Peripheral Neuropathy
NMJ and muscle diseases

Neurology Didactic Session 7
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Some important definitions

- **Central Nervous System [CNS]**
  - Brain
  - Spinal Cord

- **Peripheral Nervous System [PNS]**
  - Any nervous tissue OUTSIDE the CNS
  - Includes nerves, muscles and the NMJ
3 main parts of the PNS

- Nerves (SENSORY and motor)
  - Efferent nerves travel AWAY from spinal cord
    - Motor nerves to muscle
    - Autonomics to internal organs and skin
  - Afferent nerves travel TO the spinal cord
    - Sensory nerves from skin, bones, joints, tendons
    - Autonomics from internal organs
- Muscle
- Neuromuscular Junction [NMJ]
Neuromuscular Emergencies
[Two types]

- Nerve related
  - SENSORY disturbance proves nerve
  - Absence does not disprove it

- NMJ or muscle
  - Acute onset weakness
  - Beware of respiratory compromise

- NMJ – CPK will be NORMAL
- High CPK indicates muscle disease
Most important emergencies

- Nerve – Guillain Barre syndrome
  - Paralysis need not be ascending
  - Err on the side of overdiagnosing this
  - Tends to be subacute in presentation

- NMJ – myasthenic crisis
  - Admit to ICU
  - Support respirations

- Muscle – acute rhabdomyolysis
  - IV hydration to protect kidneys
  - Beware of compartment syndrome
3 important nerve structures:
Myelin sheath, Vasa Nervorem, Axons

- **Myelin** is blue, **blood vessels** red, **axons** white
Function of each

- **Myelin** allows for insulation and rapid conduction of nerve impulses.
- **Blood vessels** carry nutrients to the nerves and waste products away from them.
- **Axons** are the actual nerve “wires” that conduct the electrical signals.
Different nerve types

- **Heavily myelinated**
  - Proprioceptive sensory
    - Muscle spindle afferents (IA)
    - Vibration and position
  - Motor

- **Thinly myelinated**
  - Autonomics
    - Non-proprioceptive sensory (temperature)

- **Unmyelinated**
  - Pinprick sensation
  - Nociception
Myelin sheath

- Thickest on the outside; none in the center
- Functions like tape over a bare wire
- Malfunction results in:
  - Weakness with little wasting
  - “Tingling” sensations
  - Lost or absent reflexes
  - Fluctuations in HR and BP
Blood vessels

- **STOP at the nerve edge**
  - Fibers in center most at risk
- **Carry oxygen and nutrients to nerve**
- **Carry waste products away**
- **Reduced blood flow leads to:**
  - Pain in hands and feet
  - Weakness and wasting
Axons: The wires themselves

- Conduct electrical signals
- Supply growth factors to muscle
- Maintain sensory receptors
- Dysfunction leads to:
  - Symmetric problems in areas farthest from spinal cord
  - Starts in feet and works its way upward
Wallerian degeneration explained:

- Axon is separated from the cell body:
Wallerian degeneration explained:

- Axon “dies back” 2-3 nodes of Ranvier and distal segment degenerates in 2-3 weeks:
Myelinopathies

- Compression (sick nerves are more liable)
  - Median neuropathy at the wrist [Carpal tunnel]
  - Ulnar neuropathy at the elbow [Cubital tunnel]
  - Peroneal neuropathy at the fibular head

- Inherited myelinopathies
  - Charcot Marie Tooth type one
  - Déjèrine Sottas Disease

- Autoimmune

- Toxins
Stage one [neuropraxia]
- Wires intact but myelin not transmitting
- Acute function loss but rapidly reversible

Stage two [axontmesis]
- Incomplete axon loss [some wires remain]
- Recovery is still possible

Stage 3 [neurontmesis]
- All wires transected
- Recovery rarely occurs and is usually incomplete
Vasculopathies

