OBJECTIVES

1. Introduction
2. Review basic concepts of peripheral nerve anatomy and neuropathic symptoms.
3. Clinical diagnosis.
4. Classification of peripheral neuropathies. Small vs large fiber predominant.
5. Approach to underlying etiology: laboratory work-up and other investigations.
1. INTRODUCTION

- Polyneuropathy: widespread damage/dysfunction of peripheral nerves.
- Various degrees of sensory, motor and autonomic dysfunction.
- Relatively high prevalence (2-8% of adults).
- Narrow spectrum of symptoms (tingling, numbness, weakness), but many possible etiologies:
  - Inherited
  - Acquired: metabolic, toxic, nutritional, inflammatory, immune-mediated, infectious, infiltrative...

2a. PERIPHERAL NERVE ANATOMY

Peripheral nerves contain 2 types of nerve fibers (size/diameter):

- Large fibers (myelinated)
  - Motor
  - Sensory (vibration, joint position, light touch)
- Small fibers (thin or no myelin)
  - Sensory (pain, temperature -cold and hot-)
  - Autonomic

2b. NEUROPATHIC SYMPTOMS

- Positive ("gain of function") → reflect axonal membrane instability/hyperexcitability.
  - Most common in acquired, especially small fiber neuropathies.
  - Burning/coldness, pricking, stabbing, lancinating, shock-like pain (small sensory fibers)
  - Cramps, fasciculations, muscle spasms (motor fibers).
- Negative ("loss of function") → reflect axonal degeneration or demyelination.
  - Most common in large fiber predominant neuropathies.
  - Numbness, imbalance, loss of coordination and dexterity (large sensory fibers).
  - Weakness, atrophy (motor fibers).
2b. NEUROPATHIC SYMPTOMS (cont.)

- Autonomic symptoms
  - Blurred vision
  - Dry eyes and mouth
  - Dysphagia, gastroparesis
  - Constipation/diarrhea
  - Urinary retention/incontinence
  - Erectile dysfunction
  - Decreased or increased sweating
  - Orthostatic lightheadedness, resting tachycardia.

3. CLINICAL DIAGNOSIS OF PERIPHERAL NEUROPATHY

- Relies heavily on pattern recognition.
- Important questions to ask:
  - What symptoms? Where? When?
  - What is the quality of the pain? Can you feel temperature and pain?
  - How is your balance? Dexterity/fine motor skills? Any falls?
  - Autonomic symptoms?
  - Any family history of PN?
  - Comorbidities?
  - Previous toxic exposures, viral illness, weight loss?
  - BMI, how is your diet? What do you drink?

3. CLINICAL DIAGNOSIS OF PERIPHERAL NEUROPATHY

- Examination:
  - All modalities of sensation: pinprick, temperature, light touch, vibration, proprioception.
  - Motor strength and reflexes.
  - Gait and balance.
  - Pay attention to foot deformities (high arches, curled toes) and foot atrophy.
4. CLASSIFICATION OF PERIPHERAL NEUROPATHIES

**TEMPORAL COURSE**
- Acute
- Subacute
- Chronic

**PATTERN**
- Sensory
- Multifocal
- Motor

**MODALITIES**
- Length-dependent
- Non-length-dependent
- Multifocal

**Small fiber neuropathy**
- Pain is common, thermal dysesthesias ("burning feet"); worse at night.
- +/− autonomic symptoms.
- Normal strength and reflex. Abnormal pinprick and temperature.
- Nerve conduction studies normal.
- Causes significant morbidity (neuropathic pain is often difficult to treat) and mortality.

**Large fiber neuropathy**
- Numbness, tingling, ataxia/imbalance +/− weakness, atrophy.
- Frequent falls, gait disturbance.
- Abnormal light touch, vibration; loss of reflexes. Distal weakness.
- Nerve conduction studies/needle EMG.

