# *Ancillary Testing in Neuropathies and Myopathies*

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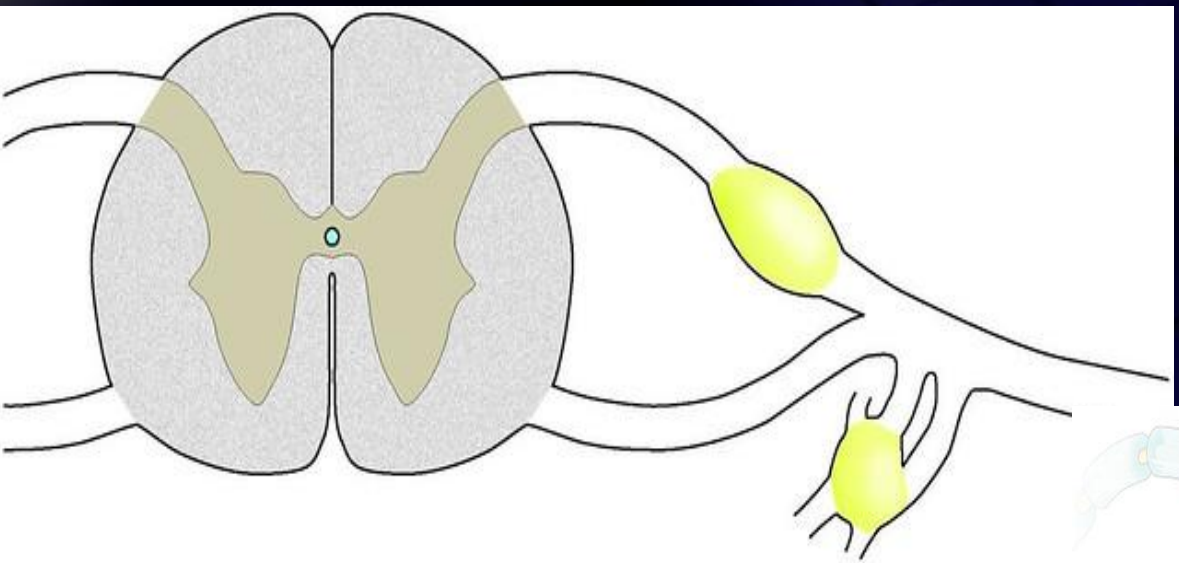
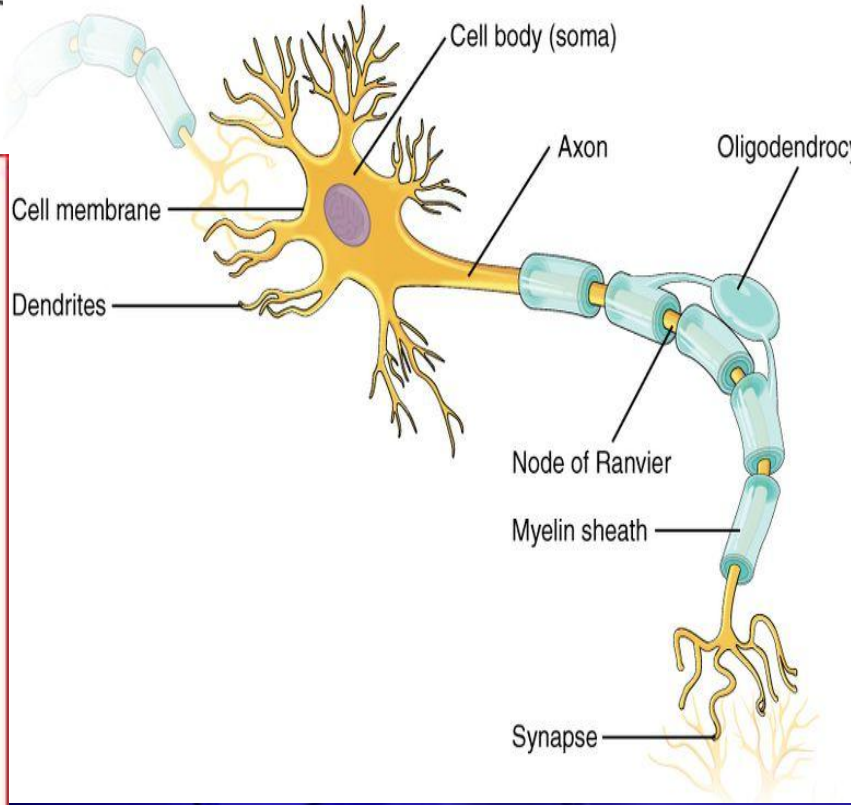
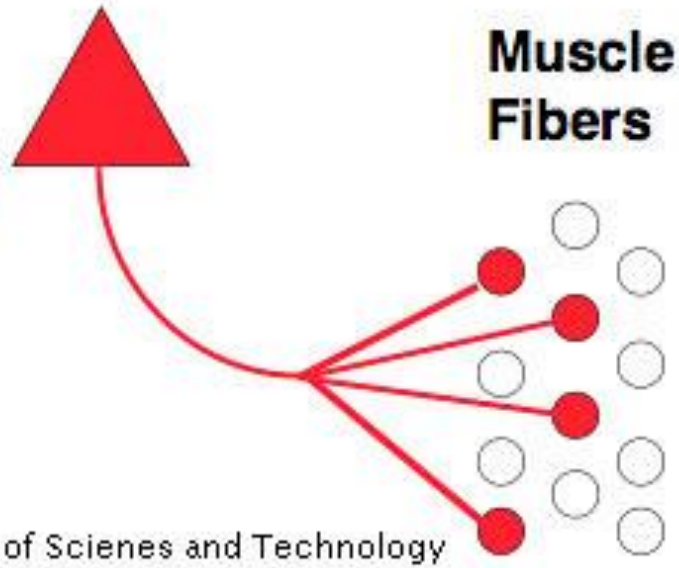





- A single neuron and all the muscle fibers it innervates are a **motor unit**
- The motor unit is the smallest division that the system can control individually

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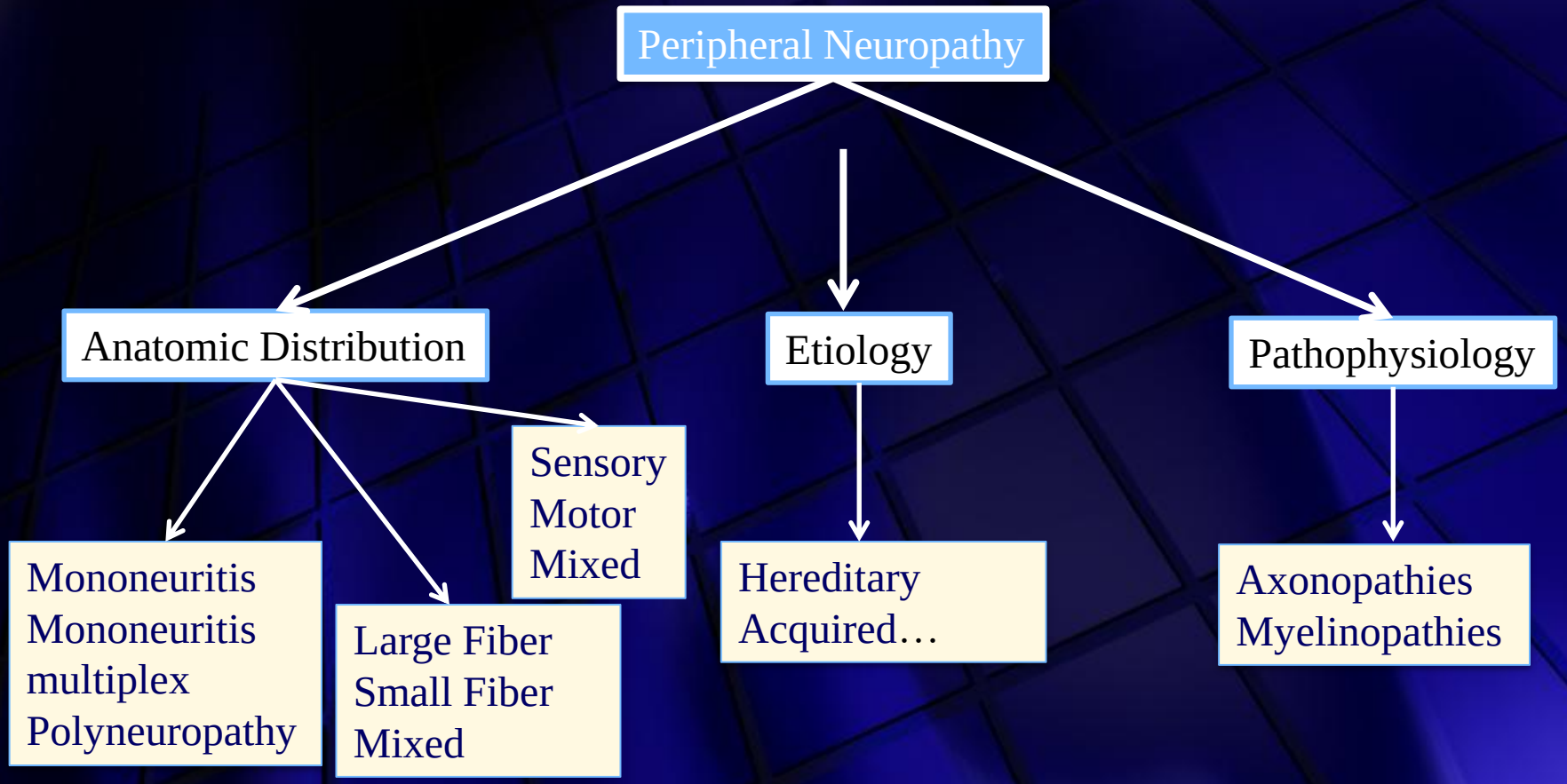
# *Classification*



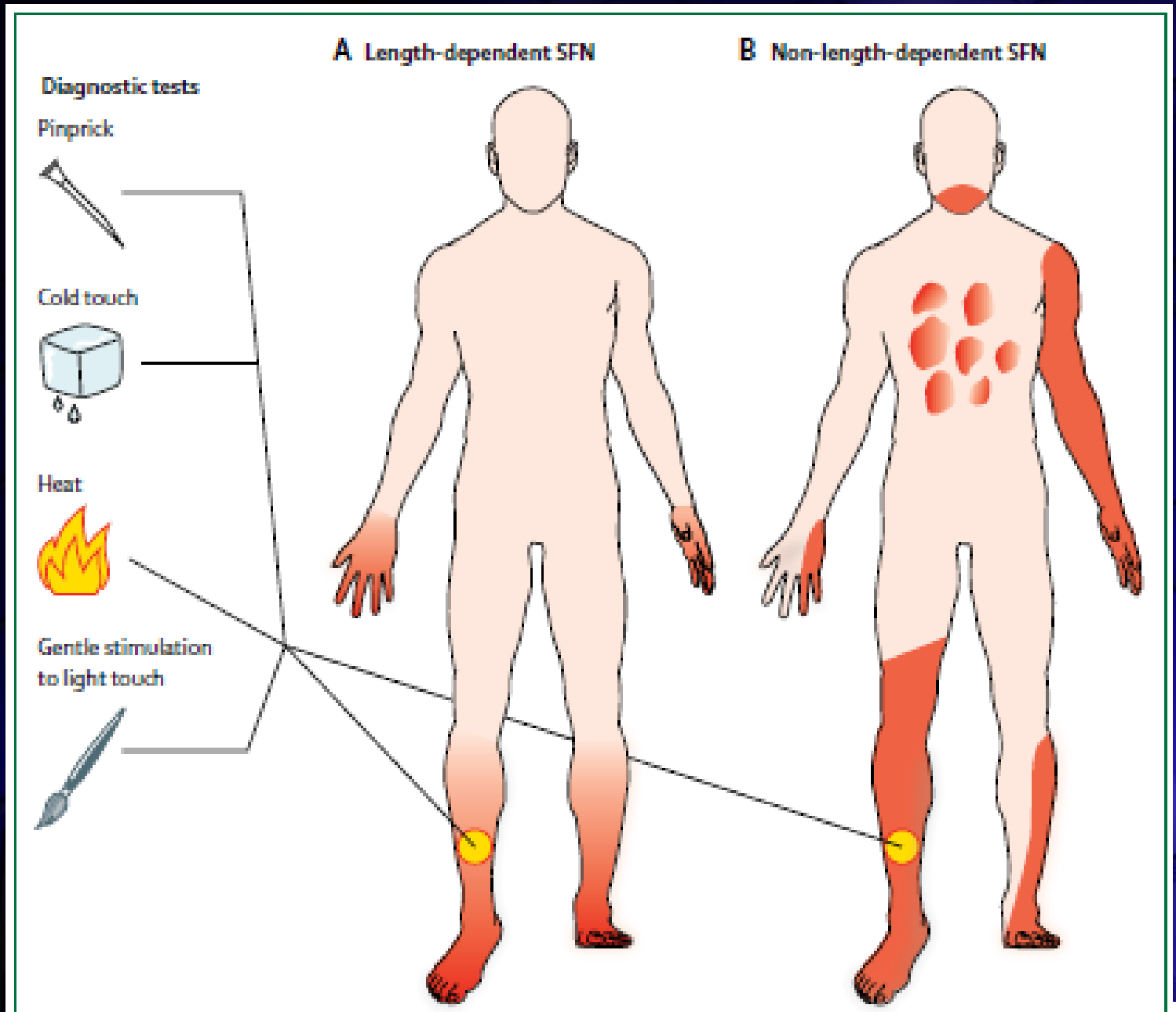

Closely related disorders: Neuronopathies, affecting the neuron cell body

- Affecting only anterior horn cells: motor neuron disease
- Affecting only sensory neurons: Sensory neuronopathies or ganglionopathies
- Autonomic neuropathies