- Secondary effects of compression
  - Median neuropathy at the wrist [Carpal tunnel]
  - Ulnar neuropathy at the elbow [Cubital tunnel]
  - Peroneal neuropathy at the fibular head

- Nerve ischemia
  - Diabetes mellitus
  - Tourniquet palsies

- Autoimmune
  - Vasculitis
  - Hypercoaguable states
Axonopathies

- Metabolic failure of cell bodies
  - Exogenous toxins
  - Medications
  - Chemotherapy

- Inherited conditions
  - Hereditary motor and sensory [HMSN]
  - Hereditary sensory neuropathies [HSN]
  - Hereditary sensory and autonomic [HSAN]
### Pathology and results

<table>
<thead>
<tr>
<th>Fibers most affected</th>
<th>Pathology</th>
<th>Respiratory Failure?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelin</td>
<td>Myelinated</td>
<td>Myelin loss</td>
</tr>
<tr>
<td>Vessels</td>
<td>Centrally located</td>
<td>Centro-fascicular atrophy</td>
</tr>
<tr>
<td>Axons</td>
<td>Most distal from cell body</td>
<td>Distal Wallerian degeneration</td>
</tr>
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Distinguish these clinically

- **Inherited**
  - Signs >> Symptoms
  - “It bothers you more than it bothers them”
  - Usually referred by another physician

- **Acquired**
  - Symptoms >> Signs
  - Deterioration from a previous level of functioning
Acquired neuropathies

[Symmetric or Asymmetric?]

- **Symmetric**
  - Most likely to be an axonopathy
  - Other causes far less likely
  - Etiology is toxic/metabolic

- **Asymmetric**
  - Think “Immune mediated”
  - Is it a myelinopathy?
  - Is it a vasculopathy?
## Asymmetric neuropathies

<table>
<thead>
<tr>
<th></th>
<th>Myelinopathy</th>
<th>Vasculopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor exam</strong></td>
<td>Weakness &gt; Atrophy</td>
<td>Weakness ≈ Atrophy</td>
</tr>
<tr>
<td><strong>Sensory exam</strong></td>
<td>Large fiber &gt; Small fiber</td>
<td>Small fiber &gt; Large fiber</td>
</tr>
<tr>
<td><strong>Reflex exam</strong></td>
<td>Reduced or absent</td>
<td>Hardly ever absent</td>
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## Asymmetric neuropathies

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<tr>
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<th>Myelinopathy</th>
<th>Vasculopathy</th>
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<tr>
<td><strong>Distribution</strong></td>
<td>Face and trunk may be affected</td>
<td>Face and trunk rarely affected</td>
</tr>
<tr>
<td><strong>CSF examination</strong></td>
<td>High protein/ few cells common</td>
<td>High protein few cells RARE</td>
</tr>
<tr>
<td><strong>Tests for systemic illness</strong></td>
<td>Usually negative</td>
<td>May be positive</td>
</tr>
</tbody>
</table>
Tempo of progression

- Rapid onset and progression is an EMERGENCY:
  - Acute myelin failure
  - Acute vasculitis

- Slower onset is less emergent
Non-emergent neuropathies

- If **symmetric** by history and exam:
  - Toxic-metabolic is the likely cause
  - Find the cause and fix it whenever possible
  - Example: Other organ dysfunction

- If **asymmetric** by history and exam:
  - Autoimmune is likely
  - Find the cause and fix it whenever possible
  - Immunosuppression if no cause is found
NMJ disorders

- Connection between motor nerve and muscle
- “Faulty,” “Incomplete” transmission
- Suspect when
  - Degree of weakness changes with exercise
    - Pre-synaptic: Exercise improves transmission
    - Post-synaptic: Exercise worsens transmission
- NO SENSORY LOSS!
- NO ATROPHY!
NMJ disorders

[NO sensory loss or atrophy]

**PRE-synaptic**
- Better with exercise
- Acetylcholine
  - Release impaired
  - Binding unaffected
- Causes
  - Immune [LEMS]
  - Botulism
- EMG test
  - 50 Hertz stimulation to improve response

