Polyneuropathy
(previously known as Peripheral Neuropathy)

Suraj Achar, MD, FAAFP

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Learning Objectives
1. Perform evidence-based differential diagnosis to differentiate peripheral neuropathy from other conditions with similar symptoms.
2. Counsel patients on how to make healthy behavior changes, including adopting a healthy diet, engaging in regular exercising, limiting heavy alcohol consumption and avoiding exposure to toxic substances.
3. Develop an evidence-based treatment plan, including pharmacologic and non-pharmacologic options, for patients with neuropathic pain.
Epidemiology

- 20 million
- Mononeuropathy (local trauma or compression i.e. CTS)
- Polyneuropathy is better term since does not include radiculopathy
- Etiology
  - DM: 44%
  - Alcoholism
  - NASH
  - Toxicity from chemotherapy

Family Medicine vs. Specialist?

- Do we always need an EMG/NCV?
- Can labs be helpful?

3 Cases: JAMA: clinical reviews

1. DM for years, + neuropathy, Ignored treatments
   1. Thought he was dying of flu—please also check my foot because it is weeping
   2. “Odd Tingling sensation in my feet, also getting numb in the feet”
      1. You have DM—not!
   3. Back Pain
      1. Serious leg pain that limited ambulation
      2. Usually worse on left leg than right

3 JAMA Patients

1. Came to ED for Flu
   - Dx: Foot infection—gas gangrene and sepsis
   - Had been Dx with DM for 15 years and even with neuropathy but had not complied with Rx and FU
   - “Feet belong to someone else”
2. Ignored symptoms because of slow
   - No DM!
   - “Feet like you are wearing 12 athletic socks, feels like walking on pillows”
   - Long history of Back Pain
3. Difficulty ambulating
   - His back symptoms were overshadowed by his leg pain
   - L leg worse than R

AES POLL QUESTION

Which is not a symptom of PN?

1) Numbness
2) Symptoms only on one side
3) Muscle weakness, wasting and even paralysis
4) Allodynia
5) Fasciculation's

National Institute of Neurological Disease and Stroke (NINDS) NcbIn. Peripheral Neuropathy Fact Sheet. NIH Publication No. 04-4853 2011;
**Natural history**

- **DM type 2**
  - Prevalence with NCV
  - 8% vs 2% gen pop
  - After 10 years (NCV abnormalities)
  - 42% of DM
  - 6% of controls

**Alcoholism**

- **Uremia**


- Evolve slowly, related to length of the nerve
- > 50% of DPN is asymptomatic
- Slowly progressive tingling and numbness
- feet and progresses up the leg and then may go to hands

**How to examine for sensory loss**

- Large sensory nerve fibers enclosed in myelin sheath: Stocking/glove
- Need 2 tests according to ADA
  - **Monofilament**
    - Screening test
    - Vibration 125 Hz
    - Hit as hard as you can
    - Place it on great toe, count seconds that pt can feel (product)
    - More than 5 sec, then discard monofilament
    - More sensitive than Monofilament
  - **Reflexes**
    - Loss of Ankle dorsiflexion? (radiculopathy)
  - **Pin prick**
  - **Temperature**

**Time course → How does it help for DX of the 3 Pts?**

**Acute: sudden in weeks!**

- Toxins and Porphyria
  - Pain >>> Numbness or tingling
- Guillain-Barre syndrome (immune attack)
  - Progress rapidly and resolve slowly
  - Motor > Sensory
  - Be careful with Cervical spinal stenosis!

**Chronic: months to years!**

- Hereditary
  - No paresthesia's or pain
- Diabetic Peripheral neuropathy
  - Why ascending pattern?
  - When neuropathy reaches the knees where does it go?

**Clanging Tuning Fork Test**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Diabetic Foot Ulcer</th>
<th>CTF score + monofilament Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>148</td>
<td>&lt;8 sec</td>
<td>32%</td>
</tr>
<tr>
<td>122</td>
<td>&lt;4 sec</td>
<td>38%</td>
</tr>
<tr>
<td>49</td>
<td>0 sec</td>
<td>67%</td>
</tr>
<tr>
<td>21</td>
<td>&lt;4sec (100%)</td>
<td>76%</td>
</tr>
</tbody>
</table>

**JAMA pts: How dx?**

- According to damage
  - Mono vs poly
  - Axon
  - Myelin sheath
- Motor/Sensory/Autonomic
- Acute vs chronic?

