Why is it Important to Know About Peripheral Neuropathy?

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DISCLOSURE

Relevant Financial Relationship(s)
None

Off Label Usage
None
I. Peripheral Neuropathy: Symptoms

Numbness

• Most numbness is physiologic (normal)
• In neuropathy: “tingling” numbness is more often acquired
• In neuropathy “dead” numbness is more often inherited
• Other causes of numbness: stroke, neck spondylosis, peripheral vascular disease
• Neuropathy numbness is persistent and tends to be worse at night (mostly feet)
• Painless numbness doesn’t respond to Rx
I. Peripheral Neuropathy: Symptoms

Pain

- Most limb pain comes from non-neuropathic sources: hip/knee/back DJD, immobility, plantar faciitis, phlebitis, DVT, etc
- In neuropathy: pain is often burning, electrical, crawly, and/or tight
- Neuropathy pain is usually persistent and tends to be worse at night (mostly feet)
- Neuropathy pain usually respond to Rx
I. Peripheral Neuropathy: Symptoms

Weakness

• Most symptoms of weakness are not from neuropathy (or other nervous system disease)
• Neuropathy weakness is persistent and worse in the toes and feet
• Causes of weakness (especially in sick inpatients): deconditioning, deconditioning, deconditioning, old back disease, old stroke, very rarely neuropathy BUT…
• Acute weakness symmetric from neuropathy is a medical emergency
I. Peripheral Neuropathy: Symptoms

- Numbness
  - most numbness isn’t neuropathy (but some is)

- Pain
  - most limb pain isn’t neuropathy (but some is)

- Paralysis
  - most paralysis isn’t neuropathy (but some is)
A region of myelinated fibers and unmyelinated fibers from a transverse section of the tibial nerve of a normal baboon. Osmium tetroxide fixation. x 7200. LMF = large myelinated fiber; SMF = small myelinated fiber; UMF = unmyelinated fiber.
### Conduction Velocities and Classifications of Primary Afferent Fibers

<table>
<thead>
<tr>
<th>Cutaneous Nerve</th>
<th>Muscle Nerve</th>
<th>Conduction Velocity (m/s)</th>
<th>Fiber Diameter (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aαβ</td>
<td>Group I</td>
<td>72-130</td>
<td>12-22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35-108</td>
<td>6-18</td>
</tr>
<tr>
<td></td>
<td>Group II</td>
<td>36-72</td>
<td>6-12</td>
</tr>
<tr>
<td>Aδ</td>
<td>Group III</td>
<td>3-30</td>
<td>3-7</td>
</tr>
<tr>
<td>C</td>
<td>Group IV</td>
<td>0.2-2</td>
<td>0.25-1.35</td>
</tr>
</tbody>
</table>

Primary afferent nerve fibers (feline) classified by conduction velocity and fiber diameter.
Drawing of the compound nerve action potential recorded from a mammalian saphenous sensory nerve with the Aα, Aδ, and C fiber components labeled.

HS Gasser 1941
II. Anatomy

• **Multiple fiber populations:** we have all but ignored the most numerous fibers in nerve (unmyelinated ones)

• Profound age changes: there are significant changes in structure and function of peripheral nerve with advancing years which must affect our understanding of what is normal
Meissner Corpuscles
(and small myelinated and unmyelinated fibers)
Meissner Corpuscles: Effect of Aging on Density

4 year old boy
49.3 mm²

43 year old man
7.3 mm²

76 year old woman
3.1 mm²
Meissner Corpuscles: Effect of Aging on Density (n=49)
II. Anatomy: 2 points

• Multiple fiber populations: we have all but ignored the most numerous fibers in nerve (unmyelinated ones)

• Profound age changes: there are significant changes in structure and function of peripheral nerve with advancing years which must affect our understanding of what is normal
III. Peripheral Neuropathy

- **Pattern**
  - pace of symptoms;
  - profile of deficits

- **Pathology**
  - interstitial findings;
  - nerve fiber findings

- **Pathophysiology**
  - "flavor" of NCS and EMG findings
III. Peripheral Neuropathy

Ultimate Reductionist EMG:

Low or Slow?