# *Diagnostic Approach*

- History and exam focus on:
  - What systems?
    - Motor, sensory, autonomic, combination
  - Distribution of weakness if present?
    - Distal only, proximal and distal, focal, symmetric/asymmetric
  - Type of sensory symptoms?
    - Pain, burning, pins and needles, stabbing, shooting
    - Imbalance worse in the dark, "wash-basin sign", numbness, "walking on pebbles or carpet"
  - Evolution?
    - Acute (days to 4 weeks)
    - Subacute (4-8 weeks)
    - Chronic (> 8 weeks)
    - Antecedent events: infections, drugs, toxin exposure
  - Hereditary?
    - Family history
    - Foot deformities
    - Lack of positive sensory symptoms

- Evidence of Upper Motor Neuron Involvement
  - Without sensory loss
  - With sensory loss




Terkelsen AJ et al. Lancet Neurology 2017; 16:934

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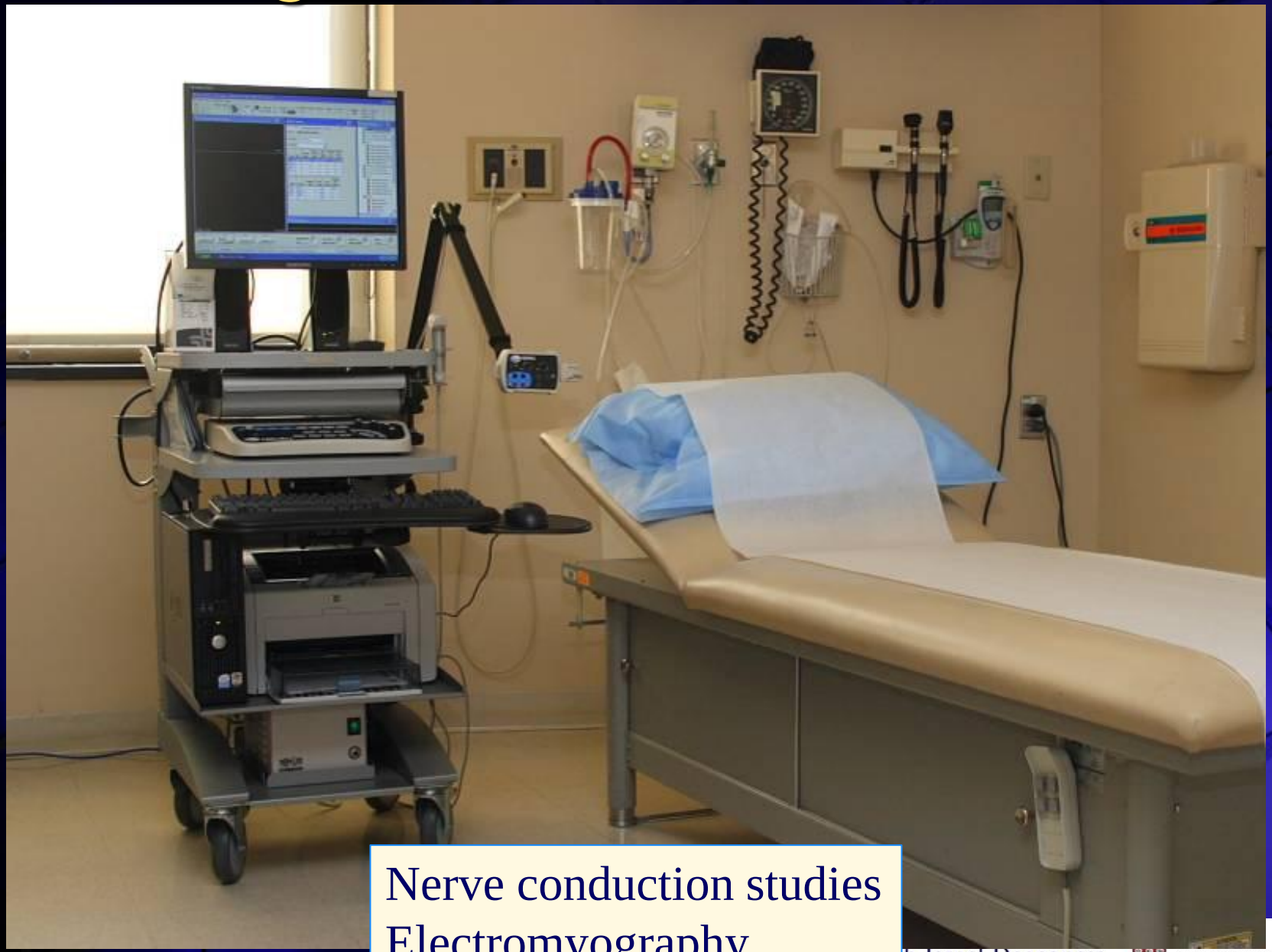
# *Laboratory Evaluation*

- **Complete blood count**
- **Renal function tests**
- **Fasting glucose* (11%), HbA1c* (26%), 2-hr oral glucose tolerance test**
- **TSH**
- **Vitamin B12* (2%), with MMA (9%)**
- **Serum immunofixation electrophoresis,* (10%),** free light chains
- Infections (if risk factors or endemic region) HIV, Lyme, Leprosy, Syphilis (sensory ataxia of tabes dorsalis)
- ESR, (ANA, SS-A,SS-B if dry mouth, dry eyes are present)
- Angiotensin converting enzyme
- Vitamin E, copper
- Paraneoplastic autoantibodies
- Other antibodies: Myelin associated glycoprotein, GM-1
- GM1 antibodies
- Genetic tests

* Highest yield tests, with percentage of cases identified

# *Electrodiagnostic Evaluation*

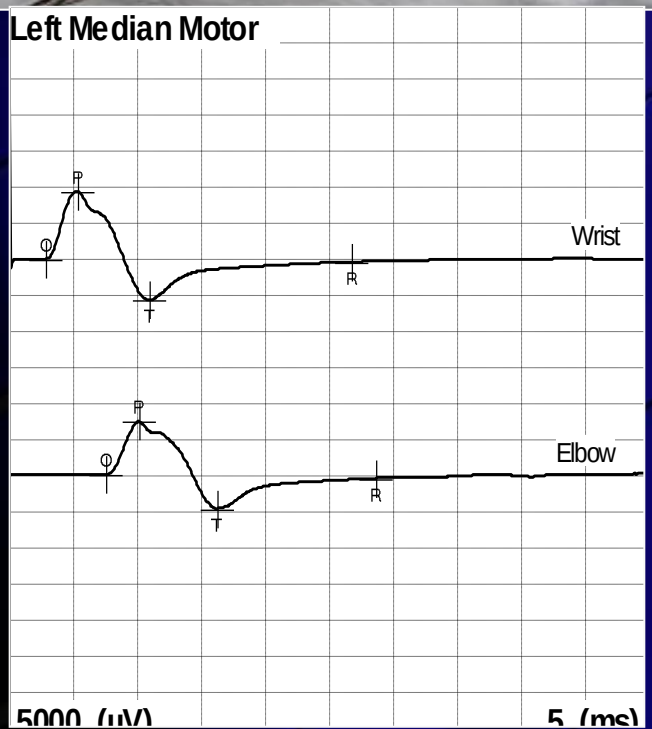


Nerve conduction studies
Electromyography

# *Components of an "EMG"*

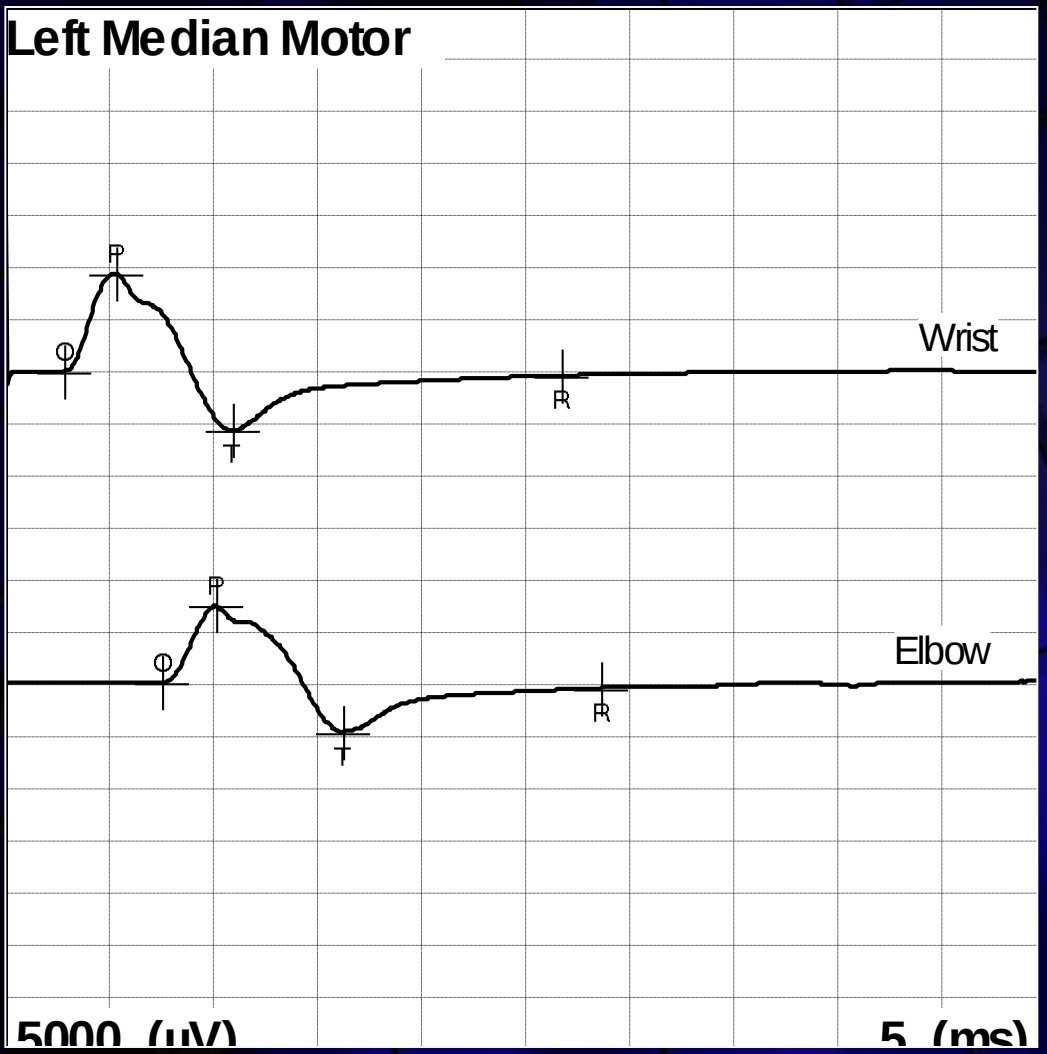
- Nerve conduction studies (NCS)
  - Motor
  - Sensory
  - F-waves
  - H-reflexes
- Electromyography (EMG)
- Special Tests: Repetitive Nerve Stimulation, Single Fiber EMG, etc.

# *Motor NCS*



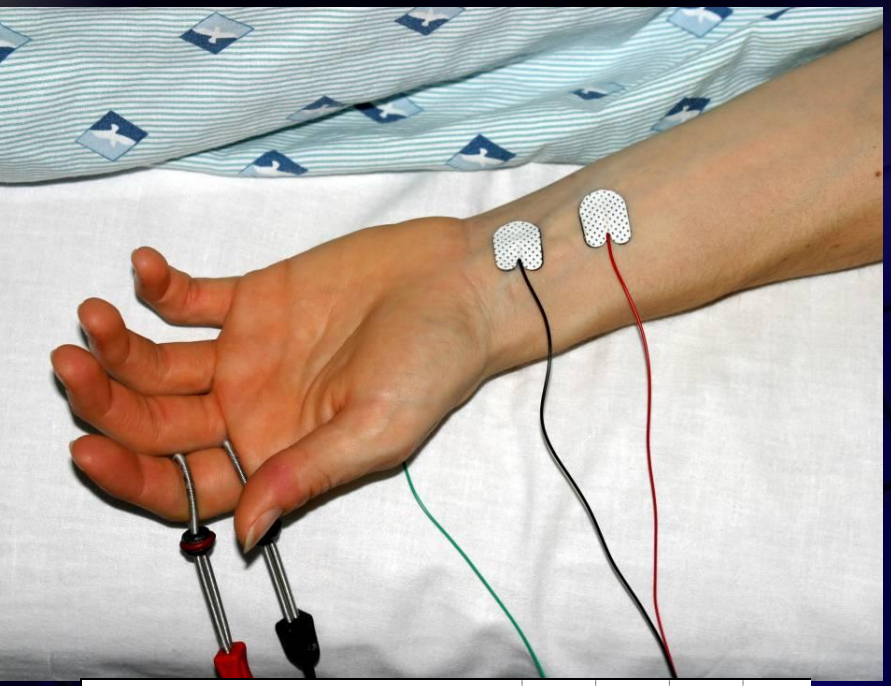

- Active recording electrode on muscle belly
- Reference electrode distal, on nearby tendon
- Motor nerve stimulated incrementally
- Recorded response = compound muscle action potential (CMAP) or M wave

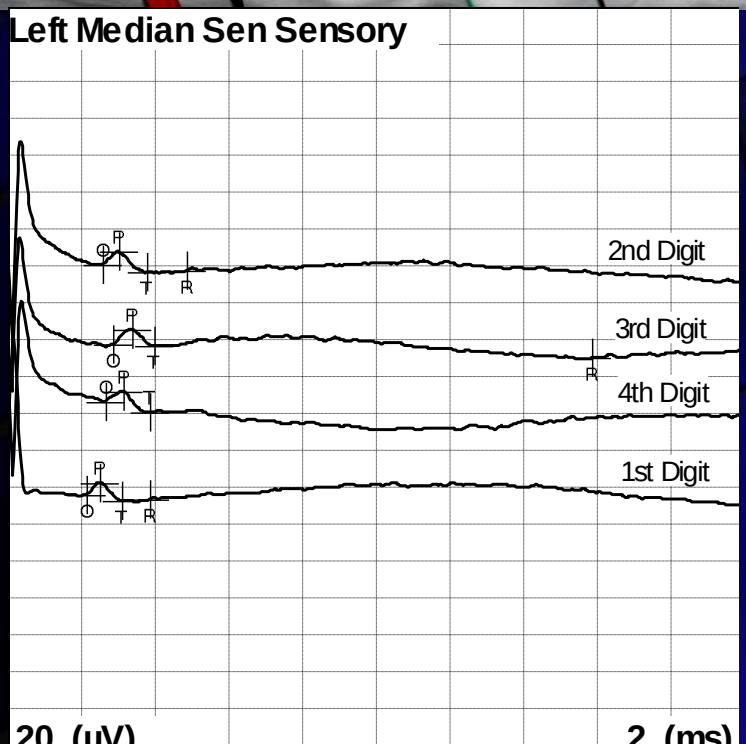
# *CMAP*
# *Compound Motor Action Potential*




