Doctor, I have dizzy feet!

Evaluation of patients with suspected neuropathy
Table 15.1

Epidemiologic features of peripheral neuropathies

<table>
<thead>
<tr>
<th></th>
<th>Prevalence per 100 000</th>
<th>Incidence* per 100 000 person-years</th>
<th>Gender predominance</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mononeuropathy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>~5000 (5%)</td>
<td>100–376</td>
<td>F &gt; M</td>
<td>Peak 50–60 years</td>
</tr>
<tr>
<td>Ulnar neuropathy</td>
<td>7–14</td>
<td>20</td>
<td>M &gt; F</td>
<td>Peak 50–70 years</td>
</tr>
<tr>
<td>Radial neuropathy</td>
<td>ND</td>
<td>2</td>
<td>M &gt; F</td>
<td>ND</td>
</tr>
<tr>
<td>Peroneal neuropathy</td>
<td>19</td>
<td>17</td>
<td>M &gt; F</td>
<td>ND</td>
</tr>
<tr>
<td>Meralgia paraesthesia</td>
<td>71</td>
<td>11–43</td>
<td>F = M</td>
<td>Peak 50–60 years</td>
</tr>
<tr>
<td><strong>Cranial nerves</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial nerve (Bell’s) palsy</td>
<td>28–143</td>
<td>12–40</td>
<td>F = M</td>
<td>Peak 15–45 years</td>
</tr>
<tr>
<td>Sixth-nerve palsy</td>
<td>ND</td>
<td>10</td>
<td>M &gt; F</td>
<td>Increasing with age</td>
</tr>
<tr>
<td>Fourth-nerve palsy</td>
<td>ND</td>
<td>6</td>
<td>M &gt; F</td>
<td>Increasing with age</td>
</tr>
<tr>
<td>Third-nerve palsy</td>
<td>ND</td>
<td>4</td>
<td>M &gt; F</td>
<td>Increasing with age</td>
</tr>
<tr>
<td><strong>Multifocal neuropathies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mononeuritis multiplex</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Multifocal motor neuropathy</td>
<td></td>
<td>1</td>
<td>M &gt; F</td>
<td>Peaks 20–50 years</td>
</tr>
<tr>
<td><strong>Acute polyneuropathy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guillain–Barré syndrome</td>
<td>ND</td>
<td>1–2</td>
<td>M &gt; F</td>
<td>Increasing with age</td>
</tr>
<tr>
<td><strong>Chronic polyneuropathy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic polyneuropathy</td>
<td>~200–600</td>
<td>23–54</td>
<td>CR</td>
<td>Increasing with age</td>
</tr>
<tr>
<td>Idiopathic polyneuropathy</td>
<td>~200</td>
<td>32</td>
<td>M &gt; F</td>
<td>Increasing with age</td>
</tr>
<tr>
<td>Hereditary polyneuropathy</td>
<td>40</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>CIDP</td>
<td>1–8</td>
<td>0.2–0.5</td>
<td>M &gt; F</td>
<td>Increasing with age</td>
</tr>
<tr>
<td>Toxic neuropathies</td>
<td>~100</td>
<td>ND</td>
<td>M &gt; F</td>
<td>Increasing with age</td>
</tr>
</tbody>
</table>

*Prevalence data for nonchronic diseases like carpal tunnel syndrome, Bell’s palsy, and Guillain–Barré syndrome is less informative. Incidence of these diseases is important from an epidemiologic perspective. These rates are mostly derived from registered new cases in a certain time period. ND, no data available; CR, conflicting results; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy.
Causes of chronic polyneuropathy

- Diabetes: 34%
- Idiopathic (CIAP): 23%
- Inflammatory: 13%
- Toxic: 13%
- Hereditary: 6%
- Connective tissue disease/vasculitis: 4%
- Metabolic: 4%
- Nutritional deficiency: 3%
- Other: 2%
Signs and symptoms

- **Large fiber modalities**
  - Ataxia esp. in the dark
  - Are you ok in the shower
  - Weakness > EHL, TA, IO
  - Vibratory sensory loss
  - Abnormal sensation to touch
  - Loss of reflexes

- **Small fiber modalities**
  - Pain -> “prickling”, “burning”, “shooting”
  - Allodynia
  - Dysethesia
  - Loss of temperature sensation ->”numbness”, “tightness”, “coldness”
  - muscle cramping!
  - Preserved reflexes
  - Non-length dependent and asymmetric!