**Fiber-type predilection (small vs. large) points towards underlying etiology and guides investigations, treatment and prognosis.**

**Small fiber neuropathy: laboratory work-up**

**Metabolic/toxins**
- Diabetes/mellitus
- Renal and/or metabolic syndrome
- Alcohol toxicity
- Uremia
- Malabsorption/chronic diarrhea

**Fasting glucose, hemoglobin Alc**
- Lipid profile, CRP
- Creatinine
- CBC, B complex vitamins

**Inflammatory/autoimmune**
- Sjögren syndrome and other connective tissue disorders
- Hepatitis C and HIV virus, postinfectious symptoms
- Other suspected immune-mediated conditions (e.g., ANCA, ANFB, autoantibodies)

- ESR, CRP
- Serologies for Hepatitis C and HIV
- Anti-dsDNA and anti-CCP antibodies

**Genetic**
- TTR anemia (FTRK, TTRK)
- Fabry disease
- Hereditary sensory and autonomic neuropathy
- Sodium channelopathies (SCN9A, 10A, 11A)

- SPEP with IF, free light chains in serum
- TTR gene analysis
- Serum alpha-galactosidase activity, GLA gene test
- HDL cholesterol level
- Genetic testing
### Small fiber neuropathy: other investigations

- In pure SFN, NCS/EMG are normal, exclude concomitant large fiber involvement.
- **Skin punch biopsies**
  - "Gold standard" for the diagnosis of SFN: sensitivity 45-80% and specificity 95%.
  - Number of nerve fibers per mm of skin = intraepidermal nerve fiber density (IENFD).
  - Normal skin biopsies DO NOT exclude SFN.
- **Thermoregulatory sweat test (TST).**
- **Autonomic reflex screen (ARS):** battery of tests to assess autonomic functions (sudomotor, cardiovagal and adrenergic).
  - **Sudomotor:** Quantitative sudomotor axon reflex test (QSART).
  - **Heart rate variability** (deep breathing).
  - **HR and BP response to Valsalva and tilt**:
    - Valsalva: healthy subjects develop tachycardia and peripheral vasoconstriction during strain, then bradycardia and increase in BP when released.
    - Tilt: BP drop >20 mmHg systolic and/or 10 mmHg diastolic consistent with OH.
- **Others:**
  - Gastric emptying studies.
  - Urodynamic studies.
  - Barium swallow.

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### Sensory predominant: laboratory work-up

<table>
<thead>
<tr>
<th>Metabolic-toxic-nutritional</th>
<th>Inflammatory-immune</th>
<th>Inherited (common)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (long-standing)</td>
<td>Rheumatologic (WBC, CRP, ESR, IgM)</td>
<td>Charcot-Marie-tooth disease and other inherited</td>
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<tr>
<td>End-stage renal disease</td>
<td></td>
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<tr>
<td>Vitamin-B12, copper, folate deficiency</td>
<td>Sjögren syndrome and other CTD</td>
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</tr>
<tr>
<td>Vitamin B6, copper, folate deficiency</td>
<td>Paraneoplastic (anti-MAG)</td>
<td></td>
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<tr>
<td>Chemotherapy-related</td>
<td>Malignant lymphoma</td>
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<td></td>
<td>HIV, Lyme, syphillis</td>
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<tr>
<td></td>
<td>Sjögren syndrome and other CTD</td>
<td></td>
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</tbody>
</table>

- Fasting glucose, hemoglobin A1c
- CRP, creatinine, BUN
- Vitamin-B12, methionine, choline, copper levels, ceruloplasmin, vitamin B6 > 80-100
- SS-A, SS-B, ANA, ds-DNA, RF, CCP, ESR, CRP
- Paraneoplastic panel
- HIV/Lyme screening, RPR
- MELAS antibodies
- CSF proteins
- IgG/DS antibodies
- Genetic testing low yield in relatively mild, sensory predominant polyneuropathy even when inherited is likely.
Motor predominant: laboratory work-up

- Guillain-Barré syndrome (AIDP, axonal variants)
- CIDP
- Multifocal motor neuropathy
- Vasculitic (mononeuropathy multiplex)
- POEMS syndrome
- Paraneoplastic (CRMP-5, amphiphysin)
- Neurolymphomatosis

