Peripheral Neuropathy for the Primary Physician

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• Disclosures: none
Objectives

• Brief overview of Anatomy
• Clinical Approach to Neuropathy
  – History
  – Exam
  – Labs
  – Ancillary Testing
• Treatment
• Clinical Case

Three major classes of nerves

1. Large myelinated
2. Small myelinated
3. Small unmyelinated

Sensory fibers
Motor fibers
Autonomic fibers

Vibration & position
Pain and temp
Three major classes of nerves

1. **Large** myelinated - Sensory fibers
   - NCV > 50 m/s
2. **Small** myelinated - Motor fibers
3. **Small** unmyelinated - Autonomic fibers

Three major classes of nerves

1. **Large** myelinated - Sensory fibers
   - BP & HR
2. **Small** myelinated - Motor fibers
   - Sweat, GI
3. **Small** unmyelinated - Autonomic fibers
• Polyneuropathy can affect the following in varying combinations

  – Small fibers -> disturbance pain and temperature

  – Small fibers -> disturbance in autonomic dysfunction

  – Large fibers -> disturbance in vibratory sense and proprioception

  – Large fibers -> weakness

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When to consider polyneuropathy

• Distal symmetric weakness
• Proximal and distal extremity weakness
• Multifocal weakness
• Hypoesthesia
• Hyperesthesia
• Paresthesias
• Allodynia
• Sensory ataxia
• Atrophy
• Fasciculations
Clinical approach to a patient with possible PN

Three goals

1. Identify where the lesion is
   - Thorough history
   - Neurological examination
   - Electrodiagnosis (NCV/EMG)
2. Identify the cause
3. Determine the treatment

Seven Key Questions

• What systems are involved?
• What is the distribution of weakness?
• What is the nature of the sensory involvement?
• Is there evidence of upper motor neuron involvement?
• What is the temporal evolution?
• Is there evidence for a hereditary neuropathy?
• Does the patient have any other medical conditions? Drug uses? Exposure to neurotoxins?
Q1: What systems are involved?

• Motor, sensory, autonomic, or a combination?
  – Pure motor weakness without sensory or autonomic dysfunction: *motor neuron disease* vs *neuromuscular transmission disorders* *(Myasthenia Gravis or Lambert Eaton Myasthenic Syndrome)* or *myopathy*
  – Pure sensory *(paraneoplastic, Sjögren’s, HIV)*
  – Autonomic involvement: orthostatic hypotension, heat intolerance, bowel, bladder or sexual dysfunction *(DM most common, amyloidosis)*

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**Large-fiber vs Small-fiber neuropathy**

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-fiber</td>
<td>Numbness</td>
<td>Absent reflexes, vibration sense, pin prick and temperature</td>
</tr>
<tr>
<td></td>
<td>Imbalance</td>
<td></td>
</tr>
<tr>
<td>Small fiber</td>
<td>Burning Pain</td>
<td>Intact reflexes and vibration sense ± Mild sensory gradient to pin prick and temperature</td>
</tr>
</tbody>
</table>

NW PADRECC - Parkinson's Disease
Research, Education & Clinical Center
Portland VA Medical Center
www.parkinsons.va.gov/Northwest
Q2: What is the distribution of weakness?

- Distal only or both proximal and distal
- Focal and asymmetric or symmetric
- If a patient has a symmetrical proximal and distal weakness and sensory findings, think of Acute Inflammatory Demyelinating Polyneuropathy (AIDP, or GBS) or the chronic form (CIDP), very treatable
- In a patient presenting with asymmetric subacute or acute sensory and motor symptoms, consider compressive neuropathy (such as CTS or ulnar nerve entrapment at the elbow), plexopathies, radiculopathies, or mononeuropathy multiplex

Q3: What is the nature of the sensory involvement?

- Loss of sensation (numbness) vs altered sensation to touch (allodynia) vs uncomfortable spontaneous sensation (tingling, burning, or aching)
- Neuropathic pain: dull, burning and poorly localized (C fibers) or sharp and lancinating (A–delta fibers)
- Loss of pain and temperature sensation, preservation of vibration and position sense, normal strength, reflexes and NCV → small fiber neuropathy (most likely DM or impaired GTT)
- Severe proprioception and vibration loss, normal strength in a non-length-dependent manner – sensory ganglionopathy (paraneoplastic, Sjögren, HIV)
Q4: Is there evidence of upper motor neuron involvement?

• Symmetric distal sensory neuropathy with additional upper motor neuron involvement (hyper-reflexia or up-going toes): combined system degeneration →
  – B12 deficiency (most common)
  – copper deficiency
  – HIV infection
  – Adrenomyeloneuropathy
• Is there weakness and upper motor neuron signs WITHOUT sensory deficits?
  – ALS

Q5: What is the temporal evolution?