Fibs or Not?
Distal SMPN: Axonal

Tibial AH

ankle amp: 1.8 mV

CV 39 m/s

knee amp: 1.3 mV

1 mV

5 ms
Axonal Neuropathy

“LOW”

- CMAP amplitude $< 70\%$ of normal with normal CV & DL, no dispersion or CB & clear fibrillation

- CMAP amplitude $< 50\%$ of normal with CV 70-100\% of normal, no dispersion or CB & clear fibrillation

- SNAPs absent with normal motor NCS and clear distal fibrillation
Distal SMPN: Demyelinating
(uniform or synchronized)

Tibial AH

ankle amp: 6.1 mV

DL 7.0 ms

CV 20 m/s

knee amp: 6.1 mV

5 mV

5 ms
Demyelinating Neuropathy
(nonuniform or desynchronized)

Fibular/EDB nerve

- ankle: amp: 0.6 mV
- fibular head: amp: 0.3 mV
- knee: amp: 0.3 mV

CV 20 m/s

Ulnar/ADM nerve

- wrist: amp: 2.0; area: 6.5
- elbow: amp: 0.5; area: 1.5
- upper arm: amp: 0.3 mV
- supraclavicular: amp: 0.3 mV
- root: amp: 0.3 mV

CV 21 m/s
Demyelinating Neuropathy

“SLOW”

• CV < 70% of normal range with normal amplitude & no fibrillation

• CV < 50% of normal range with amplitude 50-100% of normal and minimal fibrillation

• supportive evidence: DL >150% normal, CB, dispersion, prolonged F wave or blink reflex latency
Neuropathy Classification

**Pathology**
- Axonal (wires)
- Demyelinating (insulation)
- Mixed

**Pathophysiology**
- Inflammatory
- Metabolic
- Inherited
- Toxic
- Vascular

*(sometimes more than one is at work in a given neuropathy)*
Anatomical pattern (multimodality)

- Distal sensorimotor peripheral neuropathy
  length dependent

- Polyradiculoneuropathy
  length independent

- Multiple mononeuropathies (multifocal, multimodality)

Modality specific

- Motor Neuronopathy (motor neuron disease)
- Sensory Neuronopathy (polyganglionopathy)
- Autonomic Neuropathy/Neuronopathy
Practical Approach to Peripheral Neuropathy

**Peripheral Neuropathy**

**Anatomical Pattern**
- DSMPN
- PRN
- M-MPLX

**Modality Specific**
- Motor
- Sensory
- Auton

**Temporal Profile**
- (Acute, chronic)

**Severity**
- (Mild, moderate, severe)

**Pathology**
- (Axonal, demyelinating, mixed, interstitial changes)
Peripheral Neuropathy
Approach to Diagnosis

- clinical manifestations (symptoms/signs)
- electrophysiology
- blood and urine studies
- imaging (hypertrophic nerves)
- cerebrospinal fluid (protein elevation)
- biopsy: nerve/skin/muscle/marrow/other
Peripheral Neuropathy
Role of EMG/NCS/± ARS

- establish pattern
- temporal profile
- severity
- pathology
Case 1

- 69 yo. female with 5 years of numbness or a sensation of “cellophane” in the feet. In the last 2 years developed ”painful feet” (8/10 intensity)
- Meds: gabapentin 600mg bid
- PMH: HTN, hyperlipidemia, & GERD, non smoker, no alcohol, no affected relatives
- Exam: BMI 29.4, BP normal, no foot deformities, no motor or gait abnormalities, sensory impaired to vibration at great toe and absent pinprick to the distal forefoot bilaterally (Neuropathy Impairment Score 4)
- Labs: CBC, B12, fasting glucose,HbA1c, LFTs ,sTSH, monoclonal protein study, anti-gliadin antibodies: normal or negative
- EMG, NCS: normal
- Quantitative sudomotor axonal testing (QSART) & Quantitative Sensory Testing (QST): abnormal
Case 1

The most likely diagnosis:

a. HSAN type I
b. diabetic neuropathy
c. amyloidosis
d. IGT neuropathy
e. Tangier disease

Two hour oral glucose tolerance test (2h-OGTT): 195 mg/dL (<200)

Small Fiber PN associated with IGT
Mild Distal Sensorimotor Peripheral Neuropathy

**Motor:**
- mild weakness of distal LE & hand muscles

**Sensory:**
- mild distal multimodality sensory loss

**Reflexes:**
- diminished distal > proximal

- BJ: 0/0
- PP: -1/-1
- JPS: 0/0
- PP: -2/-2
- AJ: -3/-3
- KJ: -1/-1
- TF: -1/-1
- V: -1/-1
Distal Sensorimotor PN

- **NCS normal**: in mild cases
- **Sensory NCS**: affected first
- **Distal > proximal gradient**: on NCS and needle exam
- If sensory NCS normal & low amplitude distal CMAP: R/O local foot disorders, root disease, sensory CB, sural sparing neuropathy, normal anatomy
Distal Sensorimotor PN

mild, chronic, axonal or mixed:

- screen for common causes: CBC, chemistries, UA, ESR, SPEP, sTSH, vitamin B12, Chest x-ray if smoker
- family history: with particulars
- toxin exposure: industrial, medicinal, avocational, environmental
Case 2

- 55 yo. male with type IDDM since age 11 who reports years of numbness, foot pain, weakness, and more recently syncope and constipation.
- Meds: gabapentin, insulin, oxycodone, metoclopramide
- PMH: ESRD with transplant, gastroparesis, severe retinopathy, CAD s/p MI, HTN, hyperlipidemia, & thyroid cancer; non smoker, no alcohol
- Exam: orthostatic hypotension, 1.5 mm nonreactive pupils, left foot ulcers, steppage gait, severe distal quadriparesis, sensory impaired to vibration/pin/touch/JPS to knees and wrists bilaterally; global hypo- to areflexia (Neuropathy Impairment Score 80)
- Labs: glucose 128, HbA1c 6.4; Hb 9.6, with B12, LFTs ,sTSH, SPEP: normal
- EMG, NCS: very low or absent limb responses with slowed NCVs and prolonged distal latencies and normal blink reflex latencies; NEE: large MUPs in distal>thigh muscles with normal hip girdle and paraspinal muscles (sacral, lumbar, and thoracic) as well as distal UE muscles
## Severe Distal Polyneuropathy

**Case 2**

<table>
<thead>
<tr>
<th>Stimulate (Record)</th>
<th>AMPLITUDE millivolts and microvolts</th>
<th>VELOCITY Meters/sec</th>
<th>DISTAL LATENCY milliseconds</th>
<th>F-WAVE LATENCY milliseconds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R  L  Normal</td>
<td>R  L  Normal</td>
<td>R  L  Normal</td>
<td>R  L  Normal</td>
</tr>
<tr>
<td>Fibular (peroneal), motor (EDB)</td>
<td>0  (≥2)</td>
<td>(≥41)</td>
<td>NR (≤6.6)</td>
<td>(≤57)</td>
</tr>
<tr>
<td>Tibial, motor (abd.hal.brevis)</td>
<td>0  (≥4)</td>
<td>(≥40)</td>
<td>NR (≤5.9)</td>
<td>(≤57)</td>
</tr>
<tr>
<td>Sural, sensory (behind malleolus)</td>
<td>0  (≥6)</td>
<td>(≥41)</td>
<td>NR (≤4.5)</td>
<td></td>
</tr>
<tr>
<td>Median, sensory (index)</td>
<td>0  (≥15)</td>
<td>(≥54)</td>
<td>NR (≤3.5)</td>
<td></td>
</tr>
<tr>
<td>Ulnar, sensory (fifth)</td>
<td>0  (≥10)</td>
<td>(≥54)</td>
<td>NR (≤3.1)</td>
<td></td>
</tr>
<tr>
<td>Median, motor (thenar)</td>
<td>0.1  (≥4)</td>
<td>22  (≥48)</td>
<td>14.2  (≤4.5)</td>
<td>(≤32)</td>
</tr>
<tr>
<td>Ulnar, motor (hypothenar)</td>
<td>0.1  (≥6)</td>
<td>23  (≥51)</td>
<td>5.2  (≤3.6)</td>
<td>(≤33)</td>
</tr>
<tr>
<td>Fibular (peroneal), motor (anterior tibial)</td>
<td>0  (≥5)</td>
<td>(≥43)</td>
<td>NR (≤6.8)</td>
<td></td>
</tr>
</tbody>
</table>

**IPSILATERAL**

<table>
<thead>
<tr>
<th>BLINK REFLEXES</th>
<th>IPSILATERAL</th>
<th>CONTRALATERAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Trigeminal, supraorbital, orbic oculi</td>
<td>R1  Normal (≤13)</td>
<td>R2 Normal (≤41)</td>
</tr>
</tbody>
</table>
Case 2