Guillain-Barré syndrome (AIDP, axonal variants)
- Ganglioside Ab (GM1, GD1a, GD1b) in axonal GBS
- Complements, neurofascin in refractory CIDP
- CGM antibodies
- Gbx, CAP, HLA, MPO, PaCa, screening ETO
- VEGF, UPR with immunofluorescence, ETO
- Paraneoplastic panel

Charcot-Marie-Tooth disease
- Peripheral neuropathy gene panel
- TTR gene analysis
- Porphobilinogen, AUA in urine
- PMP22 deletion analysis

Thiamine deficiency
- Thiamine levels, other vitamins

Peripheral neuropathy: other investigations

- Nerve conduction studies/EMG
  - Sensitive and objective method to assess function and integrity of large sensory and motor fibers.
  - What information does it add?
  - Confirm PN and exclude other causes.
  - Evaluate severity and extent of involvement: distal, proximal/distal, multifocal.
  - Pathophysiology: axonal vs. demyelinating.
  - Prognosis and response to treatment in some cases.

DIABETIC POLYNEUROPATHY

- Most common complication of diabetes, 50-60% of all diabetic patients.
- Sensory first – small then large sensory fibers.
- Distal motor involvement later.
- Severity often correlates with glycemic control and chronicity.
- Other microvascular complications: nephropathy, retinopathy.
- Neuropathic pain and foot ulceration leading to gangrene and limb loss are the most feared complications.
- Huge economic burden. Annual costs more than $10 billion in the US.
**Diabetic Neuropathies**

<table>
<thead>
<tr>
<th>Symmetric</th>
<th>Asymmetric</th>
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<tbody>
<tr>
<td>- Small fiber neuropathy</td>
<td>- Cranial neuropathies (III, VI)</td>
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<tr>
<td>- Diabetic polyneuropathy (DPN)</td>
<td>- Entrapment neuropathies (CTS, ulnar and peroneal)</td>
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<tr>
<td>- Diabetic autonomic neuropathy (DAN)</td>
<td>- Meralgia paresthetica</td>
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<td>- Treatment-induced neuropathy of diabetes (TIND)</td>
<td>- Radiculoplexus neuropathies (diabetic amyotrophy)</td>
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<td>-</td>
<td>- Diabetic thoracic radiculopathies</td>
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Red flags for treatment-induced complications:
- Acute/subacute onset severe neuropathic pain, prominent autonomic symptoms (CH, constipation, urinary retention) → TIND
- Acute/subacute onset of leg weakness and atrophy → Lumbosacral RPN
- Weight loss
- Antecedent of rapid glycemic correction.

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**Charcot-Marie-Tooth Disease and Other Inherited**

- Probably the most overlooked cause of peripheral neuropathy.
- Insidious onset, slowly progressive course.
- Patients become symptomatic in late adulthood (>60 yo).
- Distal predominant, motor > sensory.
- Lack of positive sensory symptoms (burning, dysesthesias).
- High arches, hammertoes, inverted champagne bottled legs, skinny ankles and foot atrophy.
- Family history often under-reported.
- Genetic testing low yield if mild and sensory predominant.

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**Nutritional Neuropathies**

- Subacute onset tingling, sensory loss and ataxia/imbalance.
- Can be associated with myelopathy (subacute combined degeneration).
- Simultaneous onset in hands and feet.
- Examination: hyporeflexia, Babinski sign with absent Achilles.
- Labs: Vitamin B12, methylmalonic acid, folate, copper, thiamine, macrocytosis, anemia, celiac serologies, pernicious anemia screening.
- Axonal sensory > motor polyneuropathy on NCS/EMG
- Vitamin replacement.
NUTRITIONAL NEUROPATHIES

- Acute axonal neuropathy from thiamine deficiency can mimic GBS.
- Rapidly progressive paresthesias/numbness and ascending weakness +/- autonomic symptoms +/- CN involvement (ophthalmoparesis, hearing loss).
- Nausea/vomiting on previous days (mimics “GI illness”).
- NCS/EMG: CV slowing, axonal loss (active denervation).
- Red flags:
  - Pain refractory to medications.
  - Prominent sensory ataxia/limb incoordination.
  - Encephalopathy/confusion/memory disturbance → Wernicke’s encephalopathy.
  - Does not respond to immunotherapies.
- Obtain thiamine levels first, and immediate replacement with thiamine 500 mg IV TID.