**POST-synaptic**
- Worse with exercise
- Acetylcholine
  - Release unaffected
  - Binding impaired
- Causes
  - Immune [Myasthenia]
  - NMJ blockers
- EMG test
  - 2-3 Hertz to demonstrate worsening response
Muscle diseases (overview)

- Proximal > distal weakness
- NO SENSORY LOSS!
- Atrophy in later stages
- Three main types
  - Structural dysfunction
  - Glycolysis defects
  - Mitochondrial disorders
Structural disorders - muscle membrane breakdown

- Suspect when
  - CPK is elevated
  - Progressive muscle weakness and atrophy

- Examples
  - Muscular dystrophy
  - Polymyositis/dermatomyositis
  - Inclusion body myopathy

- Prove diagnosis by gene test or biopsy
Dermatomyositis
[SKIN and muscle- paraneoplastic?]

- Heliotrope facial rash (named after the flower)
- Muscle biopsy showing perifascicular cellular infiltrate
Dermatomyositis

- Dermatomyositis affects children and adults. It causes a purple (heliotrope) discoloration of the upper eyelids, edema around the eyes and mouth, skin rash on the face and over extensor surfaces of the extremities, muscle pain, weakness and stiffness of muscles.
- Contractures, subcutaneous calcification, intestinal ulceration, and other extramuscular manifestations are frequent in children.
- Increased risk of cancer (15-20%) in ADULTS only
Polymyositis
[Muscle only-no increased cancer risk]

- Polymyositis affects predominantly adults who present with subacute or chronic proximal weakness (without a rash) and elevated CK.
- The muscle biopsy shows endomysial mononuclear cells and myonecrosis. Polymyositis is a cell-mediated autoimmune disorder in which cytotoxic T-cells and macrophages invade and destroy myofibers.
Inclusion body myopathy

- Sporadic inclusion body myopathy (IBM) is the most common muscle disease in older people, (mostly men).
- It causes progressive proximal (deep finger flexors and quads), distal weakness and mild CK elevation.
- The filamentous inclusions of IBM have the optical properties of amyloid and contain beta amyloid, hyperphosphorylated tau protein, apolipoprotein E, presenillin 1, prion protein, and other proteins.
Glycolytic enzyme defect

- CPK usually normal
- Rapid onset of weakness
- Examples
  - McArdle’s disease
  - Debrancher enzyme disease
- Prove with ischemic exercise test
  - Lactate does not rise (failure of glycolysis)
  - Ammonia does rise (protein breakdown)
Mitochondrial myopathies

- Suspect when highly active muscles fail:
  - Extraocular muscles
  - Cranial nerve muscles
  - Speech/swallowing muscles

- Laboratory values
  - CPK usually normal
  - Lactic acid levels elevated

- Muscle biopsy shows ragged red fibers
Approach to PNS disorders

- Sensory disturbance = neuropathy
  - Symmetric = toxic metabolic process
  - Asymmetric = autoimmune
    - Myelinopathy
    - Axonopathy

- Motor weakness ONLY:
  - Anterior horn cells/motor nerve roots
  - NMJ
  - Muscle
PNS – pure motor

- No atrophy favors NMJ disorder
  - NMJ disorders affected by exercise
    - Pre-synaptic improves with exercise
    - Post-synaptic worsens with exercise

- Motor neuron/nerve root
  - Atrophy of distal/facial/trunk muscles
  - Respirations may be affected

- Muscle
  - Proximal weakness
  - Respirations rarely affected early
Which muscle disease?

- **Structural**
  - CPK elevation
  - Prove by gene test or biopsy

- **Glycolytic pathway**
  - Early onset fatigue
  - Lactate does not risk with exercise

- **Mitochondrial**
  - High baseline lactate
  - Cranial nerves/pharyngeal muscles