The most likely diagnosis:

a. CIDP
b. diabetic neuropathy

c. CMT1a
d. GBS
e. paraneoplastic neuropathy
# Case 2

## Severe Distal Diabetic Polyneuropathy

<table>
<thead>
<tr>
<th>Stimulate (Record)</th>
<th>AMPLITUDE millivolts and microvolts</th>
<th>VELOCITY Meters/sec</th>
<th>DISTAL LATENCY milliseconds</th>
<th>F-WAVE LATENCY milliseconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibular (peroneal), motor (EDB)</td>
<td>R 0 L (≥2) Normal</td>
<td>R (≥41) L NR</td>
<td>R L (≤6.6)</td>
<td>R L (≤57)</td>
</tr>
<tr>
<td>Tibial, motor (abd. hal. brevis)</td>
<td>R 0 L (≥4) Normal</td>
<td>R (≥40) L NR</td>
<td>R L (≤5.9)</td>
<td>R L (≤57)</td>
</tr>
<tr>
<td>Sural, sensory (behind malleolus)</td>
<td>R 0 L (≥6) Normal</td>
<td>R (≥41) L NR</td>
<td>R L (≤4.5)</td>
<td></td>
</tr>
<tr>
<td>Median, sensory (index)</td>
<td>R 0 L (≥15) Normal</td>
<td>R (≥54) L NR</td>
<td>R L (≤3.5)</td>
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</tr>
<tr>
<td>Ulnar, sensory (fifth)</td>
<td>R 0 L (≥10) Normal</td>
<td>R (≥54) L NR</td>
<td>R L (≤3.1)</td>
<td></td>
</tr>
<tr>
<td>Median, motor (thenar)</td>
<td>R 0.1 L (≥4) 22</td>
<td>R (≥48) L 14.2</td>
<td>R L (≤4.5)</td>
<td>R L (≥32)</td>
</tr>
<tr>
<td>Ulnar, motor (hypothenar)</td>
<td>R 0.1 L (≥6) 23</td>
<td>R (≥51) L 5.2</td>
<td>R L (≤3.6)</td>
<td>R L (≥33)</td>
</tr>
<tr>
<td>Fibular (peroneal), motor (anterior tibial)</td>
<td>R 0 L (≥5) 43</td>
<td>R (≥43) L NR</td>
<td>R L (≤6.8)</td>
<td></td>
</tr>
</tbody>
</table>

### Ipsilateral

<table>
<thead>
<tr>
<th>BLINK REFLEXES</th>
<th>R1 Normal</th>
<th>R2 Normal</th>
<th>R2 Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Trigeminal, supraorbital, orbic oculi</td>
<td>12.8 (≤13)</td>
<td>28.6 (≤41)</td>
<td>28.8 (≤45)</td>
</tr>
</tbody>
</table>

### Contralateral
Case 2

Severe Distal Diabetic Polyneuropathy with preservation of “blink reflexes”

(Knox and Litchy 1980)
Severe Distal Sensorimotor Peripheral Neuropathy

Motor:
sev. weakness of distal LE & hand muscles

Sensory:
distal multimodality sensory loss
steppage gait
Romberg sign

Reflexes: diminished distal > proximal

FDI: -4/-4
PP: -4/-4
V: -4/-4
JPS: -4/-4
PP: -4/-4
KJ: -4/-4
AT: -4/-4
AJ: -4/-4
TF: -4/-4
Distal Sensorimotor PN

**severe, acute or chronic:**

- **ischemic:** vasculitis
- **inflammatory:** CIDP, HIV, CMV, sarcoid, CTD, paraproteinemic, paraneoplastic
- **metabolic:** diabetes, liver dz, renal dz, thyroid dz, nutritional
- **inherited:** HMSN, Fabry, ataxia telangiectasia, porphyria, MSA, HNPP, others
- **toxic:** environmental toxins, chemotherapy, vit B6, metals, criminal, other medications
Practical Approach to Peripheral Neuropathy

PERIPHERAL NEUROPATHY

ANATOMICAL PATTERN
- DSMPN
- PRN
- M-MPLX

MODALITY SPECIFIC
- MOTOR
- SENSORY
- AUTON

TEMPORAL PROFILE
- (acute, chronic)

SEVERITY
- (mild, moderate, severe)

PATHOLOGY
- (axonal, demyelinating, mixed, interstitial changes)
Case 3

- 75 yo male with 15 days of ascending numbness and weakness in the feet, legs, and fingers
- PMH: BPH, HTN, hyperlipidemia, minimal alcohol, no antecedent infection
- Exam: BP normal, mild gait ataxia, flaccid paraparesis, loss of vibration and pin to knee level; areflexia (Neuropathy Impairment Score 38)
- Labs: CBC, B12, fasting glucose, HbA1c, LFTs, sTSH, SPEP, HbSag: negative or normal; CSF protein 97, WBC 1, RBC 0
- EMG, NCS: markedly slowed NCVs, prolonged distal, F wave, and blink reflex latencies with preserved amplitudes; EMG: mild reduced recruitment
- Treatment: admitted for observation and respiratory monitoring