• Determine the onset, duration, and evolution of symptoms and signs: acute (<4 w), subacute (< 8 w), or chronic (> 8w)
• Is the course monophasic, progressive, or relapsing?
• Insidious and slowly progressive
  – most neuropathies
• Acute or subacute
  – GBS, vasculitis, or radiculopathies
• Relapsing
  – CIDP or porphyria
Q6: Is there evidence for a hereditary neuropathy?

- Slowly progressive distal weakness over many years with little sensory symptoms, yet with significant sensory deficits on clinical examination → Consider hereditary neuropathy (e.g., Charcot-Marie-Tooth disease or CMT).
  - the feet may show arch and toe abnormalities (high or flat arches, hammertoes)
  - scoliosis may be present in suspected cases
  - may be necessary to perform both neurologic and electrophysiologic studies on family members in addition to the patient
Q7: Does the patient have any other medical conditions? Drug uses? Exposure to neurotoxins?

- DM? SLE?
- Preceding or concurrent infections: diarrheal illness preceding GBS
- Surgeries: gastric bypass and nutritional neuropathy
- Medications: toxic neuropathy
- OTC vitamins: B6
- Alcohol
- Dentures: fixatives contain zinc that can lead to copper deficiency

Drugs causing neuropathy

<table>
<thead>
<tr>
<th>Almitrine</th>
<th>Disulfiram</th>
<th>Nitrous oxide</th>
<th>Stavudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Doxorubicin</td>
<td>Nitrofurantoin</td>
<td>Suramin</td>
</tr>
<tr>
<td><strong>Chloroquine</strong></td>
<td>Ethambutol</td>
<td>Taxol</td>
<td>Thalidomide</td>
</tr>
<tr>
<td><strong>Cisplatin</strong></td>
<td>FK 506</td>
<td>Perhexiline</td>
<td><strong>Vincristine</strong></td>
</tr>
<tr>
<td><strong>Chochicine</strong></td>
<td>Gold salts</td>
<td><strong>Phenytoin</strong></td>
<td><strong>Vinblastine</strong></td>
</tr>
<tr>
<td>Dapsone</td>
<td><strong>Isoniazid</strong></td>
<td>Procanamide</td>
<td>Zalcitabine</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Metronidazole</td>
<td><strong>Pyridoxine</strong> (B6)</td>
<td></td>
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</tbody>
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From: Mendell, Kissel, Cornblath, 2001
Clues to diagnosis of neuropathy:
Family history

- General inquiries such as “if any family members have similar condition” are NOT productive
- Pointed questions such as
  - How many siblings? How is your brother (sister)?
  - Using canes or walkers?
  - Foot deformities?

Clues to diagnosis of neuropathy:
Social history-Habits

<table>
<thead>
<tr>
<th>Habits</th>
<th>Neuropathy</th>
</tr>
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<tbody>
<tr>
<td>Smoking</td>
<td>Paraneoplastic</td>
</tr>
<tr>
<td>Excess alcohol</td>
<td>Nutritional/vitamin deficiency</td>
</tr>
<tr>
<td>Sexual preference, IV drug</td>
<td>HIV-related</td>
</tr>
<tr>
<td>Medications/B6</td>
<td>Toxic</td>
</tr>
<tr>
<td>Nitrous oxide abuse</td>
<td>B12 deficiency</td>
</tr>
<tr>
<td>Cocaine use</td>
<td>Vasculitic neuropathy</td>
</tr>
<tr>
<td>Strict Vegetarian diet</td>
<td>B12 deficiency</td>
</tr>
</tbody>
</table>

From: Mendell, Kissel, Cornblath, 2001
What laboratory tests to order?

- Generalized symmetrical neuropathy:
  - Chem20, CBC, UA, FBS, HbA1C, UA, TFT, B12, folate, ESR, RF, ANA, SPEP, urine BJ protein
- Painful sensory neuropathies: 2HrGTT. An oral glucose tolerance test is indicated even if FBS and HbA1C are normal.
- Demyelinating neuropathy or suspects amyloidosis: serum and urine immunofixation electrophoresis (IFE) are necessary
  - CIDP and M-spikes: A skeletal survey to look for osteosclerotic or lytic lesions
  - Monoclonal gammopathy: hematology consult for bone marrow biopsy
- Mononeuropathy multiplex: vasculitis workup, including antineutrophil cytoplasmic antibodies (ANCA), cryoglobulins, hepatitis serology, HIV

What laboratory tests to order?

- Possible GBS or CIDP: lumbar puncture is indicated to look for an elevated cerebral spinal fluid (CSF) protein without pleocytosis
  - If cells are present (>10/mm$^3$), consider HIV infection, Lyme disease, sarcoidosis, lymphomatous, or leukemic infiltration of nerve roots.
- Pure sensory neuronopathy
  - Sjögren syndrome: SSA, SSB
  - Paraneoplastic: Anti-Hu. If positive, search for malignancy
What Abs to test in neuropathy?

