Evaluation and Treatment of Peripheral Neuropathy

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Goals

• Differentiate types of peripheral neuropathy

• Effectively work-up distal symmetrical PN

• Treatment of neuropathic pain
Disclosures

• None
Case – “Neuropathy”

- 31 y/o woman referred for neuropathy
  - 3+ yr h/o episodic, fleeting limb numbness
    - Hands / feet occasionally “fall asleep”
  - PHM, ROS, Exam all normal/negative
  - Has seen 2 neurologists that performed EMGs with Dx of:
    - PN of bilat LEs affecting the sensory system
    - Early, predominantly sensory peripheral polyneuropathy
Case – “Neuropathy”

• Both EMGs were misinterpreted
  – 1) Limb cooling affected sensory study
  – 2) Poor technique
• Misdiagnosis of PN led to wasteful testing
  – 3 limb EMG (not indicated)
  – 2 brain MRIs
  – 1 C-spine MRI
  – Extensive/expensive lab testing
    • Urine & serum heavy metals
    • GM1 antibodies x 2
    • MAG antibodies x 2
    • B12
    • Methylmalonic acid
    • TSH & FTI
Case – “Neuropathy”

- Anti-DS DNA antibody
- RNP AB
- Anti-Smith AB
- Anti-SSA & Anti-SSB ABs
- SCL70 AB
- Thyroperoxidase AB
- Complement levels
- Rheumatoid Factor
- GQ1B AB
- GD1A AB
- GD1B AB
- Anti-Hu AB
- Anti-Ri AB
- Anti-Yo AB
- Lyme AB
- Folate
- ESR
- CMP & CBC
Case – “Neuropathy”

• Shotgun approach to PN workup
  – dangerous
  – expensive
  – misdiagnosis of PN

• Need an organized approach to neuropathy
Stepwise Evaluation of PN

1. Characterize the neuropathy
   – “what, when, where and what setting?”

2. Classify into acquired or inherited
   – Acquired, inherited or idiopathic?
     • Avoid the “shotgun” approach

3. Emphasize the red flags of neuropathy
   – What warrants aggressive evaluation?

4. What’s the work-up if no red flags?
### Acquired

**“M I N I”**

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### Comments

- "Garden-variety", gradual onset neuropathy
- Vasculitis - mononeuritis multiplex (painful); GBS/CIDP- prox & distal motor & sens
- Presentations differ based on whether paraneoplastic, paraproteinemic, compressive
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Motor: weakness, atrophy, cramps, fasciculations
- All large fiber (A fiber, myelinated 6-12µ, 35-75m/sec)

Sensory:
- Large fiber: (Aβ fiber, myelinated 6-12µ, 35-75m/sec)
  - Vibration, JP
  - Areflexia
  - Sensory ataxia
  - Negative sensory symptoms
- Small fiber: (Aδ fiber, myelinated 1-5µ, 5-30m/sec)
  - (C fiber, unmyelinated 0.2–1.5µ, 1-2m/sec)
  - PP, temp
  - Dysesthesias, burning/stinging sensory complaints

Autonomic: lightheadedness, diarrhea, constipation, impotence, bladder, postprandial bloating, pupils, sweating, dry mouth/eyes
Sensory Complaints
Feet feel odd
Sensation is Subjective

My feet are just freezing!

Buddy, You think You have problems!
Weakness
Autonomic Nervous System Involvement in Neuropathy

• Diabetes mellitus
• Amyloidosis
• Guillain-Barre Syndrome
• Paraneoplastic
• Porphyria
• Idiopathic pandysautonomia, likely autoimmune
• Autoimmune autonomic neuropathy
• Vincristine induced
• HIV-related autonomic neuropathy (late)
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“Where?”

• Focal
  – Cranial neuropathy, Mononeuropathy, Radiculopathy

• Segmental
  – Plexopathy, Motor neuron disease

• Multifocal
  – Mononeuritis multiplex, Neuronopathy

• Widespread
  – Distal symmetrical
    • DM, Idiopathic PN
  – Proximal
    • Myopathy, Porphyria
  – Distal & proximal
    • CIDP, Myelopathy
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“When?”