Acute Inflammatory Demyelinating Polyradiculoneuropathy
Case 3

The toxic neuropathy that can mimic AIDP is:

a. amiodarone neuropathy
b. arsenical neuropathy
c. nitrofurantoin neuropathy
d. phenytoin neuropathy
e. pyridoxine neuropathy
**Motor:**
mod. to severe weakness of proximal & distal muscles

**Sensory:**
multimodality sensory loss proximal & distal areas

**Reflexes:**
Diminished or absent distal & proximal

**Motor:**
- Mass: -2/-2
- Bic: -2/-2
- FDI: -2/-2

**Sensory:**
- PP: -2/-2
- Vib: -3/-3
- JPS: -3/-3
- PP: -3/-3

**Reflexes:**
- BJ: -4/-4
- PP: -2/-2
- RF: 0/-2
- AT: -2/-2
- AJ: -4/-4
- KJ: -3/-3
- TF: -3/-3
Polyradiculoneuropathy

**acute:**

- **ischemic:** vasculitis, diabetes
- **inflammatory:** HIV, Lyme, GBS, sarcoid, PSPPSP*
- **toxic/metabolic:** lead, arsenic, critical illness
- **inherited:** porphyria, Tangier
- **non-neuropathy:** botulism, tick paralysis, MG, LES, polymyositis, others

*painful sensory polyradiculoneuropathy a/w pig slaughter plants (Daniel Lachance 2008)*
Spectrum of GBS (don’t miss it in the ED!)

- antiGD1a
- antiGM1
- antiGQ1b

AIDP
- sensory > motor

AMSAN

AMAN

AMNIN

MFS

AIDP
- motor > sensory

AIDP
- sensory = motor
Case 4

- 66 yo. male with gradual onset of sensory symptoms in the feet over months, unsteadiness, and distal flaccid weakness more in the legs than hands
- PMH: unremarkable
- Exam: moderate gait ataxia, moderate distal flaccid quadriparesis, sensory impaired to vibration to knees and wrists bilaterally, hypo- to areflexia (Neuropathy Impairment Score 61)
- Labs: CBC, B12, fasting glucose, HbA1c, LFTs, sTSH, CK, ENA antibodies: normal; SPEP/IEP: IgM kappa MGUS; antiMAG 1:20,000; CSF protein 70 mg/dL
- EMG, NCS: low amplitude responses, slowed NCVs, prolonged distal and FWLs; distal>proximal MUP enlargement, fibrillations in feet
- Bone marrow, skeletal survey, rectal bx: negative or normal
Case 4

The most likely diagnosis is:

a. amyloid neuropathy
b. chronic inflammatory demyelinating neuropathy
c. lymphomatous neuropathy
d. paraproteinemic neuropathy
e. Waldenström macroglobulinemia neuropathy
Case 4

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- EMG, NCS: low amplitude responses, slowed NCVs, prolonged distal and FWLs; distal>proximal MUP enlargement, fibrillations in feet
- Bone marrow, skeletal survey, rectal bx: negative or normal
- Treatment: Rituximab 375mg/m² (2 cycles). Over 1 year NIS 61 → 24

Paraproteinemnic Polyradiculoneuropathy with antiMAG activity
Polyradiculoneuropathy

**Chronic:**
- **ischemic:** vasculitis, diabetes
- **inflammatory:** CIDP, HIV, CMV, Lyme, sarcoid, paraprotein, paraneoplastic, connective tissue diseases
- **neoplastic:** CA/Lymph meningitis
- **toxic/metabolic:** lead, arsenic, RöRx
- **inherited:** porphyria, Tangier
Polyradiculoneuropathy

Nerve conduction studies:
- examine proximal segments
- less helpful if purely axonal polyradiculopathy

Needle examination:
- changes in proximal & distal muscles (NOT just in paraspinals!)
Practical Approach to Peripheral Neuropathy

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TEMPORAL PROFILE
- (acute, chronic)

SEVERITY
- (mild, moderate, severe)

PATHOLOGY
- (axonal, demyelinating, mixed, interstitial changes)
Case 5

- 61 yo. male with recurrent right foot drop followed by insidious onset of left hand weakness, unresponsive to IVlg
- PMH: Colon polyp, hyperlipidemia, hypercalcemia; father had bilateral foot drops in his late 70s
- Exam: right foot drop with normal ankle inversion, intrinsic left and right hand muscle weakness, sensory impaired to vibration at ankles and absent pinprick to the distal forefoot bilaterally
- Labs: CBC, B12, fasting glucose, HbA1c, LFTs, sTSH, SPEP: normal
- EMG, NCS: low amplitude right fibular and ulnar CMAPs with slowed NCVs and disproportionate prolongation of motor distal latencies
Case 5