- Summation of individual muscle fiber AP's
- Not a reflection of muscle contraction
- Recorded parameters: latency, amplitude, conduction velocity

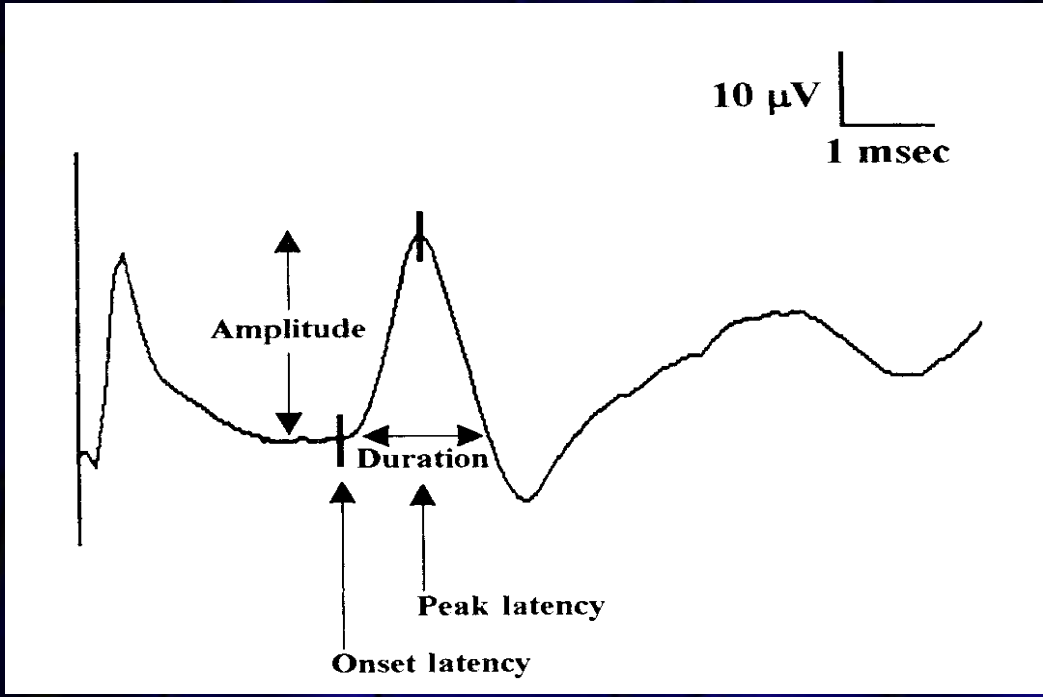
# Sensory Nerve Conduction Studies






- Recording electrodes over skin in area innervated by single sensory nerve

# *SNAP*
# *Sensory Nerve Action Potential*



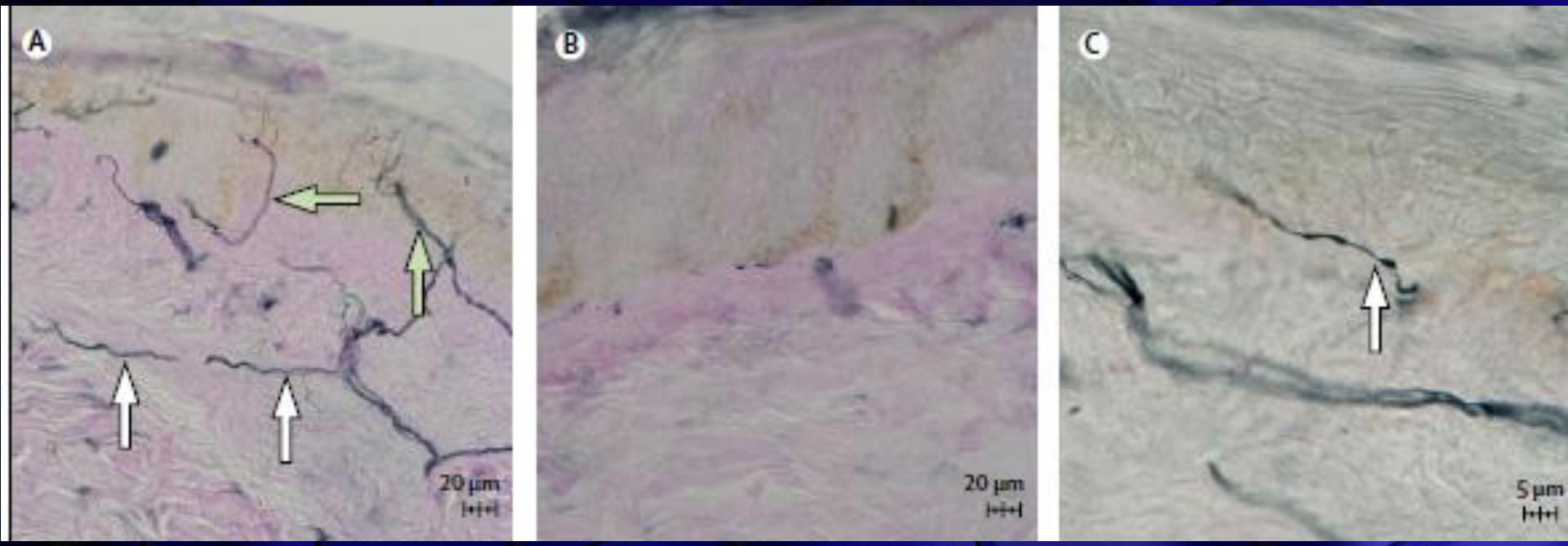

- Measured in microvolts
- Summation of all individual sensory fiber action potentials
- Recorded parameters: latency, amplitude, conduction velocity (CV)

# *Nerve Conduction Studies*

| Pathology | Latency/ Distal Latency | Amplitude | Conduction Velocity |
|---|---|---|---|
| Axonal | Normal<br>↑ when severe | ↓↓ | Normal<br>↓ when severe |
| Demyelinating | ↑ | Normal<br>↓ with temporal dispersion/<br>Conduction block | ↓↓ |

•Skin biopsy : validated technique for determining intraepidermal nerve fiber density (somatic unmyelinated C-fiber nerve terminals)

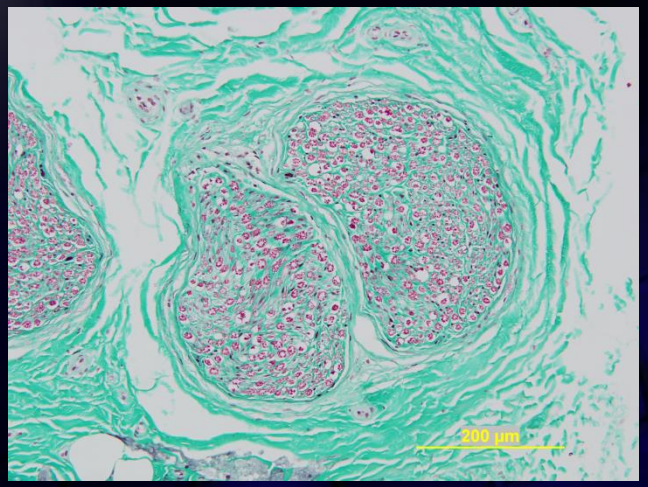
•Sensitivity 90% specificity  95% to 97%.

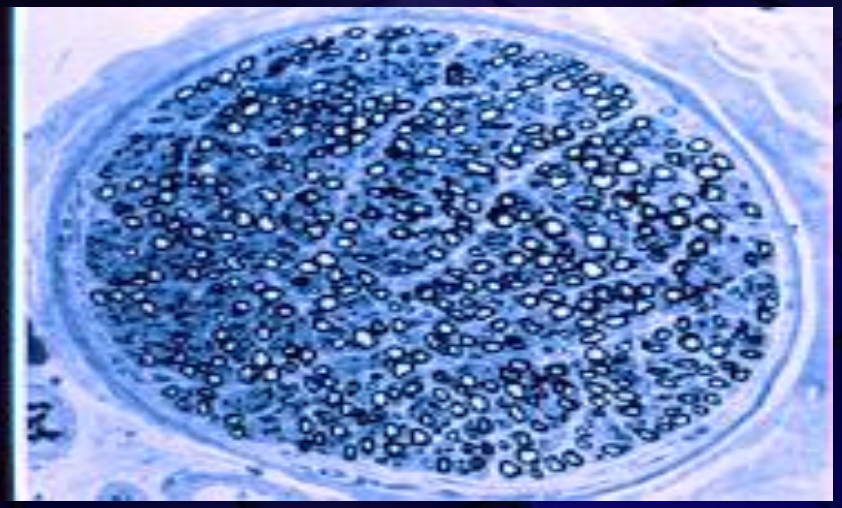


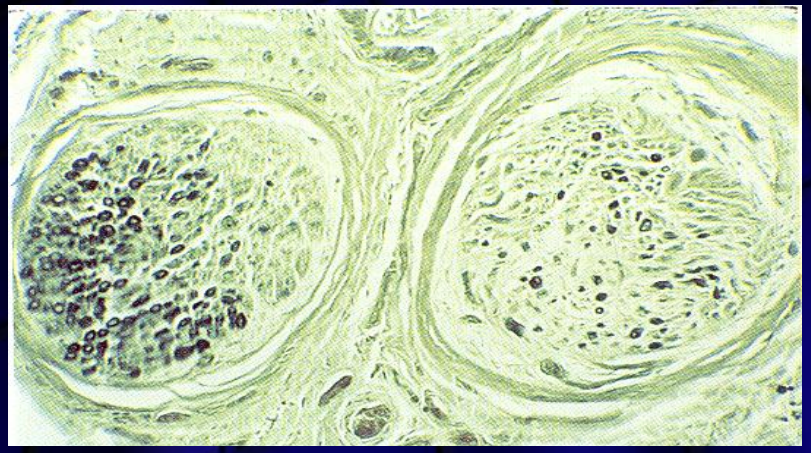

Terkelsen AJ et al. Lancet Neurology 2017; 16:934

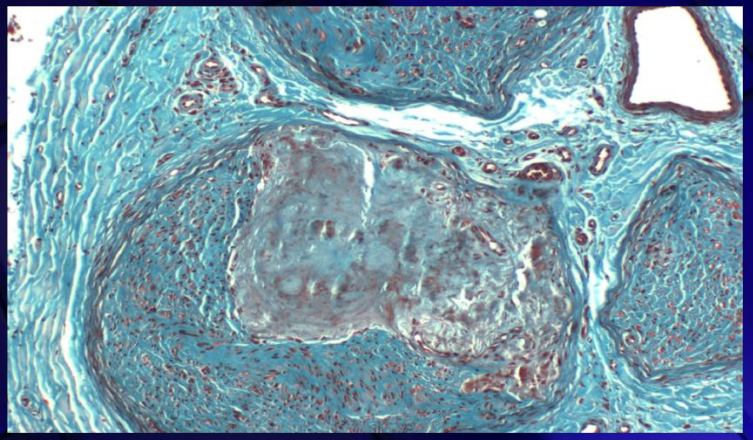
# *Other tests*

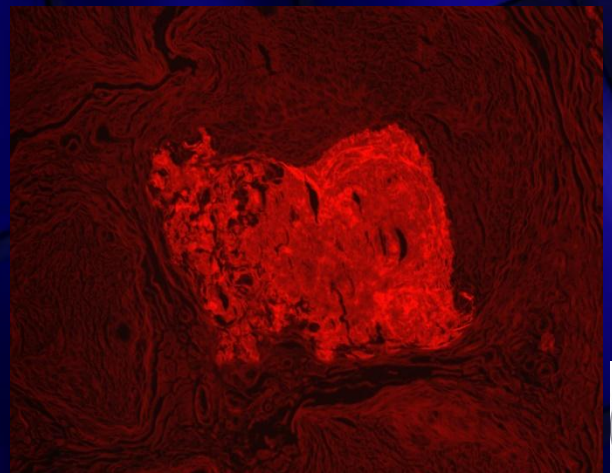
- Quantitative sensory testing : controlled applications of large- and small fiber (touch, pressure, vibration, thermal) sensations to the skin to determine the threshold for detection
- Autonomic Function tests
- Nerve biopsy: Limited utility
  - vasculitis, sarcoidosis, CIDP
  - infectious neuropathies (leprosy)
  - infiltrative neuropathies (carcinoma, lymphoma, amyloidosis, polyglucosan bodies)
- Nerve Ultrasound









# *Myopathies*

- Disorders of skeletal muscle
- May affect the channels, structure or metabolism of skeletal muscle

