How to work up Peripheral Neuropathy and Effectively Treat: Case Based Presentation

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The Scope of the Problem

- **The Burden:** Peripheral neuropathy is incredibly common, affecting approximately 2-7% of the general population and up to 50% of patients with diabetes. It is a major cause of morbidity, falls, and chronic pain.
- **The Diagnostic Dilemma:** With over 100 potential etiologies—ranging from metabolic and toxic to hereditary and inflammatory—the "shotgun approach" (ordering every test available) is costly, inefficient, and often confusing.
- **The Objective:** The goal of this talk is to provide a structured, algorithmic approach to diagnosis. We move from **phenotype** (what does the patient look like?) to **anatomy** (what part of the nerve is damaged?) to **etiology** (what caused it?).

The 5 Key Questions (Pattern Recognition)

This is the most critical part of the clinical assessment. Categorizing the patient correctly here narrows the differential diagnosis by 90%.

Which systems are involved?

- **Motor:** Look for weakness (distal vs. proximal), atrophy, and fasciculations. *Pearl: Early motor involvement without significant sensory loss should raise red flags for motor neuron disease (ALS) or multifocal motor neuropathy.*
- **Sensory:** Differentiate "negative" symptoms (numbness, deadness) from "positive" symptoms (tingling, burning, shooting pain).
- **Autonomic:** Ask about orthostatic lightheadedness, erectile dysfunction, constipation/diarrhea, and early satiety. *Significant autonomic involvement suggests Diabetes, Amyloidosis, or GBS.*

What is the distribution

- **Length-dependent (Distal Symmetric Polyneuropathy):** The most common pattern. Pathology affects the longest nerves first. Symptoms start in the toes, progress up the legs. When they reach the knees, symptoms usually appear in the fingertips ("Stocking-Glove").
  - *Differential:* Diabetes, Alcohol, Chemo, B12 deficiency.
- **Non-length dependent:** Symptoms appear in proximal limbs, face, or trunk early on. This violates the "longest nerve first" rule.
  - *Differential:* Demyelinating neuropathies (GBS, CIDP), Porphyria, Lyme.
- **Multifocal (Mononeuritis Multiplex):** Painful, asymmetric, sequential nerve infarcts. For example, a right wrist drop followed a week later by a left foot drop.
  - *Differential:* Vasculitis (PAN, ANCA), Leprosy, Sarcoidosis, Diabetes (can present this way, though rare).

What is the time course?

- **Acute (< 4 weeks):** Rapid progression is a medical emergency. The concern is respiratory failure (GBS).
  - *Causes:* Guillain-Barré Syndrome, Vasculitis, Porphyria, Toxins (Arsenic).
- **Subacute (4–8 weeks):** Often inflammatory, toxic, or paraneoplastic.
- **Chronic (> 8 weeks):** The vast majority of neuropathies.
  - *Causes:* Diabetes, Hereditary (CMT), Metabolic.
- **Relapsing-Remitting:** Suggests an immunologic cause like CIDP.

What fibers are involved?

- **Small Fibers (A-delta and C fibers):** Unmyelinated or thinly myelinated. Responsible for pain and temperature.
  - *Symptoms:* Burning, stabbing, electric shock sensations.
  - *Signs:* Reduced pinprick/temperature sensation. **Reflexes and motor strength are preserved.**
- **Large Fibers (A-alpha and A-beta fibers):** Heavily myelinated. Responsible for vibration, proprioception, and motor function.
  - *Symptoms:* Walking on cotton wool, imbalance, wash basin sign (falling when closing eyes to wash face).
  - *Signs:* Loss of vibration/proprioception, **loss of deep tendon reflexes**, ataxia.

Is there family history?

- Many hereditary neuropathies are insidious. Patients may not realize they have a problem because they've "always been clumsy" or "never could run fast."
- *Exam:* Look for Pes Cavus (high arches), Hammertoes, and "Champagne bottle legs" (inverted bottle appearance due to distal atrophy).

The Diagnostic "Fork in the Road": Electrodiagnostics

- Once the clinical phenotype is established, Electrodiagnostic Testing (EMG/NCS) serves as the extension of the physical exam. Its primary role is to determine the **underlying pathology**.

The Big Divide: Axonal vs. Demyelinating

- **Axonal Neuropathy (80-90% of cases):**
- **Pathology:** The axon itself is damaged (Wallerian degeneration). "Dying back" phenomenon.
- **NCS Findings:** Reduced **Amplitudes** (signal strength is lower because fewer axons are firing). Conduction velocities are normal or mildly slow.
- **EMG Findings:** Fibrillation potentials (active denervation) and positive sharp waves.
- **Etiologies:** Diabetes, Alcohol, B12, Uremia, HIV, Chemotherapy (Vinca alkaloids, Taxanes).

- **Demyelinating Neuropathy:**
- **Pathology:** The myelin sheath is damaged, or Schwann cells are dysfunctional.
- **NCS Findings:** Slowed **Conduction Velocities** (<70% of lower limit of normal), Prolonged Distal Latencies, Temporal Dispersion, and Conduction Block (signal drops off between stimulation points).
- **Etiologies:**
  - *Acquired:* Guillain-Barré (AIDP), CIDP, Anti-MAG.
  - *Hereditary:* Charcot-Marie-Tooth Type 1 (Uniform slowing).

A Tiered Approach to Laboratory Testing
Tier 1

Tier 1: The "High Yield" Screen (For Chronic, Distal Symmetric, Axonal Polyneuropathy)

- **Glucose Metabolism:** Fasting Glucose + HbA1c + 2-hour Oral Glucose Tolerance Test (OGTT).
  - *Pearl:* Impaired Glucose Tolerance (Pre-diabetes) is a very common cause of painful small fiber neuropathy, even with normal A1c.
- **Vitamin B12:** Always check Methylmalonic Acid (MMA) if B12 is low-normal (200-400 pg/mL). MMA is more sensitive.
- **Serum Protein Electrophoresis (SPEP) with Immunofixation (IFE):** Screening for monoclonal gammopathy (MGUS), Multiple Myeloma, or Amyloidosis.
  - *Note:* If positive, check serum free light chains.
- **Comprehensive Metabolic Panel (CMP):** Renal function (uremia) and Liver function.
- **Thyroid Function:** TSH.