The most likely diagnosis is:

a. vasculitic neuropathy
b. multifocal motor neuropathy
c. spinal muscular atrophy
d. polyglucosan body disease
e. inherited tendency to pressure palsies
Case 5

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- Exam: right foot drop with normal ankle inversion, intrinsic left and right hand muscle weakness, sensory impaired to vibration at ankles and absent pinprick to the distal forefoot bilaterally
- Labs: CBC, B12, fasting glucose,HbA1c, LFTs ,sTSH, SPEP: normal
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Genetic testing: deletion of the PMP22 locus on 17p11.2

Inherited Tendency to Pressure Palsies (PMP22 deletion)
**Motor:** severe weakness left hand/wrist extensors, right knee flexor & ankle dorsiflexor muscles

**Sensory:** multimodality sensory loss in distribution of left radial and right sciatic nerves
Multiple Mononeuropathies

- **ischemic:** vasculitis, diabetes
- **inflammatory:** CIDP (MADSAM), HIV, zoster, Lyme, leprosy, sarcoid, paraneoplastic
- **neoplastic:** lymphoma, NFT
- **toxic/metabolic:** lead, arsenic
- **inherited:** HNPP, porphyria, Tangier
Practical Approach to Peripheral Neuropathy

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**TEMPORAL PROFILE**
- (acute, chronic)

**SEVERITY**
- (mild, moderate, severe)

**PATHOLOGY**
- (axonal, demyelinating, mixed, interstitial changes)
Motor Neuronopathy/Neuropathy

Manifestations

• weakness, atrophy, cramps, fasciculations

• absence of (or only minor) sensory, autonomic deficits

• multifocal or diffuse distribution
Case 6

- 65 yo. female with several months of difficulty spreading the right fingers followed weeks later by problems extending the left fingers
- PMH: non smoker, 4 glasses of wine weekly, no family history of neurologic disease
- Exam: severe weakness in the right ulnar and left radial territories, normal sensation, reflexes, gait, station, coordination
- Labs: CBC, B12, fasting glucose, HbA1c, LFTs, sTSH, SPEP, anti-GM1 ganglioside antibodies: normal or negative
- EMG, NCS: partial right median and complete right ulnar and left radial motor conduction blocks, relative preservation of corresponding SNAPs; low grade fibs in most affected muscles, few MUPs under voluntary activation in involved territories
- Treatment: IVIg
- Outcome: marked improvement in hand strength bilaterally
Case 6

The most likely diagnosis is:

a. vasculitic neuropathy
b. multifocal motor neuropathy
c. spinal muscular atrophy
d. polyglucosan body disease
e. inherited tendency to pressure palsies
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Multifocal Motor Neuropathy with Conduction Block
Multifocal Motor Neuropathy/Motor Neuronopathy

Motor:
Asymmetric weakness, atrophy & fasciculations
- Proximal & distal left arm
- Distal right arm & legs

Sensory:
Normal

Reflexes:
Asymmetric loss

VIB: 0/0
JPS: 0/0
PP: 0/0

BJ: 0/-2
KJ: 0/-2
AJ: 0/-3
Motor Neuronopathy/Neuropathy

Acute:

- Poliomyelitis (WNV, enterovirus) GBS, (Botulism), gold (old RA Rx)

Chronic:

- motor neuron disease
- MMN with CB
- CIDP, paraneoplastic, paraproteinemnic, lead
Motor Neuronopathy

Nerve conduction studies:
• “axonal” pattern (except MMN): sensory NCS normal
• symmetric or asymmetric

Needle examination:
• MUP changes, fibrillation & fasciculation potentials often in clinically unaffected muscles
Sensory Neuropathy:

3 Sub-patterns

- length dependent sensory neuropathy
- sensory neuronopathy/polyganglionopathy
- spinocerebellar syndrome
Length Dependent Sensory Neuropathy

Small fiber

• Similar differential to DSMPN (idiopathic, vasculitis, connective tissue disease, toxic including B6, diabetes, uremia, HSN)

Large fiber

• Less likely to be idiopathic: CIDP (DADS*), B12, diabetes, leprosy, thalidomide, cis-platinum, HSN, etc.

*Distal acquired demyelinating symmetric
Length Dependent Sensory Neuropathy

Small fiber

• NCS typically normal

• TST, QSART other autonomic tests helpful in many because of subclinical autonomic involvement, skin punch bx, CHEPS

• Beware of CNS disease!!! (thalamus, etc.)

