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Diagnosis of peripheral neuropathies

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DISCLOSURES

Nothing to disclose.

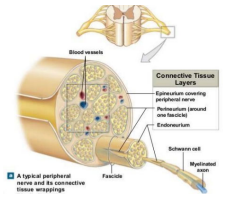
OBJECTIVES

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

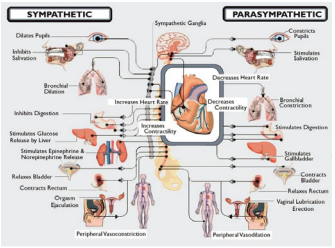
2b. NEUROPATHIC SYMPTOMS

- ✓ **Positive** ("gain of function") → reflect **axonal membrane instability/hyperexcitability.** Spontaneous axonal "misfiring".
  - ✓ Most common in acquired, especially small fiber neuropathies.
  - ✓ Burning/coldness, prickling, stabbing, lancinating, shock-like pain (small sensory fibers) **PAINFUL!**
  - ✓ 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). **PAINLESS!**
  - ✓ 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.



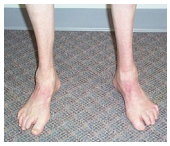
3. CLINICAL DIAGNOSIS OF PERIPHERAL NEUROPATHY

- ✓ 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?
  - ✓ Any weakness? Tripping? Dropping things? Cramping?
  - ✓ Autonomic symptoms?
  - ✓ Any family history of PN?
  - ✓ Comorbidities?
  - ✓ Previous toxic exposures, viral illness, weight loss?
  - ✓ BMI, how is your diet? What do you drink?

Watson JC, Dyck PJ. Peripheral Neuropathy: A Practical Approach to Diagnosis and Symptom Management. Mayo Clin Proc. 2015 Jul;90(7):940-51.

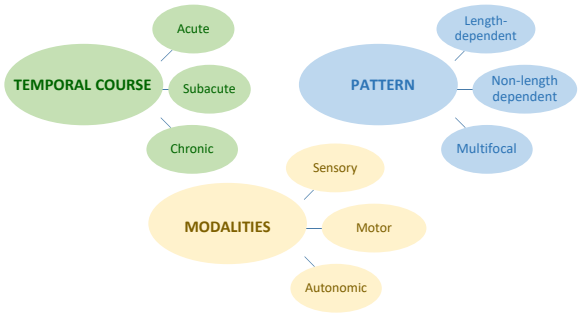
3. CLINICAL DIAGNOSIS OF PERIPHERAL NEUROPATHY

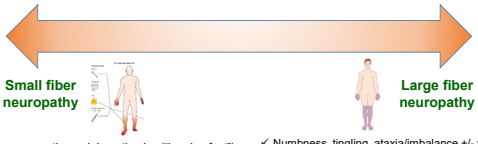
- ✓ Examination:
  - ✓ All modalities of sensation: pinprick, temperature, light touch, vibration, proprioception.
  - ✓ Motor strength and reflexes.
  - ✓ Gait and balance.
  - ✓ Pay attention to foot deformities (high arches, curled toes) and foot atrophy.



Watson JC, Dyck PJ. Peripheral Neuropathy: A Practical Approach to Diagnosis and Symptom Management. Mayo Clin Proc. 2015 Jul;90(7):940-51.

4. CLASSIFICATION OF PERIPHERAL NEUROPATHIES





Small fiber neuropathy

Large fiber neuropathy

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

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

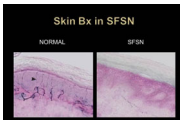
Fiber-type predilection (small vs. large) points towards **underlying etiology** and guides **investigations, treatment and prognosis**.