- **Acute**
  - Spontaneous painful sensorimotor mononeuropathy
  - Acute onset weakness and paresthesias following a URI

- **Subacute**
  - Unilateral hand and forearm weakness for 2 weeks
  - Difficulty walking due to weakness for 3 weeks

- **Chronic**
  - Weakness and sensory loss for 3 years

- **Insidious**
  - Tripping over feet since high school, never ran that well
  - Numb feet, doesn’t remember onset
### Acquired

#### Metabolic
- Sensory

#### Immune
- Variable, most often sensorimotor
- Not insidious (e.g. acute/subacute)

#### Neoplastic
- Not distal, symmetrical (e.g. proximal, asymmetrical)

#### Infectious
- Sxs or risk factors for infection?

### Inherited

#### Motor or sensorimotor
- Distal, symmetrical
- Insidious

#### Family History, Foot deformities (high arches, hammer toes, Charcot joints)

### Comments

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- Presentations differ based on whether paraneoplastic, paraproteinemic, compressive

### Differential Diagnosis

#### Acquired
- Diabetic
- Pre-diabetes
- Uremic
- Alcohol
- Vitamin B12 deficiency
- Vitamin B1 deficiency
- Hypothyroidism
- Medications
- Heavy Metals
- Other toxins

#### Inherited
- Charcot-Marie-Tooth (CMT)
- Hereditary Sensory Neuropathies (HSN or HSAN)
- Other less common inherited neuropathies
“What Setting?”

- Tobacco
- Weight loss
- Rheumatologic complaints – eg polyarthralgias, dry eyes, abdominal pain, – weight loss, rash
- Preceding URI or GI illness?
- Malnutrition
- Critically ill hospitalized patient
- DM
- Alcohol
- Family history of PN
- Travel exposure
- Onset insidious in a healthy individual?
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- **Acquired**
  - Motor or sensorimotor
  - Distal, symmetrical
  - Insidious

- **Inherited**
  - Family History, Foot deformities (high arches, hammer toes, Charcot joints)

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- **Other less common inherited neuropathies**
  - Charcot-Marie-Tooth (CMT)
  - Hereditary Sensory Neuropathies (HSN or HSAN)
“W’s of Neuropathy”

• 44 y/o man with:
  – Numb feet with paresthesias in Jan
  – Numbness ascended to level of thighs by Feb
  – ROS – didn’t feel right
  – Tingling in 4\textsuperscript{th}/5\textsuperscript{th} digits by March
  – Paresthesias evolved into burning dysesthesias
    followed by onset of pain in the trunk and face
“W’s of Neuropathy”

• PMH
  – Pneumonia in Jan before Sx’s

• ROS
  – Felt sick

• SH
  – Smokes 1 ppd x 30 yrs

• FH
  – Negative

• Exam
  – Widespread sensory loss arms, legs, face; sensory ataxia, areflexia
  – Normal strength
“W’s of Neuropathy”?

• What?
  – Sensory
    • Large & small fibers
    • Sensory ataxia
    • Areflexia
  – Where?
    • Entire body (not distal symmetric)
• When?
  – Subacute onset (over days, progressing over 3 months)
• What setting?
  – Preceding URI
  – H/o tobacco
  – Feels ill
“W’s of Neuropathy”

• PLAN
  – Neurology referral
    • EMG
    • LP
    • CT Chest
    • Serum immunofixation
    • Antineuronal antibodies
  – Dx: Sensory CIDP
‘W’s of Neuropathy’

• 63 y/o smoker with 12 weeks of:
  – Constipation
  – Lightheaded on standing
  – Impotence
  – Numbness in hands and feet

• Exam
  – Stocking-glove sensory loss
  – Distal areflexia
  – Orthostatic hypotension
  – Normal strength
“W’s of Neuropathy”

• **What?**
  - Sensory
    - Large & small fibers
    - Distal areflexia
  - Autonomic
    - Orthostasis
    - Impotence

• **Where?**
  - Distal symmetrical

• **When?**
  - Subacute onset (over 3 months)

• **What setting?**
  - H/o tobacco
“W’s of Neuropathy”

• PLAN
  – Neurology referral
    • EMG
    • Autonomic Test
    • Nerve biopsy
    • Serum immunofixation
    • 24 hour urine immunofixation
  – Dx: Amyloidosis
Red Flags

1. Proximal involvement/ non-length dependent
2. Ataxia
3. Finger joint position loss (severe ataxia)
4. Autonomic Nervous System Involvement
5. Multifocality
6. Setting of smoking
7. Setting of concerning ROS
8. Acute or subacute onset
Common Clinical Scenarios
Clinical Presentation

Sensory Loss
Distal Symmetric Polyneuropathy

- What
  - Small > Large fiber Sensory
- Where
  - Distal symmetrical
- When
  - Insidious, slowly progressive
- What Setting
  - Diabetes
    - 10% of patients have a neuropathic condition not related to DM
      - Other neuropathy (alcohol, inherited, paraproteinemic, amyloid)
      - Lumbar radiculopathy or spinal stenosis
- Red flags?
- What is a cost effective workup?

