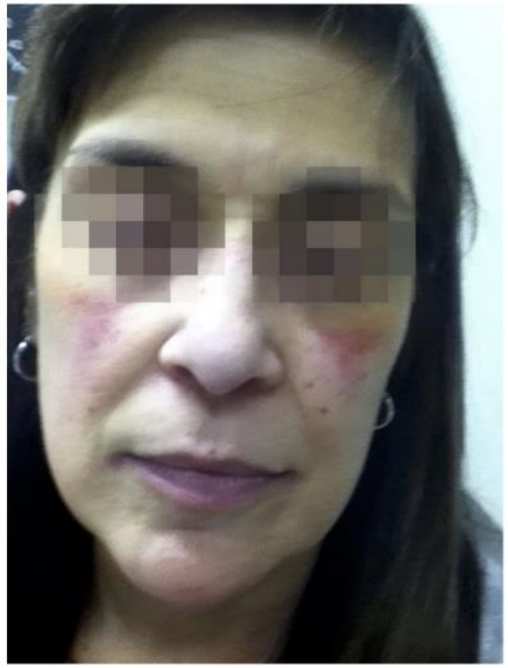
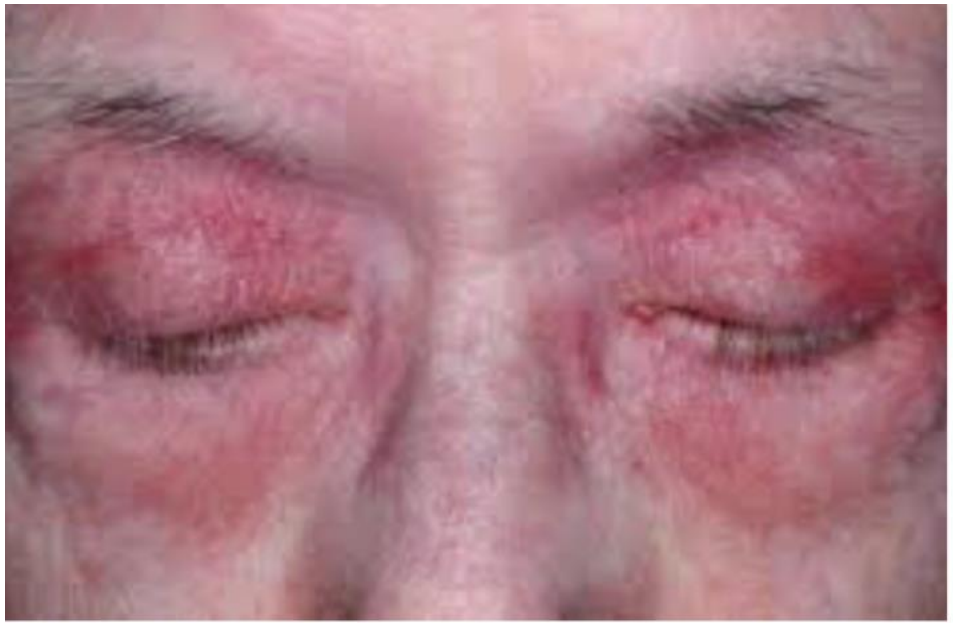