DYSPROTEINEMIAS

- Monoclonal proteins found in 10% of patient with peripheral neuropathy (IgM most commonly associated).
- SPEP with immunofixation increases the sensitivity.
- Some distinctive clinical syndromes:
  - DADS (distal acquired demyelinating symmetric) neuropathy.
    - IgM monoclonal protein.
    - 2/3 of patients have anti-MAG antibodies.
    - Demyelinating + axonal on NCS.
    - Often poor response to immunotherapies.
  - POEMS: Polyneuropathy, Organomegaly, Endocrinopathy, M-spike, Skin changes.
    - Ig G or Ig A lambda.
    - Osteosclerotic myeloma.
    - Mixed axonal and demyelinating on NCS.
    - Elevated VEGF.

MEDICATIONS

- Chemotherapies: cisplatin, taxanes, vincristine, thalidomide, bortezomib, pembrolizumab/nivolumab.
- Anti-infectious: metronidazole, chloroquine, isoniazid, nitrofurantoin, HIV drugs.
- Antirheumatic: colchicine.
- Cardiovascular: amiodarone, hydralazine.
- Others: phenytoin, vitamin B6, monoclonal ab, anti-TNF inhibitors.
POLYRADICULONEUROPATHIES

- Proximal and distal weakness.
- Subacute onset, motor >> sensory, often cranial nerve involvement.
- Recommended investigations:
  - NCS/EMG
  - CSF
  - MRI cervical and lumbar spine with and without contrast
  - Screening tests in serum.
  - +/- nerve biopsy.
- Potentially treatable.

CAUSES
- GBS/CIDP
- POEMS
- Lymphoma
- Diabetes
- Sarcoidosis
- West Nile, HIV, Lyme

MULTIPLE MONONEUROPATHIES

- Subacute onset, stepwise progression.
- Asymmetric.
- Motor involvement may be prominent.
- Investigations:
  - NCS/EMG
  - CSF
  - Imaging studies
  - +/- nerve biopsy

CAUSES
- Vasculitis
- MMN
- Diabetes
- Multifocal CIDP
- Leprosy

When to refer to a specialist?

- No cause found despite thorough clinical history and investigations.
- Severe and rapidly progressive (weeks/months).
- Asymmetry, multifocal \(\rightarrow\) mononeuropathy multiplex, multifocal motor neuropathy (MMN).
- Motor predominant symptoms \(\rightarrow\) CIDP, MMN, TTR amyloidosis. Alternative diagnosis (ALS, myopathy, NMJ disorder).
- Prominent sensory loss and ataxia \(\rightarrow\) sensory ganglionopathy.
- Systemic symptoms, weight loss.
- “Refractory” to medications.
When to consider a nerve biopsy?

- Acute/subacute
- Multifocal
- Severe/rapidly progressive

When suspected etiologies are:
- Inflammatory: vasculitis, sarcoidosis.
- Infectious: leprosy.
- Infiltrative: neoplastic (lymphoma), amyloid.

Take Home Points

- Peripheral neuropathies are a common problem.
- Often a thorough clinical history and examination, lab work-up and electrodiagnostic testing point towards etiology.
- Think metabolic when painful paresthesias and obesity (BMI >30), metabolic syndrome, high carbohydrate consumption.
- Think inherited when painless numbness, foot atrophy, foot drop, indolent course.
- EDX criteria for axonal vs. demyelinating should be carefully considered to avoid misdiagnosis and ensure adequate management, particularly concerning the use of immunotherapies.

Thank you!