- **Glut:**
  - Acute
  - Demyelinating
  - Affects motor → weakness
  - Sensory spared early

Classify PN >100 (confusing)
AES POLL QUESTION
Which is not consistent with a motor nerve involvement?
1) Fasciculation's
2) Painful cramps
3) Inability to sweat
4) Atrophy
5) Decreased reflexes

Should laboratory testing be an initial step?
• Yes:
  – simple history, PE and simple labs
• Get EMG/NCV
  – if confusing picture
  – Not responding to Rx

Simple lab tests >50% of pts
- ngds
- bld
- crp
- lft
- spep
- upep

How do labs help?
• LFTs ➔ chronic liver disease
• Glucose: DM
• Creatinine ➔ CRF
• TSH
• Lyme
• CBC ➔ lymphoma
• Vit B12/B6
• Spep/Upep
  – Amyloidosis (sensory)
  – M myleoma (ms)
  – Plasmacytoma
  – Monoclonal gammopathy
    - Axonal
    - Demyelinating
  - Porphyria Tilters
  - RPR

Drug exposures
- Amiodarone
- Digoxin
- INH
  - 20% at Rx doses
  - B6 minimize PN
- Lithium
- Flagyl
- Dilantin
- Captopril
- Vinblastine
  - Comes from plant in Madagascar
  - Can be severe
  - Can cause foot drop
- Nitrofurantoin

Autonomic nerve damage (everyday functions): can be caused by most including DPN, Hereditary and PBC
- Inability to sweat ➔ heat intolerance
- GI ➔
  - Frequency, urgency, incontinence and retention
  - Inability to control muscles that expand/contract blood vessels
    - Porphyria ➔ DI ➔ falls
    - Diastasis
- GI
  - Hypoglycemia because absorption of medication is delayed
  - Sluggish movement of small intestine ➔ bacterial overgrowth ➔ bloating, gas and diarrhea.
AES POLL QUESTION

Why do those with PN sometimes feel like they have gloves or stockings on when they don’t?

1. Damage to large sensory fibers
2. Damage to smaller sensory fibers without myelin sheaths
3. Affect on parasympathetic nerves
4. Motor nerve damage

Worst symptom of PN: Neuropathic Pain!

- Difficult to control
- Affect emotional well being
- Often worse at night
- Alloodynia: over sensitization of pain receptors

Common Diff Dx

- Acquired
  - Systemic diseases
    - DM
    - HIV
    - Critical Illness: uremia
    - Amyloidosis
    - Hypothyroidism
    - Vitamin Deficiencies
    - Lyme disease
  - Environmental
    - Vibration, cold, hypoxemia
- Inherited
  - CMT
  - Metabolic diseases of childhood
  - Idiopathic
    - CIDP
    - Sensory PN
    - Relation to systemic disease?

Causes of Acquired

- Physical trauma (most common)
  - Accidents, sports injuries, surgery
  - Crush, severe, compress, stretch nerve
- Nerve Squeeze?
  - Irritation of tendons/muscles\(\rightarrow\) constricting nerves
- CTS, Cubital Tunnel
- Pregnancy
- Women
- Repetitive?

Diseases or disorders

- Metabolic and endocrine
  - DM
    - 60-70% of patients eventually have mild to severe forms of nervous damage
    - sensory, motor, +/- autonomic
    - impaired blood flow to nerves?
  - Hypothyroidism\(\rightarrow\) retention and swelling\(\rightarrow\) pressure on tissues

Chronic Inflammatory Demyelinating Neuropathy CIDP

- More prevalent in DM
- Motor weakness > sensory loss
- Testing
  - EMG
  - CSF\(\rightarrow\) Protein >100
  - Biopsy?/MRI\(\rightarrow\) enlarged nerve roots?
Name this Diff dx?