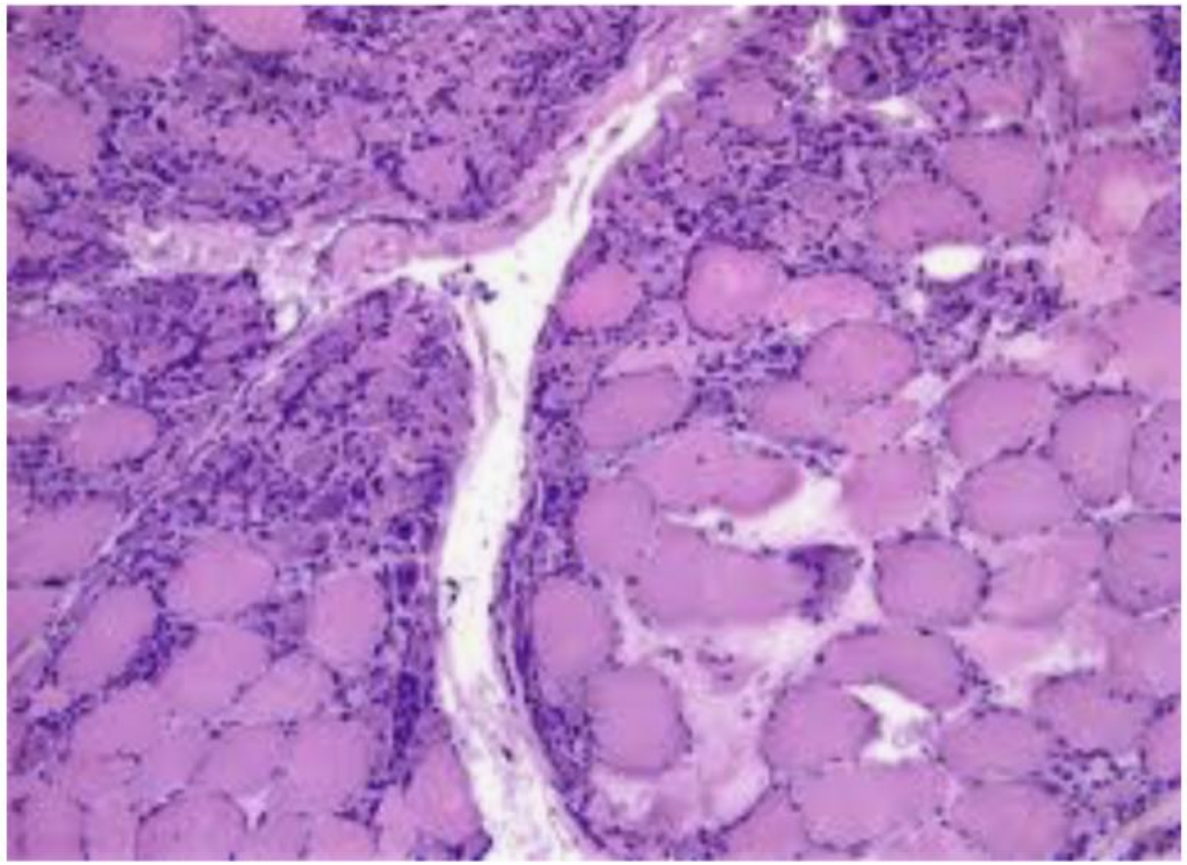




Acquired,cont.
Laboratory

- CK, LFT, RFT
- Myositis-specific antibodies
- Antinuclear antibody levels
- Pulmonary function studies with diffusion capacity
- Electrocardiography
- esophageal manometry
- CT CAP or PET scan and Colonoscopy to screen for underlying malignancy
- CA-125 and CA-19-9 for malignancy screening

Muscle biopsy



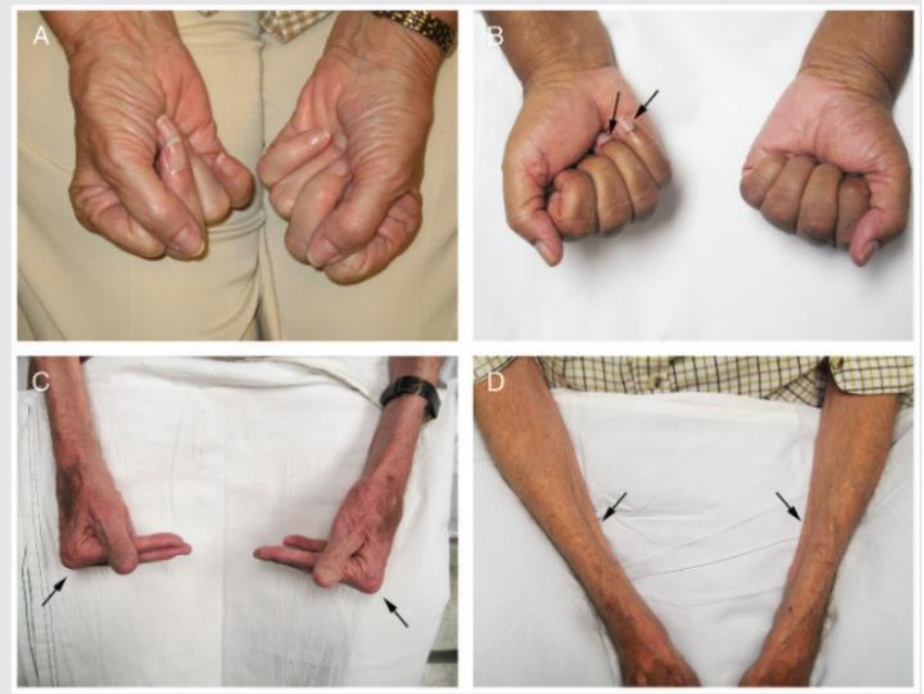
Acquired myopathies, cont.