- Demyelination sensory or sensorimotor PN
  - check anti-MAG (IgM)
- Pure sensory syndromes
  - anti-Hu
- Motor neuropathy
  - anti-GM1 and AntiGD1a if no UMN sign
- GBS with severe axonal loss
  - antiGM1 (not diagnostic, but prognostic, worse)
- possible Miller Fisher syndrome
  - check GQ1b, sensitive and specific

What laboratory tests NOT to order?

- Various anti-ganglioside antibodies (commercially available as “neuropathy panel”) -- $$$$$$$$$$$$, not useful
- Heavy metal screening: not necessary unless
  - Severe painful and autonomic neuropathy with alopecia $\rightarrow$ thallium
  - Severe painful sensorimotor neuropathy with Mee’s line $\rightarrow$ arsenic
  - Wrist or finger extensor weakness and anemia with basophilic stippling of RBC $\rightarrow$ lead
Neuropathy Testing

NCS/EMG

Autonomic Tests

Skin biopsies

Electrodiagnosis plays a crucial role in evaluating patients with PN
Goals of NCV/EMG

1. **Localization of the lesion:**
   - **Nerve:** mononeuropathy, mononeuritis multiplex, polyneuropathy, plexopathy, radiculopathy, polyradiculopathy, neuronopathy
   - **Neuromuscular Junction:** presynaptic or postsynaptic
   - **Muscle:** muscular dystrophy

2. **Underlying nerve pathophysiology:**
   - **Fiber type involved:** motor, sensory, motor and sensory
   - **Pathology:** primary demyelination (AIDP or CIDP) or primary axonal

3. **Assessment of severity:**
   - Correlation with clinical finding

4. **Assessment of temporal course:**
   - hyperacute, acute, subacute or chronic
Autonomic Testing

• Consider if suspect small fiber neuropathy with autonomic dysfunction
• Assess small myelinated (A-delta) or unmyelinated (C) nerve fiber involvements
  1. HR and BP response to the Valsalva maneuver
  2. HR response to deep breathing
  3. HR and BP response to tilt-table testing
  4. Quantitative sudomotor axon reflex testing (sweat response)

Skin Biopsy

• May be helpful with small fiber neuropathy
• Punch skin biopsy of distal leg and proximal thigh
• Stain to measure the density of small unmyelinated fibers (the density is reduced in patients with small fiber neuropathy)
### Treatment of painful sensory neuropathies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST-LINE</strong></td>
<td></td>
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<tr>
<td>Amitriptyline or nor triptyline</td>
<td>10 - 100 mg po qhs</td>
<td>Cognitive changes, sedation, dry eyes and mouth, urinary retention, constipation</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300-1200 mg po tid</td>
<td>Cognitive changes, sedation, peripheral edema</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>50-100 mg po tid</td>
<td>Cognitive changes, sedation, peripheral edema</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30-60 mg po qd</td>
<td>Cognitive changes, sedation, dry eyes, diaphoresis, nausea, diarrhea, constipation</td>
</tr>
<tr>
<td><strong>SECOND-LINE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>200-400 mg po tid or qid</td>
<td>Cognitive changes, dizziness, leukopenia, liver dysfunction</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>200-400 mg po qhs</td>
<td>Cognitive changes, dizziness, liver dysfunction</td>
</tr>
<tr>
<td>Other agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin 0.025%-0.075 cream</td>
<td>Apply locally</td>
<td>Painful burning skin</td>
</tr>
</tbody>
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### Case: CL

- 26 year old left handed female with progressive weakness and numbness in her arms and legs
- She initially developed onset of weakness and numbness in her hands and feet in October 2007, which worsened over the next few weeks to the point where she was falling frequently and tripping over objects.
- She was having numbness and tingling in her fingers and hands.
- Symptoms then improved for several weeks.
Case CL

<table>
<thead>
<tr>
<th></th>
<th>Nadir</th>
<th>Relapses?</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDP</td>
<td>Within 4 weeks</td>
<td>Very rare</td>
<td>NO steroids</td>
</tr>
<tr>
<td>CIDP</td>
<td>&gt;8 weeks</td>
<td>Typical</td>
<td>Yes steroids</td>
</tr>
</tbody>
</table>

In July, 2008, she again developed weakness and numbness in her hands and feet. She eventually had problems standing from a sitting position and climbing stairs. She started using a wheelchair in October 2008.
Case: CL

