APPROACH TO NEUROPATHIES
56TH ANNUAL PRIMARY CARE REVIEW

Anson Wilks, MD

Assistant Professor, Neurology – Oregon Health & Science University

February 10, 2025

NO RELEVANT DISCLOSURES

SCOPE

- The non-specialist evaluation of neuropathy in the outpatient setting
- Does *not* include neuromuscular medicine specialist approach or practice guidelines
- Does *not* include non-specialist evaluation in the emergency department

LEARNING OBJECTIVES

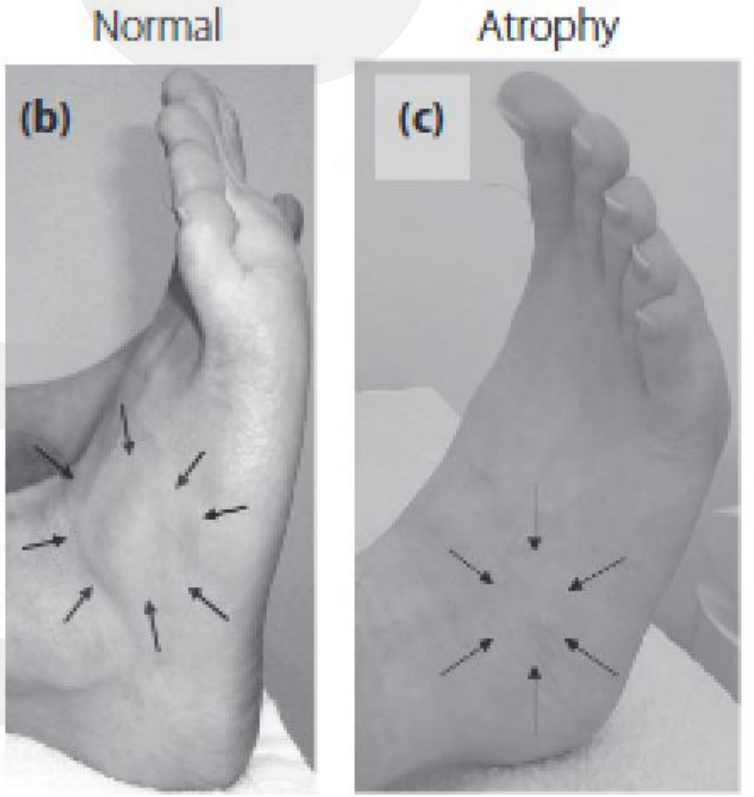
- Recognize urgent/emergent presentations of neuropathy
- Implement first-tier neurological evaluation of neuropathy
- Integrate pharmacological management of neuropathic pain in clinical practice
- Identify clinical situations in which neuromuscular medicine referral is warranted

HISTORY

- Acuity
  - Acute, subacute, chronic
- Pattern
  - Symmetry, length dependence, distal predominance
- Symptom characteristics
  - Positive sensory symptoms: paresthesia, lancinating / burning pain, allodynia
  - Negative sensory symptoms: numbness (hypoesthesia / anesthesia)
  - Imbalance
  - Weakness
- Associated features
  - Autonomic features (heat or cold intolerance, abnormal sweating, orthostasis)
  - Weight loss
- Medications
  - History of chemotherapy
- Toxic exposure
  - Alcohol use
- Past Medical history
  - ESRD, HIV infection
- Family history

FOCUSED NEUROLOGICAL EXAMINATION

- Motor
  - Bulk (particularly extensor digitorum brevis)
  - Power (Toe extension weakness not uncommon in many neuropathies, ankle dorsiflexion weakness would be unexpected in diabetic polyneuropathy or idiopathic polyneuropathy)
- Sensory
  - Vibration, joint position sense, Romberg testing
  - Pinprick
- Reflexes
  - Achilles reflex (absent in many axonal polyneuropathies, may be a physiologic finding in patients of advanced age)
  - Diffuse hyporeflexia/areflexia (suggestive of a demyelinating neuropathy)



J Diabetes Investig. 2021 Mar;12(3):398-408.

FIBER INVOLVEMENT

- Small fiber sensory
- Large fiber sensory
- Motor fibers
- Autonomic

LABS

- B12
  - With metabolites (i.e. methylmalonic acid [MMA])
- Test of glucose tolerance
  - HgbA1c
- Screen for gammopathy
  - Serum protein electrophoresis with reflex to immunofixation, serum free light chains

England JD et al. American Academy of Neurology. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2009 Jan 13;72(2):185-92.