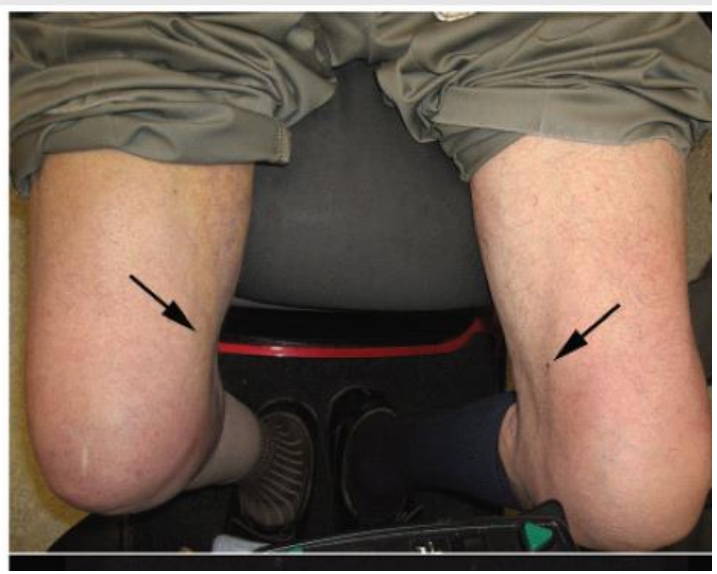
Inclusion body myositis (IBM):

- Progressive slow-onset inflammatory/degenerative myopathy
- Common after age 50(prevalence:35-71/1000000)
- M:F → 2:1
- Unique clinical and pathological features
- Relentless progression, lacks effective therapies