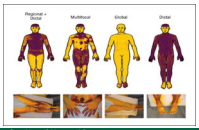
Small fiber neuropathy: laboratory work-up

Metabolic-toxic-nutritional	Diabetes/prediabetes Obesity and metabolic syndrome Alcohol toxicity Uremia Malabsorption/chronic diarrhea Treatment induced neuropathy of diabetes (TIND)	• Fasting glucose, hemoglobin A1c • Lipid profile, CMP • LFTs • Creatinine, BUN • CBC, B complex vitamins, MMA, folate
Inflammatory-immune	Sjögren syndrome and other connective tissue disorders Hepatitis C and HIV viruses, postinfectious Sarcoidosis Other suspected immune-mediated Monoclonal protein (AL amyloidosis)	• SS-A, SS-B, ANA, rheumatoid factor, anti-dsDNA and anti-CCP antibodies, ESR, CRP • Serologies for hepatitis C and HIV • ACE • TS-HDS?, FGFR3? • SPEP with IF, free light chains in serum
Genetic (rare)	TTR amyloidosis (transthyretin) Fabry disease Tangier disease Hereditary sensory and autonomic neuropathy Sodium channelopathies (SCN9A, 10A, 11A)	• 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 45-90% 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).**





Farhad K. Current Diagnosis and Treatment of Painful Small Fiber Neuropathy. Curr Neurol Neurosci Rep. 2019 Nov 26;19(12):103.

Small fiber neuropathy: other investigations

- **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.

Farhad K. Current Diagnosis and Treatment of Painful Small Fiber Neuropathy. Curr Neurol Neurosci Rep. 2019 Nov 26;19(12):103.

Sensory predominant: laboratory work-up

Metabolic-toxic-nutritional	Diabetes (long-standing) End-stage renal disease Vitamin B12, copper, folate deficiency Vitamin B6 toxicity Chemotherapy-related	• Fasting glucose, hemoglobin A1c • CMP, creatinine, BUN • Vitamin B12, methylmalonic acid, folate, thiamine, copper levels, ceruloplasmin, Vitamin B6 > 80-100
Inflammatory-immune	Sjögren syndrome and other CTD Paraneoplastic (ANNA-1, ANNA-2) HIV, Lyme, syphilis DADS neuropathy (anti-MAG) Sensory CIDP and CISP Miller-Fisher syndrome	• SS-A, SS-B, ANA, ds-DNA, RF, CCP, ESR, CRP • Paraneoplastic panel • HIV, Lyme screening, RPR • MAG antibodies • CSF protein • GQ1b antibodies
Inherited (common)	Charcot-Marie-tooth disease and other inherited	• Genetic testing low yield in relatively mild, sensory predominant polyneuropathy even when inherited is likely

Motor predominant: laboratory work-up

Inflammatory-immune	Guillain-Barre syndrome (AIDP, axonal variants)	• Ganglioside Ab (GM1, GD1a, GD1b) in axonal GBS
	CIDP	• Contactin, neurofascin in refractory CIDP
	Multifocal motor neuropathy	• GM1 antibodies
	Vasculitic (mononeuropathy multiplex)	• ESR, CRP, ANCA, MPO, PR3, screening CTD
	POEMS syndrome	• VEGF, SPEP with immunofixation, FLC
	Paraneoplastic (CRMP-5, amphiphysin)	• Paraneoplastic panel
	Neurolymphomatosis	
Genetic/inherited	Charcot-Marie-Tooth disease	• Peripheral neuropathy gene panel
	TTR amyloidosis	• TTR gene analysis
	Acute intermittent porphyria	• Porphobilinogen, ALA in urine
	Hereditary neuropathy with liability to pressure palsies (HNPP)	• PMP22 deletion analysis
Nutritional	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.

Sasaki H, Kawamura N, Dyck PJ, Dyck PJB, Kihara M, Low PA. Spectrum of diabetic neuropathies. Diabetol Int. 2020 Jan 8;11(2):87-96.

DIABETIC NEUROPATHIES

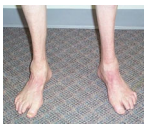
Symmetric	Asymmetric
• Small fiber neuropathy • Diabetic polyneuropathy (DPN) • Diabetic autonomic neuropathy (DAN) • Treatment-induced neuropathy of diabetes (TIND) ♦	• Cranial neuropathies (III, VI) • Entrapment neuropathies (CTS, ulnar and peroneal) • Meralgia paresthetica • Radiculoplexus neuropathies (diabetic amyotrophy) ♦ • Diabetic thoracic radiculopathies ♦

♦ **Red flags for treatment-induced complications:**
- Acute/subacute onset severe neuropathic pain, prominent autonomic symptoms (OH, constipation, urinary retention) → TIND
- Acute/subacute onset of leg weakness and atrophy → Lumbosacral RPN
- Weight loss
- Antecedent of rapid glycemic correction.