- **Autonomic features**
  - Dizziness on standing
  - Orthostatic hypotension or intolerance
  - Dry eyes/mouth
  - Nausea/constipation/nocturnal diarrhea/early satiety/dyuria
  - Abnormal flushing
  - Abnormal sweating
  - “brain fog”
Signs and symptoms

- Onset
- Distribution: symmetric vs. asymmetric, distal vs. proximal
- Systemic features:
  - Skin changes
  - Joint inflammation
  - Fevers chills
  - Autonomic features
- If non-length dependent features, acute or subacute onset, and systemic signs -> 96% sensitive, 89% specific for inflammatory etiology
Exam:

Trophic changes:
- Altered hair growth
- Altered nail growth
- Skin dryness
Special patterns

- Gangionopathy/sensory neuronopathy:
  - Severe large fiber sensory loss that is not length dependent i.e. in fingers + pseudoathetosis
    - Anti-HU, Sjogren’s, Pyridoxine toxicity
- Mononeuritis multiplex:
  - Vasculitis
  - Lewis-Sumner variant of CIDP
  - Could just be DM
  - Cranial nerve involvement
- Multiple mononeuropathies at compression sites:
  - CTS, ulnar neuropathy at elbow, fibular neuropathy at fib head
  - HNPP PMP22 deletion
- Diabetic radiculoplexus neuropathy -> e.i. diabetic amyotrophy
  - Unilateral proximal leg muscles
Assessment/Plan

• Neuropathy? What kind based on exam/clinical presentation?
• Is something else going on:
  • Spinal stenosis esp. in elderly?
  • Superimposed mononeuropathy -> CTS and/or ulnar and fibular neuropathies
  • Superimposed radiculopathy -> most common C7 and L5/S1

• Plan:
  • EMG/NCS
  • Labs
  • consider : LP nerve BX
  • PT if gait imbalance
  • Neuropathic pain treatment
### Carpal tunnel syndrome

**Table 17-2. Clinical Symptoms and Signs**

<table>
<thead>
<tr>
<th>Highly Suggestive of Carpal Tunnel Syndrome</th>
<th>Possible Carpal Tunnel Syndrome</th>
<th>Inconsistent with Carpal Tunnel Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal paresthesias awakening patient from sleep</td>
<td>Hand, wrist, forearm, arm, and/or shoulder pain</td>
<td>Neck pain</td>
</tr>
<tr>
<td>Shaking or ringing the hands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain/paresthesias associated with driving or holding a phone, book, or newspaper</td>
<td>Perception of paresthesias involving all five digits</td>
<td>Paresthesias radiating from neck and shoulder down the arm</td>
</tr>
<tr>
<td>Sensory disturbance of digits 1, 2, 3, and 4, splitting the fourth digit</td>
<td>No fixed sensory disturbance, or sensory disturbance of digits 1, 2, 3, and/or 4</td>
<td>Unequivocal numbness over the thenar eminence</td>
</tr>
<tr>
<td>Weakness/wasting of thenar eminence</td>
<td>Decreased hand dexterity</td>
<td>Weakness/wasting of hypothenar muscles, thumb flexion (interphalangeal joint), arm pronation, and/or elbow flexion/extension</td>
</tr>
<tr>
<td>Phalen’s maneuver reproduces symptoms</td>
<td>Tinel’s sign over the median nerve at the wrist</td>
<td>Reduced biceps or triceps reflexes</td>
</tr>
</tbody>
</table>
CTS etiology