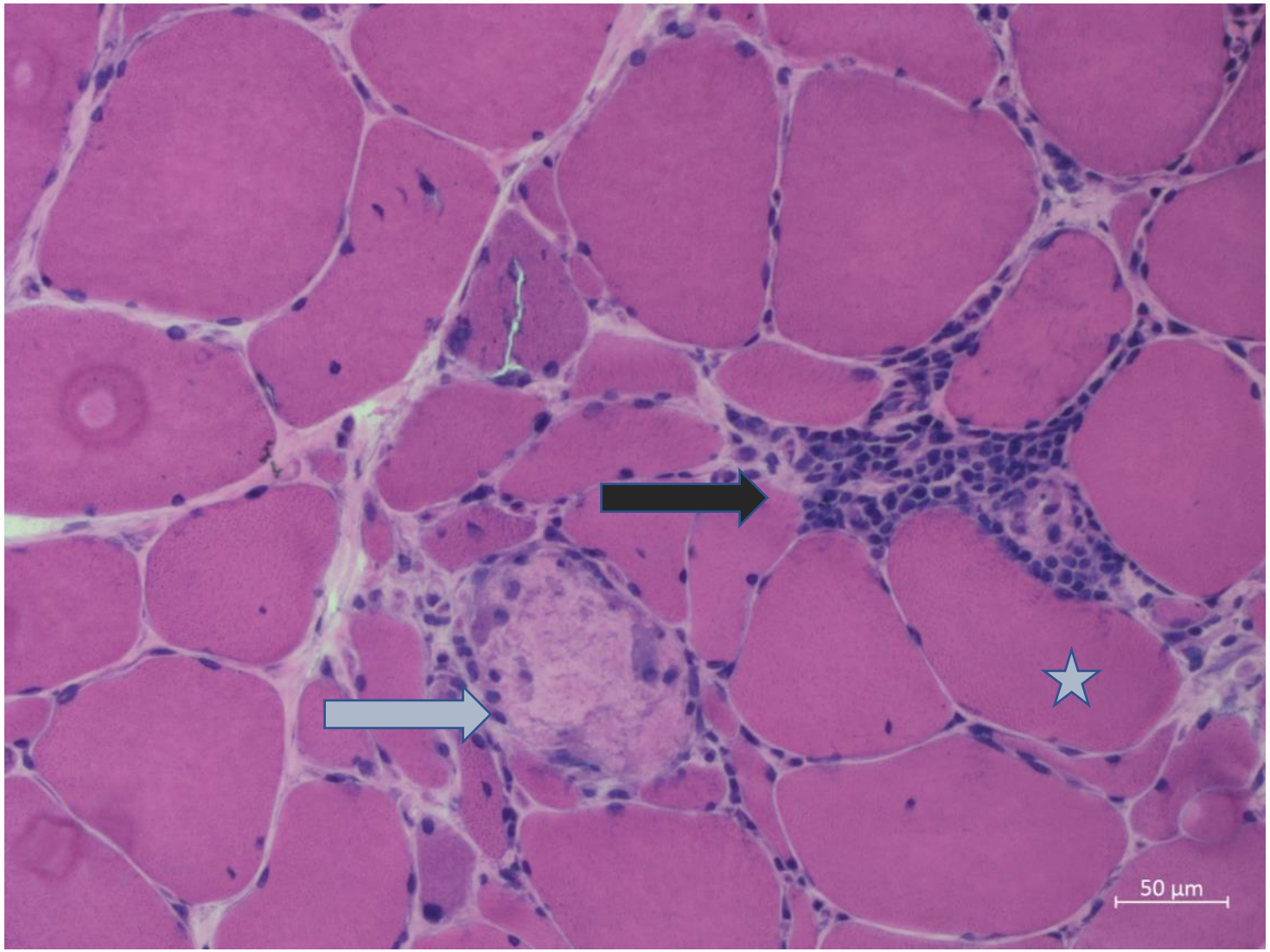
Clinical presentation

- Quadriceps femoris +/- long finger flexors
- Biceps, foot dorsiflexors
- paraspinal muscles: camptocormia or dropped head syndrome
- oropharyngeal dysphagia : 40–86% (upper esophageal sphincter dysfunction)
- heart muscle: usually unaffected