Large fiber

• NCS abnormal in length dependent pattern

• Beware of CNS disease if NCS not significantly abnormal for age in setting of large fiber clinical deficit!!! (dorsal columns, etc.)
Small Nerve Fiber Pathology

Epidermal skin biopsy: significantly reduced nerve fiber density in the right calf of 4.25/mm (normal >5) with a normal nerve fiber density in the thigh of 10.13/mm (normal >8).
CHEPS
(Contact Heat Evoked Potential Stimulator)

Atherton et al. *BMC Neurology* 2007;7:21
Case 7

- 39 yo. female with 1 month of numbness in the legs spreading over weeks to thighs, arms, face, and perineum associated with 25 lb weight loss
- PMH: 10 pack year history of smoking, no alcohol, no drugs
- Exam: gait ataxia, asymmetric sensory impairment to pinprick and in the toes to vibration; normal strength, global areflexia
- Labs: CBC, B12, fasting glucose, HbA1c, LFTs, sTSH, SPEP, HIV serology, HBV antibodies: normal or negative; ANNA1 antibody (anti-HU): positive at >1:7000
- EMG, NCS: low amplitude to absent SNAPs, normal blinks, normal EMG
- Quantitative sudomotor axonal testing (QSART) & Quantitative Sensory Testing (QST): abnormal
- Chest xray: 2 cm mass in right lower lobe, confirmed on chest CT
- Biopsy: small cell carcinoma of the lung

Malignant Inflammatory Sensory Polyganglionopathy
Case 7

What % of malignancies causing MISP originate in the lung?

a. 0-10%

b. 20-30%

c. 40-50%

d. 60-70%

e. 80-90%
**Sensory Polyganglionopathy/Neuronopathy**

**Motor:**
Normal (except poor activation)

**Sensory:**
Loss of large & small fiber modalities
Often multifocal early, diffuse late or early in some cases
Pseudoathetosis

**Reflexes:**
Severe loss in symptomatic areas

- **VIB:** -3/-4
- **JPS:** -3/-4
- **PP:** -3/-4
- **BJ:** 0/-4
- **KJ:** -1/-4
- **AJ:** -2/-4
- **CR:** -4/0
Sensory Polyganglionopathy/Neuronopathy

Nerve conduction studies

- low amplitude or absent SNAPS
- proximal and distal
- normal motor NCS

Needle examination

- poor activation - loss of proprioception
Sensory Polyganglionopathy/Neuronopathy

- **Most common:**
  - Sjögren, paraneoplastic (small cell lung > breast, lymphoma)

- **Less common** (with rare to spared motor dysfunction):
  - Lyme, Parsonage-Turner (BPN), vasculitis, syphilis
Spinocerebellar Syndrome

- Large fiber sensory deficit with or without cerebellar ataxia
- Loss of SNAPS, abnormal SEPS
- Motor nerve involved to varying degree
- Causes: nitrous oxide, Vit B12 or Vit E deficiency, syphilis, SCAs (4 and 25), leukodystrophy, Biemond ataxia (rare)
Autonomic Neuropathy

- Symptoms/signs of abnormal regulation of sweating, vascular reflexes, GI/GU motility, pupillary

- Absence of CNS signs or pure IOH

- Usually some clinical evidence of a mild DSMPN
Autonomic Neuropathy

Nerve conduction studies

• Normal or mild distal “axonal” pattern
• TST, QSART, vascular, GI/GU motility studies abnormal

Needle examination:

• Minimal MUP changes +/- fibrillation potentials in distal muscles
Autonomic Neuropathy

• **Inflammatory**: AIDP, amyloid, paraneoplastic, ?POTS

• **Toxic/metabolic**: thallium, vincristine, ETOH, diabetes

• **Inherited**: HSAN, MSA, porphyria, Tangier, mitochondrial disease
Practical Approach to Peripheral Neuropathy

PERIPHERAL NEUROPATHY

ANATOMICAL PATTERN
- DSMPN
- PRN
- M-MPLX

MODALITY SPECIFIC
- MOTOR
- SENSORY
- AUTON

TEMPORAL PROFILE
- (acute, chronic)

SEVERITY
- (mild, moderate, severe)

PATHOLOGY
- (axonal, demyelinating, mixed, interstitial changes)
IV. Do I Really Need to Worry About this Neuropathy?