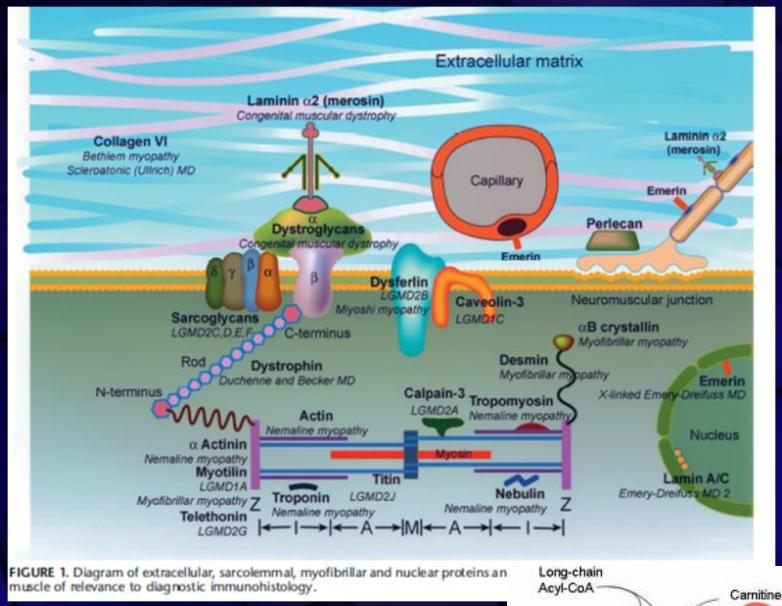
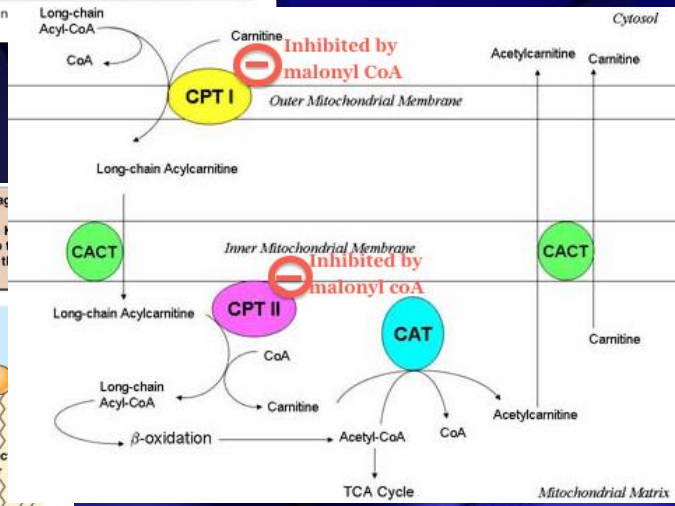
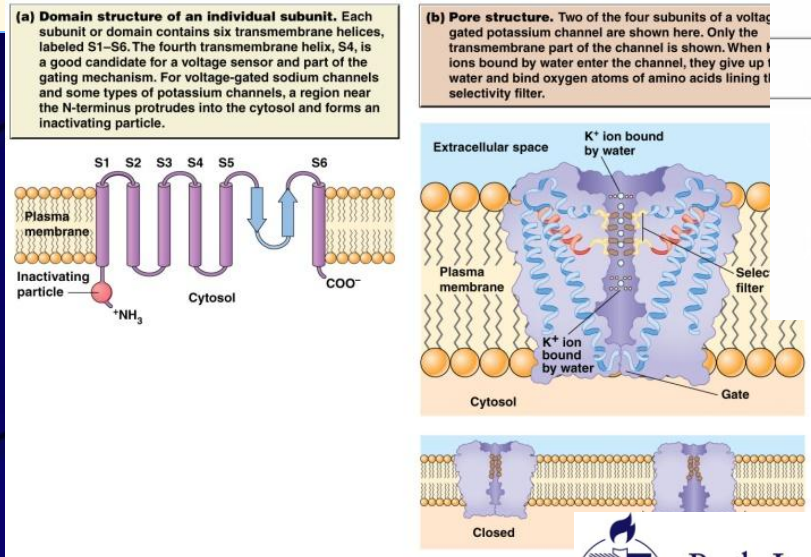



FIGURE 1. Diagram of extracellular, sarcolemmal, myofibrillar and nuclear proteins an muscle of relevance to diagnostic immunohistology.



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# Acquired Myopathies

Inflammatory/ Immune Necrotizing

- *Polymyositis*
- *Dermatomyositis*
- *Inclusion Body Myositis*
- *Immune mediated necrotizing myopathy*

Endocrine

- *Hypothyroidism*
- *Thyrotoxic*
- *Cushing's/steroid*
- *Vit D. deficiency*
- *Hyperparathyroidism*

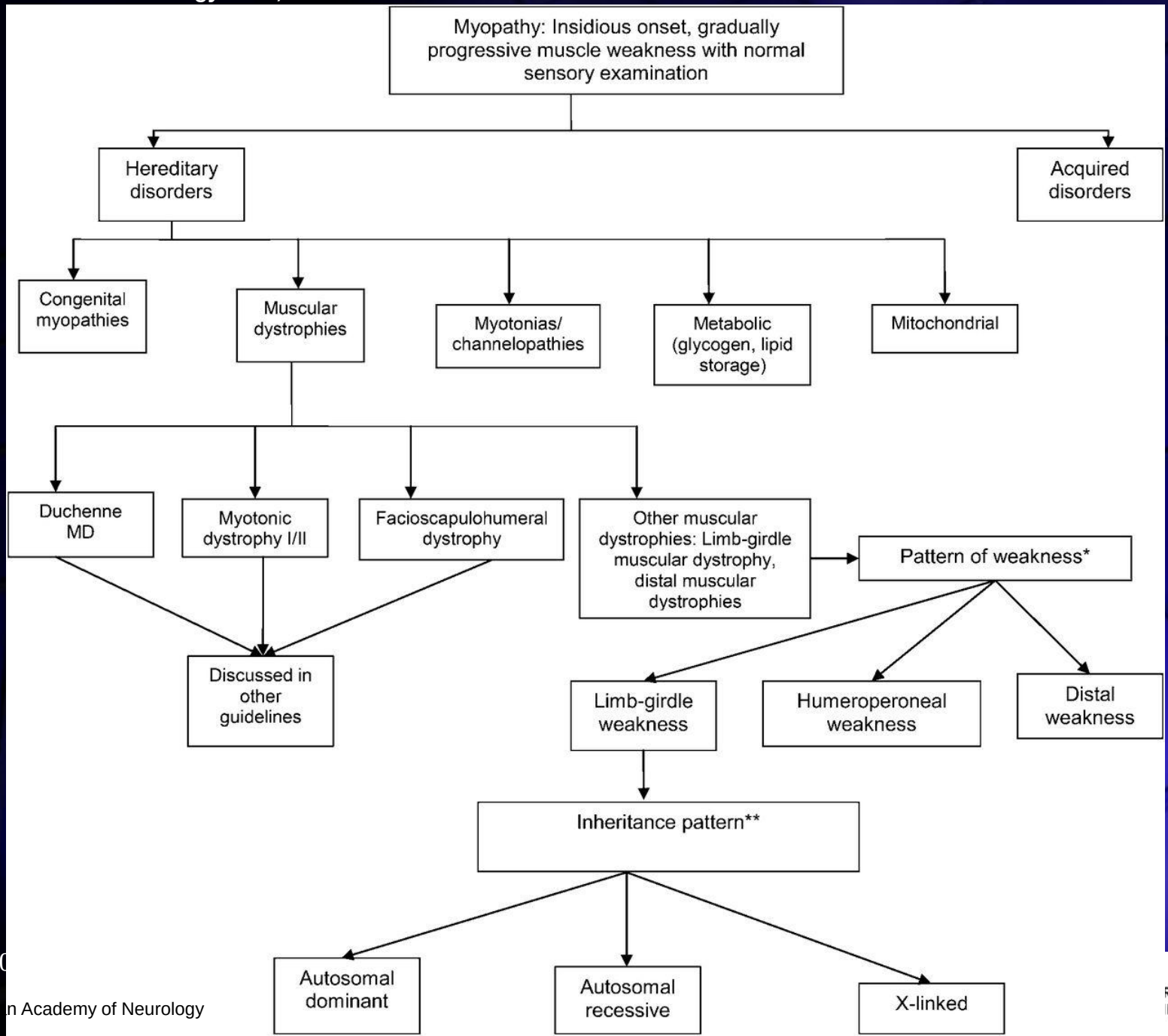
Drug-induced/ Toxic

- *Statins*
- *colchicine,*
- *Chloroquine/ hydroxychloroquine*
- *Amiodarone*
- *Zidovudine*
- *Cimetidine, D-penicillamine*
- *Alcohol*
- *Cocaine, heroin, amphetamines*

Associated with systemic illnesses

- *Paraneoplastic*
- *Connective tissue disease- MCTD*
- *Infections*
- *Critical illness*

Narayanaswami P et al. Neurology 2014;83:1453-1463



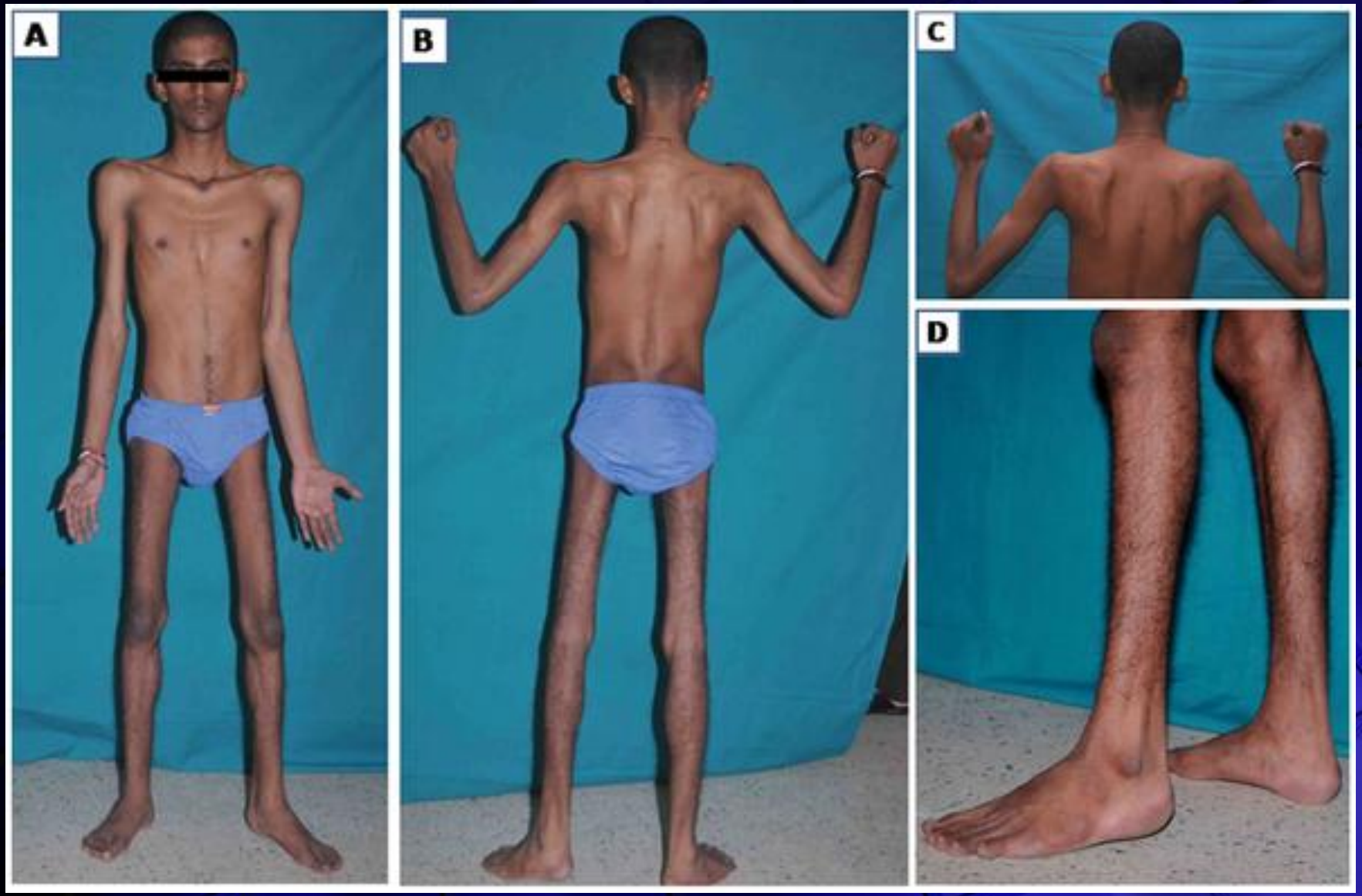
# *Features that assist in determining etiology*

- Temporal evolution: age at onset, course
- Constant weakness vs. episodic periods of weakness
- Family history and likely mode of inheritance
- Precipitating factors triggering or exacerbating weakness
- Systemic involvement

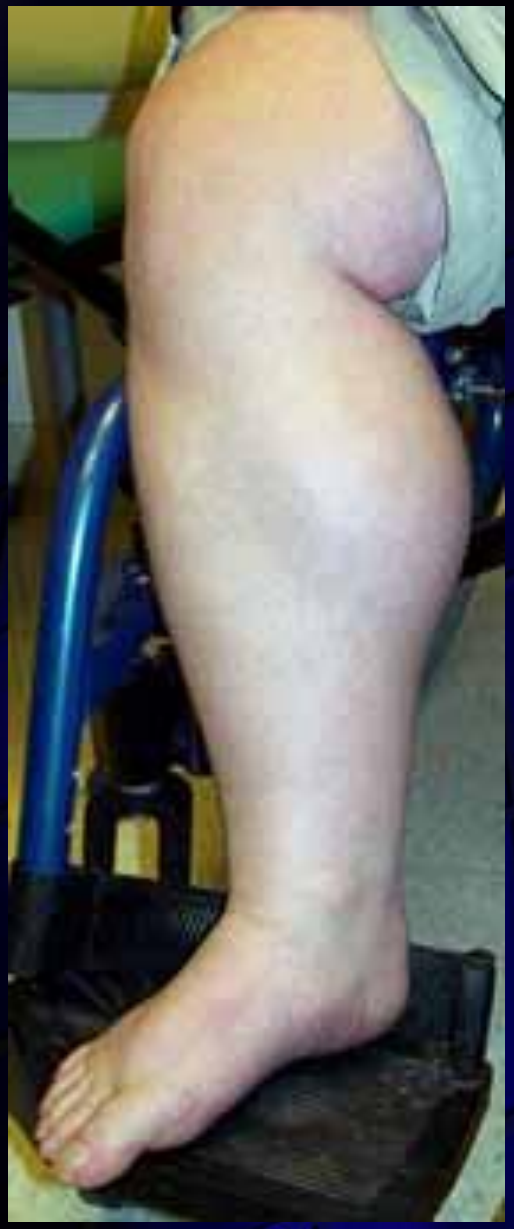
Barohn R et al. Neurologic Clinics 32; 2014

