Peripheral Neuropathy for the Primary Physician

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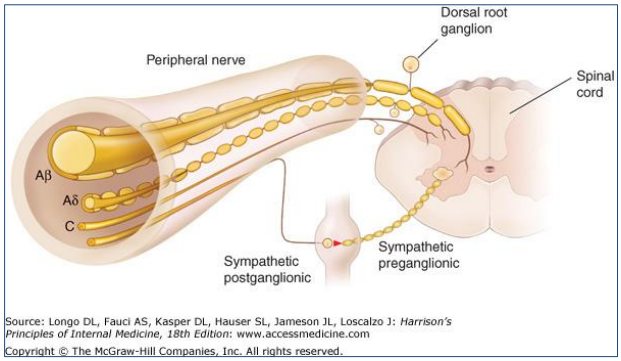
- Disclosures: none

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 — Vibration & position → Sensory fibers
2. **Small** myelinated — Pain and temp → Motor fibers
3. **Small** unmyelinated — Pain and temp → Autonomic fibers

Three major classes of nerves

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

NCV >50 m/s

Sensory fibers

Motor fibers

Autonomic fibers

Three major classes of nerves

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

BP&HR, sweat, GI

Sensory fibers

Motor fibers

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

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**)

Large-fiber vs Small-fiber neuropathy

Type	Symptoms	Signs
Large-fiber	Numbness Imbalance	Absent reflexes, vibration sense, pin prick and temperature
Small fiber	Burning Pain	Intact reflexes and vibration sense ± Mild sensory gradient to pin prick and temperature

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 S & S, 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 ganlionopathy (**paraneoplastic, Sjögren, HIV**)

Q4: Is there evidence of upper motor neuron involvement?

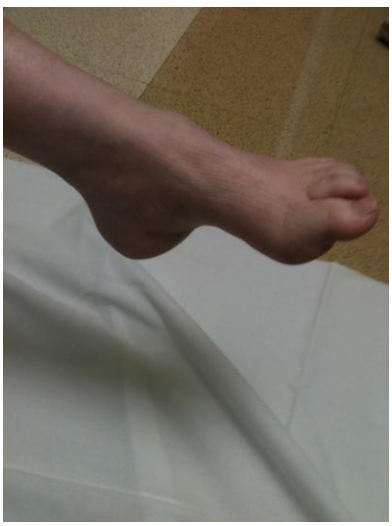
- Symmetric distal sensory neuropathy with additional upper motor neuron involvement (hyper-reflexia or up-going toes): combined system degeneration →
  - **B12 deficiency** (most common)
  - **copper deficiency**
  - **HIV infection**
  - **Adrenomyeloneuropathy**
- Is there weakness and upper motor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

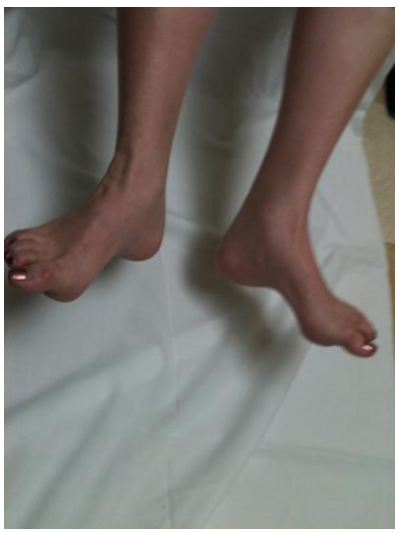
Q5: What is the temporal evolution?

- 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

Almitrine	Disulfiram	Nitrous oxide	Stavudine
Amiodarone	Doxorubicin	Nitrofurantoin	Suramin
Chloroquine	Ethambutol	Taxol	Thalidomide
Cisplatin	FK 506	Perhexiline	**Vincristine**
Chochicine	Gold salts	**Phenytoin**	**Vinblastine**
Dapsone	**Isoniazid**	Procanamide	Zalcitabine
Didanosine	Metronidazole	**Pyridoxine** (B6)	

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

Habits	**Neuropathy**
Smoking	Paraneoplastic
Excess alcohol	Nutritional/vitamin deficiency
Sexual preference, IV drug	HIV-related
Medications/B6	Toxic
Nitrous oxide abuse	B12 deficiency
Cocaine use	Vasculitic neuropathy
Strict Vegetarian diet	B12 deficiency

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

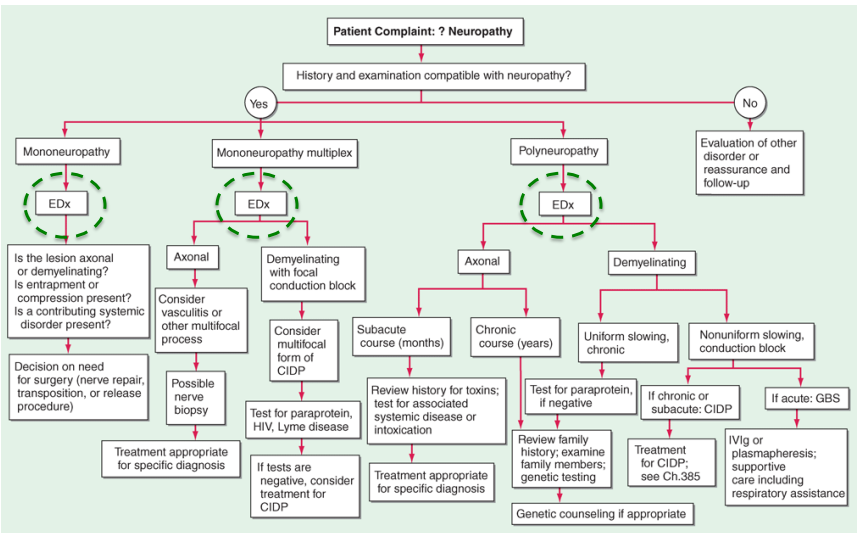
What laboratory tests NOT to order?