- most are idiopathic
- compression from repeated stress to connective tissue (edema, vascular sclerosis, fibrosis) causes ischemia and demyelination with possible wallerian degeneration and axonal loss

- **DDx**: C6-7 radiculopathy, proximal median nerve lesion, brachial plexopathy

### Box 17-1. Conditions Associated with Carpal Tunnel Syndrome

<table>
<thead>
<tr>
<th>Idiopathic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetitive stress</td>
</tr>
<tr>
<td>Occupational</td>
</tr>
<tr>
<td>Endocrine disorders</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Acromegaly</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Connective tissue disease</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Tumors</td>
</tr>
<tr>
<td>Ganglia</td>
</tr>
<tr>
<td>Lipoma</td>
</tr>
<tr>
<td>Schwannoma</td>
</tr>
<tr>
<td>Neurofibroma</td>
</tr>
<tr>
<td>Hemangioma</td>
</tr>
<tr>
<td>Congenital disorders</td>
</tr>
<tr>
<td>Persistent median artery</td>
</tr>
<tr>
<td>Congenital small carpal tunnel</td>
</tr>
<tr>
<td>Anomalous muscles (palmaris longus, flexor digitorum sublimis)</td>
</tr>
<tr>
<td>Infectious/inflammatory</td>
</tr>
<tr>
<td>Sarcoid</td>
</tr>
<tr>
<td>Histoplasmosis</td>
</tr>
<tr>
<td>Septic arthritis</td>
</tr>
<tr>
<td>Lyme</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Fractures (especially Colles’ fracture)</td>
</tr>
<tr>
<td>Hemorrhage (including anticoagulation)</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Spasticity (persistent wrist flexion)</td>
</tr>
<tr>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Amyloidosis (familial and acquired)</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Any condition that increases edema or total body fluid</td>
</tr>
</tbody>
</table>
Spinal stenosis

- Insidious onset of usually symmetric symptoms
- Low back pain and morning stiffness
  - Usually relieved by activity
- Low back, calf/thigh discomfort -> cramping
- Numbness and tingling in legs and thighs
- Weakness after prolonged standing/walking

- Sx worse when spine extended -> walking/standing , better when spine is flexed (leaning on shopping cart) -> sitting bending forward
- Latency between spine extension and onset of sx decreases with worsening stenosis -> neurogenic claudication
- Descending stairs worse than ascending stairs (as opposed to vascular claudication
- Exam is usually normal at rest but can see sensory loss/hyporeflexia/mild weakness if examined immediately after extended period of walking
The purpose of nerve conduction studies

- Is it a neuropathy?
- Sensory, motor, or both?
- Assess for demyelinating features?
- Is there muscle denervation?
- Is there radiculopathy?
- Are symptoms commensurate with EDX findings?
Basic EDX principles for assessment of neuropathies:

**Large-fiber sensorimotor polyneuropathy:**
Longest nerves affected first
Usually symmetrically
Sensory nerves affected before motor
sural/superficial fibular > ulnar > radial > median
F waves prolonged
If neuropathy is severe, can see denervation on EMG in distal > proximal muscles