- **Neuro:**
- **Motor:** Deltoid and triceps 4+/5 bilaterally, biceps 4/5, wrist extensors 2/5, FDI 4+, hip flexors 4+, knee extensors 2 on right, 3 on the left, knee flexors 3/5, ankle dorsiflexors 4, plantar flexors 4+
- **Sensory:** Proprioception intact at toes and fingers. Intact to pinprick upper and lower extremities bilaterally
- **Coord/Gait:** Able to rise from a chair but very unsteady, takes a few steps w/ bilateral foot drop, requires support.
- **DTR’s:** Absent throughout
Case CL

- NCS/EMG:
  - Conduction block in right median and ulnar nerves
  - Absent SNAPs
  - Moderate axonal degeneration in distal muscles on EMG

- Conclusion: Acquired Demyelinating Polyneuropathy

Case: CL

- CSF: WBC 2, RBC 8, glucose 62, protein 89
- CSF Cx and gram stain: neg
- HIV negative, RPR negative
- B12, ANA, ENA, ANCA, antithyroid antibodies, vit B1, B6, D, E, CK, aldolase, heavy metals, SPEP: all negative or within normal limits
- MRI brain w/out 10/08: normal per report
- MRI C-spine w/out: normal per report.
- Chem 7, CBC: wnl
# Acquired Demyelinating Neuropathy

- Clinical Features of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
  - Proximal and/or distal weakness
  - Paresthesias and sensory loss are common
  - Absent or reduced reflexes
  - Cranial Nerve involvement in 10–20%
  - Usually slowly progressive (>2mths), may be relapsing/remitting
  - Peak incidence 40-60 years, can present in kids

# Demyelinating Neuropathy

- Acquired Demyelinating Neuropathy
- Subtypes:
  - Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
  - Multifocal Acquired Demyelinating Sensory and Motor neuropathy (MADSAM)
  - Distal Acquired Demyelinating Sensory Neuropathy (DADS)
  - Multifocal Motor Neuropathy (MMN)
  - Multifocal Acquired Motor Axonopathy (MAMA)
Acquired Demyelinating Neuropathy

• Differential Diagnosis
  – Disorder of Neuromuscular Junction (myasthenia gravis)
  – Myopathy
  – Motor Neuron Disease (ALS)
  – Hereditary Neuropathy
  – Vasculitic Neuropathy (mononeuropathy multiplex)
  – Axonal Neuropathy
  – Other causes of polyradiculopathy
  – Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS)

Diagnostic Work up

• Electrodiagnosis
• Many different criteria
• Features:
  – Conduction block and temporal dispersion*
  – Reduction in conduction velocity *(<80% LLN)
  – Prolonged distal latencies (>125% ULN)
  – Absent or prolonged F-Waves (>120% ULN)
  – Secondary axonal degeneration

• Remember: Check temp and warm limbs
Diagnostic Work up

• Electrodiagnostics
  – Differentiate from axonal neuropathy, polyradiculopathies, myopathies
  – Guide additional laboratory work up
  – May be sufficient information to warrant treatment

Diagnostic Work up

• Lumbar Puncture
• Albuminocytologic dissociation
• If pleocytosis, think other diagnoses
• HIV, Lyme, sarcoid, lymphoma
• SPEP/Immunofixation
• Other labs: Hgb A1C, TSH, HIV, CBC, COMP, Lyme serologies, Hepatitis profiles, CRP, ESR, ANA, SSA, SSB, ACE
Antibody Testing

• Demyelination sensory or sensorimotor PN with prolonged distal latencies
  – check anti-MAG (IgM)
• Pure sensory syndromes
  – anti-Hu
• Motor neuropathy
  – anti-GM1 and AntiGD1a
• GBS with severe axonal loss
  – antiGM1 (not diagnostic, but prognostic)
• Possible Miller Fisher syndrome
  – check GQ1b, sensitive and specific

• Various antiganglioside antibodies (commercially available as “neuropathy panel”) – expensive / not useful

Case CL: Treatment

• January, 2009: Prednisone 80 mg po qday, Azathioprine 50 mg po bid
• April, 2009: Complete resolution of symptoms and normal exam
• Weight gain noted on steroids, steroids gradually tapered over 8 weeks.
• Continued on Imuran.
Acquired Demyelinating Neuropathy: Treatment

• First line
  – Prednisone (start 50mg – 80mg day for 1-3 mths)
  – Plasmapheresis
  – IVIG

• Steroid sparing
  – azathioprine
  – methotrexate
  – mycophenolate mofetil
  – rituximab
References

- Mendell JR, Kissel JT, Cornblah DR. Diagnosis and management of peripheral nerve disorders (Contemporary Neurology), Oxford University Express, 2001

The Neuromuscular Center at VA/OHSU

- Consultation
- EMG/NCV
- Autonomic Function tests
- Skin Biopsy
- Muscle Biopsy