Peripheral Neuropathy

Practical Points and Update

Devon I. Rubin, M.D.
Professor of Neurology
Mayo Clinic
Jacksonville, Florida
Learning Objectives
After completion of this talk you should be able to:

• Perform a practical, cost-effective evaluation
• Identify “atypical” neuropathies
• Understand treatment options for various neuropathies
Peripheral Neuropathy: A Practical Approach to Diagnosis and Symptom Management

James C. Watson, MD, and P. James B. Dyck, MD

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66 yo man with 2 years of foot numbness/ burning.

Exam: Decreased sensation (to mid shins), absent Achilles reflexes

6 months ago diagnosed with type 2 DM
DEFINE:

- Signs & Symptoms (M, S, Auto)
- Anatomic Distribution
- Temporal Profile

Differential diagnosis?
Tests?
Treatments?
Perform a careful neuromuscular examination!

- Distal Symmetric
- Focal Multifocal Asymmetric (mononeuropathy, mononeuritis multiplex)
- Proximal & Distal Symmetric or Asymmetric (polyradiculopathy)
Distal Sensorimotor Peripheral Neuropathy

- “Length-dependent” (Legs before arms)
- Symmetric

Sensory loss (“glove-stocking”)
  Joint position/Vibration
  Pin/Temperature

Hypo-Reflexia
  Achilles > Quads > UEs

Weakness
  Toes > Ankles > Interossei / Hand muscles
<table>
<thead>
<tr>
<th>Feature</th>
<th>Consider</th>
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<tbody>
<tr>
<td><strong>Hands &gt; Feet</strong></td>
<td>Mononeuropathy (median, ulnar)</td>
</tr>
<tr>
<td></td>
<td>Polyradiculopathy (CIDP)</td>
</tr>
<tr>
<td></td>
<td>Cervical cord</td>
</tr>
<tr>
<td><strong>Asymmetric</strong></td>
<td>Mononeuropathy (peroneal, ulnar)</td>
</tr>
<tr>
<td></td>
<td>Radiculopathy (L5, S1)</td>
</tr>
<tr>
<td></td>
<td>Polyradiculopathy</td>
</tr>
<tr>
<td></td>
<td>ALS</td>
</tr>
<tr>
<td><strong>Motor without sensory</strong></td>
<td>Motor neuron disease/motor neuropathy</td>
</tr>
<tr>
<td></td>
<td>Distal myopathy</td>
</tr>
<tr>
<td><strong>Proximal (with distal) weakness</strong></td>
<td>Polyradiculopathy</td>
</tr>
<tr>
<td></td>
<td>Myopathy (IBM) +/- neuropathy</td>
</tr>
<tr>
<td></td>
<td>NMJ disorder</td>
</tr>
</tbody>
</table>
What workup is needed?

- EMG
- Labs
- Genetic testing
- Nerve biopsy
Goals of EMG

1) Confirm “peripheral neuropathy”
2) Determines pathophysiology (axonal vs demyelinating)
3) Identify / exclude “mimicking” disorders
Uniform Demyelination

Inherited etiologies
CMT 1a

Segmental Demyelination

Acquired etiologies
AIDP (GBS)
CIDP
MGUS (esp IgM), anti-MAG neuropathy, Osteosclerotic myeloma
Hereditary neuropathy with pressure palsy
Laboratory Testing
How Extensive?

<table>
<thead>
<tr>
<th>Test</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>OGTT</td>
<td>61%</td>
</tr>
<tr>
<td>Hgb A1C</td>
<td>26%</td>
</tr>
<tr>
<td>F.glucose</td>
<td>11%</td>
</tr>
<tr>
<td>ANA</td>
<td>3%</td>
</tr>
<tr>
<td>SPEP</td>
<td>3%</td>
</tr>
<tr>
<td>Vit B12</td>
<td>2%</td>
</tr>
<tr>
<td>TSH</td>
<td>0%</td>
</tr>
<tr>
<td>ESR</td>
<td>0%</td>
</tr>
</tbody>
</table>

(n=138  Smith AG 2004)
The yield of screening laboratory tests is 37% - 58%.

Conclusion:

“Screening laboratory tests are possibly useful in determining the cause . . .”