- Charcot-Marie-Tooth
  - most common inherited neurologic disorder
  - 1886, Professor Jean Martin Charcot of France and his student Pierre Marie
  - (1853-1940) published the first description of distal muscle weakness and wasting beginning in the legs, calling it peroneal muscular atrophy
  - 1/2,500 pop
  - Spinal deformities (eg, thoracic scoliosis) occur in 37-50%
  - Deep tendon reflexes (DTRs) are diminished markedly or are absent
  - Testing EMG/Genetic testing for some variations

No Rx?

What is the first step in the management of Diabetic PN?

1. Glycemic Control
2. Foot Care
3. Treatment of Pain


Glycemic control

- Prevention and Rx
  - Improves NCV and vibration thresholds
  - Can we reverse established PN?
  - SORT B: improves after gastric bypass
    - No level A evidence
    - we need to emphasize prevention!

AES POLL QUESTION

What is incorrect about Foot Care in DPN?

1. Exam should be daily for the presence of dry or cracking skin, fissures, plantar callosity formation, and signs of early infection
2. The majority of patients with DPN have painful symptoms
3. If pain is unilateral or acute onset should consider radicular
4. Diabetic neuropathy can be seen with rapid weight loss
5. Symptoms can be self limited

- Feldman et al. Treatment of diabetic neuropathy. Up-to-date retrieved 6/2/2017

AES POLL QUESTION

What is correct about Diabetic PN?

1. Treatment induced neuropathy can happen if you bring down A1c > 1 point per month.
2. Good glucose alone has a minimal effect on neuropathy in type 2 DM
3. Development of neuropathy in type 2 DM is more related to lipid control, htn and obesity than glucose control
4. In type 1 DM you can reduce the complication rate of DPN by 60%
5. All of the above are correct

DPN: Self Limited?

- Prospective study
  - 29 patients
  - pain remitted within 12 months in 16 patients (55 percent)
  - Remission was more likely if
    - the onset of symptoms had followed a sudden metabolic change (either an episode of diabetic ketoacidosis or occasionally an improvement in glycemic control)
    - when the duration of diabetes was relatively short
    - when marked weight loss preceded the onset of pain

Evaluation

- Time consuming:
  - should not be an oh by the way!
- PE is focused
- Terminology?
  - Types
  - EMG/NCV

Advanced tests?

- EMG/NCV
  - yup have neuropathy
- ¼ get MRI not usually helpful

AES POLL QUESTION

Full diagnostic evaluation should be pursued if this feature is present:

1. Asymmetry
2. Sensory predominance
3. Chronic onset


Warning Signs

- Asymmetry
- Comes on quickly
- Non-length dependent
  - Hands and feet together
- Motor more involved than sensory
  - Most neuropathy affect the sensory system
- Prominent autonomic involvement

NCV: How robust a response and how fast

- Amplitude
  - Axons get damaged
- Conduction Velocity
  - How good the myelin sheath is developed

EMG: needle into individual muscles

Nerve Pattern
- Nerve root
- Plexus
- Multiple individual nerves
- Length dependent polyneuropathy

Muscle pattern
- Proximal myopathy
How to use EMG/NCV

- Neuropathy vs myopathy
- Polyneuropathy vs peripheral nerve disorder (polyradiculopathy from lumbar stenosis)
- Axonal vs demyelinating
  - Axonal → reduced amplitude but normal NCV
  - Demyelinating
    - Prolonged distal latencies and CV → CIDP

Biopsy?

- Nerve: asymmetry
- Low yield
- Uses sural nerve
  - Amyloid
  - Leprosy
  - CIDP
  - Vasculitis
  - sarcoidosis

Skin

- Small unmyelinated nerves
- Typical symptoms, pain (distal burning), numbness, paresthesia's
- Remove a small piece of skin proximal to ankle
- Quantitative data
- Monitor Rx?

Rx

Little can be done about the numbness

What can be treated is the pain!

Pain control: Expense?

- Antidepressants
  - Amitriptyline
  - Nortriptyline
  - Duloxetine
  - Venlafaxine?
  - Anticonvulsants
    - Gabapentin?
    - Pregabalin
    - Valproate?

- MIT
  - 1 drug, think cost
  2. Combination Rx different class
  - Unable to tolerate any?
    - Capsaicin
    - Lidocaine patch
    - TENS
    - Isosorbide dinitrate topical

AES POLL QUESTION

What is true about Antidepressants?