**Small fiber neuropathy:**
Normal

**Radiculopathy:**
Hallmark: *preserved sensory responses low motor responses and signs of denervation*

**Spinal stenosis:**
Normal sensory response. Motor responses are normal in half of cases especially mild/early.

**Motor neuropathy:**
Low compound muscle action potentials but sensory action potential preserved
Muscle denervation on EMG
DDX: myopathy, motor neuron disease, LEMS radiculopathy
Demyelination
<table>
<thead>
<tr>
<th>Fiber Type(s)</th>
<th>Name</th>
<th>Subtype</th>
<th>Diameter (mm)</th>
<th>Conduction Velocity (m/s)</th>
<th>Alternative Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myelinated Somatic Afferent/Efferent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous afferent</td>
<td>A β</td>
<td>δ</td>
<td>6–12</td>
<td>35–75</td>
<td>α</td>
</tr>
<tr>
<td>Muscle afferent</td>
<td>A α</td>
<td>β, δ</td>
<td>12–21</td>
<td>80–120</td>
<td>I, Ia, Ib</td>
</tr>
<tr>
<td>Muscle efferent</td>
<td>A</td>
<td>δ</td>
<td>1–5</td>
<td>5–30</td>
<td>III</td>
</tr>
<tr>
<td>Anterior horn cells (α and γ motor neurons)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Myelinated Autonomic Efferent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preganglionic efferent</td>
<td>B</td>
<td></td>
<td>3</td>
<td>3–15</td>
<td></td>
</tr>
<tr>
<td><strong>Unmyelinated Somatic/Autonomic Afferent/Efferent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postganglionic efferent</td>
<td>C</td>
<td></td>
<td>0.2–1.5</td>
<td>1–2</td>
<td>IV</td>
</tr>
<tr>
<td>Afferent to dorsal root ganglion (pain)</td>
<td>C</td>
<td></td>
<td>0.2–1.5</td>
<td>1–2</td>
<td></td>
</tr>
<tr>
<td><strong>Sensory Receptor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair follicle</td>
<td>A β</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin follicle</td>
<td>A β</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spindle</td>
<td>A a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint receptor</td>
<td>A β</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain, temperature</td>
<td>A δ, C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Demyelinating Findings on NCS

- slowing of conduction velocity
- prolonged distal latency
- abnormal temporal dispersion
- conduction block
- prolonged/absent late responses (F-waves)
Demyelinating Lesions

FIGURE 16-2. Demyelination and nerve conduction studies. Demyelination results in marked slowing of conduction velocity and, if severe enough, conduction block. The underlying axon remains intact, however, and Wallerian degeneration does not occur. Nerve conduction parameters vary in demyelination, depending on the site(s) of demyelination. 

A: Demyelination affecting proximal, intermediate, and distal segments of nerve. This distribution results in conduction velocity slowing, prolonged distal latencies (DLs), prolonged late responses, reduced distal amplitudes, and conduction block between distal and proximal stimulation sites.  

B: Demyelination affecting only distal nerve segments. This distribution results in prolonged DLs and reduced distal amplitudes, when the nerve is stimulated at the wrist and elbow. Because late responses also travel through the distal segment, they are prolonged as well. Conduction velocities are normal, however, and no conduction block is seen between the usual distal and proximal stimulation sites. If a more distal site can be stimulated (e.g., the palm), then a conduction block pattern may be seen between the more distal stimulation site (palm) and the usual distal stimulation site (wrist).  

C: Demyelination affecting only proximal nerve segments. In this pattern, DLs, amplitudes, and conduction velocities are normal. The only abnormality on routine studies may be prolongation of late responses. If it is possible to stimulate a very proximal site, a conduction block pattern may be seen between the very proximal stimulation site and the usual proximal stimulation site (elbow).
Conduction velocity slowing
Distal latency prolongation

• Normal CV in arms is > 48 m/s
• Normal CV in legs is > 40 m/s
• any motor or sensory CV lower than 35m/s in the arms or 30m/s in the legs are due to demyelination
• Conduction velocity can be slow due to axonal loss if larger, more highly myelinated axons are preferentially lost
FIGURE 3–21 Temporal dispersion without conduction block. A marked drop in proximal compound muscle action potential (CMAP) amplitude usually means conduction block. In the figure above, there is no conduction block between distal and proximal stimulation sites. The drop in amplitude was entirely due to abnormal temporal dispersion from a demyelinating lesion. To differentiate conduction block from abnormal temporal dispersion requires a drop in area >50%, which is not seen here.
Conduction Block

FIGURE 3-19 Model of conduction block. In acquired demyelinating lesions, demyelination is often a patchy, multifocal process. When the nerve is stimulated proximal to the conduction block, the compound muscle action potential (CMAP) drops in amplitude and area and becomes dispersed (bottom). In a normal nerve (top), the CMAP morphology usually is similar between distal and proximal stimulation sites.