The "Focused" Workup (For Atypical features, aggressive course, or negative Tier 1) Tier 2

- **Rheumatologic:** ANA, SSA/SSB (Sjogren's is a key cause of non-length dependent sensory neuropathy), Rheumatoid Factor, ESR/CRP.
- **Infectious:** HIV, Hepatitis C (associated with Cryoglobulinemia), Lyme Serology (if relevant exposure).
- **Nutritional/Toxic:** Copper (if Zinc overload or history of gastric bypass), Vitamin E, Heavy Metals (only if history supports; rare in developed world).
- **Celiac Disease:** Tissue transglutaminase (tTG) IgA.

Tier 3: The "Specialized" Workup: Referral to a Neurologist

- **Genetic Testing:** Panels for Charcot-Marie-Tooth (CMT) or Hereditary Transthyretin Amyloidosis (hATTR).
- **Paraneoplastic Panel:** If rapid progression + weight loss + smoking history (Anti-Hu, etc.).
- **Lumbar Puncture:** Essential for suspected CIDP or GBS (Cytoalbuminologic dissociation: High protein, normal cells).
- **Nerve/Muscle Biopsy:** Reserved for suspected Vasculitis or Amyloidosis.

Trouble with walking

- KK is a 77-year old man with longstanding well controlled Type II diabetes with an %HgBA1C of 7.2
- For some months now, he complains of **pain in his buttocks and legs when walking that forces him to stop**. There is no rest pain.
- He has persistent numbness in his feet and he has been told that he has a neuropathy related to his longstanding diabetes.
- There is no evidence of vascular claudication. He has undergone a left carotid endarterectomy for a symptomatic left carotid, related to his diabetes. He has had a left common iliac stent.

Relevant Neurological Examination

- Motor: Normal bulk, tone throughout.
- The motor strength is 5/5 in all muscle groups tested except for some wasting of both EDB's and mild EDB weakness.
- Sensory: **Stocking hyperesthesia to the level of the ankles to light touch, pinprick**. There is mild loss bilaterally to pinprick in an **S1 distribution**.
- Normal cold sensation, vibratory sense, throughout.
- **Slight distal decrease in proprioception**.

Neurological Assessment

- There are 3 components to the examination
  - Peripheral neuropathy

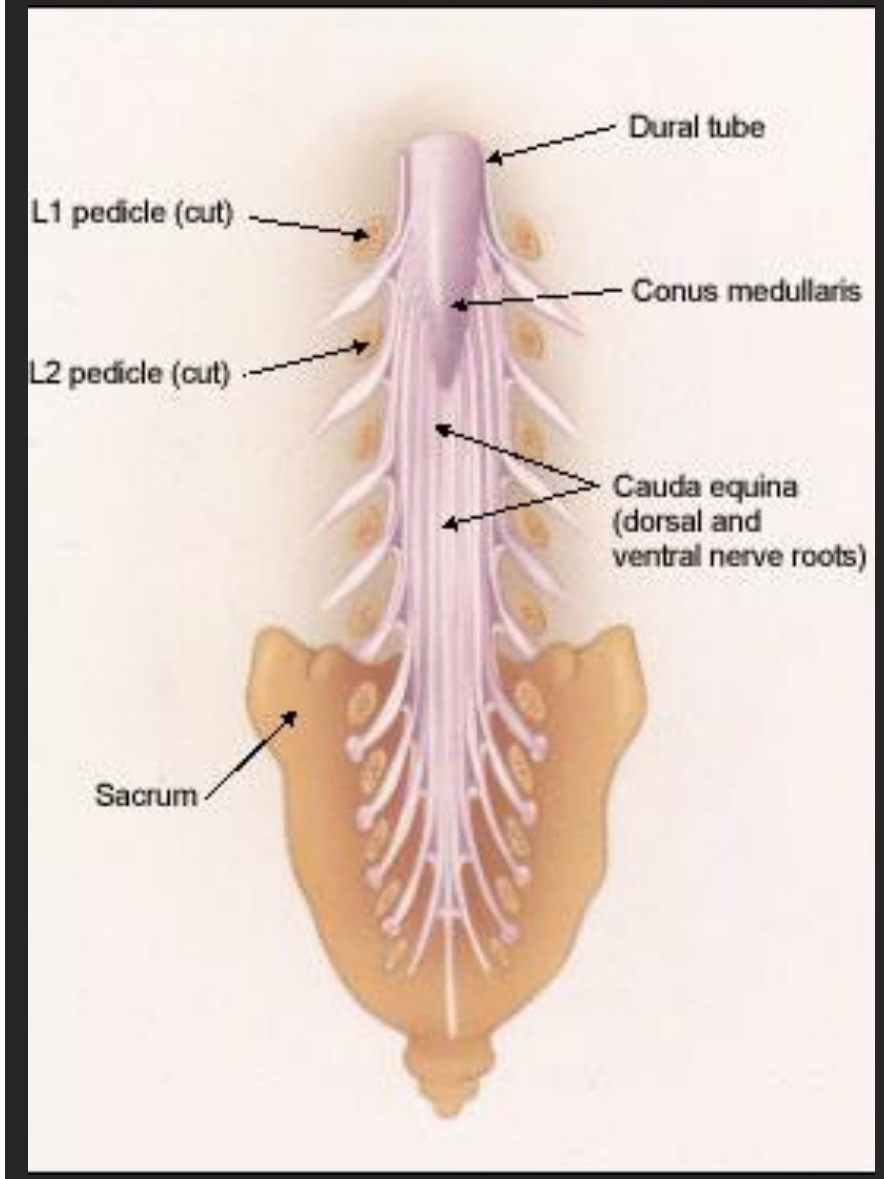
    Stocking loss to pinprick and light touch
  - Poor distal peripheral pulses
  - Wasting of the EDB muscles and