1. SSRI’s have also been found to be helpful
2. Benefit requires six weeks of therapy
3. Only amitriptyline has been found effective
4. The therapeutic effect occurs at a lower dose

RCT

Amitriptyline vs. Desipramine

- Equally effective > Fluoxetine
- Benefit at 2 weeks & increased to 6 weeks
- Desipramine less SE
- Ave effective dose:
  - 111mg/day desipramine
  - 105 mg/day amitriptyline
- No correlation between pain relief & drug concentration

RCT Amitriptyline vs Duloxetine

- Equal benefits (55 vs 59%)
- SE
  - A = Dry mouth
  - D = Constipation


Should we use amitriptyline?

- Nortriptyline has less side effects
  - N: more NE
  - A: balanced S and NE
- Both are contraindicated in patients with cardiac disease
  - Delay in inhibition of fast sodium channels
  - Slow CV and prolong PR, QT, QTc
- Do not use if using fluoxetine

Duloxetine

- Dual SSRI/NERI
- RCT (12 week)
  - 48% vs 29% (placebo)
- Onset
  - ~ 1 week
- Helpful at night!
- SE
  - Nausea (take on full stomach), somnolence, dizziness, constipation

Venlafaxine

- Mixed evidence?

Unusual Medications?

- Capsaicin (0.075%)?
  - Many are intolerant
  - 4 times a day?

- Anesthetics?
  - Mexiletine: conflicting evidence
  - Lidocaine patches (open label data only)

- Isosorbide topical spray?
  - 22 pts? DM did well

Pregabalin

- Structurally similar to gabapentin
  - + Effective: Pooled analysis of seven randomized trials 5-13 weeks
  - Start at 50mg BID + max dose 150mg BID
- SE
  - Dizziness, vertigo, incoordination, ataxia, diplopia, blurred vision, agitation, confusion
  - Weight gain 2-3.9% vs 0.7%
- Gabapentin (data is inconclusive)

Venlafaxine

- Mixed evidence?

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- ALA (alpha-lipoic acid)
  - Potent anti-oxidant, Dietary supplement
  - Sydney trial
  - 50/62 improved >50%

- Optimal dose 600mg qd
  - (increasing dose increases SE without benefit)

- Russian Medical Academy for Advanced Studies, Moscow, Russia.
- German Diabetes Research Institute, Leibniz Institute at the Heinrich Heine University.
Opioids

- AAN & Authors of Up-to-date
  - Not indicated
- Trials
  - Dextromethorphan, Tramadol, Oxycontin
    - Limited by small size and short term and bias
- 2009, 2013 systemic review
  - Paucity of evidence for long term effectiveness and risks of abuse, addiction and overdose!


Non-pharmacologic Rx

- PT → weakness
- Ankle foot orthosis
- Splints?
- Walking assistance devices
- Proper foot and nail care

Surgery?

- Decompression of multiple peripheral nerves
  - Controversial
  - No adequately designed trials

Summary

History

- Onset?
  - Exposure to medication?
  - Acute or subacute
- Sensory vs Motor
- Diff Dx
  - Alcohol, DM, Chemo Rx

Exam

- Isolated muscle wasting or general
- Monofilament
- Tuning fork
- Pin
- Reflex hammer

Screening | SORT Category
--- | ---
We should screen patients with Diabetic PN with at least 2 modalities | SORT B
Vibration Testing is more sensitive than monofilament testing in DPN | SORT B
Focused history, exam and inexpensive blood tests can lead to diagnosis in > 50% of PN | SORT C

Rx of PN | SORT CATEGORY
--- | ---
Little can be done about numbness but significant benefits can be achieved for pain control with 1 or multiple medications | SORT B
TCA’s, Duloxetine and Pregabalin are all effective modalities | SORT B
Opioids: Risks > benefits | SORT B
Therapeutic effect of TCA occurs at a lower dose | SORT B
1. Ask a few simple questions to sort out most common etiologies
   - Symmetrical?
   - Painful or painless
   - Distal vs length dependent
   - Alcohol or drug exposure

2. Order Simple labs
   - (BMP, HgA1c, b12, CBC, SPEP)

3. Most cases do not need
   - EMG/NCV
   - neurology