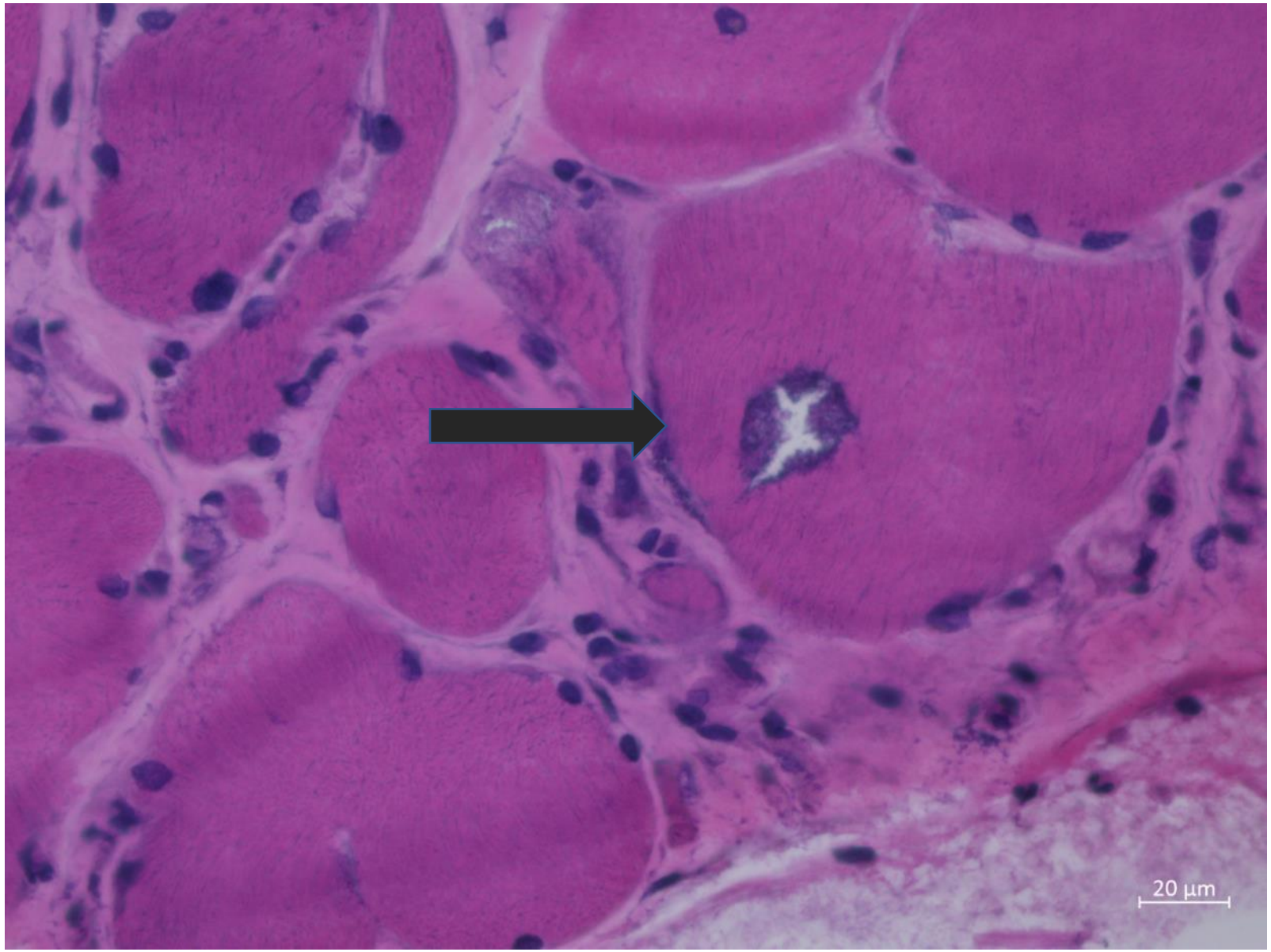




Continuum December,2016



H&E



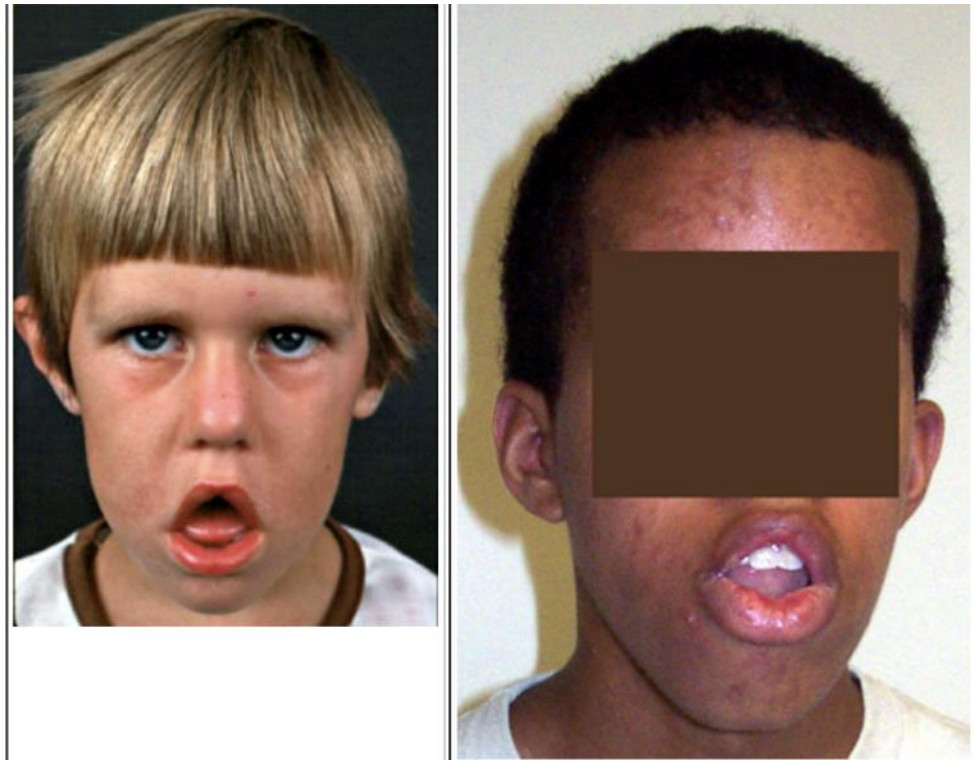
H&E

Inherited myopathies

Myotonic dystrophies : autosomal dominant

- Most prevalent dystrophy in adult
- characterized by progressive muscle wasting and weakness.
- prolonged muscle contractions (myotonia) and are not able to relax certain muscles after use.
- difficulty releasing hand grip on a doorknob or handle.
- slurred speech or temporary locking of their jaw.
- Cataracts
- Diabetes and other endocrine
- cardiac conduction defects
- anticipation

Myotonic dystrophies, cont.



Percussion and grip myotonia

Frontal balding

Cognitive impairment

Myotonic dystrophies, cont.

Lab:

- CK
- EMG : myopathic plus myotonic discharges
- ECG and echo
- Genetic testing; type 1 and type 2

Inherited myopathies

Dystrophinopathy : X - linked

- Duchenne – most common dystrophy
- Becker

Inherited myopathies

Duchenne

- Weakness
  - Onset age: 2 to 5 yrs
  - Distribution
    - Proximal > Distal
    - Symmetric
    - Legs & Arms
  - Course
    - Reduced motor function by 2 to 3 years
    - Steady decline in strength: After 6 to 11 years
  - Gowers sign
    - Standing up with the aid of hands pushing on knees
  - Loss of Ambulation
    - Age: 9 - 13 years
    - Later with: Steroid treatment

Inherited myopathies

Duchenne

Muscle hypertrophy

- Especially calf
- May be generalized
- Increases with age
- Most commonly due to: Muscle replacement by fat & connective tissue

Inherited myopathies

Duchenne

- Scoliosis
- Dilated cardiomyopathy : common after age 15
- Cognitive impairment
- Death: 15-25 years

Inherited myopathies

- Duchenne

- CK : very high, usual is 100 X ULN
- Muscle biopsy : absent dystrophin staining
- Genetic testing is gold standard

Inherited myopathies

Becker

- Onset age: Usually > 7 yrs
- Weakness
  - Proximal > Distal; Symmetric; Legs & Arms
  - May be especially prominent in quadriceps or hamstrings
  - Slowly progressive
  - Severity & onset age correlate with muscle dystrophin levels
- Calf pain on exercise
- Muscle hypertrophy: Especially calves
- Failure to walk 16 - 80 years