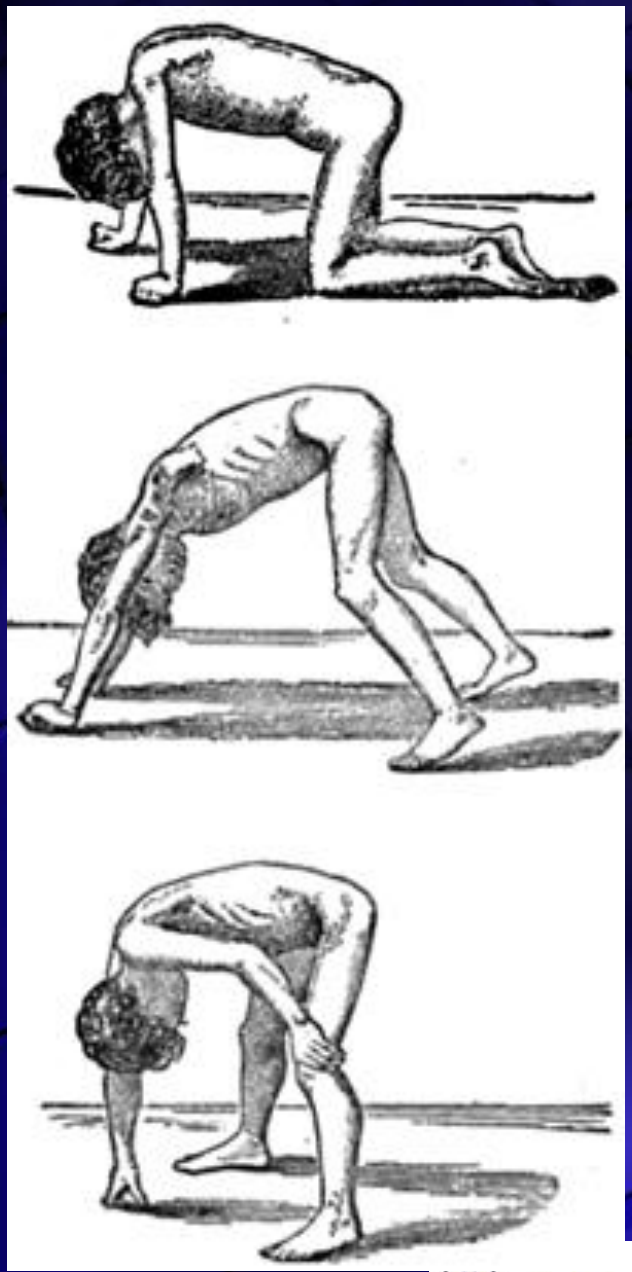
# *Myopathy: Patterns of weakness*

- Limb-girdle: Symmetric weakness affecting predominantly the proximal muscles of the legs and arms
- Distal: Predominantly involves the distal muscles of the upper or lower extremities
- Humeroperoneal: Proximal arm/distal leg
- Distal arm/proximal leg: wrist and finger flexors and quadriceps: IBM
- Ptosis with or without ophthalmoparesis
- Prominent neck extensor weakness: Dropped head syndrome, bent spine syndrome
- Myotonia: stiffness, decreased ability to relax




Francis A et al. LGMD 2G. PLOS ONE 2014





https://neuromuscular.wustl.edu/musdist/dmd.html

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# *Laboratory Evaluation:*

- Serum creatine kinase elevation, variable degree, may be normal in some myopathies
  - False positive: in neurogenic disorders (ALS), hypothyroidism, hypoparathyroidism, trauma, seizures, strenuous exercise
  - Race, sex
    - < 3- fold unusual to be associated with myopathy in absence of objective muscle weakness or pain
- Other tests: TSH, Vit. D, PTH, myositis specific antibodies, HMGCoA- reductase antibodies

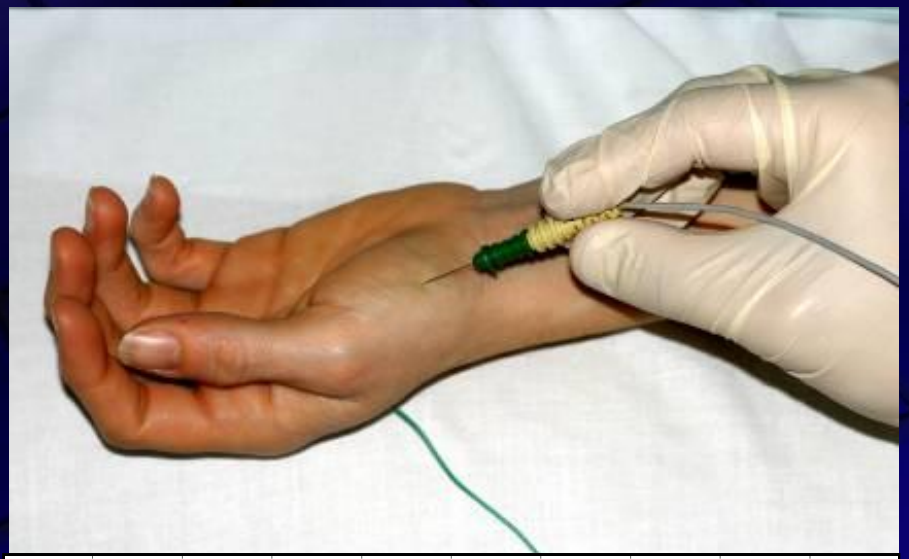
# *Prevalence and Clinical Association of Myositis Specific Autoantibodies*

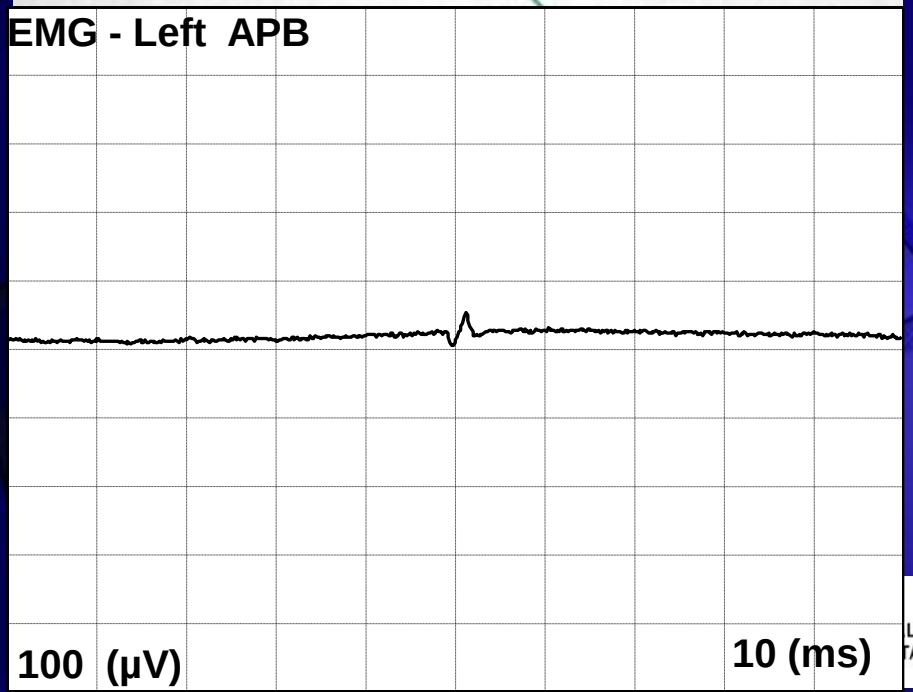
| Autoantibodies | Prevalence (%) | Disease association | Clinical association/significance |
|---|---|---|---|
| Aminoacyl tRNA synthetases | | | |
| Jo-1 | 15–30 | PM, DM | Anti-synthetase syndrome (myositis, ILD, polyarthritis, Raynaud's phenomenon, mechanic's hands) |
| PL-7 | <5 | PM, DM | Anti-synthetase syndrome |
| PL-12 | <5 | PM, DM, CADM, ILD | Anti-synthetase syndrome, ILD, CADM |
| EJ | <5 | PM, DM | Anti-synthetase syndrome |
| OJ | <5 | PM, DM | Anti-synthetase syndrome, ILD |
| KS | <1 | PM, DM, ILD | ILD |
| ZO | Rare | | Myositis |
| YRS (HA) | Rare | | Myositis |
| SRP | 5 | PM | Myositis (necrotizing) |
| Mi2 | 10 | DM | DM with typical skin lesions and mild myositis |
| MDA5/CADM140 | 15–20 | CADM/ADM | CADM, rapidly progressive ILD, severe skin manifestations |
| TIF1γ/α | 10–15 | DM, | Malignancy-associated DM |
| MJ/NXP2 | 1–5 | DM | Adult and juvenile DM with severe skin disease |
| SAE | 1 | DM | DM |

Satoh et al. Clin Rev Allergy Immunol 2017; 52

# *Electrodiagnostic studies in myopathy*

- Confirm that a myopathy is present
- Add diagnostic information based on presence and type of spontaneous activity
- Exclude an alternate diagnosis to explain clinical picture
- Guide muscle biopsy
  - Select a muscle which is involved but not end-stage