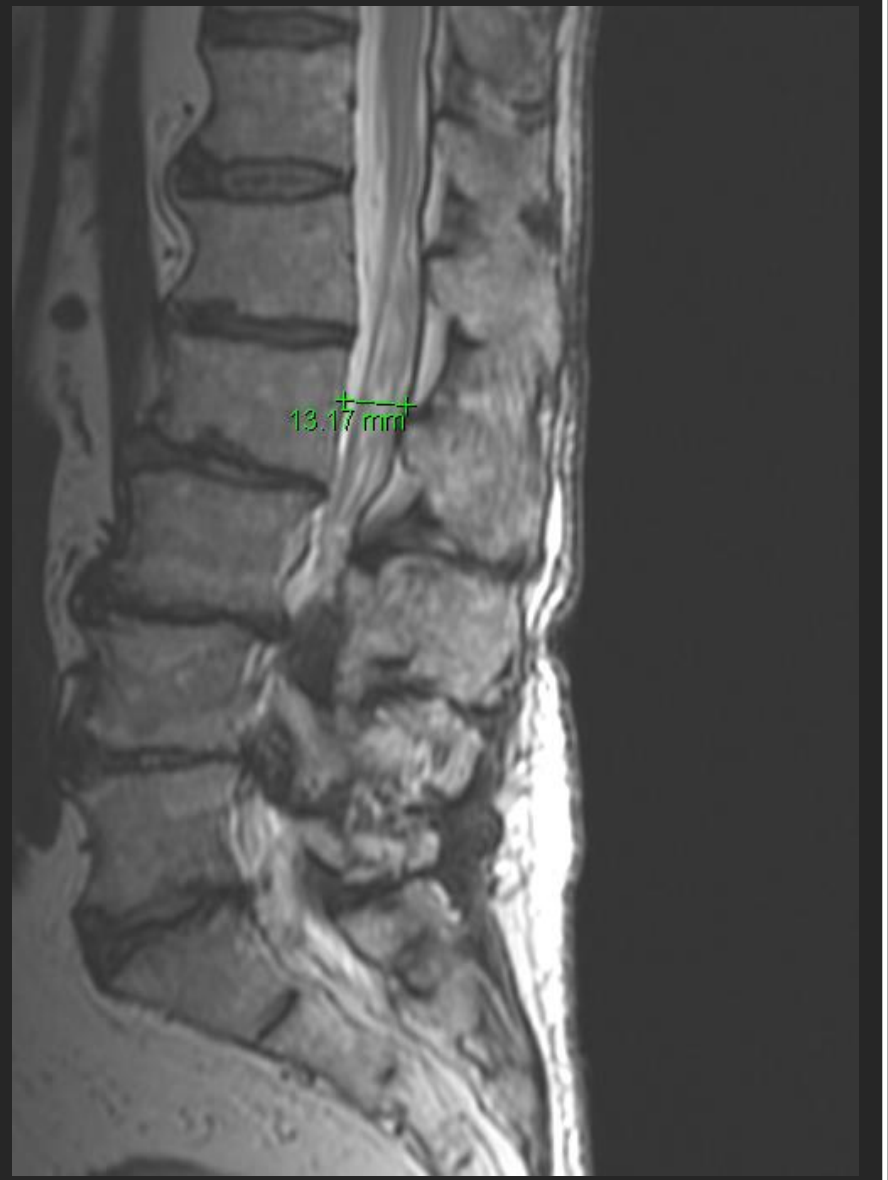
    S1 sensory loss

Does his neuropathy account for his chief complaint and signs on examination?

How do we manage the pain?

- Mild vascular peripheral disease
- Lumbar spinal stenosis with lumbar radiculopathy
- Peripheral neuropathy
- Of note: there is no rest pain and his numbness does not bother him.


Dural tube
L1 pedicle (cut)
Conus medullaris
L2 pedicle (cut)
Cauda equina
(dorsal and
ventral nerve roots)
Sacrum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Discussion

Lumbar Spinal Stenosis:	• Pain management options
Peripheral Neuropathy	• Pain Management options
Vascular Claudication	• Pain management options

The tingles

- RS is a 38 year old electrical engineer who complained of tingling in his hands and feet.
- These symptoms were present for 9 months and involved his hands to the forearms and then spread to his feet and upper thighs.
- He also volunteered that when he **flexed his neck**, he would get an **electric-like sensation** in his hands and legs.
- He is a homosexual man whose partner recently tested HIV positive. He did practice safe sex.

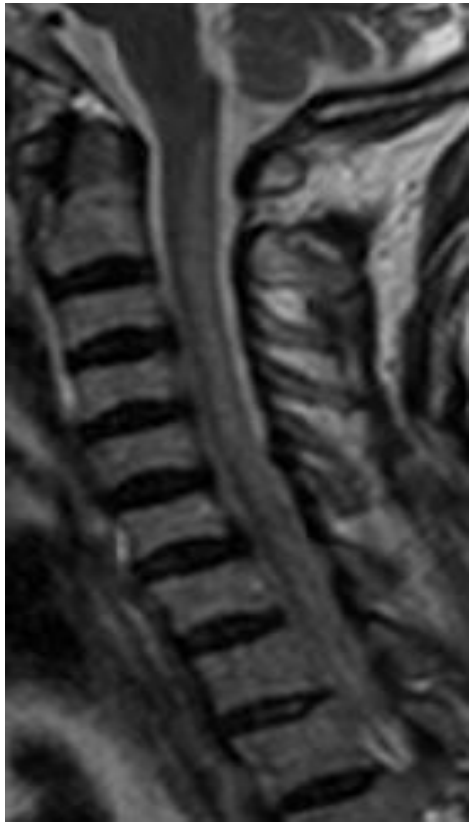
Next steps:

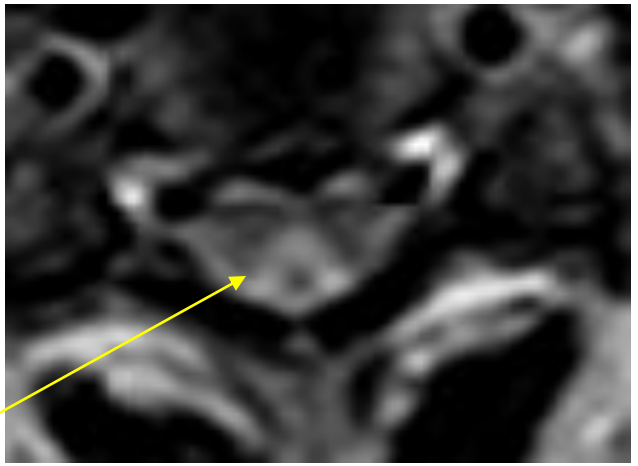
- He saw his primary care physician who obtained an MRI scan of the cervical spine.
- He was then referred to a neurosurgeon who obtained nerve conduction studies and did not think that he required surgery and referred Mr. RS to a neurologist.
- He was told by multiple physicians that he may have a problem that could antecede becoming HIV positive, despite multiple negative HIV tests.

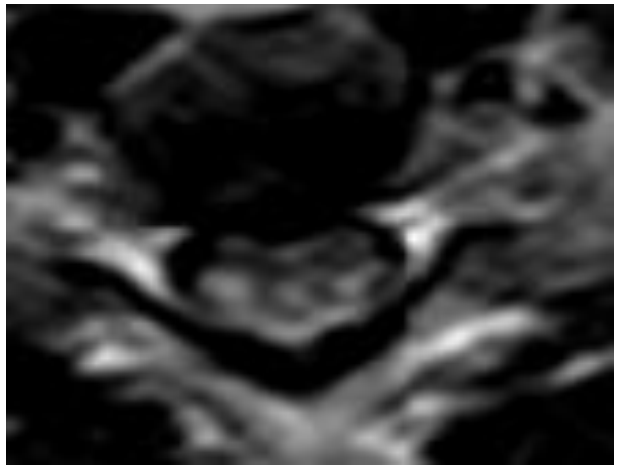
Lhermitte’s sign

- Sudden electric-like sensation with flexion of the neck
  - It usually implies PATHOLOGY of the posterior columns and we see this with:
    - Demyelinating disease
    - Vacuolar myelopathy (AIDS)
    - B12 deficiency