Prolonged latency of F-waves
# Acquired Demyelinating Neuropathies

## Table 1 | Clinical presentation and therapy

<table>
<thead>
<tr>
<th>Neuropathy</th>
<th>Common clinical presentations</th>
<th>First-line therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
<td>Typical: proximal and distal weakness with large-fibre sensory loss (50% of cases) Atypical: distal large fibre sensorimotor neuropathy (24–35% of cases); multifocal sensorimotor neuropathy (8–15% of cases)</td>
<td>Intravenous immunoglobulin Corticosteroids Plasmapheresis</td>
</tr>
<tr>
<td>Anti-MAG (myelin-associated glycoprotein) neuropathy</td>
<td>Distal large fibre sensorimotor neuropathy</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Multifocal motor neuropathy</td>
<td>Multifocal weakness</td>
<td>Intravenous immunoglobulin</td>
</tr>
<tr>
<td>POEMS syndrome</td>
<td>Distal sensorimotor neuropathy; severe pain (75% of cases)</td>
<td>Melphalan with autologous bone marrow transplant Lenalidomide</td>
</tr>
</tbody>
</table>

Latov, N. (2014) Diagnosis and treatment of chronic acquired demyelinating polyneuropathies

*Nat. Rev. Neurol.* doi:10.1038/nrneurol.2014.117
**CIDP**

**Table 4 Clinical diagnostic criteria**

(1) Inclusion criteria
(a) Typical CIDP
   - Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and
   - Absent or reduced tendon reflexes in all extremities
(b) Atypical CIDP (still considered CIDP but with different features)
   - One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):
     - Predominantly distal (distal acquired demyelinating symmetric, DADS) or
     - Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis–Sumner syndrome] or
     - Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)
   - Pure motor or
   - Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)

(2) Exclusion criteria
- Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy
- Hereditary demyelinating neuropathy
- Prominent sphincter disturbance
- Diagnosis of multifocal motor neuropathy
- IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein
- Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features

**Weakness (distal +/- proximal)**
**Large fiber sensory loss**
**Arreflexia**
**Table 1  Electrodiagnostic criteria**

(1) **Definite:** at least one of the following
   
   (a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
   
   (b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or
   
   (c) Prolongation of F-wave latency ≥30% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP < 80% of LLN values), or
   
   (d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN + ≥1 other demyelinating parameter\(^a\) in ≥1 other nerve, or
   
   (e) Partial motor conduction block: ≥50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter\(^a\) in ≥1 other nerve, or
   
   (f) Abnormal temporal dispersion (> 30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves, or
   
   (g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms)\(^b\) + ≥1 other demyelinating parameter\(^a\) in ≥1 other nerve

(2) **Probable**

 ≥30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter\(^a\) in ≥1 other nerve

(3) **Possible**

 As in (1) but in only one nerve
CIDP supporting criteria

Table 5: Supportive criteria

1. Elevated CSF protein with leukocyte count < 10/mm³ (level A recommendation)
2. MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses (level C recommendation)
3. Abnormal sensory electrophysiology in at least one nerve (good practice points):
   a. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or
   b. Conduction velocity < 80% of lower limit of normal (< 70% if SNAP amplitude < 80% of lower limit of normal); or
   c. Delayed somatosensory evoked potentials without central nervous system disease
4. Objective clinical improvement following immunomodulatory treatment (level A recommendation)
5. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis (good practice point)
CIDP Diagnostic Challenges