Inherited myopathies

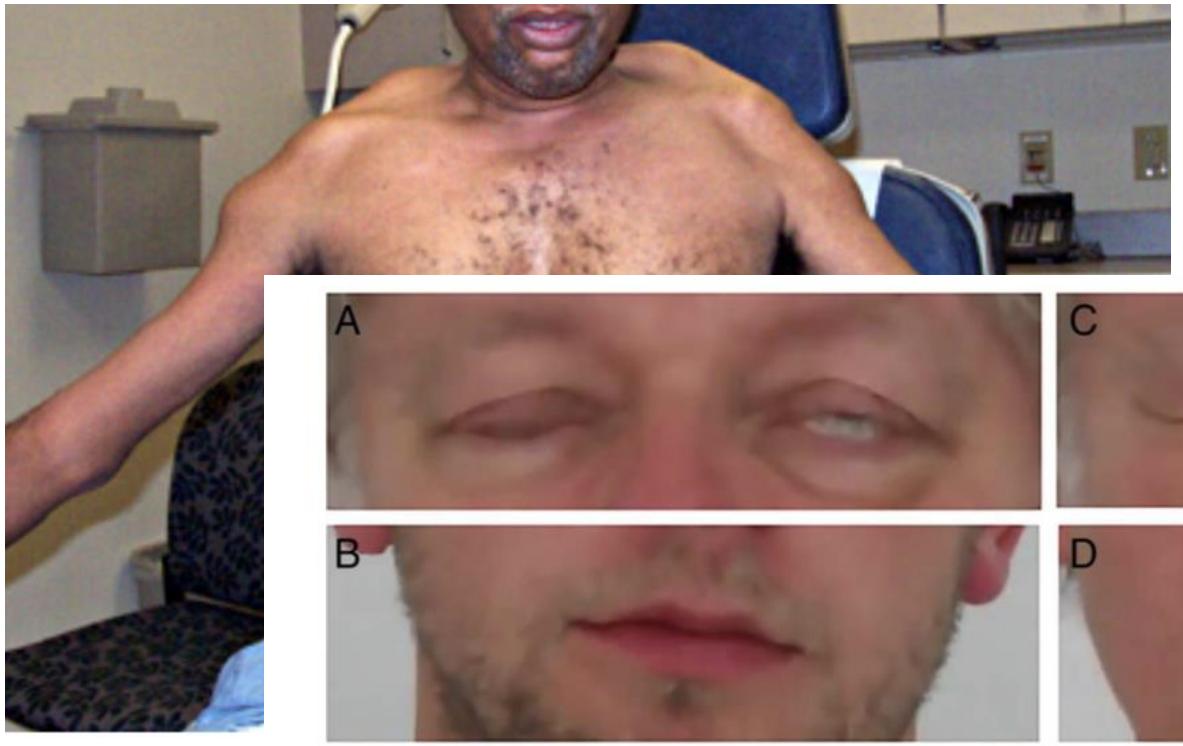
Becker:

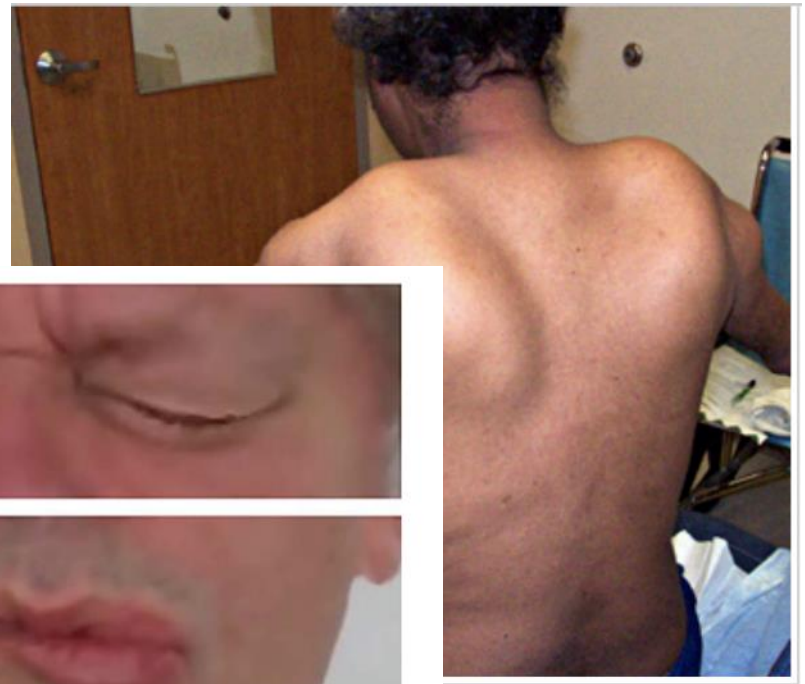
- Cardiomyopathy may occur before weakness
- ck high: 2000 to 20,000
- Partial loss of dystrophin staining
- Genetic testing