RED FLAGS

- Acute onset
- Asymmetry
- Significant sensory ataxia
- Motor predominance
- Significant autonomic symptoms

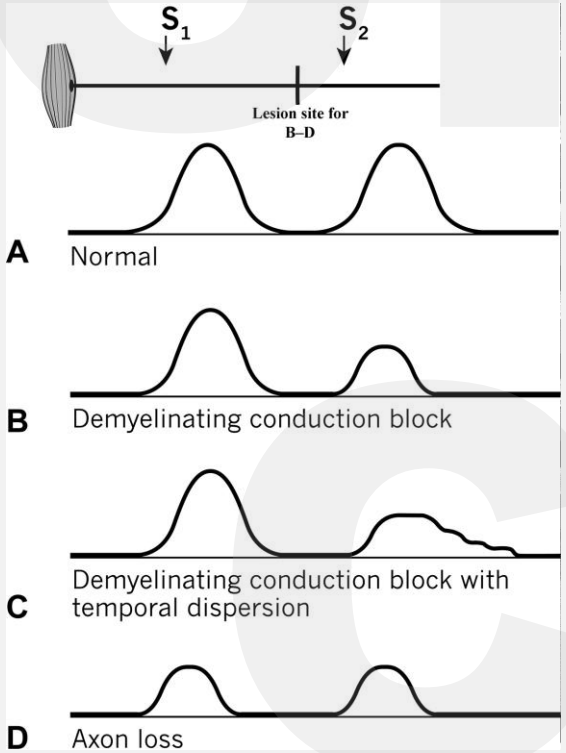
WHEN TO DIRECT PATIENT TO THE EMERGENCY DEPARTMENT

- Acute onset of sensory symptoms typically with an ascending pattern
- Gait impairment within two weeks of onset
- Concerning of Guillain-Barré syndrome
  - Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
  - Acute motor axonal neuropathy (AMAN) / acute motor sensory axonal neuropathy (AMSAN)
- May have antecedent event (e.g., vaccination, infection)
- IVIg or plasma exchange (PLEX) given within two weeks in ambulatory patients hastens improvement and likely improves outcomes
- Corticosteroids are not indicated

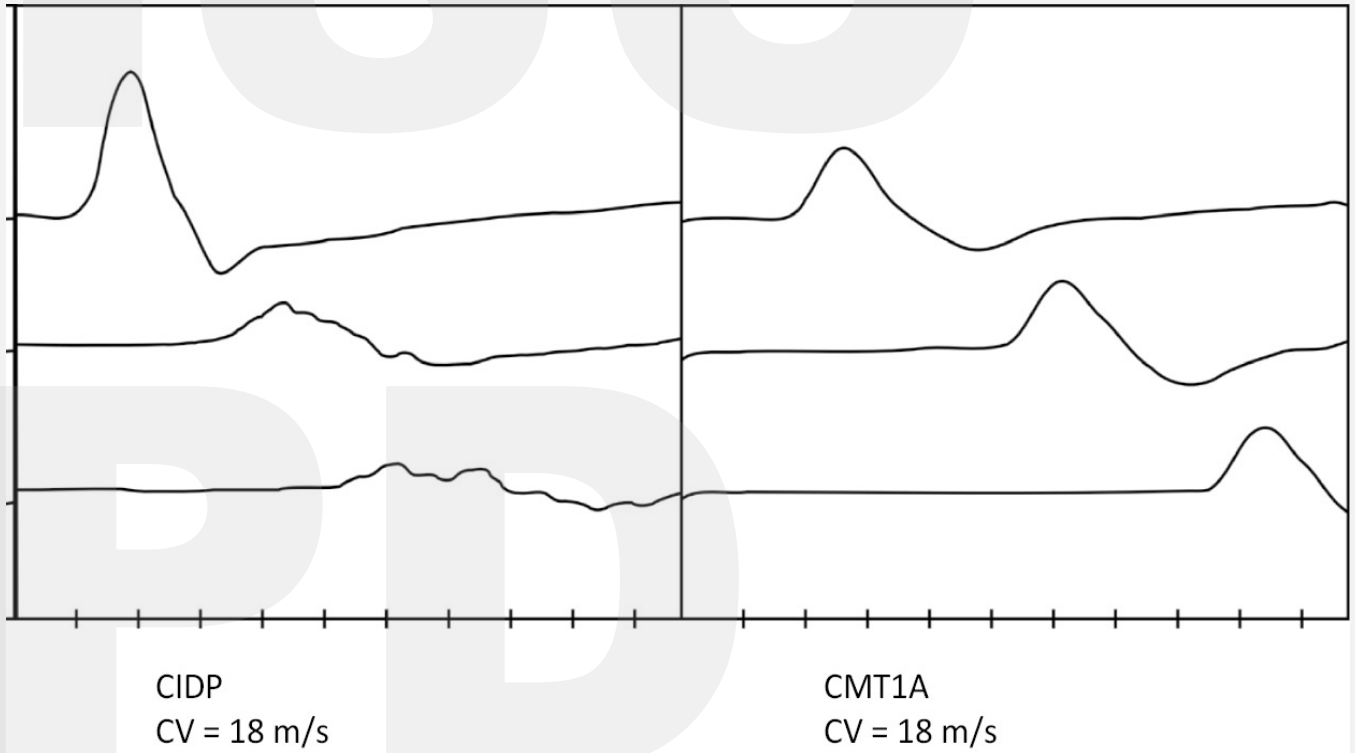
ELECTRODIAGNOSTICS (EMG/NERVE CONDUCTION STUDIES)