<table>
<thead>
<tr>
<th>TABLE 2 Classification of Charcot-Marie-Tooth disease</th>
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<tbody>
<tr>
<td><strong>Type</strong></td>
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<tr>
<td>----------</td>
</tr>
<tr>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>CMT1 (AD CMT1)</td>
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<tr>
<td>CMT1A</td>
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<tr>
<td>Dp 17p (PMP22)</td>
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<tr>
<td>PMP22 (point mutation)</td>
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<tr>
<td>CMT1B</td>
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<td>MPZ</td>
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<td>CMT1C</td>
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<tr>
<td>LITAF</td>
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<td>CMT1D</td>
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<tr>
<td>EGR2</td>
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<tr>
<td>CMT1</td>
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<tr>
<td>NEFL</td>
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<tr>
<td>Hereditary neuropathy with liability to pressure palsies (HNPP)</td>
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<tr>
<td>HNPP</td>
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<tr>
<td>PMP-22 (point mutation)</td>
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<tr>
<td>X linked CMT1 (CMT1X)</td>
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<tr>
<td>CMT1X</td>
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<tr>
<td>GJB1</td>
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<tr>
<td>Autosomal recessive CMT1 (AR CMT1)</td>
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<tr>
<td>CMT4A</td>
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<td>Autosomal dominant CMT2 (AD CMT2)</td>
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<td>Autosomal recessive CMT 2 (AR CMT2)</td>
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<tr>
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<td>LMNA</td>
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<tr>
<td>ARCM2B</td>
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<td>MED25</td>
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<td>MED25</td>
</tr>
</tbody>
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AD, autosomal dominant; AR, autosomal recessive; Dup, duplication; Del, deletion; PMP-22, peripheral myelin protein 22; MPZ myelin protein zero; LITAF, lipopolysaccharide-induced tumour necrosis factor; EGR2, early growth response 2; GJB1, gap junction protein, beta 1; GDAP1, ganglioside-induced differentiation-associated protein 1; MTM12, myotubularin-related protein 2; MTM13, myotubularin-related protein 13; KIAA1885, KIAA1885 protein; NDRG1, N-myc downstream-regulated gene 1; PRX, peroxin; CTD1, CTD phosphatase, subunit 1; KIF1B, kinesin family member 1B-B; MFN2, mitofusin 2; RAB7, RAS-associated protein RAB7; GARS, glycol-RNA synthetase; NEFL, neurofilament, light polypeptide 68 kDa; HSP 27, heat shock 27 kDa protein 1; HSP 22, heat shock 22 kDa protein 8; LMNA, lamin A/C; MED25, mediator of RNA polymerase II, subunit 25; DN2-M2, dynamin 2; YARS, tyrosyl-RNA synthetase; SEPT9, septin 9;
IV. Do I Really Need to Worry About this Neuropathy?

Is it one of the 39 most common causes of inherited neuropathy?
The Three Lists of Neuropathy

- **Common causes** (you would be embarrassed to miss)

- **Treatable causes** (the patient would feel bad if you missed)

- **Dangerous causes** (your lawyer would feel bad if you missed)
The Three Lists of Neuropathy

- **Common causes** (you would be embarrassed to miss)

  Diabetes
  Impaired glucose tolerance (75g 2 hour OGTT – a pain)
  Vitamin B12 deficiency (B12, MMA, homocysteine, N2O)
  Hypothyroidism
  HIV infection
The Three Lists of Neuropathy

• Treatable causes (the patient would feel bad if you missed)

Diabetes
Impaired glucose tolerance (75g 2 hour OGTT)
Vitamin B12 deficiency (B12, MMA, homocysteine, N₂O exposure)
Hypothyroidism
HIV infection
Vasculitis (PAN, Wegener, HCV, Sjogren, GCA, etc)
Toxic (B6, chemo, antibiotics, metals, solvents, Zn, etc)
Copper deficiency
Immune (CIDP, GBS, MMN, MGUS, etc)
Lyme disease
The Three Lists of Neuropathy

• Dangerous causes (your lawyer would feel bad if you missed)

Diabetes
Impaired glucose tolerance (75g 2 hour OGTT)
Vitamin B12 deficiency (B12, MMA, homocysteine, N₂O exposure)
Hypothyroidism
HIV infection
Vasculitis (PAN, Wegener, HCV, Sjogren, GCA, etc)
Toxic (B6, chemo, antibiotics, metals, solvents, Zn, etc)
Copper deficiency
Immune (CIDP, GBS, MMN, MGUS, etc)
Lyme disease
Fulminant GBS (+ICU Neuromyopathy, Tick paralysis, etc)
Amyloid
Paraneoplastic (lymphoma, POEMS, SCCL, etc)
Arsenic
Porphyria