A Practical Approach to Peripheral Neuropathy

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Disclosures

• None
Learning Objectives

• Understand the types of presentations of peripheral neuropathy
• Discuss utility of laboratory testing in peripheral neuropathy
• Recognize the role of EMG in PN evaluation
• Implement evaluation tool for peripheral neuropathy
Peripheral Neuropathy

- Peripheral neuropathy – means disease or dysfunction of peripheral nerves

- Root – radiculopathy
- Multiple roots - polyradiculopathy
- Plexus – plexopathy
- Individual nerve – mononeuropathy
  - Multiple, multifocal – mononeuritis multiplex
Scope of the Problem

- Peripheral neuropathy has an estimated prevalence of 2-3% in the general population.
- As high as 8% in people older than 55 yrs.
- Evaluation for etiology important as it may identify a treatment and prevent progression to disability.

Olmsted county Peripheral Neuropathy prevalence

England, JD Lancet 2004
Hughes, RA. BMJ 2002

Hoffman et al. Neurology 2015
Scope of the Problem

• Diabetic Peripheral Neuropathy (DPN)
  • 20% of Type 2 DM at presentation
  • Increasing with duration of disease, 50%
• Dyck RDS
  • Diabetic microvessel disease, chronic hyperglycemic exposure, and type of diabetes associated with severity

Scenarios

1. Screening for PN in patients with chronic diseases in which PN is prevalent
   - DM
   - Chemotherapy
   - Dysproteinemias

2. Evaluating those with symptoms of PN
   - Define who would benefit from neurology consultation
   - Fine tune differential diagnosis and work-up
Screening for Peripheral Neuropathy

- Neurologic symptoms
- Neurologic signs

- 128 Hz tuning fork and monofilament > 90% sensitivity of Diabetic LD PN

CI vs NPhys Investigators. Arch Neurol 2012;69(12):1609-14
Algorithm for approach to PN

- **What?** Which nerve fibers are involved

- **Where?** The distribution of nerve involvement

- **When?** The onset and progression of neuropathy

- **What setting?** Clues from the patient
Stratification of Peripheral Neuropathy

- **Modality**
  - Sensory
  - Motor
  - Autonomic

- **Pattern**
  - LD
  - Non-LD
  - MF

**Timing** – Definite Date of Onset/Rapid progression or Gradual/Insidious

**Setting** – other comorbid diseases, medications, family history
Pearls in PN History

- Definite date of onset - immune, vasculitic, infectious or neoplastic
- Stepwise progression – multiple mononeuropathies
- Relapsing/remitting – intermittent exposure or CIDP illness
- Positive neuropathic symptoms more common in acquired vs. inherited neuropathies
**Inherited**

- **“What”**
  - Motor or sensorimotor
  - PNSS uncommon

- **“Where”**
  - distal, symmetric

- **“When”**
  - Insidious/gradual onset, slow progression

- **“What Setting”**
  - Family history, foot deformities, foot ulcers

**Differential Diagnosis**
- CMT/HMSN
- HNPP

**Acquired**

- **“M I N I”**
  - Metabolic
    - Sensory > motor
  - Immune
    - Variable
  - Neoplastic
    - PNSS very common
  - Infectious

- **“Where”**
  - Not distal, symmetric

- **“When”**
  - Definite date of onset, more rapid progression

- **“What Setting”**
  - Risk factors, diseases or exposures?
  - Symptoms of vasculitis or systemic illness?
  - Symptoms of cancer? Paraproteinemia?
  - Symptoms / risks for infection?

