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.

Alpha Motor Neuron

Muscle Fibers

Cell body (soma)
Axon
Oligodendrocyte
Node of Ranvier
Myelin sheath
Synapse
Cell membrane
Dendrites

Harvard-MIT Division of Sciences and Technology
Beth Israel Deaconess Medical Center
Peripheral Neuropathy

Anatomic Distribution
- Mononeuritis multiplex
- Polyneuropathy
- Sensory Motor Mixed
- Large Fiber Small Fiber Mixed

Etiology
- Hereditary Acquired...

Pathophysiology
- Axonopathies Myelinopathies

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
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

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Latency/Distal Latency</th>
<th>Amplitude</th>
<th>Conduction Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axonal</td>
<td>Normal</td>
<td>↓↓</td>
<td>Normal ↓ when severe</td>
</tr>
<tr>
<td></td>
<td>↑ when severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demyelinating</td>
<td>↑</td>
<td>Normal ↓ with temporal dispersion/Conduction block</td>
<td>↓↓</td>
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</table>
• Skin biopsy: validated technique for determining intraepidermal nerve fiber density (somatic unmyelinated C-fiber nerve terminals)
• Sensitivity 90% specificity 95% to 97%.
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
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
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
9/8/2019
**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 ophthalmoplegia**
- **Prominent neck extensor weakness:** Dropped head syndrome, bent spine syndrome
- **Myotonia:** stiffness, decreased ability to relax
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

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

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

- Rise Time
- Duration
- Amplitude
- Phase
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
<table>
<thead>
<tr>
<th>Pathology</th>
<th>Insertion Activity</th>
<th>Fibrillations/Positive sharp waves</th>
<th>Amp</th>
<th>Dur</th>
<th>Phases</th>
<th>Recruitment</th>
<th>Interference Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurogenic (Acute)</td>
<td>Normal/Increased</td>
<td>+++</td>
<td>N</td>
<td>N</td>
<td>Normal</td>
<td>Red</td>
<td>Incomplete</td>
</tr>
<tr>
<td>Neurogenic (Chronic)</td>
<td>Normal (may be increased in chronic ongoing lesion)</td>
<td>+/-</td>
<td>Inc</td>
<td>Inc</td>
<td>Poly</td>
<td>Red</td>
<td>Incomplete</td>
</tr>
<tr>
<td>Myopathic</td>
<td>Normal (may be increased in inflammatory or necrotizing myopathies, etc.)</td>
<td>Normal (may be increased in inflammatory or necrotizing myopathies, etc.)</td>
<td>Red</td>
<td>Red</td>
<td>Poly</td>
<td>Early</td>
<td>Complete</td>
</tr>
</tbody>
</table>
**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)
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?