Tests with the highest yield of abnormality are: glucose, B12, SPEP/IEP.
<table>
<thead>
<tr>
<th>Test</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Anemia, myeloproliferative</td>
</tr>
<tr>
<td>AST, ALT, creatinine</td>
<td>Hepatic or renal disease</td>
</tr>
<tr>
<td>Fasting glucose, Hgb A1C, OGTT</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
</tr>
<tr>
<td>B12, Methylmalonic acid (Vitamin E, copper)</td>
<td>Vitamin deficiencies</td>
</tr>
<tr>
<td>SPEP</td>
<td>Paraproteinemia</td>
</tr>
<tr>
<td>Monoclonal protein study</td>
<td>Osteosclerotic myeloma</td>
</tr>
<tr>
<td>Metastatic bone survey</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Fat aspirate</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>Hypo-, Hyperthyroidism</td>
</tr>
<tr>
<td>ESR, ANA, ENA, ds-DNA</td>
<td>Vasculitis, connective tissue disease</td>
</tr>
</tbody>
</table>
Other Tests if:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV, Hepatitis serologies, RPR</td>
<td>Risk factors</td>
</tr>
<tr>
<td>Urine heavy metal screen</td>
<td>Risk factors (wrist drop, GI symptoms, hair loss, abdominal pain, etc.)</td>
</tr>
<tr>
<td>Antibody testing</td>
<td></td>
</tr>
<tr>
<td>GM1</td>
<td>Motor only neuropathy</td>
</tr>
<tr>
<td>MAG</td>
<td>If monoclonal protein (IgM) and demyelination</td>
</tr>
<tr>
<td>SGPG, anti-sulfatide</td>
<td>Rapid or subacute onset, severe sensory loss/ataxia</td>
</tr>
<tr>
<td>CSF</td>
<td>Polyradiculopathy</td>
</tr>
</tbody>
</table>
Hereditary Clues

- “Always clumsy”, childhood onset
- Foot deformities (high arches/hammertoes), foot pain, gait difficulties, podiatrist consultations
- Examine accompanying family members
When to Consider Genetic Testing

AAN Practice Parameter

Useful for patients who exhibit a classic hereditary neuropathy phenotype.
(+ Family History, Early onset, Demyelinating)

Insufficient evidence in cryptogenic PN without hereditary phenotype.
Nerve Biopsy

When to order?

- Subacute
- Severe
- Rapidly progressive

Diagnosable disorders

- Vasculitis
- Amyloid
- Sarcoid
- Leprosy
- CMT 1, 3
- Micrometastases
- Neurogenic tumors

*AAN Practice Parameter 2009*
Skin Biopsy
Intraepidermal Nerve Fiber Quantification

- Validated, reproducible marker of small fiber sensory pathology
- AAN Practice Parameter: “Possibly useful”
- Abnormal in 88% of pts with small fiber PN and normal NCS

But . . . not a perfect test.

66 yo man with 2 years of foot numbness/burning.

Exam: Decreased sensation (to mid shins), absent Achilles reflexes

6 months ago diagnosed with type 2 DM
Types of Neuropathy Associated with Diabetes
Diabetes and Neuropathy

PN may precede DM dx
(no definite increase in small fiber PN in prediabetes)***

Tight glycemic control may delay PN

?? Optimal treatment and outcome

***Kassardjian et al. J Neurol Sci 2015
75 yo woman with 6 months of foot and hand numbness and imbalance.

EMG: Demyelinating PN

IgM lambda monoclonal gammopathy.
Monoclonal Gammopathy

- Present in ~10% of PN
  - 50% - IgM (often MAG antibody)
- Assess/follow for systemic amyloidosis or hematologic malignancy (lymphoma, osteosclerotic myeloma)
- Treatment: Rituximab, IVIg
- Cochrane Review (IgA and IgG PN) (2015)
  - 1 RCT trial (n=18) of PLEX: modest improvement in weakness of NDS score (no difference in overall score)
  - Observational studies: Limited support for cyclophosphamide + prednisone, IVIG, corticosteroids
- Autologous stem cell transplant improved POEMS PN (n=60), Class IV evidence (Neurology 2015)
- 65 yo woman
- 3 months - numbness in hands and face
- 1 month – numb feet and leg weakness

Exam:
- Symmetric, proximal and distal weakness
- Areflexia
- Distal sensory loss in hands/feet

Thoughts?

Hands 1st, Subacute, Proximal weakness
Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP)

Classic Features

- Progressive or relapsing motor and sensory symptoms (≥2 months)
- Symmetric
- Distal and proximal weakness
- Motor > sensory
- EMG: (true) demyelinating features
- CSF: elevated protein

BEWARE!