Subacute Combined Degeneration of the Spinal Cord



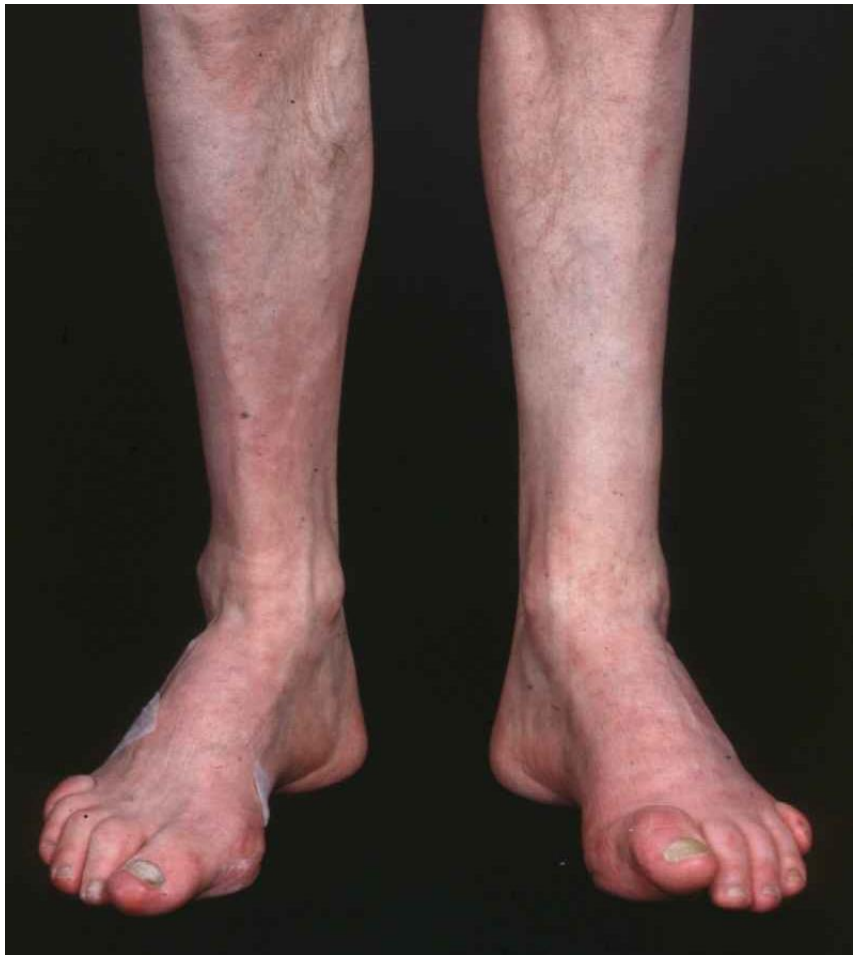


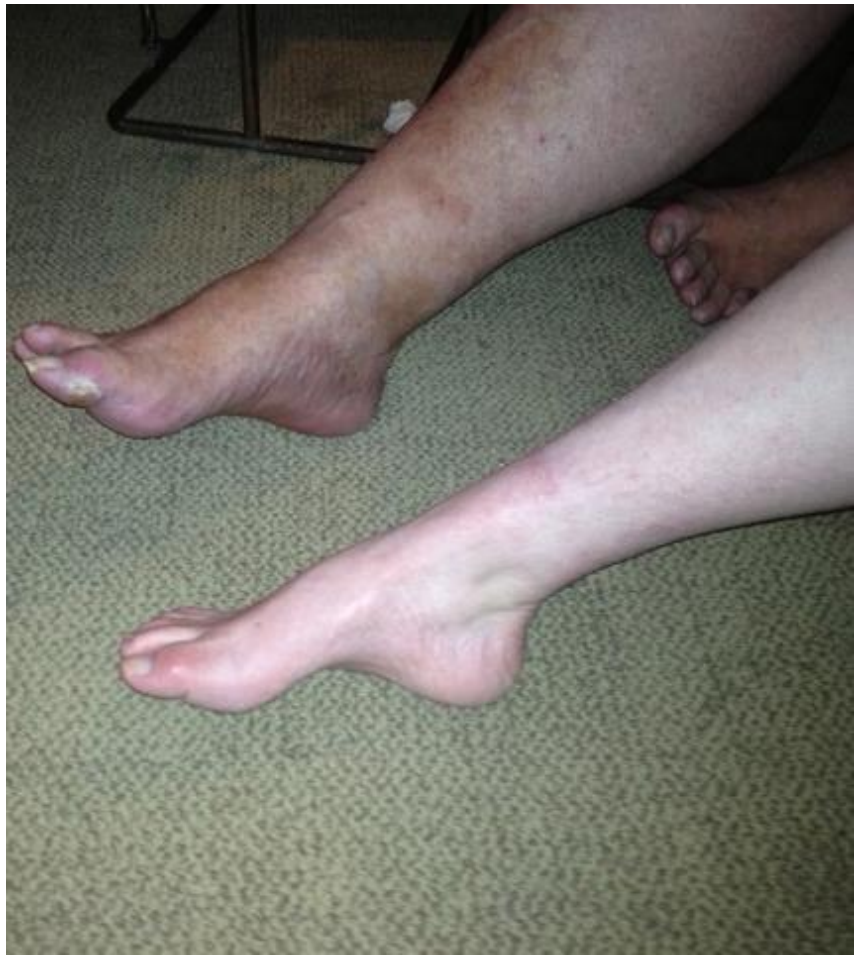


Treatment of this neuropathic pain and take home messages

- The patient was treated with monthly B12 shots and his MMA levels followed. These returned to normal within 6 months.
- It took 12 months for the tingling to slowly disappear and he was left with residual tingling in his toes.
- He also had antiparietal cell and antimicrosomal antibodies present.
- **Final diagnosis: Pernicious Anemia**
- In other words, we have to find a treatable cause and then treat accordingly

A 32 year old woman with Type 1 Diabetes comes to your office complaining about her feet. Her father comes with her….



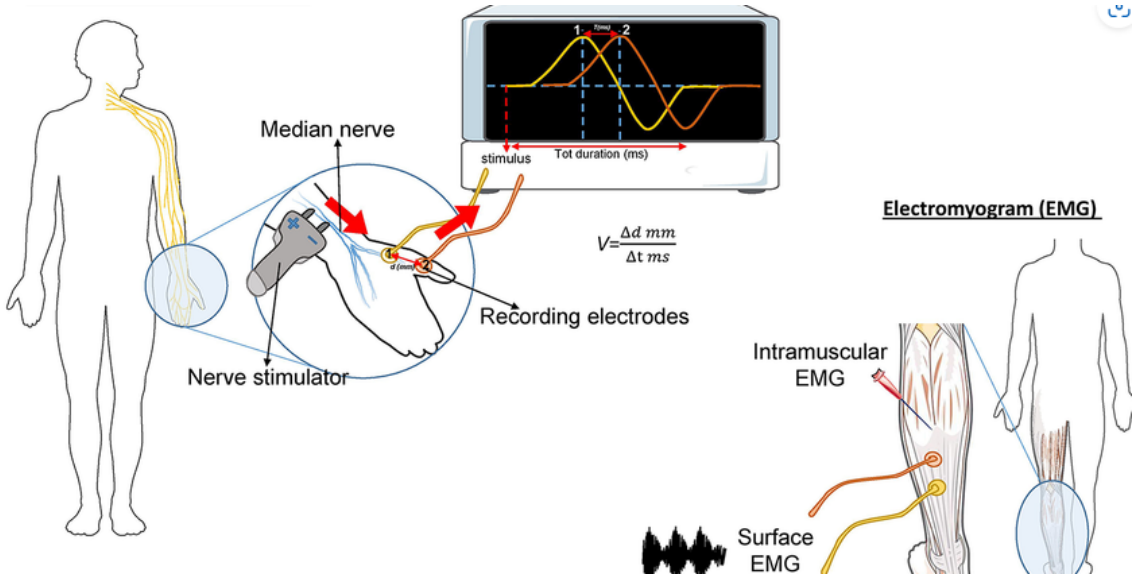


Next steps

EMG and nerve conduction studies were performed.