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<td>Charcot-Marie-Tooth (CMT) Hereditary Sensory Neuropathies (HSN or HSAN) Other less common inherited neuropathies</td>
<td>Hepatitis C e.g. HCV-cryoglobulin Lyme HIV Sarcoïdosis West Nile Poliomyelitis Syphilis</td>
</tr>
</tbody>
</table>
Distal Symmetric Polyneuropathy

- Fasting blood glucose = 130 mg/dl
- 2 hr 75 gram OGTT = 210 mg/dl
- B₁₂
- TSH
- BUN/Cr
- EMG c/w sensorimotor PN
- Autonomic test: decreased distal sweat
- Dx
  - Diabetic polyneuropathy
Distal Symmetric Polyneuropathy

• Dx known 74-82% of patients

• Highest Yield Evaluation
  – Glucose screening (11%)
    • Glucose tolerance test- increases yield
  – Serum Immunofixation (9%)
    • More sensitive than SPEP
  – Vitamin B12 (3.6%)
    • Methylmalonic acid and homocysteine
      – 5-10% of patients with B12 200-500 pg/dL
# Definitions

1. **DM**
   - Fasting blood glucose $\geq 126$ mg/dl
   - 2 hr glucose $\geq 200$mg/dl on 75-g OGTT

2. **Impaired fasting glucose**
   - Fasting blood glucose 101-125 mg/dl

3. **Impaired glucose tolerance**
   - 2 hr glucose 140-199 mg/dl on 75-g OGTT
89 patients w/ idiopathic PN

- 28 pts (31%) DM
- 12 pts (13%) IGT
- 3 pts (3%) IFG

-------------------------

- 43 pts (48%) abnormal glucose metabolism
- 2 hr OGTT is the most sensitive measure of demonstrating abnormal glucose metabolism in cases of idiopathic PN

Value of OGTT in PN Work-Up

- 100 patients with idiopathic PN (previously screened for DM)
  - 2003 Revised ADA Criteria
    - 61% normal glucose metabolism
    - 39% abnormal glucose metabolism
      - 36% impaired fasting glucose
      - 3% diabetes mellitus
  - 2hr-OGTT (23 out of 61 patients)
    - 38% normal glucose metabolism
    - 62% abnormal glucose metabolism (37% increase Dx)
      - 38% impaired glucose tolerance
      - 24% diabetes mellitus

Clinical Scenarios

• 70 y/o man with numbness and tingling in feet for 10 years. Does not recall onset, not sure if it’s progressing

• PMH
  – Obese, chronic back pain

• ROS
  – Walking hurts feet

• Exam
  – Stocking sensory loss to pin, temperature, vibration, absent ankle jerks
Clinical Scenarios

- **What**
  - Small / Large fiber, Sensory
- **Where**
  - Distal symmetrical
- **When**
  - Chronic
- **What setting**
  - Obese, back pain
- **Red flags?**
- **What is a cost effective workup?**
Clinical Scenarios

- Fasting blood glucose = 90 mg/dl
- 2 hr 75 gram OGTT = 100 mg/dl
- B12
- TSH
- BUN/Cr
- EMG – Sural sensory normal.
- Chronic neurogenic changes L5/S1 muscles bilaterally
- Autonomic test - normal
- Dx
  - Chronic, inactive bilateral L5/S1 radics
Dermatome Map
Clinical Scenarios

- 70 yr old man with burning stinging pain in feet for 10 years. Onset insidious, slowly progressive
- PMH
  - Obese
- SH
  - Several martinis per day
- ROS
  - Walking hurts feet
- Exam
  - Stocking sensory loss to pin & temperature
  - Reflexes normal
Clinical Scenarios

• What
  – Small fiber, Sensory
• Where
  – Distal symmetrical
• When
  – Insidious, slowly progressive
• What setting
  – Obese, ETOH
• Red flags?
• What is a cost effective workup?
Clinical Scenarios

- Fasting blood glucose = 85 mg/dl
- 75 gram 2 hr OGTT = 90 mg/dl
- B12
- TSH
- BUN/Cr
- EMG – normal
- Autonomic test – decreased distal sweat
- Dx
  - Alcohol related small fiber sensory PN
For many reasons, I prefer... marijuana over alcohol. Does that make me a bad person?