- Burning feet only
- Normal reflexes
- Normal strength
- Normal CSF protein
- No demyelination
CIDP - Atypical Forms

DADS (Distal Acquired Demyelinating Symmetric)
- Distal weakness
- Distal sensory loss

MADSAM (Multifocal acquired demyelinating sensory and motor; Lewis-Sumner)
- Motor or motor and sensory
- Asymmetric
- Multifocal

CISP (chronic immune sensory polyradiculopathy)
- Sensory only

Focal CIDP
Treatment of CIDP

- *IVIg* (Lancet Neurol 2008 Feb;7:136-144)
  - 0.4 g/kg x 5 days, then weekly x 1 month, then every other week

- Corticosteroids*
  - 60 mg daily, slow taper (over months)

- Plasmapheresis

- Other immunosuppressants
  - Azathioprine
  - Cyclophosphamide
  - Cyclosporine
  - Rituximab
  - Methotrexate†
  - Interferon β †

*Positive response in up to 87%. Viala et al, 2010
† No statistically significant benefit
Peripheral neuropathy news
@RubinPNCMETalk
brief key updates in PN
Boca Raton, FL

Folate-deficiency Neuropathy @FolatePN
Distal, symmetric, sensory>motor, axonal neuropathy. Slow progression (mos – yrs). +/- anemia, macrocytosis; folate < 3.0 ng/mL. 5/18 improved with replacement.

Celiac Disease Neuropathy @GlutenPN
68 pts (44 CD; 24 + gliadin abs); 11 with PN (2º to other deficiencies – Vit E, Cu, Folate – or other autoimmune). Other causes in majority. 6 with PN without cause. (McKeon, Neurology 2014)

Statin Neuropathy @StatinPN?
2002 Neurology. Case control study: 1 case per 2200 (880 – 7300) person-years of statin use.
Systematic review (2006) Meta-analysis 4 cohort studies: OR 1.8 (1.1 – 3.4); Incidence 12/100,000 person-years
1. Treat the medical disorder (DM, nutritional deficiency, etc.)

2. Remove offending agent (EtOH, medications, etc.)

3. If immune-mediated (CIDP, MMN, vasculitis): immune modulating Rx (IVIg, prednisone, immunosuppressants)

4. Symptomatic treatment
   Neuropathic pain
   Numbness
   Weakness (AFO, PT/OT)
## Symptomatic Treatment
### Neuropathic Pain

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>Antidepressants</th>
<th>Topical Agents</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclics</strong></td>
<td><strong>SSRI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin*</td>
<td>Amitriptyline</td>
<td>Capsaicin</td>
<td></td>
</tr>
<tr>
<td>(Level A)</td>
<td>(Level B)</td>
<td>(Level B)</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Gabapentin*</td>
<td>Nortriptyline</td>
<td>Duloxetine*</td>
<td>Dextromethorphan</td>
</tr>
<tr>
<td>(Level B)</td>
<td></td>
<td>(Level B)</td>
<td>(Level B)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Venlafaxine</td>
<td>Venlafaxine</td>
<td>Morphine</td>
</tr>
<tr>
<td>(Level B)</td>
<td>(Level B)</td>
<td>(Level B)</td>
<td>(Level B)</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Fluoxetine</td>
<td>Fluoxetine</td>
<td>Oxycodone</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Desipramine</td>
<td>Desipramine</td>
<td>Mexiletine</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Imipramine</td>
<td>Imipramine</td>
<td>NSAIDS</td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
<td>Alpha-lipoic acid</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
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<tr>
<td>Topiramate</td>
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</tbody>
</table>

*Treat with maximal (tolerated) dose
*Adequate length of treatment (4-6 weeks)

*FDA approved

**Bril V. Muscle Nerve 2011**
<table>
<thead>
<tr>
<th>Medication</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>900-3600 mg/day</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>300 – 600 mg/day</td>
</tr>
<tr>
<td>Amitriptyline, nortriptyline</td>
<td>25-100 mg/day</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75-225 mg/day</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60-120 mg daily</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>100 mg daily</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>400 mg TID</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>Tramadol</td>
<td>200 mg/day</td>
</tr>
<tr>
<td>Lidocaine (5%) patch</td>
<td>3 patches to skin, 12 hrs on/12 hrs off</td>
</tr>
<tr>
<td>1% amitriptyline + 0.5% ketamine</td>
<td>Apply up to 5 times daily</td>
</tr>
<tr>
<td>Alpha lipoic acid</td>
<td>600 mg/day</td>
</tr>
</tbody>
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Take Home Points

• Define anatomic distribution and fiber type involvement
• EMG to determine axonal vs demyelinating
• Red flags (“HAMP”er)
  • Hands, Asymmetric, Motor, Proximal
• Adequate dose and 4-6 week trial of neuropathic pain medications
References

• Bright R, et al. Therapeutic options for chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review. BMC Neurology
• Stork AC, et al. Treatment for IgG and IgA paraproteinaemic neuropathy. Cochrane Database Syst Rev. 2015 Mar 24
• Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006; 97[suppl]: 52C-60C.
Differential Diagnosis
Distal Sensorimotor Neuropathy