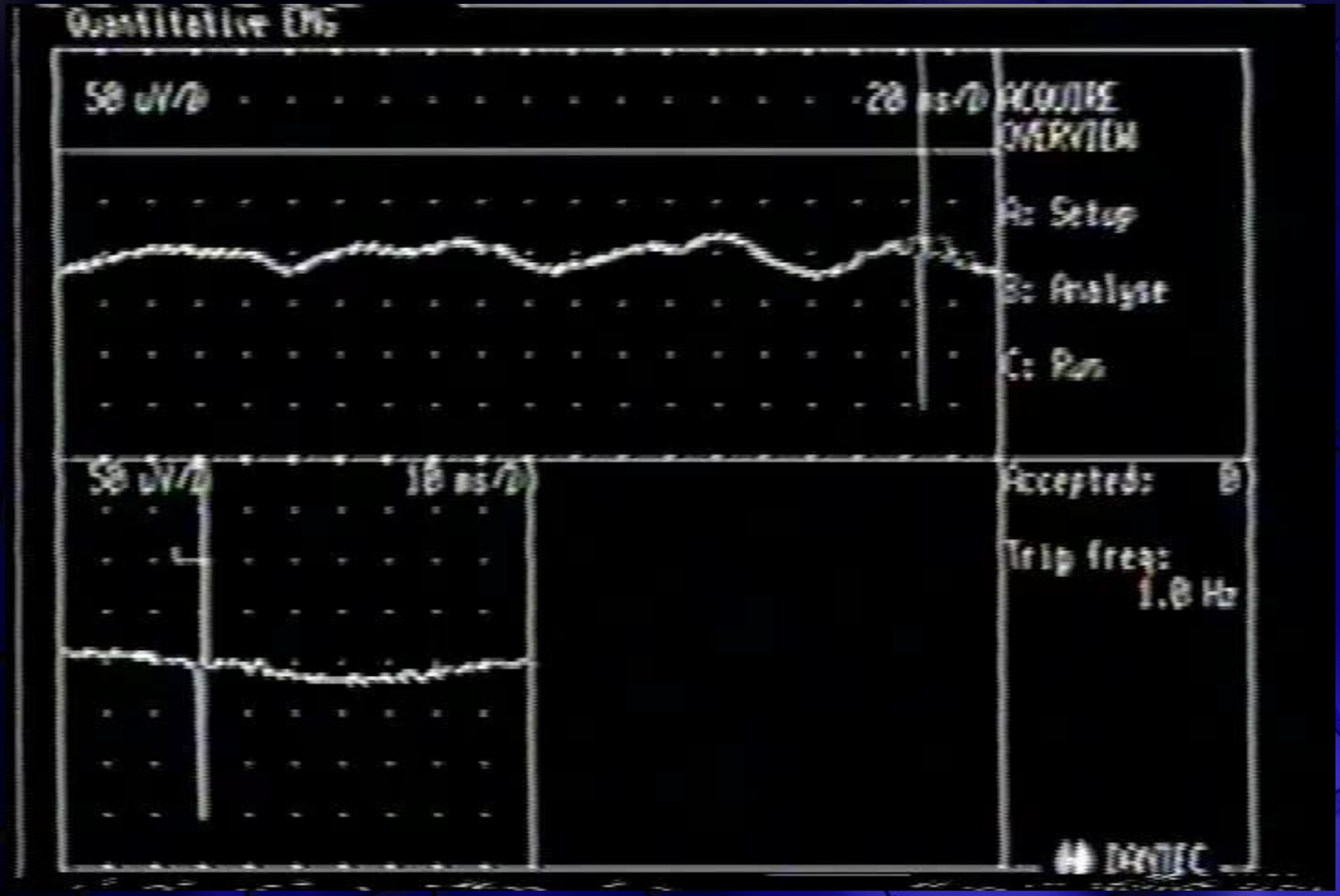


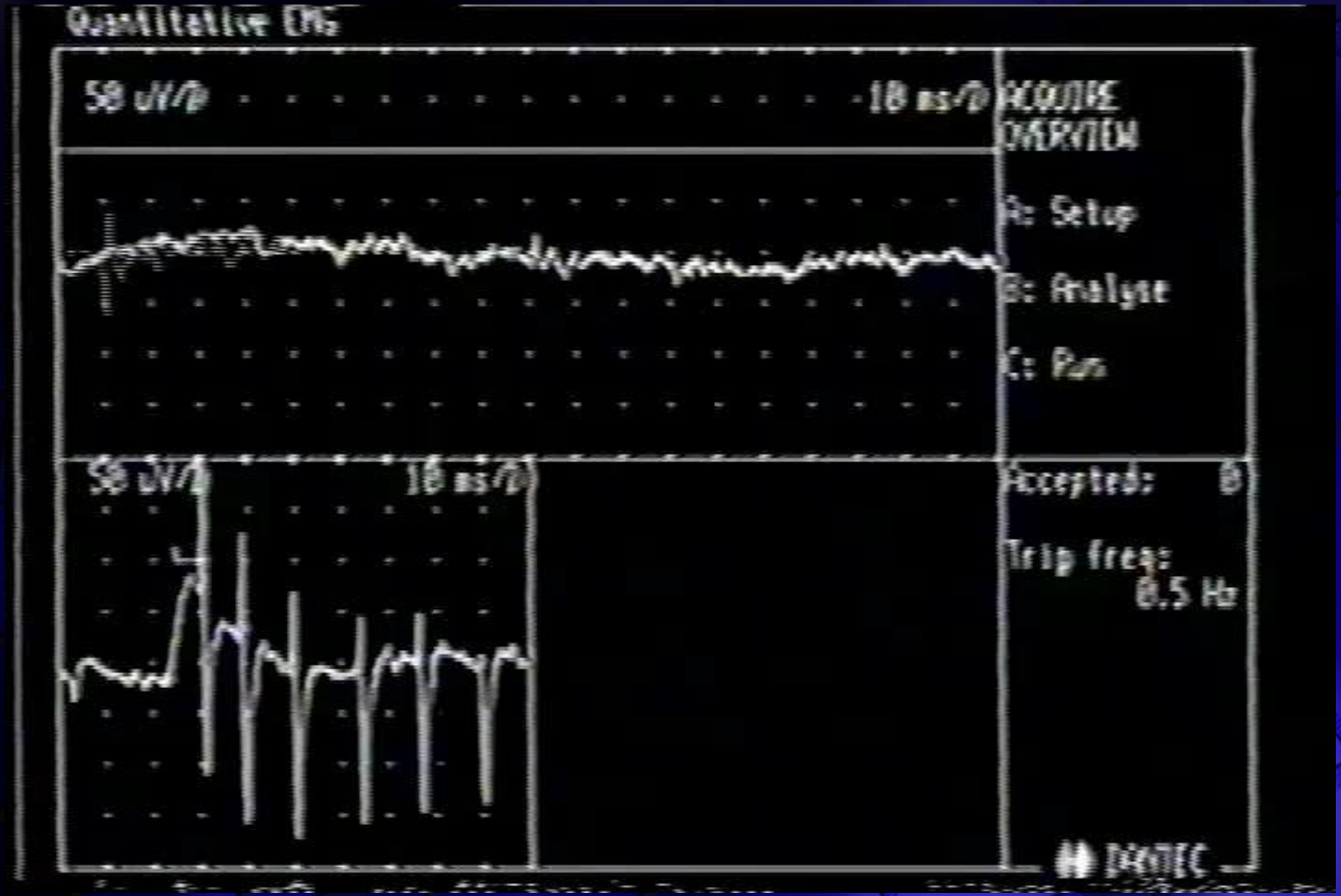
# *Needle EMG*

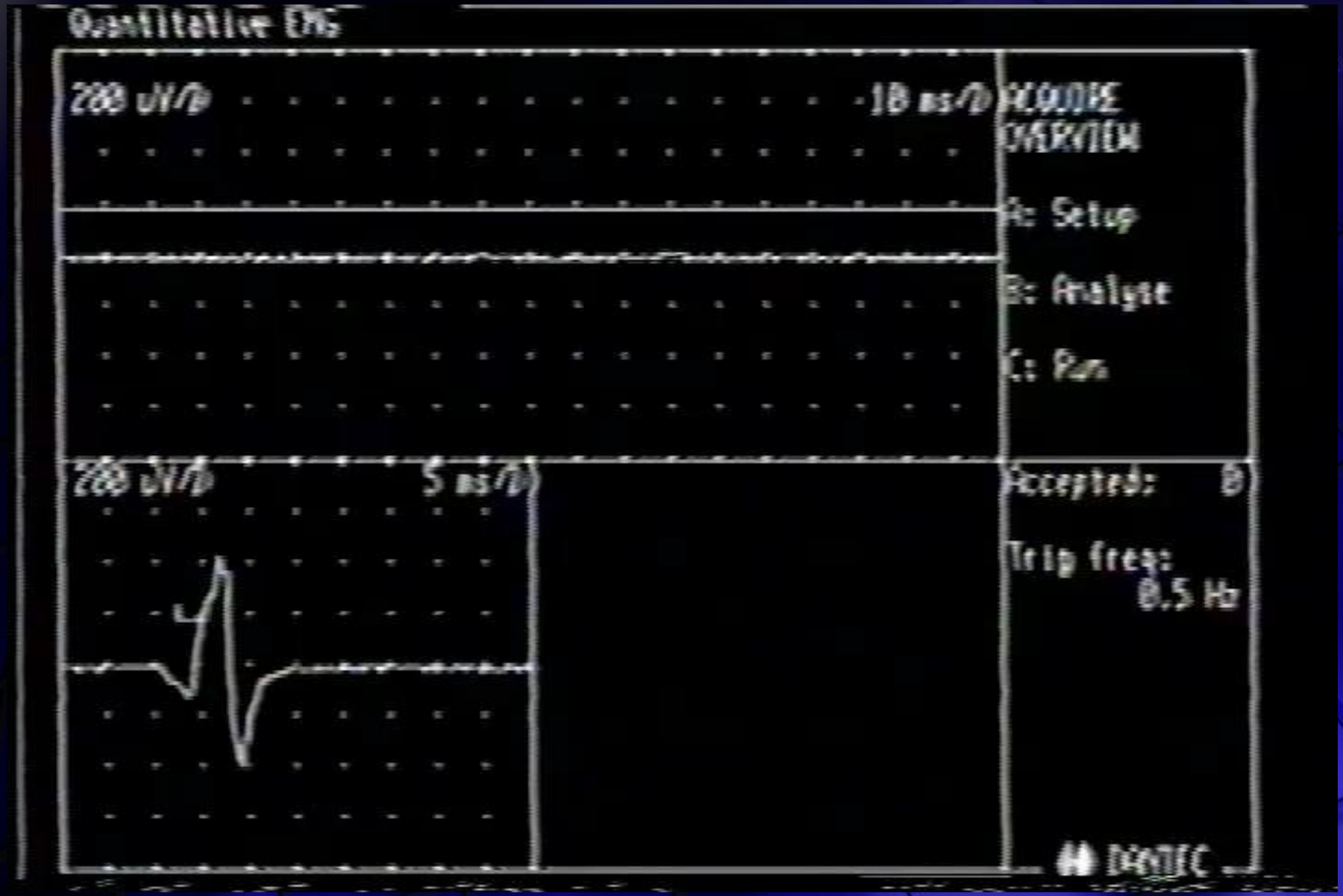
- Insertion Activity
- Spontaneous Activity
- Motor Unit analysis:
  - Morphology: amplitude, duration, phases
  - stability, firing patterns
  - recruitment
  - Interference patterns

# *Insertional Activity*

- When needle moved quickly through muscle, muscle fibers depolarize in a brief burst
- Insertional activity that lasts longer is “increased”
- Seen in neurogenic and some myopathic conditions



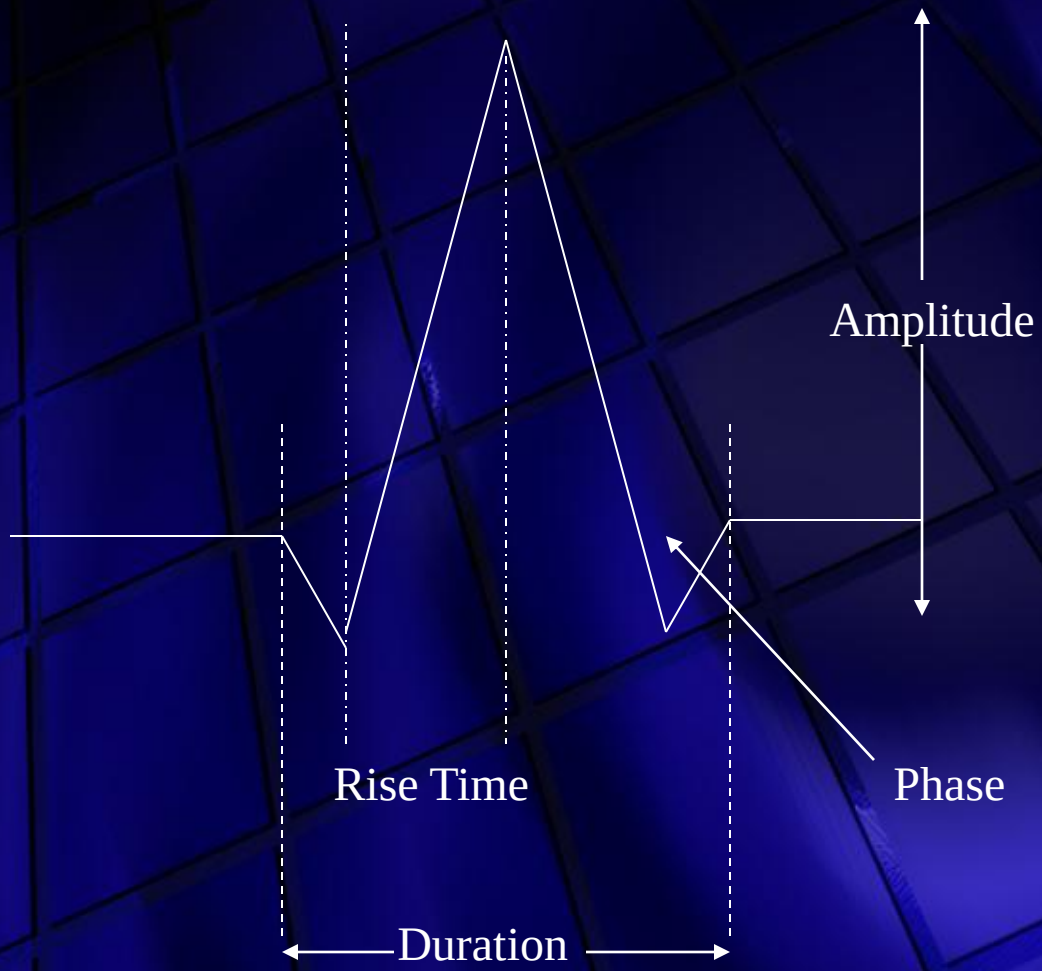




# *Motor Unit Action Potentials:*
## *Parameters Evaluated*

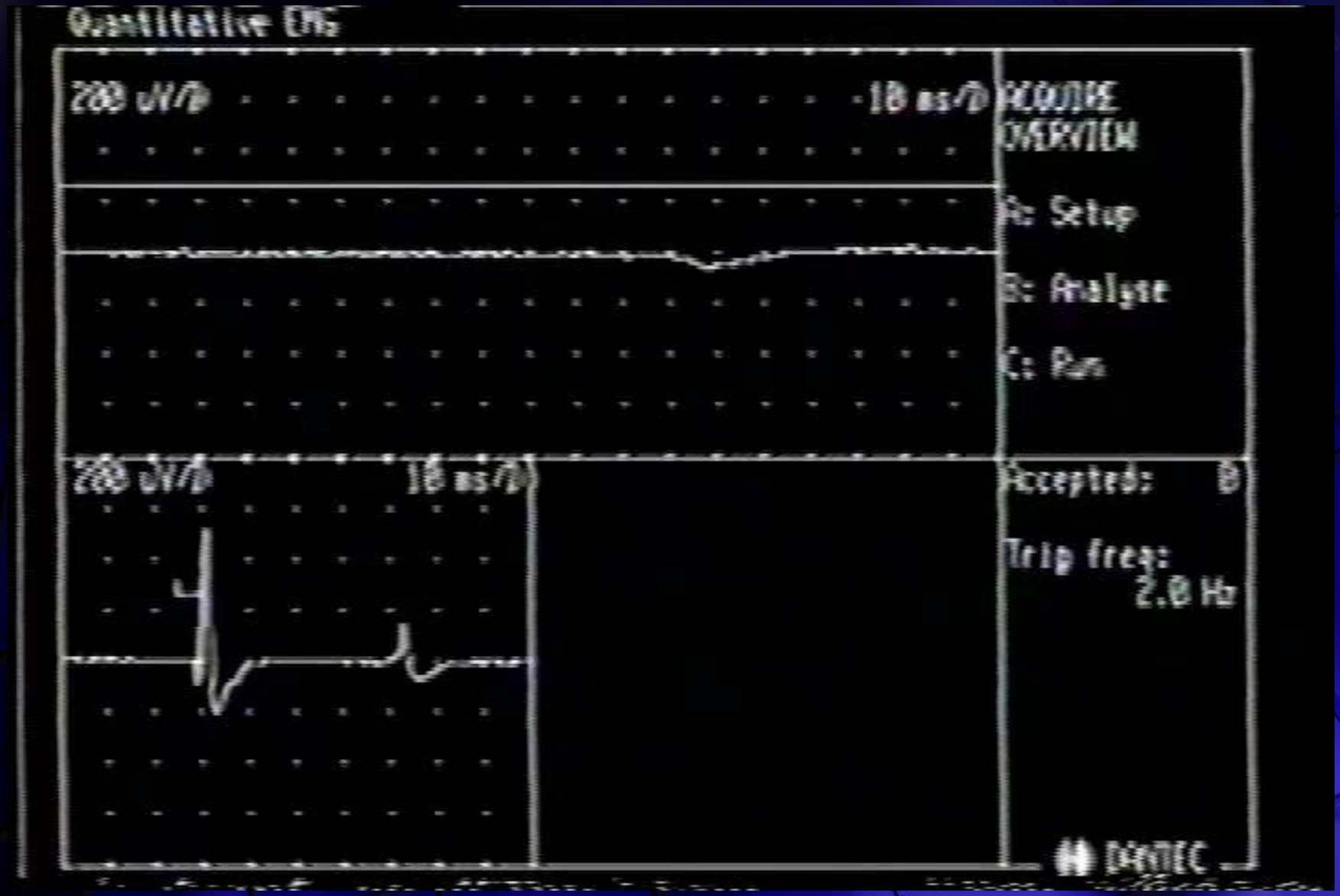
- Motor Unit Configuration
  - Muscle is volitionally activated at different force levels
  - Single motor units are assessed
  - Amplitude, duration, morphology
- Motor Unit Recruitment
  - Pattern of motor unit activation with increasing volitional activation
- Interference Patterns
  - Motor unit pattern with maximal voluntary activation