Sasaki H, Kawamura N, Dyck PJ, Dyck PJB, Kihara M, Low PA. Spectrum of diabetic neuropathies. Diabetol Int. 2020 Jan 8;11(2):87-96.

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.



Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of referred unclassified neuropathies yields improved diagnosis. Ann Neurol. 1981 Sep;10(3):222-6.

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: hyperreflexia, 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.

Gwathmey KG, Grogan J. Nutritional neuropathies. Muscle Nerve. 2020 Jul;62(1):13-29.

NUTRITIONAL NEUROPATHIES

- ✓ Acute axonal neuropathy from **thiamine deficiency** can mimic GBS.
- ✓ Risk factors: bariatric surgery, malnutrition/restrictive diets, malabsorption, alcoholism.
- ✓ 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.

Shible AA, et al. Dry Beriberi Due to Thiamine Deficiency Associated with Peripheral Neuropathy and Wernicke's Encephalopathy Mimicking Guillain-Barré syndrome: A Case Report and Review of the Literature. Am J Case Rep. 2019 Mar 13;20:330-334.

DYSPROTEINEMIAS

- ✓ Monoclonal proteins found in 10% of patient with peripheral neuropathy (Ig M most commonly associated).
- ✓ SPEP with immunofixation increases the sensitivity.
- ✓ Some distinctive clinical syndromes:
  - ✓ DADS (distal acquired demyelinating symmetric) neuropathy.
    - ✓ Ig M monoclonal protein.
    - ✓ 2/3 of patients have anti-MAG antibodies.
    - ✓ Demyelinating > axonal on NCS.
    - ✓ Often poor response to immunotherapies.
  - ✓ POEMS: **P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**-spike, **S**kin changes.
    - ✓ Ig G or IG A lambda.
    - ✓ Osteosclerotic myeloma.
    - ✓ Mixed axonal and demyelinating on NCS.
    - ✓ Elevated VEGF.

Mauermann ML. Paraproteinemic neuropathies. Continuum (Minneap Minn). 2014 Oct;20 (5 Peripheral Nervous System Disorders):1307-22.

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

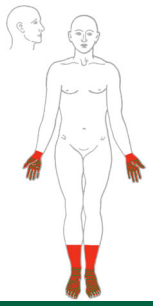
- ✓ Subacute onset, stepwise progression.
- ✓ Asymmetric.
- ✓ Motor involvement may be prominent.
- ✓ Investigations:
  - ✓ NCS/EMG
  - ✓ CSF
  - ✓ Imaging studies
  - ✓ +/- nerve biopsy

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** → mononeuropathy multiplex, multifocal motor neuropathy (MMN).
- ✓ **Motor predominant** symptoms → CIDP, MMN, TTR amyloidosis. Alternative diagnosis (ALS, myopathy, NMJ disorder).
- ✓ Prominent sensory loss and **ataxia** → sensory ganglionopathy.
- ✓ Systemic symptoms, weight loss.
- ✓ "Refractory" to medications.

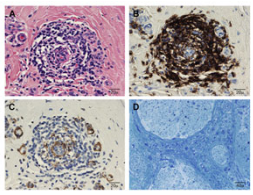


When to consider a nerve biopsy?

- ✓ Acute/subacute
- ✓ Multifocal
- ✓ Severe/rapidly progressive

When suspected etiologies are:

- ✓ Inflammatory: vasculitis, sarcoidosis.
- ✓ Infectious: leprosy.
- ✓ Infiltrative: neoplastic (lymphoma), amyloid.



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Said G. Indications and usefulness of nerve biopsy. Arch Neurol. 2002 Oct;59(10):1532-5.

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.**

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Thank you!