Results:

DEMYELINATING PHYSIOLOGY



Single Gene Causes of CMT Hereditary Neuropathy

Type 1	Pathology	Mode of Inheritance	Proportion of CMT
CMT1	Abnormal myelin	AD	~50%
CMT2	Axonopathy	AD	~20-40%
Intermediate form	Combination of myelin and axonopathy	AD	Rare
CMT4	Either myelinopathy or axonopathy	AR	Rare
CMTX	Axonopathy with secondary myelin changes	X-linked	~10-20%

CMT1: Molecular genetics

Disease Name	Proportion of CMT1	Gene	Chromosome Locus	Protein product
CMT1A	70-80%	PMP22	17p11.1	Peripheral myelin protein 22
CMT1B	5-10%	MPZ	1q22	Myelin P_0 protein
CMT1C	Unknown	LITAF (lipopolysaccharide induced TNF- alpha factor)	16p13.1-12.3	SIMPLE
CMT1D	Unknown	EGR2	10q21.1-22.1	Early growth response protein 2

X-linked CMT: Molecular genetics

Disease Name	Proportion of X-linked CMT	Gene	Chromosome Locus	Protein Product
CMTX	90%	GJP1	Xq13.1	Gap junction beta-1 protein (connexin 32)
Other X-linked forms	10%	Unknown	Unknown	Unknown

Diabetes Causes Eight Well-Characterized Peripheral Nerve Syndromes

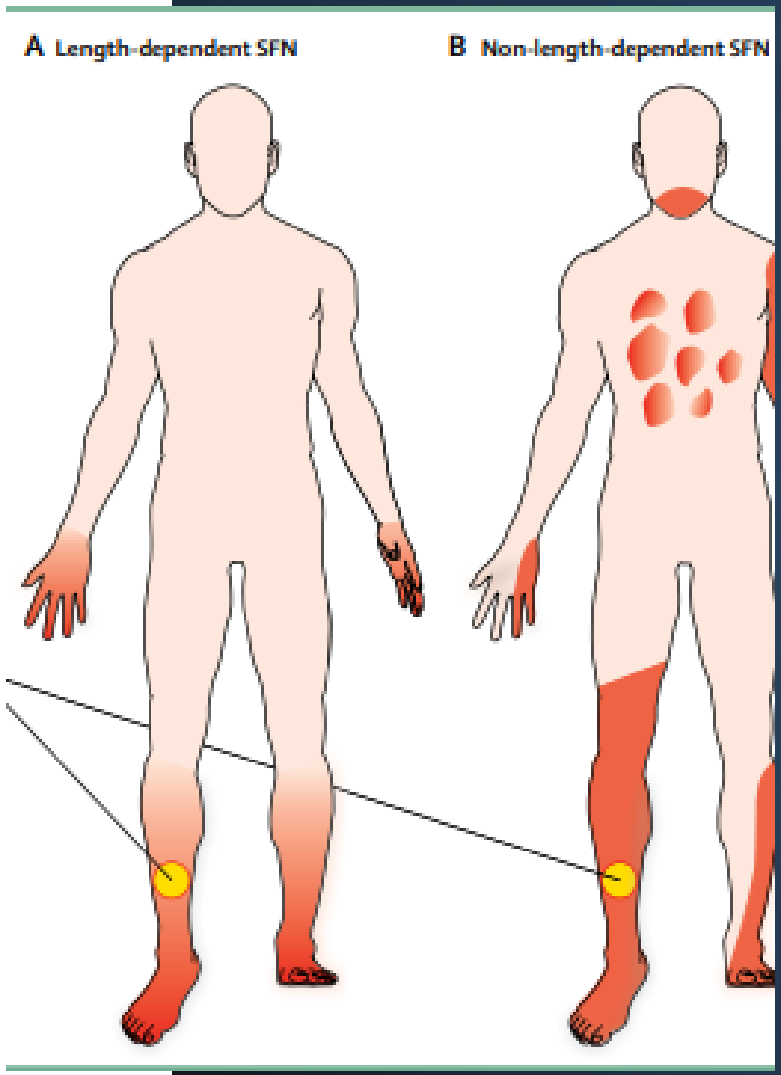
- Distal symmetric polyneuropathy in diabetes.
- Small-fiber diabetic neuropathy.
- Autonomic neuropathy in diabetes.
- Metabolic syndrome and neuropathy.
- Diabetic radiculoplexus neuropathy (diabetic amyotrophy) or high lumbosacral plexopathy
- Insulin neuritis/treatment induced neuropathy.
- Thoracoabdominal radiculopathy.
- Diabetic oculomotor palsy.

Small fiber Neuropathy (SFN)

- There is selective or predominant impairment of peripheral afferent thinly myelinated Aδ-fibers and unmyelinated C-fibers
- 30% of all cases are attributable to Diabetes
- SFN might develop insidiously in patients with diabetes and be present before the metabolic syndrome is diagnosed, or it might occur acutely, as is the case in treatment-induced neuropathy caused by fast glycemic diabetic regulation
- In patients with type 2 diabetes, SFN symptoms can occur early in the course of the disease and are followed by gradual large fiber involvement
- This raises the question whether, in diabetic neuropathy and possibly also other neuropathies, there is a continuum of features that starts as pure SFN and develops into mixed neuropathies, with the involvement of both small and large fibers