More common
- Diabetes
- Paraproteinemia
- Hereditary (CMT type 2)
- Systemic medical illnesses
  - Hypothyroidism
  - Renal failure
  - Hepatic failure
- B12 deficiency

Less common
- Toxins - thallium, mercury, gold, arsenic, hexacarbons
- Medications
  - colchicine, phenytoin, ethambutol, metronidazole, nitrofurantoin, chloroquine, disulfiram, lithium, amiodorone
- Infectious
  - HIV, syphilis, Lyme
- Alcohol
- Systemic vasculitis - RA, PAN, SLE, scleroderma
- Sarcoidosis
- Amyloidosis
- Critical illness neuropathy
Sensory Neuropathy
Small fiber (autonomic)

- Idiopathic
- Amyloidosis
- Diabetes
- EtOH (thiamine def)
- Vasculitis
- Fabry’s disease
- Tangier’s disease
- Hereditary sensory neuropathy
Severe Sensory Neuropathy / Ganglionopathy

• Severe sensory loss
• Poor proprioception
• Sensory ataxia
• Pseudoathetosis

• Sjogren’s
• Lyme
• Syphilis
• Sarcoid
• HIV, HTLVI
• Paraneoplastic (Small cell lung)
• B6 toxicity
• B12 deficiency
• Vitamin E deficiency
• Cisplatinum, thalidomide
• Spinocerebellar ataxia
• Friedreich’s ataxia
# Demyelinating Neuropathies

**Uniform**
- Charcot Marie Tooth type 1
- Adrenomyeloneuropathy
- Metachromatic leukodystrophy
- Krabbe’s disease
- Cerebrotendinous xanthomatosis

**Segmental**
- CIDP (AIDP)
- MGUS (esp IgM)
- Anti-MAG neuropathy
- Osteosclerotic myeloma
- Toxic (amiodarone, perhexiline, arsenic, hexane)
- Hereditary neuropathy with pressure palsy (HNPP)
Mononeuritis Multiplex
Etiologies

- Vasculitis
- Hepatitis C (Cryoglobulinemia)
- Diabetes
- Sarcoidosis
- Amyloidosis
- Hereditary neuropathy with liability to pressure palsies (chrom 17 del)
- Leprosy (sensory only)
- Multifocal motor neuropathy with conduction block (motor only)
Motor Predominant “Neuropathies”

- Neuropathy / Polyradiculopathy
- CIDP / Guillain-Barre syndrome
- Multifocal motor neuropathy with conduction block (*asymmetric)
- GM1-antibody associated motor neuropathy
- Porphyria
- Lead intoxication
- Diphtheria
- Dapsone, Vincristine
- Hereditary (CMT)

Motor Neuron Diseases
- ALS (hyperreflexia) (*asymmetric)
- Spinal muscular atrophy
- Kennedy’s disease

Distal Myopathies
- Inclusion body myositis
- Distal muscular dystrophies

NMJ disorders
- Lambert Eaton myasthenic syndrome
Subacute Polyradiculopathy

- Inflammatory (GBS, CIDP)
- Vasculitis
- Diabetes
- Infectious (HIV, CMV, Lyme)
- Sarcoid
- Paraproteinemia
- Infiltrative (amyloid, neoplastic)
- Vascular malformation (dural AVF)
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- Inclusion body myositis
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- Lambert Eaton myasthenic syndrome
“Mononeuritis Multiplex”
Etiologies

• Vasculitis, Vasculitis, Vasculitis
  • Hepatitis C (Cryoglobulinemia)
  • Diabetes
  • Sarcoidosis
  • Amyloidosis
• Hereditary neuropathy with liability to pressure palsies (chrom 17 deletion)
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• Multifocal motor neuropathy with conduction block (motor only)
Medications that Cause Neuropathy

**Sensorimotor**
- Amiodarone
- Colchicine (+myopathy)
- Disulfiram
- Isoniazid
- Nitrofurantoin
- Phenytoin
- Tacrolimus
- Taxanes (paclitaxel, docetaxel)
- Thalidomide
- Vinca alkaloids

**Sensory**
- Cisplatin
- Ethambutol
- Metronidazole
- Nitrous oxide
- Nucleoside analogues (ddC, ddI)
- Pyridoxine

**Motor**
- Chloroquine (+myopathy)
- Dapsone
- Vincristine
• 50 yo man
• 3 months of painless, progressive right wrist drop
• 6 months later - left wrist drop
• No sensory loss
Multifocal Motor Neuropathy with Conduction Block (MMN)

Clinical:
- Single or multiple nerves
- Not at common sites of compression
- Radial nerve predilection

GM1 antibodies + (~ 50%)

Treatment:
- IVIg
- Cyclophosphamide
- Rituximab (3 pts)*

* Stieglbauer et al. Neuromuscular Disorders 2009