- Clinically heterogeneous
- No biomarkers
- Elevated CSF protein in 83-95% (Dyck, 1981)
- In atypical CIDP (eg. Lewis-Sumner) protein elevated in 33-42% (Viala, 2004)
- Diabetes can cause elevated protein (mean 77mg/dl, as high as 440mg/dl)
- Nerve biopsy may be non-diagnostic in multifocal or proximal disease
- 14 different criteria requiring different numbers of demyelinating findings

- Bottom line: diagnosis may be tricky at times. Demyelinating findings are sometimes called erroneously.
- IVIG is rather safe BUT has HIGH placebo effect and is very EXPENSIVE
- Consider Expert referral
Workup for Neuropathy

**Sensory Large Fiber Neuropathy/ gangionopathy**

Hemoglobin A1c/ oral glucose tolerance test
B12
Pyridoxine (B6 level)
SPEP with IFE
UPEP
Quantitative immunoglobulins
Anti-MAG
Anti-Gliadin ab (IgA and IgG)
Tissue transglutaminase Ab IgA
ENA panel (Sjogrens panel)
ANA
RF
ANCA
Copper level
Lyme Antibody titer
Anti-Hu

Hepatitis B/C
Anti-GD1b
Anti-sulfatide
Vitamin E level (if ataxia/cerebellar)
Heavy Metal screen
RPR
Thiamine (in alcoholics/bariatric surgery)
ESR (if multifocal)
TTR amyloid
Small Fiber Neuropathy
Hemoglobin A1c/ oral glucose tolerance test
B12
ENA panel (Sjogrens panel)
Anti-MAG
SPEP/IFE serum and urine (quantitative immunoglobulins)
ESR
ANA
RF
TTR Amyloid

Anti-Hu
Anti-sulfatide
Hepatitis B/C
Anti-GD1b
Alpha-galactosidase (if there is Family history for Fabry’s disease)
Pyridoxine (B6 level)

Skin Biopsy- if painful (consider Autonomic testing)
Sensorimotor neuropathy Labs
Hemoglobin A1c/ oral glucose tolerance test
Serum and urine IFE
Quantitative immunoglobulins
B12
GM1 ganglioside Ab
Anti-MAG
Hepatitis B/C
ESR
ANA
RF
Anti-GD1b
Anti-sulfatide Ab
ANCA
Copper
Paraneoplastic panel
Workup for Neuropathy

- **When to consider LP:**
  - If clinical suspicion for CIDP or inflammatory neuropathy is high but NCS?EMG is equivocal or in some case small fiber neuropathy

- **When to consider nerve bx:**
  - If vasculitis or amyloid is considered
Monoclonal Gammopathy

- Proliferation of a single clone of plasma cells/B-Cells, which produce a homogenous monoclonal protein (M protein)

- Each monoclonal protein consists of two heavy chains of the same class and two light chains of the same type

- Polyclonal gammopathy consists of one or more heavy chain classes and both light chain types: Reactive or due to an inflammatory disease.
Immunoglobulin: heavy and light chains

- **Heavy chains:** IgG (γ), IgM (μ), IgA (α), IgE (ε), IgD (δ)

- **Light chains:** Kappa (κ) and Lambda (λ)
Protein Electrophoresis & IFE

• In 1937, Tiselius used electrophoretic techniques to separate serum globulins into three components: alpha, beta, gamma.
Monoclonal Gammopathy

- Limited monoclonal B-cell/plasma cell proliferation in the bone marrow
- The most common plasma cell dyscrasia
- A heterogeneous group of disorders, ranging from the subclinical MGUS (a premalignant disorder) to malignant disorders such as MM, amyloidosis, Waldenström macroglobulinemia, POEMS syndrome or other lymphoproliferative disorders.
- The prevalence of monoclonal gammopathy increases with age:
  - 1% in > 25 years
  - 3% in >50 years
  - 5% in >70 years
  - 10% in >80 years
MGUS