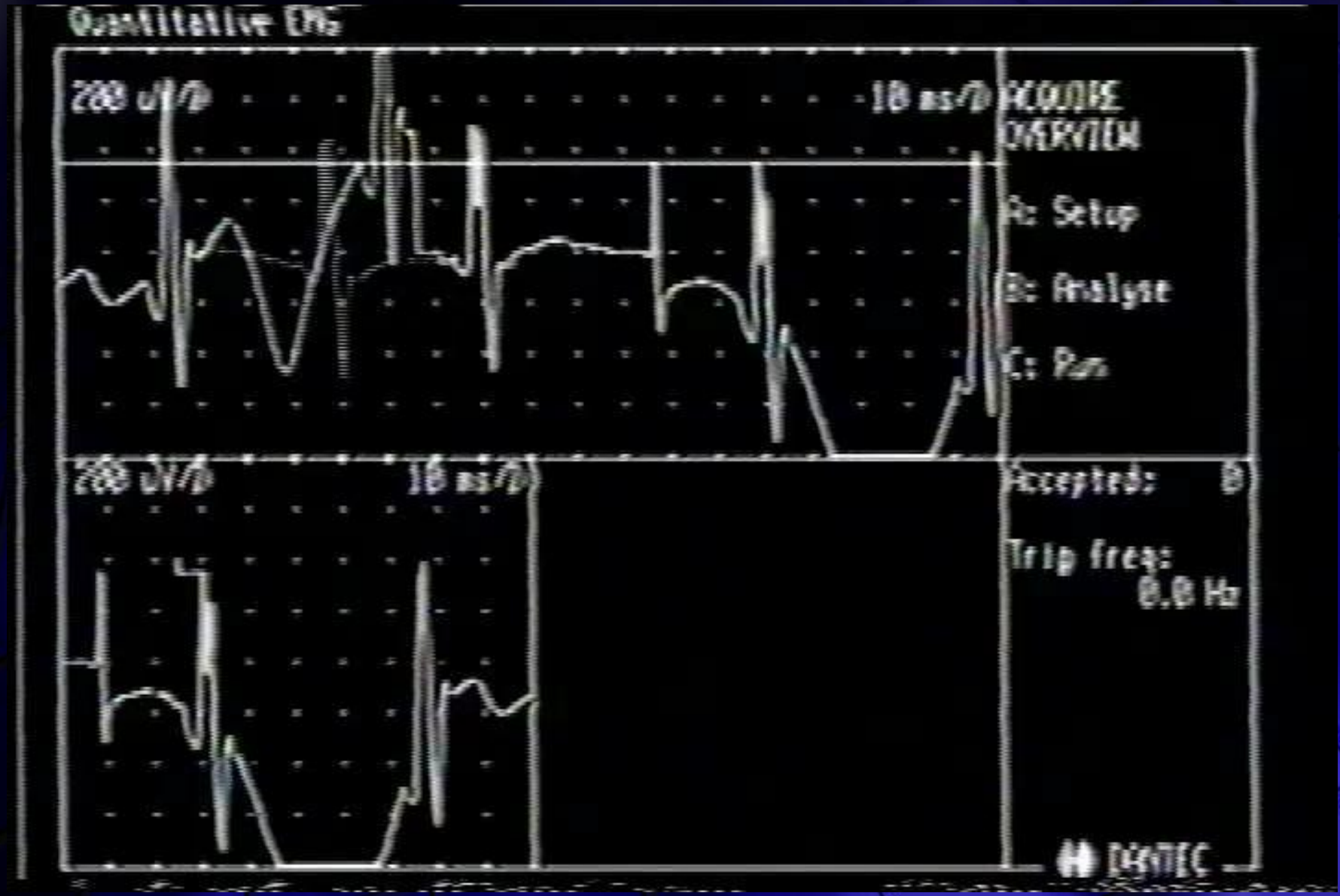
# *MUAP Morphology*



# *Recruitment*

- To increase muscle force:
  - Motor units can increase firing rate
  - Additional motor units can fire
- Normal recruitment:
  - Smaller motor units recruited first
- During maximal contraction, multiple MUAPs overlap and create an interference pattern

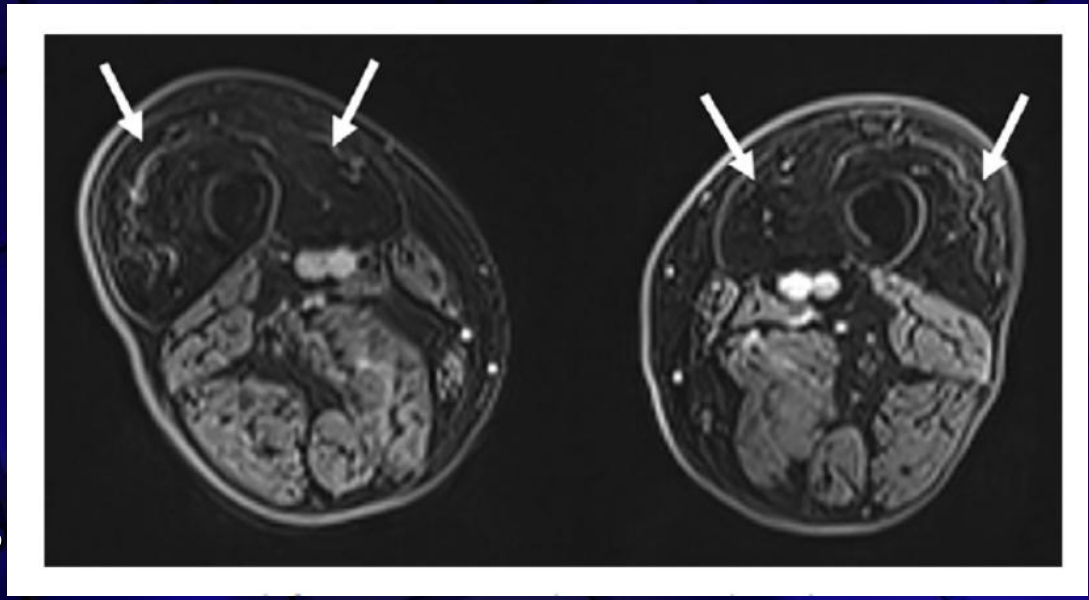

Quantitative EMG
200 uV/D
10 ms/D
A: Setup
B: Analyse
C: Run
200 uV/D
10 ms/D
Accepted: 0
Trig freq:
2.0 Hz
DANTEC



| Pathology | Insertion Activity | Fibrillations/ Positive sharp waves | Amp | Dur | Phases | Recruitment | Interference Pattern |
|---|---|---|---|---|---|---|---|
| Neurogenic (Acute) | Normal/Increased | +++ | N | N | Normal | Red | Incomplete |
| Neurogenic (Chronic) | Normal (may be increased in chronic ongoing lesion) | +/- | Inc | Inc | Poly | Red | Incomplete |
| Myopathic | Normal (may be increased in inflammatory or necrotizing myopathies, etc.) | Normal (may be increased in inflammatory or necrotizing myopathies, etc. | Red | Red | Poly | Early | Complete |

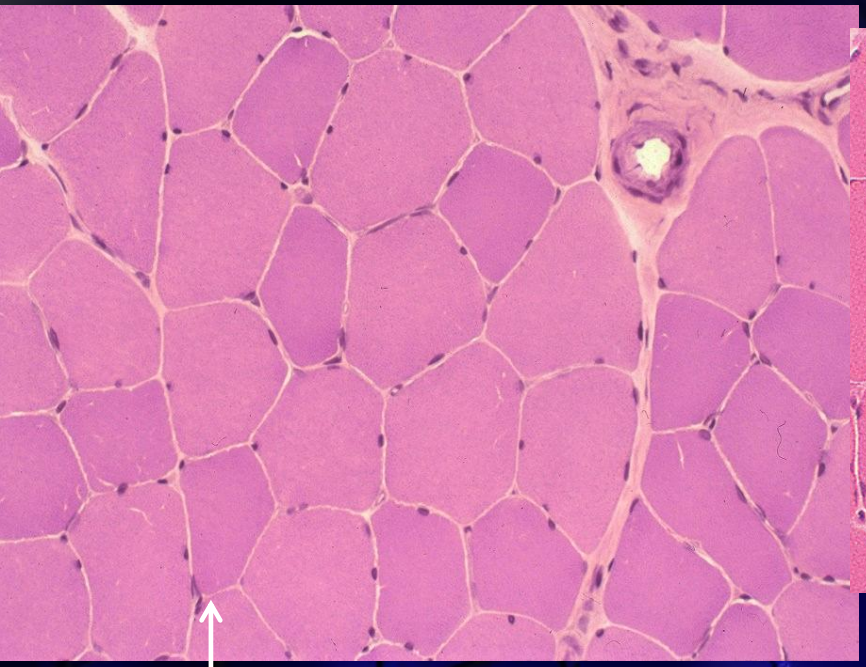
# *Whole Body Magnetic Resonance Imaging*

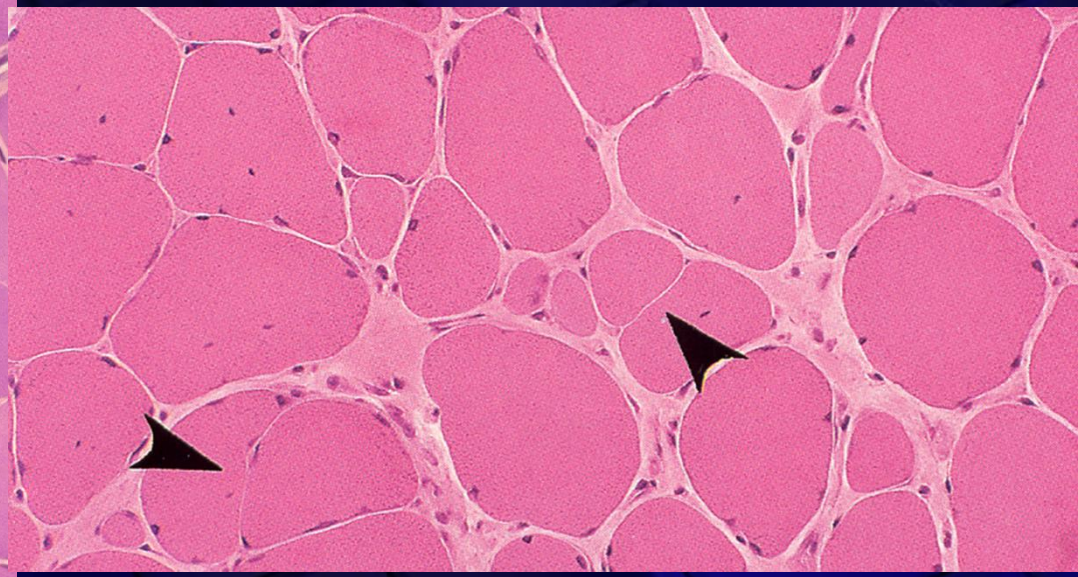
- Muscle edema and fatty degeneration can be imaged
  - Non-specific
  - Distribution of changes suggests certain diseases
- Can detect clinically silent involvement
- Select muscle biopsy site
- Treatment response



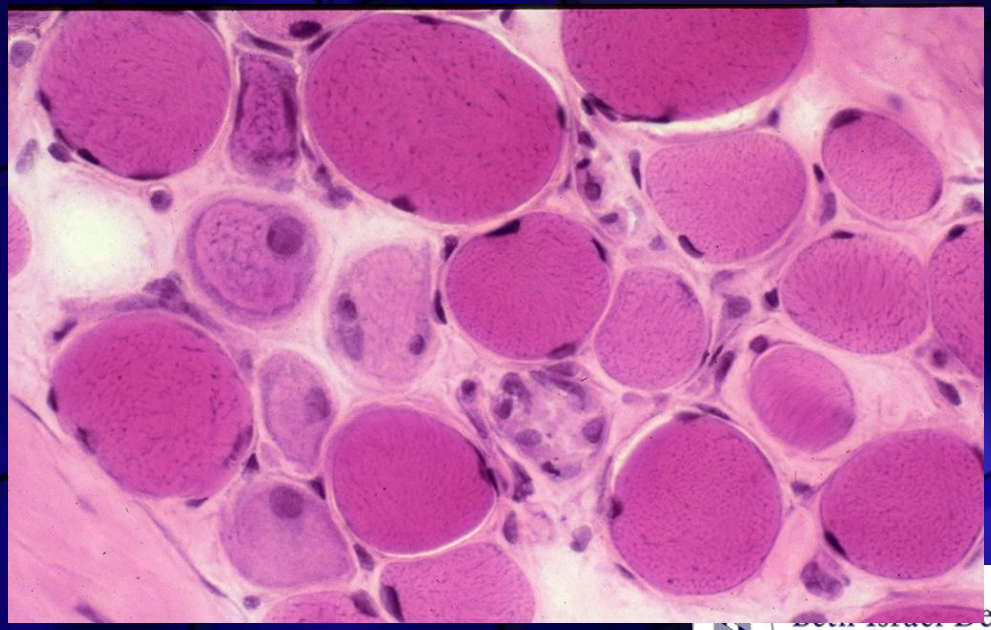
75 year old male with sporadic IBM: Bilateral, symmetric quadriceps atrophy with fatty replacement.