**Differential Diagnosis**
- Diabetic
- Uremic
- Alcohol
- B12 deficiency
- B1 deficiency
- Hypothyroid
- Meds

- Non-vasculitic
  - GBS
  - CIDP
  - MMN
  - Sarcoid
  - Sjogren’s

- Paraneoplastic
  - Paraproteinemic (monoclonal gammopathies)

- Hepatitis B & C
- Lyme
- HIV
- West Nile
- Syphilis
- Diphtheria
- Leprosy
Stratification of Peripheral Neuropathy

- Electrophysiological tests
  - “EMG” – NCS and EMG
  - Autonomic tests
EMG in the evaluation of PN

- Nerve conduction studies have sensitivity of 70% for LD PN

- What information does it add?
  - Confirm diagnosis
  - Extent of involvement – distal, proximal/distal, MF
  - Provide unique information that cannot be reliably determined from the history / exam
    - Axonal vs. demyelinating
  - For some (AIDP, CIDP) –provides prognostic information and information on response to treatment
### Inherited
- **What**: Motor or sensorimotor
- **Where**: Distal, symmetric
- **When**: Insidious/gradual onset, slow progression
- **What Setting**: Family history, foot deformities, foot ulcers
- **Differential Diagnosis**: CMT/HMSN, HNPP

### Acquired
#### Metabolic
- **What**: Sensory > motor
- **Where**: Not distal, symmetric
- **When**: Definite date of onset, more rapid progression
- **What Setting**: Risk factors, diseases or exposures?
- **Differential Diagnosis**: Diabetic, Uremic, Alcohol, B12 deficiency, B1 deficiency, Hypothyroid, Meds

#### Immune
- **What**: Variable
- **Where**: PNSS very common
- **When**: Definite date of onset, more rapid progression
- **What Setting**: Symptoms of vasculitis or systemic illness?
- **Differential Diagnosis**: Non-vasculitic GBS, CIDP, MMN, Sarcoid, Sjogren’s, Vasculitic PAN, GPA, EGPA, SLE, RA

#### Neoplastic
- **What**: PNSS uncommon
- **Where**: Not distal, symmetric
- **When**: Definite date of onset, more rapid progression
- **What Setting**: Symptoms of cancer? Paraproteinemia?
- **Differential Diagnosis**: Non-vasculitic Paraproteinemic (monoclonal gammopathies)

#### Infectious
- **What**: PNSS very common
- **Where**: Not distal, symmetric
- **When**: Definite date of onset, more rapid progression
- **What Setting**: Symptoms / risks for infection?
- **Differential Diagnosis**: Hepatitis B & C, Lyme, HIV, West Nile, Syphilis, Diphtheria, Leprosy

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Limitations of EMG

• Timing (3 weeks)
• Dynamic process – spinal stenosis normal
• Old processes remain so can make localization difficult

• Small fiber neuropathy – EMG normal
Who to refer?

- Acute/subacute
- Progressive
- Severe, functionally limiting
- Non length-dependent (proximal and distal, multifocal)
- Modality specific – motor, severe dysautonomia
Case of Typical LD SMPN

• 64 yr old man with 2 year history of numb feet.
• Started in toes and has progressed gradually to the ankles
• Associated tingling/prickling, occasional shooting pain
• Examination – loss of vibration at big toe, decreased touch to the ankle, ankle reflex reduced, normal strength and gait
LD SMPN

- Most common
- Symmetric
- Stocking-glove
  - Proprioceptive generally preserved unless severe (Posterior column dysfunction)
  - Weakness – distal > proximal
  - DTR reduced distally >> proximal
## Large fiber vs Small fiber neuropathy

<table>
<thead>
<tr>
<th></th>
<th>Large Fiber PN</th>
<th>Small Fiber PN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful</td>
<td>Sometimes</td>
<td>Common</td>
</tr>
<tr>
<td>Numbness</td>
<td>Yes – Abnormal light touch, vibration</td>
<td>Yes – Abnormal pinprick, temperature</td>
</tr>
<tr>
<td>Proprioception</td>
<td>Late</td>
<td>No</td>
</tr>
<tr>
<td>loss/sensory ataxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>Often, could be mild</td>
<td>No</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Lost, often length-dependent</td>
<td>Normal</td>
</tr>
<tr>
<td>EMG</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Small fiber neuropathy