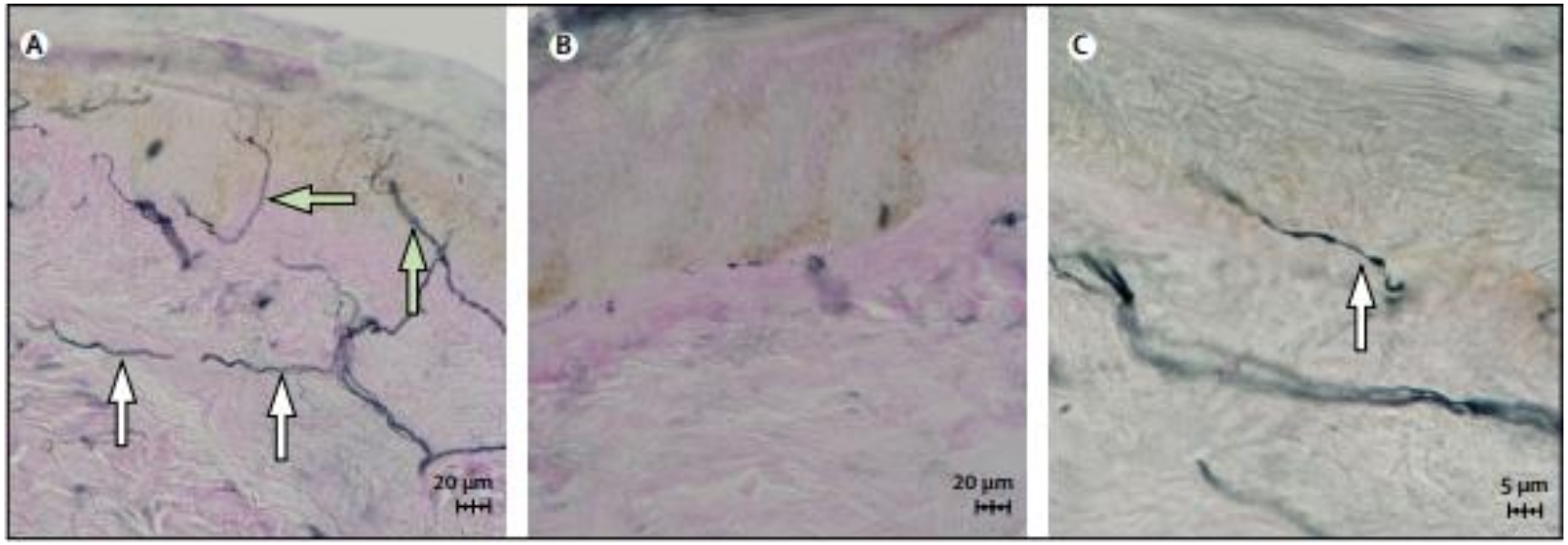
Clinical presentations in Small Fiber Neuropathy

- A: patient with typical length-dependent polyneuropathy (A) might have pain, sensory loss, or hypersensitivity to cold, warm, light touch, or pinprick in a characteristic stocking-glove distribution, with intact deep tendon reflexes and preserved proprioception and sensation to vibration.
- B: A patient with patchy non-length-dependent neuropathy (B) might have either reduced or increased small fibre function corresponding to a single or to multiple nerves.



Skin biopsy of a patient with Diabetes and small fiber neuropathy

- (A) Intraepidermal nerve fibres (green arrows) and dermal nerve fibres (white arrows) in a healthy individual. (B) Loss of skin nerve fibres in a patient with painful diabetic neuropathy. (C) Axonal swelling of intraepidermal nerve fibres (white arrow) in a patient with painful diabetic neuropathy



Terkelsen, Karlsson, Lauria, et al
2017:16:934-944

The EMG/NCS is an extension of the physical examination

Distinctive features of demyelination

- Conduction block & Non-uniform slowing of NCV: Suggest acquired demyelination
- Selectively prolonged distal latencies: Suggest IgM M-protein related neuropathy

Asymmetry: Suggests vasculopathy or demyelination; Nerve biopsy can be useful

Focal nerve lesions

Always test upper & lower extremities to document diffuse vs. focal neuropathy

Interpretation of tests in the pursuit of a diagnosis of neuropathy

- **Again the physical examination is paramount**
  - All the tests that we order should be interpreted in the context of the physical examination
  - Involvement of the posterior columns points to a large fiber neuropathy
  - If only pinprick and pain are present, usually means there is small fiber neuropathy
- The EMG/Nerve conduction studies:
  - Slowed velocity implies slowed nerve conductions and usually points to demyelinating disease
  - Low amplitudes on the physiology implies injury to the axon

Management of neuropathic pain: Principles

- All treatable causes of neuropathic pain should be excluded.
  - Especially in patients with diabetes. Additional causes can be found in up to 53% of patients which includes:

    Neurotoxic medications

    Alcohol overuse

    Monoclonal gammopathy

    Vitamin deficiencies/Vitamin overuse

    Renal disease

Neurotoxic Medications Selected chemotherapeutic agents associated with polyneuropathy:

- Vinka alkaloids: 30% of patients develop sensorimotor axonal injury from vincristine
- Taxane: Paclitaxel, docetaxel cause a sensory neuropathy which is mild to moderate and is rarely dose limiting. Resolves on stopping medication
- Platinum analogues: Cisplat/carboplat: axonal injury and may cause acute neuropathy
- Bortezomib (protease inhibitor) axonal injury with vasculitis
- Thalidomide: Axonal and autonomic injury

Other medications associated with polyneuropathy

- Linezolid: sensory polyneuropathy
- Chloramphenicol: Sensory axonal polyneuropathy
- Metronidazole: all forms of neuropathy
- Nitrofurantoin: sensorimotor axonal neuropathy
- INH: Sensorimotor neuropathy
- Reverse transcriptase inhibitors
- Amiodarone: Mixed axonal and demyelinating neuropathy
- Disulfiram: sensorimotor polyneuropathy
- Phentyoin: Axonal polyneuropathy
- Colchicine: Myopathy usually, but can cause neuropathy
- Vitamin B6: overuse is a common cause of painful sensory ganglionopathy. Resolves with cessation of the vitamin

Management of neuropathic pain: Principles

- All treatable causes of neuropathic pain should be excluded.
  - Especially in patients with diabetes. Additional causes can be found in up to 53% of patients which includes:

    Neurotoxic medications

    Alcohol overuse (check a PETH level)

    Monoclonal gammopathy

    Vitamin deficiencies/Vitamin overuse

    Renal disease

Nutrient deficient neuropathies

- Vitamin B12 (remember diabetics on metformin- 20% of patients can have low B12 with neuropathy)
- Folate
- Copper large fiber sensory neuropathy and myeloneuropathy
- Thiamine
- Vitamin B6 deficiency causes a small fiber neuropathy, excess causes a sensory ganglionopathy
- Vitamin E: large fiber sensory neuropathy