Filli L et al; Radiol Clin N Am 55 (2017)

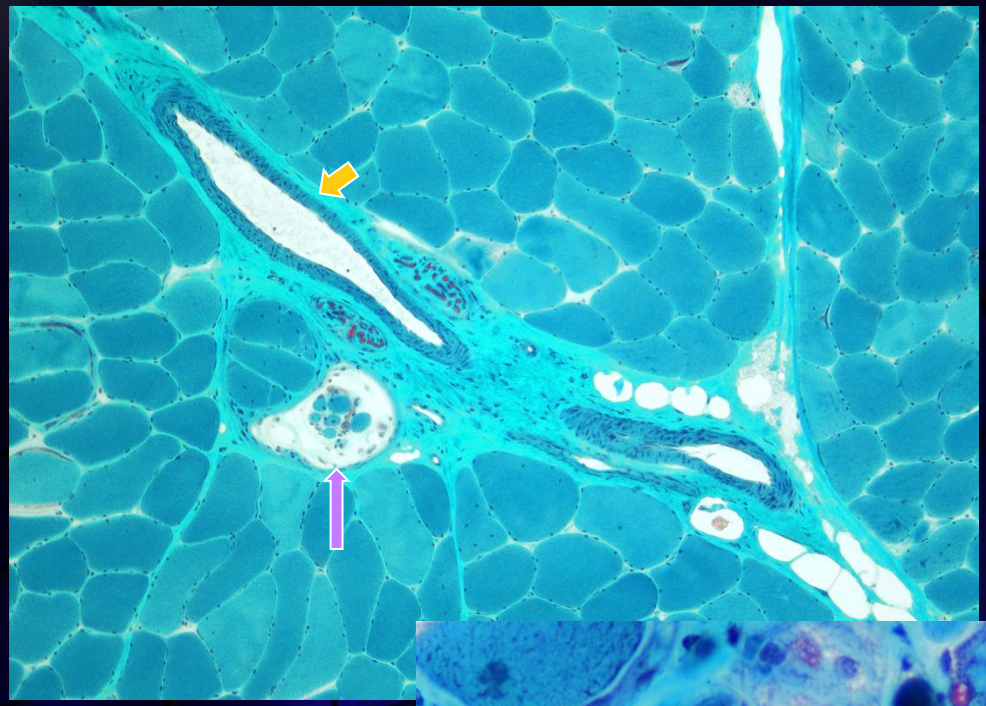




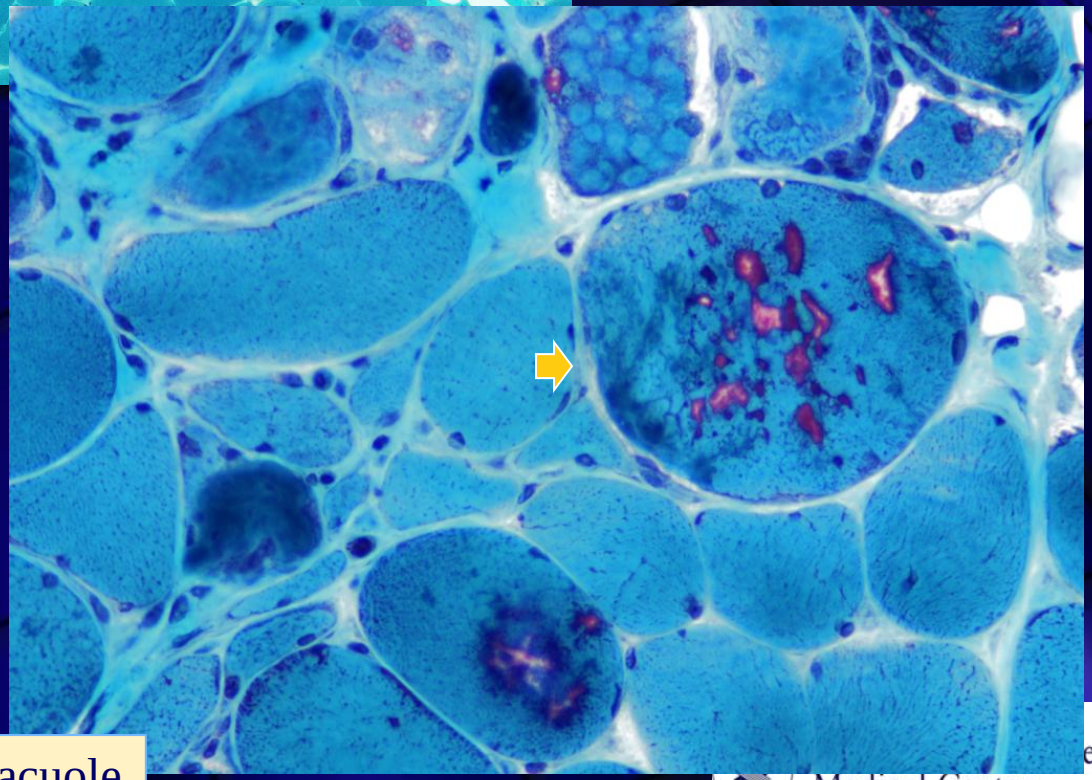
Normal H and E



Myopathic

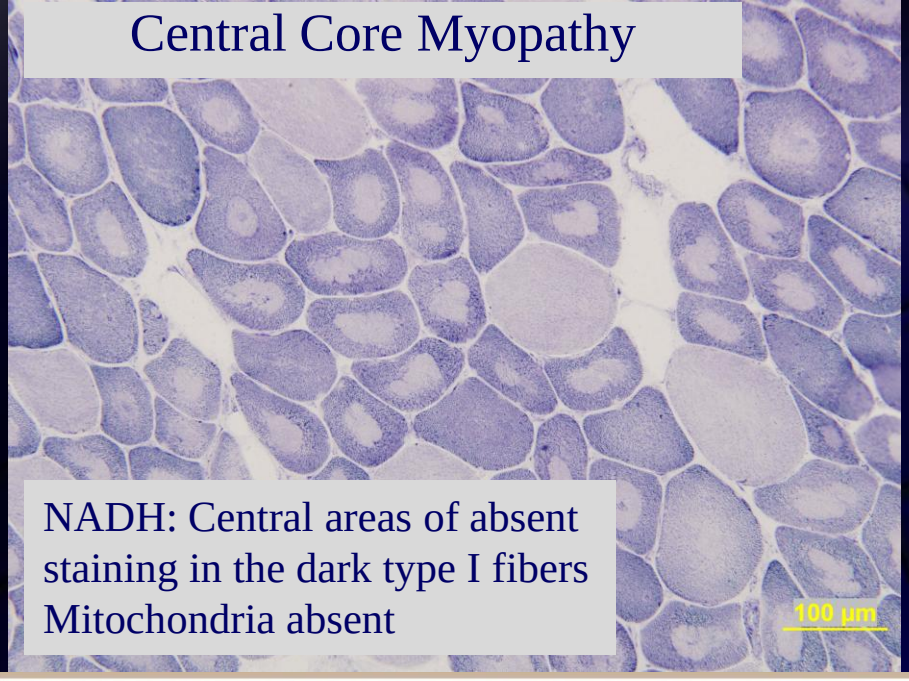


Modified Gomori Trichrome: Normal.



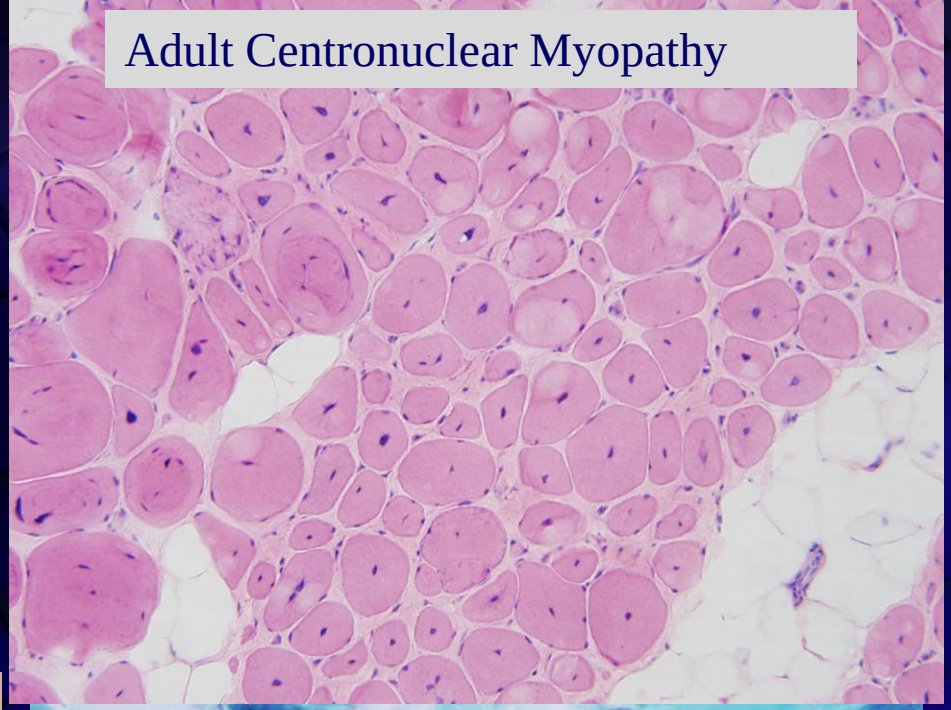
IBM: Rimmed vacuole

## Central Core Myopathy

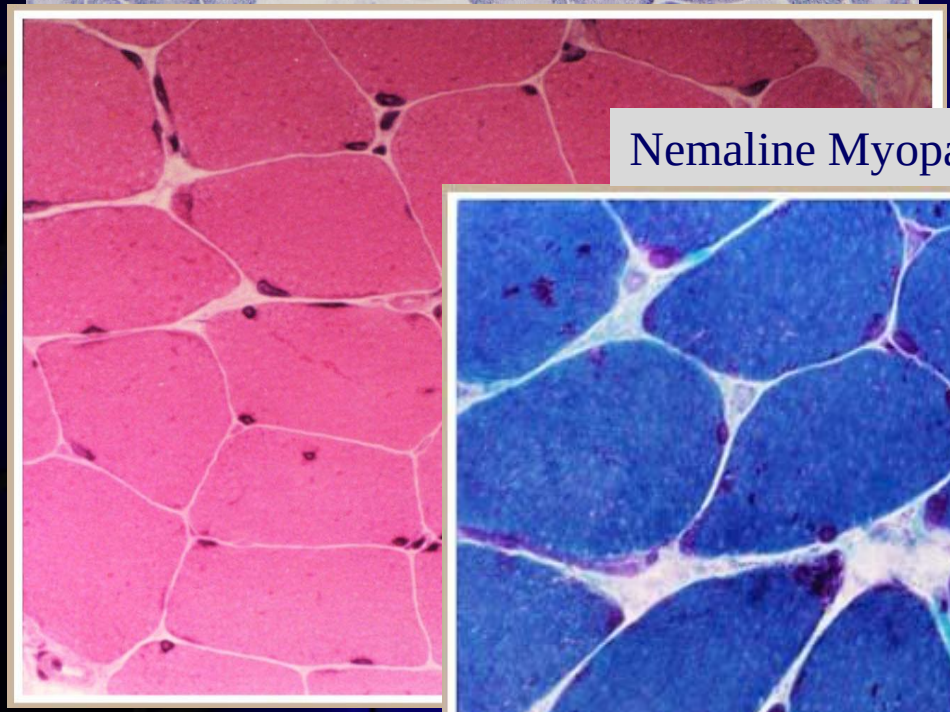



NADH: Central areas of absent staining in the dark type I fibers
Mitochondria absent

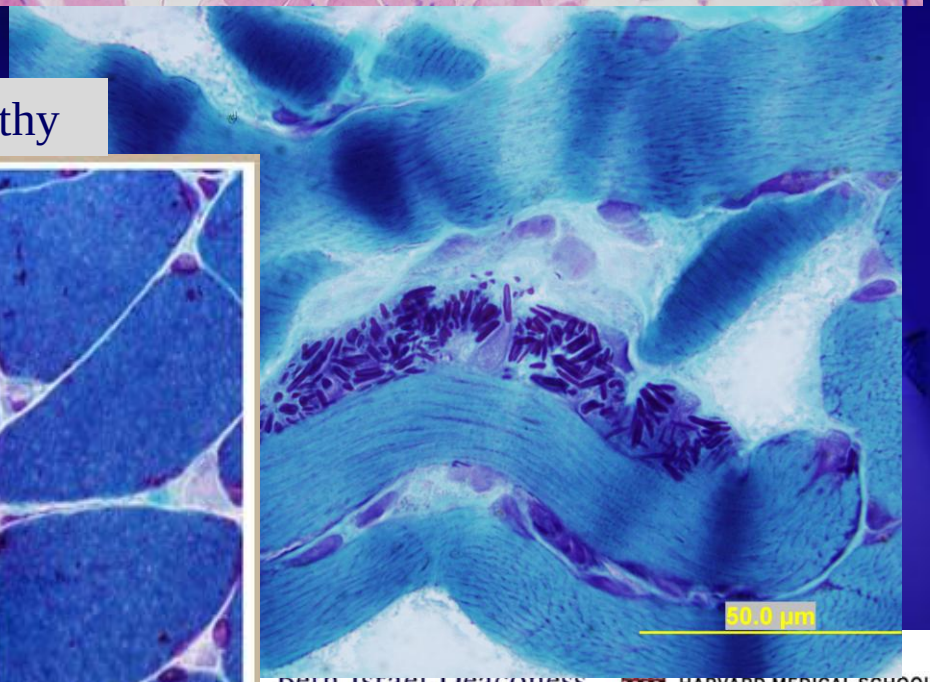
## Adult Centronuclear Myopathy



## Nemaline Myopathy







# *Why establish a genetic diagnosis?*

- In general, 5 answers that patients/families seek to know about any condition involving themselves or their family members:
  - What is the diagnosis?
  - How did it happen?
  - Who else in the family might be at risk?
  - What can be expected in the future?
  - Is there any treatment or cure?

# *Questions?*

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