<table>
<thead>
<tr>
<th>Associated Dysautonomia?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Satiety</td>
</tr>
<tr>
<td>Gastroparesis</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Orthostatism</td>
</tr>
<tr>
<td>Resting tachycardia</td>
</tr>
<tr>
<td>Urinary retention</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Sudomotor (sweat) dysfunction</td>
</tr>
<tr>
<td>Dry eyes/mouth</td>
</tr>
</tbody>
</table>
Evaluation of LD SMPN

• History/Exam, EDX, Labs yield etiology 74-82%

• Mild/chronic
  • CBC
  • Renal function
  • LFTs
  • ESR
  • FGS (11%, HgA1c 26%)
  • TSH
  • Monoclonal protein SPEP/SIFE – 3-9%
  • B12 – 2%
  • Infectious (risk factors, endemic): Lyme, HIV
  • Family history
## Diabetic Neuropathies

<table>
<thead>
<tr>
<th>Symmetric</th>
<th>Asymmetric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic polyneuropathy (DPN) 75%</td>
<td>Cranial neuropathy</td>
</tr>
<tr>
<td>Diabetic autonomic neuropathy (DAN)</td>
<td>Mononeuropathy (compression)</td>
</tr>
<tr>
<td>Neuropathy with IGT</td>
<td>Radiculoplexus neuropathies (diabetic amyotrophy)</td>
</tr>
<tr>
<td>Diabetic cachexia</td>
<td>Thoracic radiculopathy</td>
</tr>
<tr>
<td>Treatment induced neuropathy of diabetes</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemic neuropathy</td>
<td></td>
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<tr>
<td>CIDP in DM</td>
<td></td>
</tr>
</tbody>
</table>
Diabetic Peripheral Neuropathy

- Sensory first – distal small then large fiber
- Distal motor involvement later
- Microvascular disease, chronic hyperglycemic exposure, and type of diabetes associated with severity
IGT – still controversy

• Evidence that DPN, especially painful small fiber type, present in 10-30% of IGT patients

• Increased risk of PN in IGT and metabolic syndrome

• RDS - No difference in prevalence of typical or atypical PN in IGT vs non-IGT
  • No difference in prevalence of retinopathy or nephropathy
  • New DM2 vs IGT and or non-IGT cohorts
    • Increased prevalence of PN, retinopathy and nephropathy

Dyck PJ et al. Diabetes Care 2012;35:584-91
Treatment Induced Neuropathy of Diabetes (TIND)

- More common in T1DM
- LD or generalized - severe burning, shooting pain, allodynia
- SFN with autonomic
- Occurs within weeks of onset of glucose control
- Improves over 12-24 mos

DLRPN (Diabetic amyotrophy)

• Clinical features
  • Begins in one lower limb
  • Spreads to contralateral limb but remains asymmetric
  • Often femoral or sciatic predominant
  • Pain with contact sensitivity
  • Weight loss

• Assoc. with mild diabetes

• CSF and MRI fairly normal

Dyck, P. J. B. et al. Neurology 1999;53:2113
Vitamin B\textsubscript{12} Deficiency (Subacute Combined Degeneration)

- **Clinical Features**
  - Sensory loss and ataxia
  - Simultaneous onset in hands and feet (due to myelopathy)
  - Abrupt onset of symmetric symptoms

- **Setting** - Vegan diet, GI malabsorption, autoimmune, IBD, nitrous oxide toxicity or resection of terminal ileum
  - Labs – macrocytosis, anemia, ↓ Vitamin B\textsubscript{12}, ↑ Methylmalonic acid
Dysproteinemias

- Occur in up to 10% of patients with PN

- SPEP with immunofixation more sensitive
  - 17% of all monoclonal proteins missed by SPEP
  - 30% of IgM’s missed by SPEP

MGUS
Prev-3.2%

Kyle et al. Oncology 2011
Immunoglobulin Type Matters in Neuropathy

- IgG 73%
- IgM 15%
- IgA 12%

Does a discovered MGUS cause the polyneuropathy?