Medication Management

- FDA has approved **Duloxetine** and **Pregabalin** as first-line medications to treat Diabetic Neuropathy
- **Gabapentin** is often used as a first-line drug
- FDA has also approved the 8% **topical capsaicin patch**, initially approved for post herpetic neuralgia in 2009.
- FDA has also approved tapentadol (but only rarely useful).
- Medications must be tailored with special attention to drug drug interactions.
- Please check the GFR particularly if you are using Gabapentin

Medication	Typical Dose Range	Common Side-effects	AAN Level of Rec	Notes
Gabapentin	300-1200 mg three times daily	Sedation, weight gain, peripheral edema	B	Adjust dose in renal dysfunction
Pregabalin	150-600mg per day in 2-3 divided doses	Sedation, weight gain, peripheral edema	A	Adjust dose in renal dysfunction
Nortriptyline and Amitryptiline	10-25mg at bedtime to max 150mg/d	Sedation, dry mouth, weight gain, orthostatic hypotension	B	Watch QTC interval, avoid in patients with dysautonomia
Duloxetine	30mg/d to 90mg/d	Nausea, dizziness, hypertension	A	Watch LFT's and GFR<30ml/min
Venlafaxine	37.5mg to start and increase to 225mg/day (max)	Nausea, dizziness, hypertension, hyperhidrosis	B	Extended release is better tolerated

Multimodal Options for Painful Polyneuropathy Treatment

Continuum 2020

	Pharmacologic Therapies	Complementary/ Nonpharmacologic Therapies	Exercise
First-level therapies (clinically proven with placebo-controlled studies, FDA approved, Level A and B evidence-based recommendations)	Pregabalin, duloxetine, gabapentin	α-Lipoic acid 600 mg/d	Aerobic exercise 4 h/wk at 50–85% maximum heart rate
Second-level therapies (smaller studies, prospective studies without placebo control, greater side effects)	Tricyclic antidepressants, venlafaxine, valproate, lidocaine patches	Levomefolate/*Schizochytrium*/ pyridoxal phosphate/ methylcobalamin, B vitamin supplements (avoiding excess vitamin B_6), spinal cord stimulation	Balance exercises to decrease fall risk, tai chi
Third-level therapies (anecdotal, case studies)	Topiramate, lacosamide, oxcarbazepine, lamotrigine, mexiletine	Acupuncture	Yoga

A little about Alpha-Lipoic Acid

- Antioxidant that has shown some benefit in patients with painful diabetic peripheral neuropathy.
- Used as adjunctive therapy.
- Conflicting evidence in large studies: The ALADIN III trial was a 7-month multicenter randomized Controlled trial showed an improvement in the Neuropathy Impairment Score, but not in the Total Symptom score.
- The SYDNEY 2 Trial compared 3 doses of A-lipoic acid (600mg/day, 1200mg/day and 1800mg/day) to placebo. All 3 doses were superior to placebo in pain relief, but not to Total Symptom Score.
- The NATHAN 1 trial suggested patients with fewer co-morbidities were more likely to improve in the lower limbs.
- Common adverse effects: Nausea and acid reflux.
- Most commonly discontinued because of ineffectiveness

Opiates and Cannabanoids

- **Tramadol** has a mixed mechanism of action. It is both a *u*-opioid and an SNRI.
- Should never be used as first or even second line option to treat pain.
- There are complicated drug-drug interactions
- Watch for opioid-induced hyperalgesia
- **Cannabanoids:** Popular pharmacotherapy in many neurological disorders.
- There is anecdotal improvement, and a Cochrane review evaluated 16 placebo-controlled studies with small differences between placebo and cannabis products (28%-22%)
- More adverse effects in the elderly because of slower metabolism

GLP-1 Agonists and Peripheral Neuropathy Promising Avenue with cautious optimism

- Important in the management of glycemic control
- Research has shown improved nerve conduction velocity and axonal function in animal models
- Reduction of neuropathic pain: In animal models by reduction of inflammation
- Promote nerve fiber regeneration

Suzetrigine: new non-opioid voltage gated Na channel inhibitor

- Found in Peripheral pain-sensing neurons
- FDA approved in 2025 for post operative pain
- Blocks transmission of pain from the periphery without activating the brain’s reward system
- Non-addictive potential
- Phase 2 trial results: Preliminary results look promising in patients with severe painful diabetic neuropathy
- Ongoing Phase 3 trials

Summary Take home points

- **1. Phenotype is Priority**
  - **Don't rely on a "Shotgun" workup.** Use the **5 Questions** (Systems, Distribution, Time, Fibers, History) to narrow your differential first.
  - **Pattern Recognition:**
  - *Stocking-Glove:* Think Metabolic/Toxic (Length-dependent).
  - *Asymmetric/Multifocal:* Think Vasculitis or Infectious.
  - *Rapidly Progressive:* Think GBS or Vasculitis (**Emergency!**).

- **2. The Diagnostic "Fork in the Road"**
  - **EMG/NCS is the compass:** It separates **Axonal** (common, metabolic) from **Demyelinating** (rare, inflammatory/hereditary).
  - **Small Fiber Neuropathy:** Remember that patients can have severe burning pain with **normal** EMG/NCS and reflexes. *Diagnosis is clinical or via skin biopsy.*

- **3. Testing Strategy**
  - **Tier 1 for everyone:** A1c, B12 (with MMA), SPEP/IFE.
  - **Diabetes is #1, but:** If the neuropathy is rapid, asymmetric, or motor-predominant, look for another cause—even in a diabetic.
  - **Don't forget the "Pre-Diabetic":** Impaired Glucose Tolerance is a major cause of painful sensory neuropathy.

- **4. Management Realities**
  - **Set Expectations:** The goal of pain management is **30–50% reduction** in pain and improved function, not zero pain.
  - **First Line Meds:** Gabapentinoids (Gabapentin/Pregabalin), SNRIs (Duloxetine), TCAs (Nortriptyline).
  - **Disease Modification:** Strict glycemic control prevents neuropathy in Type 1 Diabetes but primarily slows progression in Type 2.