Peripheral Neuropathy

The pattern is the diagnosis · three labs find most treatable causes · and a normal EMG never excludes small fiber disease

Stepwise + asymmetric
= vasculitis until proven otherwise

READ THE PATTERN FIRST *it does the diagnostic work the lab panel cannot*

Pattern	What it means and what to do
Distal symmetric (DSP) *the overwhelming majority*	Length-dependent, so the longest axons fail first: toes upward, hands involved as symptoms reach the knees (**stocking-glove**). Diabetes, alcohol and idiopathic disease dominate. First-tier labs, foot protection, pain control
Mononeuropathy	One nerve at a known compression site: median (carpal tunnel), ulnar (elbow), peroneal (fibular head foot drop). A different workup entirely
⚠ Mononeuritis multiplex	Multiple discrete nerves failing **stepwise** (wrist drop today, foot drop next month). **This is nerve infarction from vasculitis of the vasa nervorum: urgent.** ANCA, cryoglobulins, hepatitis B/C, ESR, complements. Every untreated week accumulates permanent axonal loss
Polyradiculoneuropathy	Proximal *and* distal weakness with areflexia. **Acute (days to 4 weeks) = GBS**: monitor vital capacity and bulbar function. **Progressive or relapsing beyond 8 weeks = CIDP**, which responds to IVIG or steroids and is the diagnosis not to miss
Small fiber	Burning pain and allodynia with **normal strength, normal reflexes and a NORMAL EMG**, often with autonomic features (dry eyes/mouth, orthostasis). Diagnosis is clinical ± skin biopsy for intraepidermal nerve fiber density

LARGE FIBER vs SMALL FIBER

Large: vibration and proprioception loss, sensory ataxia (worse in the dark, positive Romberg), reduced reflexes. **Falls are the danger. Small:** pain and temperature loss, burning, electric shocks, allodynia. **Ulcers and Charcot joints are the danger**, because painless injury goes unnoticed. Most DSP is mixed, but which predominates guides both testing and counseling.

⚠ RED FLAGS THAT CHANGE THE CLOCK

Acute over days to weeks (GBS: check vital capacity, not just reflexes). **Asymmetric, multifocal or stepwise** (vasculitis now). **Motor-predominant, proximal, or prominent autonomic failure** (prompt EMG and neurology). **Prominent ataxia with demyelinating EMG** (paraproteinemic neuropathy, CIDP variants). None of these are "diabetic neuropathy, follow up in a year."

THE FIRST-TIER WORKUP *three tests find most treatable causes of symmetric disease*

Test	Why it earns its place
A1c or fasting glucose → then GTT	**If normal, get a 2-hour glucose tolerance test**: impaired glucose tolerance causes painful small-fiber neuropathy *before* diabetes is diagnosable, so a normal A1c does not close the question
B12 WITH methylmalonic acid	The serum assay is poorly sensitive at 200-400 pg/mL, where patients can be functionally deficient. **Elevated MMA unmasks the deficiency the level missed**. Then find the reason: metformin, PPIs, gastric surgery, pernicious anemia
SPEP with immunofixation	A paraprotein reroutes the entire case to hematology: MGUS, myeloma, **amyloid**, POEMS, anti-MAG disease each carry specific treatment. Add free light chains where suspicion is high
Exposure history (a lab test in disguise)	**Alcohol quantified**, chemotherapy named (platinums, taxanes, vincristine, bortezomib), isoniazid without pyridoxine, and **supplements asked about by ingredient: B6 causes neuropathy in EXCESS as well as deficiency**, and gram doses hide in "nerve support" products taken for these very symptoms
By context	TSH, CMP, CBC, ESR, HIV and hepatitis serologies, Lyme where endemic. **High arches, hammertoes and lifelong clumsiness** point to hereditary neuropathy (CMT) and spare the rest of the workup

EMG: ORDER IT FOR A QUESTION *not as a reflex, and not to rule out neuropathy*

WHEN IT HELPS

Skip it for classic mild length-dependent DSP with an obvious cause: it confirms what you already know. **Order it** for atypical features (asymmetry, motor predominance, rapid course), unclear cause, or when the **axonal vs demyelinating** distinction will change management.

WHY THE DISTINCTION MATTERS

Axonal is the common final pathway of metabolic and toxic causes and mostly confirms the usual suspects. **Demyelinating is a different disease list**: CIDP (treatable), paraprotein-associated neuropathy, and hereditary disease (uniform slowing in CMT1 vs the patchy conduction block of acquired disease). Demyelination is the branch point toward SPEP, referral and immunotherapy.

⚠ A NORMAL EMG PROVES NOTHING

EMG/NCS tests **only large myelinated fibers**. Burning pain with preserved strength, reflexes and a normal study is **small fiber neuropathy**, not an absent one. **MRI of the spine is not a neuropathy test**: order it for radiculopathy or myelopathy (dermatomal pattern, hyperreflexia, sphincter involvement), not stocking-glove numbness.

TREAT THE CAUSE, THEN THE PAIN *and say the pain goal out loud*

Target	Detail
Modifiable causes	**Glycemic control clearly slows type 1 neuropathy** (more modest in type 2, so foot protection carries the weight). **Alcohol cessation plus thiamine** partially reverses if early. **Replete B12** and find its reason. **A third remain idiopathic**: name it, protect the feet, re-examine yearly
⚠ Set expectations	**A 30-50% reduction in pain is a successful outcome.** Patients expecting zero pain will call every effective drug a failure
Pick by comorbidity	**Duloxetine** 30→60 mg (co-existing depression). **Pregabalin** 75→150-300 mg BID or **gabapentin** 300→3,600 mg/day divided (co-existing insomnia; **both need renal dosing**, both cause sedation, edema, weight gain). **Nortriptyline** 10-25→75 mg qHS, **preferred over amitriptyline** for far less anticholinergic and orthostatic burden at equal analgesia; avoid in cardiac conduction disease
Trial then combine	Adequate dose for several weeks before a verdict, then switch or **combine two mechanisms at moderate doses**, which often beats maximizing one. Topical lidocaine or the 8% capsaicin patch for focal or medication-intolerant patients. **Opioids are not recommended for chronic neuropathic pain**; tramadol adds serotonergic and seizure risk
Protect the feet and the balance	**Annual monofilament, daily self-inspection, footwear review, early podiatry**: painless injury is how ulcers, infection and Charcot arthropathy begin. **Balance-focused PT and a look at sedating medications** address the fall risk that sensory ataxia creates

PEARLS & PITFALLS

- **Both directions of vitamin B6 are on the differential:** deficiency (classically with isoniazid) and excess (gram-dose supplements) each cause neuropathy, and the second only improves if you ask about the bottle.
- **Metformin and PPIs deplete B12 over years**, so a long-standing diabetic with worsening numbness deserves an MMA before the neuropathy is blamed on glucose alone.
- **Stepwise asymmetric deficits are infarcts, not a slow neuropathy.** Mononeuritis multiplex runs on a rheumatologic timescale of days.
- **CIDP is the treatable one.** Progressive or relapsing proximal-plus-distal weakness with areflexia beyond 8 weeks deserves EMG and referral, because IVIG and steroids work.

References: AAN practice parameter on the evaluation of distal symmetric polyneuropathy · AAN guideline on oral and topical treatment of painful diabetic neuropathy · ADA standards of care (neuropathy and foot care) · EAN/PNS guidance on CIDP.

Educational aid; verify against current guidance, local formulary and patient factors.