No Neuropathy
- IgG 37%
- IgM 48%
- IgA 15%

With Neuropathy

## Paraproteinemic Neuropathies

<table>
<thead>
<tr>
<th>Hematologic Disorder</th>
<th>Monoclonal Protein type</th>
<th>PN Type</th>
<th>EDX</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM-MGUS</td>
<td>IgM Kappa</td>
<td>LD large fiber sensory with ataxia</td>
<td>Demyelinating</td>
</tr>
<tr>
<td>Waldenstrom Macroglobulinemia</td>
<td>IgM Kappa</td>
<td>LD large fiber sensory Mononeuritis multiplex</td>
<td>Variable (demyelinating or axonal)</td>
</tr>
<tr>
<td>POEMS</td>
<td>Lambda</td>
<td>CIDP</td>
<td>Demyelinating</td>
</tr>
<tr>
<td>AL amyloid</td>
<td>Lambda&gt; kappa</td>
<td>Sensorimotor or small fiber Autonomic</td>
<td>Axonal</td>
</tr>
</tbody>
</table>
Hereditary Neuropathy

Final classification

- Inherited: 42%
- Inflammatory demyelinating: 13%
- Other acquired: 21%
- Undiagnosed: 24%

Hereditary Neuropathy

- Motor > Sensory
- 30% are de novo – no Family history
- Heterogeneity – genetic and phenotypic

- EMG characteristics
  - Type 1 Demyelinating
  - Type 2 Axonal
- Genetic testing demyelinating
Medications

- Anti-infectious
  - Chloroquine
  - Dapsone
  - Isoniazid
  - Metronidazole
  - Nitrofurantoin
  - HIV “d” drugs
- Chemotherapy
  - Cisplatinum
  - Taxanes
  - Thalidomide/Bortezomib
  - Vincristine
  - Pembrolizumab/Nivolumab
- Antirheumatic
  - Colchicine
- Cardiovascular
  - Amiodarone
  - Hydralazine
  - Perhexilene
  - Propafenone
- Psychiatric
  - Disulfiram
- Others
  - B6
  - Phenytoin
  - Monoclonal Ab, anti-TNFα

### Other causes to consider in SFN

<table>
<thead>
<tr>
<th>Causes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic</td>
<td>Alcohol, Chemotherapy</td>
</tr>
<tr>
<td>HIV</td>
<td>Disease and “d” drugs</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Light chain and Hereditary</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Anti-TTG Ab most sensitive adults</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td></td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>Sicca symptoms, SSA, SSB</td>
</tr>
<tr>
<td>Fabry’s disease</td>
<td>Alpha-galactosidase</td>
</tr>
<tr>
<td>Sarcoid</td>
<td></td>
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<tr>
<td>Nav1.7 mutations of SCN9A</td>
<td></td>
</tr>
</tbody>
</table>
Polyradiculoneuropathies

- Clinical Clues:
  - Proximal and distal weakness
  - Cranial nerves
  - Motor > sensory
  - Subacute onset
  - Maybe episodic (relapses/remissions)
  - CSF protein ↑
  - Nerve trunk sometimes enlarged

- Potentially treatable

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDP/CIDP</td>
</tr>
<tr>
<td>POEMS</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Sarcoid</td>
</tr>
<tr>
<td>Lyme</td>
</tr>
<tr>
<td>West Nile</td>
</tr>
<tr>
<td>AMAN (axonal GBS)</td>
</tr>
</tbody>
</table>
Multiple Mononeuropathies

- Multiple nerves
- Asymmetric neuropathy
- Subacute or stepwise

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculitis</td>
</tr>
<tr>
<td>Diabetic</td>
</tr>
<tr>
<td>Leprosy</td>
</tr>
<tr>
<td>MMN</td>
</tr>
<tr>
<td>Compression</td>
</tr>
</tbody>
</table>
Autonomic Testing