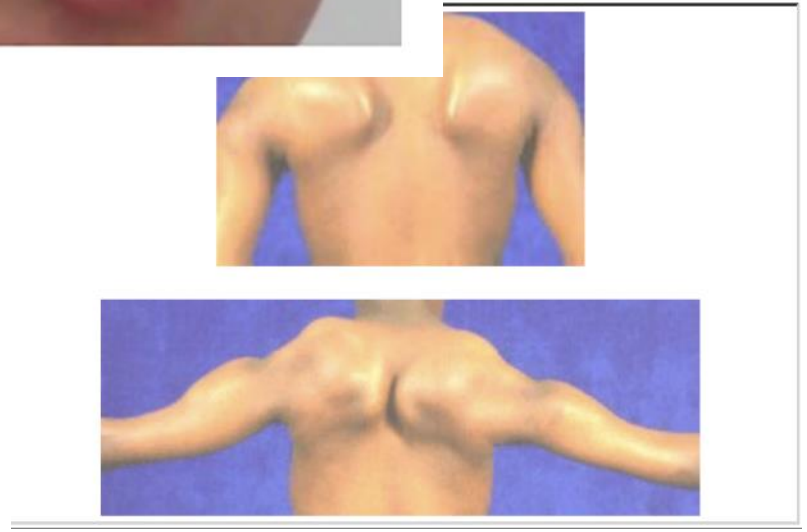
Inherited myopathies

Fascioscapulo - humeral dystrophy

- 3rd most common dystrophy in adult
- Autosomal dominant
- Face: Initial manifestation: Frequency: 95% at age 30 with examination
- Asymmetry
- Eyes: Often early in disease course Lid closure: Incomplete
- Sleeping: With eyes open
- Bulbar dysfunction
- Using straws -blowing up balloons







- Screen for hearing loss
- Screen for retinal vascular disease
- No screening for cardiac needed unless symptomatic

Inherited myopathies

Emery – dreifuss muscular dystrophy

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

Emery – dreifuss muscular dystrophy, cont.

- Contractures: Often more limiting to function than weaknessElbow
- Spine
  - Posterior neck (extension)
  - Lower back: Usually later onset, but may present with rigid spine syndrome
- Testing:
  - CK
  - EMG
  - CARDIAC SCREENING FOR ARRYTHMIA AND CARDIOMYOPATHY

Rhabdomyolysis

- Definition & General features
  - Acute syndrome due to extensive injury of skeletal muscle
- Weakness: Proximal > Distal
- Pain + swelling
- Cola or tea color urine
- May have fever, leukocytosis
- Serum CK: > 10,000, Usually > 30,000
- Most common causes: Exercise, Drugs & Alcohol
- More likely hereditary etiology:
  - Rhabdomyolysis on minimal exertion or fasting
  - Family history
  - Multiple episodes

Rhabdomyolysis,cont.

- Common etiologies
- Metabolic myopathy: glycogen, lipid, mitochondrial
- Statins
- Muscular dystrophy: baseline ck high
- Malignant hyperthermia!!!!!

Rhabdomyolysis, cont.

Management:

- IV hydration to avoid acute tubular necrosis and renal failure!!!
- Other treatment according to underlying etiology.

Thank you

A Pattern Recognition Approach to Patients with a Suspected Myopathy

Richard J. Barohn, MD[a,*], Mazen M. Dimachkie, MD[b], Carlayne E. Jackson, MD[c]

KEYWORDS

• Myopathy • Limb-girdle • Distal myopathy • Inflammatory myopathy
• Metabolic myopathy • Myotonia

KEY POINTS

- The initial key to the diagnosis of myopathies is recognition of a clinical pattern.
- There are 6 key questions the clinician should consider in arriving at the pattern that fits the patient.
- After arriving at the pattern that fits best, then the clinician can better determine the most appropriate diagnostic tests and management.