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

Neuropathy Testing

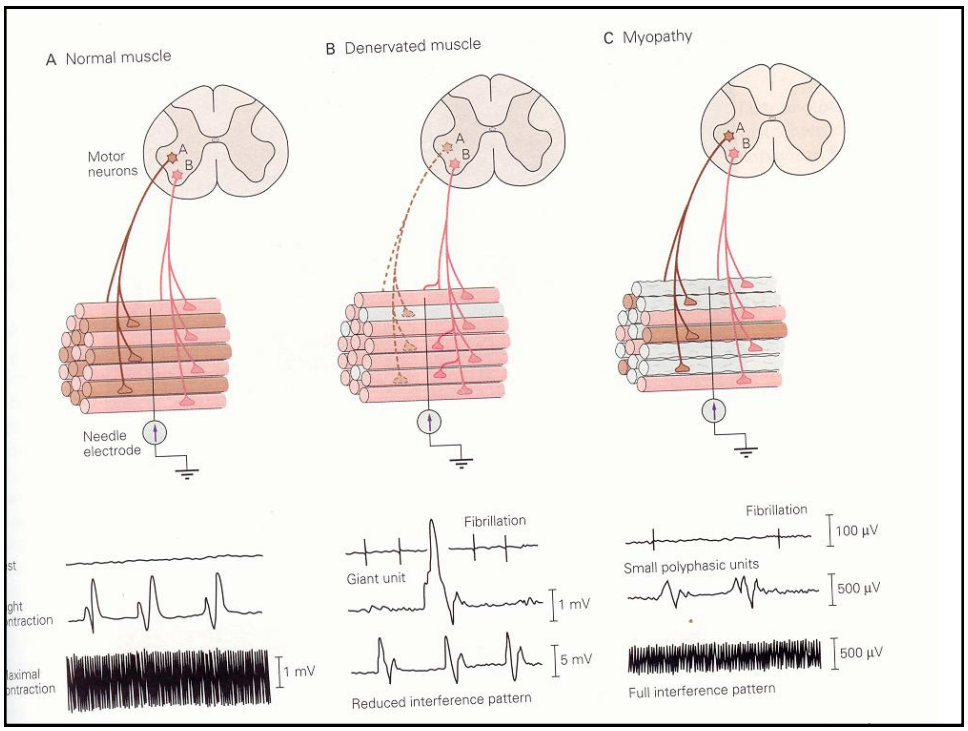
NCS/EMG
Autonomic Tests
Skin biopsies

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

Therapy	Dose	Side Effects
	FIRST-LINE	
Amitriptyline or nortriptyline	10 -100 mg po qhs	Cognitive changes, sedation, dry eyes and mouth, urinary retention, constipation
Gabapentin	300-1200 mg po tid	Cognitive changes, sedation, peripheral edema
Pregabalin	50-100 mg po tid	Cognitive changes, sedation, peripheral edema
Duloxetine	30-60 mg po qd	Cognitive changes, sedation, dry eyes, diaphoresis, nausea, diarrhea, constipation
	SECOND-LINE	
Carbamazepine	200-400 mg po tid or qid	Cognitive changes, dizziness, leukopenia, liver dysfunction
Phenytoin	200-400 mg po qhs	Cognitive changes, dizziness, liver dysfunction
	Other agent	
Capsaicin 0.025%-0.075 cream	Apply locally	Painful burning skin

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

	Nadir	Relapses?	Treatment
AIDP	Within 4 weeks	Very rare	NO steroids
CIDP	>8 weeks	Typical	Yes steroids

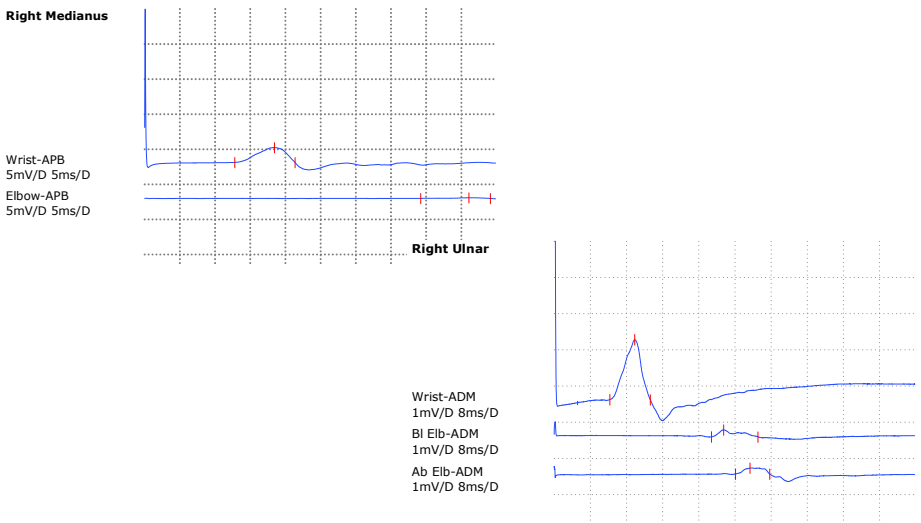
Case CL

- 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



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

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The Neuromuscular Center at VA/OHSU

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