- Autonomic reflex screen
  - QSART - sudomotor
  - HRDB - vagal
  - Valsalva maneuver - adrenergic
- Tilt table - adrenergic
Autonomic Testing

• Thermoregulatory Sweat Test – pre and post ganglionic sudomotor fibers (test for small fiber function)
Skin biopsy

- Skin punch biopsy
  - No sutures
  - Complication rate 0.5%

- Assess intraepidermal nerve fiber density (IENFD)
  - Sensitivity 45-90%
  - Specificity 95-97%
  - Normal IENFD doesn’t exclude small fiber neuropathy

Hlubocky A Neurologist 2010;16:61
England JD. Neurology 2009

Stino AM et al. JDI 2017;8:646-55.
Devigilli G Brain 2008 131:1912
Nerve Biopsy

• Consider for PN that is:
  • Acute/subacute
  • Multifocal
  • Severe and/or progressive

• Recommended when suspect:
  • Inflammatory
    • Vasculitis
    • Sarcoid
    • CIDP
  • Infectious
    • Leprosy
  • Infiltrative
    • Neoplastic
    • Amyloid
    • Polyglucosan bodies

No role for biopsy in idiopathic length-dependent axonal SM PN
Non-systemic treatments

- Soaking the feet in cool water
- Lidocaine patch
  - 5% patch
  - maximum of 3 patches daily for a maximum of 12-18 hours, trial for 3 weeks
    - No significant adverse effects
- Combination gels/creams
  - Amitriptyline 2%/Ketamine 0.5%
    - Also can use Baclofen, Clonidine, Lidocaine
  - Trial twice a day for 2 weeks
Calcium channel $\alpha_2$-$\delta$ ligands

- Gabapentin
  - Start with 100 mg to 300 mg at bedtime
  - Increase by 300 mg every 3-7 days as tolerated
  - TID dosing
  - Maximum dose is 3600 mg/d
  - Trial for 3-8 weeks, 2 weeks at max dose

- Pregabalin
  - Start with 75 mg twice per day
  - Increase by 75 mg every 3-7 days as tolerated
  - BID dosing
  - Maximum dose 600 mg/d
  - Trial for 4 weeks
Calcium channel $\alpha_2$-$\delta$ ligands

- Can produced dose-dependent dizziness and sedation and lower extremity edema
- Dose adjustment in renal insufficiency
- Pregabalin has more consistent bioavailability and linear pharmacokinetics

![Graphs of PGB and GBP](image-url)
Tricyclic Antidepressants

- Both norepinephrine and serotonin reuptake inhibition
- Nortriptyline or desipramine (less side effects)
  - Start with 25 mg at bedtime
  - Increase by 25 mg/day every 3-7 days as tolerated
  - Maximum dosage 1 mg/kg
    - Some say 150 mg/day, <100 mg/day in those with ischemic cardiac disease or ventricular conduction abnormalities with screening EKG in those over 40 years
  - Trial for 6-8 weeks with at least 2 weeks at maximum tolerated dose
- Common side effects – dry mouth, OH, constipation, urinary retention, weight gain
SSNRI’s

• Duloxetine
  • Start with 30 mg daily
  • Increase to 60 mg daily after 1 week
  • Maximum dose is 60 mg twice a day
  • Trial for 4 weeks
  • Most common side effect is nausea

• Venlafaxine
  • Start with 37.5 mg once or twice a day
  • Increase by 75 mg weekly
  • Maximum dose is 225 mg/day
  • Trial for 4-6 weeks
  • Taper because a withdrawal syndrome has been reported
Summary

- Length-dependent sensorimotor peripheral neuropathy is common and can usually be evaluated and managed without specialty consultation

- The highest yield tests/history in evaluation of LDSM PN
  - Diabetes
  - SPEP with immunofixation
  - B12/MMA
  - Family history

- EMG testing useful in distinguishing axonal and demyelinating neuropathies