- Men > Women
- African Americans (x3) > White
- Other factors: Family Hx, Immunosuppression and pesticide exposure.
- The risk of progression from MGUS to malignant plasma cell dyscrasia, is 1% per year
Monoclonal Gammopathy

- Nonmalignant monoclonal gammopathy:
  - Serum M protein < 3 g/dl
  - Bone marrow clonal plasma cells less than 10%
  - Absence of organ or tissue impairment:
    - NO lytic bone lesions, anemia, hypercalcemia, renal insufficiency, amyloidosis, or recurrent bacterial infections
  - No weight loss or bone tenderness
MGUS: Neuropathy

- In 1936, Bing and Neel reported the first case of peripheral neuropathy associated with macroglobulinemia

- After adjusting for age, the prevalence of monoclonal gammopathy is greater than 10% in patients with idiopathic neuropathy (Kelly 1981)

- 85 to 100% of the patients with the osteosclerotic Multiple Myeloma have neuropathy

- Up to 1/3 of MGUS patients have neuropathy
IgM related Peripheral Neuropathy

- The majority of patients with IgM gammopathy have MGUS, and remaining have Waldenström macroglobulinemia or other lymphoproliferative disorders.

- IgM protein can directly bind to peripheral nerve myelin sheaths and IgM Ab to neural antigens have been found in MGUS patients with neuropathy, but not in those without neuropathy. (Nobile-Orazio 1994)

- 50% have anti-MAG Ab and EM reveals deposition of IgM on nerve myelin with associated separation of the outer layers of compacted myelin.
IgG and IgA related Peripheral Neuropathy

- The association with neuropathy is not well understood.

- IgG is the most common M protein and is associated with MGUS, MM and POEMS.

- Most patients with IgG MGUS do not have neuropathy and neuropathies associated with IgG MGUS include the full spectrum of neuropathic disorders.

- Patients with CIDP and IgG MGUS are similar to other CIDP patients.

- IgG monoclonal gammopathy, unless in a patient with myeloma, amyloid, or POEMS, may be an incidental finding and have no relationship to the neuropathy.
Initiating treatment of inflammatory neuropathies

- If real demyelinating findings on NCS consider trial of IVIG.
- EARLY expert referral if no clear improvement
- Consider expert referral when demyelinating findings but small fiber neuropathy phenotype
- If anti-MAG positive expert referral for consideration of rituximab
- If SPEP/UPEP abnormal referral to hematology
- If IgG lambda check VEGF levels, refer to hematology for consideration of POEMS
- If elevated inflammatory markers, refer to rheum, trial of steroids prednisone 20-40 mg
Symptomatic treatment for neuropathic pain

- NNT for most tested drugs is at least 4-5
- Try one at a time, if not working at medium to high dose, stop and switch
- If working somewhat add another agent e.g. SNRI+GBP/lyrica + AED combos

- GBP (sedation, leg swelling)
- Lyrica (sedation, leg swelling, weight gain)
- Cymbalta (nausea/Gi distress psychiatric/sexual)
- Oxcarbazepine (sedation, hyponatremia)
- Lamotrigine (rash)
- Lacosamide
- Tramadol
- Amitriptyline (sedation, cardiac)
- Topamax, nortriptyline, venlafaxine

- Adjunctive measures:
  - lidocaine cream
  - Namenda
  - Ketamine cream
  - Botox
  - Neudexta
  - spinal cord stimulator

- Future:
  - Growth factor injections (clinical trials)
What we tell patients

• Even pre-diabetes can cause small fiber neuropathy and improved glycemic control results in improved symptoms

• Idiopathic neuropathies are usually indolent and do not progress a lot; prognosis is good

• Manage expectations re: pain control. We can usually achieve a level of pain control that lets you function and doesn’t keep you up at night. You are unlikely to have complete recovery of sensation. It may take a lot of medication switches to achieve control

• PT really does work. If it doesn’t may need to switch PT providers