RegulateMarijuana.org
Idiopathic Polyneuropathy

- Late adult onset
- Symmetrical
- Very gradual or insidious onset
- Axon loss
- Behaves like metb/tox/vitamin but work-up negative
Clinical Scenario

• 25yo presented with 2-3yrs of fatigue during exercise, leg cramps, no sensory complaints
• 2yr hx of progressive foot deformity
• FHx of foot deformities in father and sister
• Exam:
  – Mild distal atrophy in foot and hands with mild weakness
  – Reflexes were reduced
  – Reduced sensation to vibration in feet
Clinical Scenario

• What
  – Motor; Large fiber; painless

• Where
  – Distal Symmetric

• When
  – Insidious

• What Setting
  – Foot Deformity
Clinical Scenario

- EMG-
  - Uniform Demyelination/Slowing of all motor nerves; Absent sensory potentials

- Dx
  - Inherited Neuropathy- CMT1/ HMSN1A
Genetic Testing

Neurology 2008 AAN Guidelines
AAN Guidelines 2009

• Distal symmetrical PN
  – Fasting blood glucose
  – 75 gram 2 hour OGTT if FBG negative
  – Vit B12, homocysteine, & MMA
    • (↑ 5-10% detection where B12 200-500)
  – Serum immunofixation
  – EMG
  – Autonomic test
    • 75-90% sensitive small fiber neuropathy
  – Skin biopsy may be useful
Treatment of Painful Diabetic Neuropathy

• 16% of all patients with DM
• 39% are untreated
• Uniform cause of neuropathic pain to study
• At best 11-30% improvement
# Treatment of Painful Diabetic Neuropathy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Anti-epileptic</th>
<th>Anti-depressant</th>
<th>Opioids</th>
<th>Other</th>
<th>Non-Rx</th>
<th>Doesn’t Work</th>
<th>Don’t Know</th>
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</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>11-13%</td>
<td>Venlafaxine +add on 18-23%</td>
<td>Dextromethorphan 16%</td>
<td>Capsaicin 40%</td>
<td>Electrical Nerve Stim. (TENS) 11-42%</td>
<td>Lamictal, Trileptal, Vimpat</td>
<td>Other TCA’s, fluoxetine</td>
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<tr>
<td>Gabapentin</td>
<td>11%</td>
<td>Duloxetine 8-13%</td>
<td>Morphine 15%</td>
<td>Lidoderm Patch 20-30%</td>
<td>Clonidine, Mexiletine, pentoxifylline</td>
<td>A-lipoic acid</td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>27-30%</td>
<td>Amitriptyline 20-63%</td>
<td>Tramadol 16-20%</td>
<td>Laser Treatment</td>
<td>Surgical Decompression</td>
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<tr>
<td>Oxycodone</td>
<td>9-27%</td>
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<td>Magnets</td>
<td>Isosorbide dinitrate</td>
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<tr>
<td>* Develop chronic pain syndromes and tolerance</td>
<td>Reiki therapy</td>
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<td></td>
<td></td>
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<td>Neurology 2011 AAN Guidelines</td>
<td></td>
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</tbody>
</table>
Lifestyle Intervention

• 32 patients with IGT and neuropathy

• 1yr diet and exercise intervention
  – Improved nerve fiber density
  – Improved pain

Smith et al Diabetes Care 2006
The change in IENFD for each patient from the baseline visit to the 12-month visit is displayed for the distal leg (A) and the proximal thigh (B).

Smith A G et al. Dia Care 2006;29:1294-1299

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There was a significant correlation between improvement in proximal IENFD and improvement in pain assessed by the 100-mm VAS (Pearson correlation coefficient $-0.4$, $P < 0.05$).

Smith A G et al. Dia Care 2006;29:1294-1299
Top Five Take-home Points

1. Characterize the neuropathy
2. Classify into acquired or inherited
3. Cost-effective workup for distal symmetrical PN
4. Look for the red flags – neurology referral
5. EMG and autonomic tests are valuable
The End
References