- Length-dependent sensorimotor axonal polyneuropathy
- Primary demyelinating polyneuropathy
  - CMT1, CIDP
- Sensory neuronopathy/ganglionopathy
- Mononeuropathy multiplex
- Bilateral carpal tunnel syndrome
  - Diabetes, amyloidosis
- Brachial plexopathy / lumbosacral plexopathy

NERVE CONDUCTION STUDY FINDINGS



Tavee T. Nerve conduction studies: Basic concepts. In: *Handbook of Clinical Neurology*, Elsevier; 2019: 217-224.



Bromberg MB. Hereditary Neuropathies (Charcot Marie Tooth Neuropathies). In: *Peripheral Neuropathies: A Practical Approach*. Cambridge University Press; 2018:175-180.

ELECTRODIAGNOSTICS IN DISTAL SYMMETRIC SENSORY(SENSORIMOTOR) POLYNEUROPATHY (AXONAL)

- Sural sensory nerve action potential (SNAP) absence or amplitude reduction most frequently used criterion
- Sural / radial amplitude ratio (SRAR)
- Medial plantar mixed nerve action potential (MNAP) absence or amplitude reduction
- Active denervation (fibrillations, positive sharp waves) in an intrinsic foot muscle (dorsal interosseous pedis)

AUTONOMIC REFLEX TESTING

Composite Autonomic Scoring Scale (CASS)	
Sudomotor index	
1	Single site abnormal or quantitative sudomotor axon reflex test *or* Length-dependent pattern (distal sweat volume < 1/3 of proximal value) *or* Persistent sweat activity at foot
2	1 site < 50% of lower limit on quantitative sudomotor axon test
3	≥ 2 sites < 50% of lower limit on quantitative sudomotor axon reflex test
Adrenergic index	
1	Phase II MAP decrease of > 20 mmHg but < 40 mmHg *or* Phase II does not return to baseline *or* Decrease in pulse pressure to ≤ 50% of baseline
2	Phase II MAP decrease of < 40 mmHg *or* Phase II MAP decrease of > 20 mmHg + phase II or IV absent
3	Phase II decrease of > 40 mmHg + absent phases II and IV
4	Criteria for 3 *and* Orthostatic hypotension (Δ SBP ≥ −30 mmHg *and* Δ DBP ≥ −20 mmHg)
Cardiovascular heart rate index	
1	HR or VR decreased but > 50% of min
2	HR or VR decreased to ≤ 50% of min
3	HR decreased to ≤ 50% of min *and* VR decreased to ≤ 50% of min

Composite score of 1–3 indicates mild autonomic failure, 4–6 moderate, and 7–10 severe

BP blood pressure; *MAP* mean arterial blood pressure; *min* minimum; *VR* Valsalva ratio

Adapted from Low PA "Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure." *Mayo Clin Proc* 1993;68:748–752

Curr Oncol Rep. 2021 Jan 8;23(2):14.

MOST COMMON ETIOLOGIES OF PERIPHERAL POLYNEUROPATHY

- Diabetic polyneuropathy
  - Red flags: Prominent weakness (toe weakness allowed)
- Monoclonal gammopathy of undetermined significance (MGUS)
  - Association versus causality
  - Special considerations: IgM paraprotein (e.g., with anti-MAG antibodies), lambda-restricted paraprotein (i.e., POEMS syndrome), high lambda free light chain (AL amyloidosis)
- B12 deficiency
  - Caveat: Causes a myeloneuropathy. If superimposed myelopathy is suspected, evaluation for concomitant vitamin deficiencies (e.g., copper) is warranted
- Chronic idiopathic axonal polyneuropathy
  - Red flags: Acute onset, prominent weakness (toe weakness allowed)

DIABETIC POLYNEUROPATHY - EPIDEMIOLOGY

- Most common neuropathy in developed countries
- Approximately 50% of patients will develop neuropathy but rates vary based on definition used
  - Of 4400 patients followed for 25 years, approximately half developed neuropathy (decreased sensation in the feet and depressed or absent reflexes)
  - Cohort study of adolescents and young adults with type 1 (N=329) and type 2 diabetes (N=70) followed for 6 – 7 years showed 8.2% vs 25.7% (P <0.0001) developed neuropathy
- Contributes to morbidity increasing risk for infection, ulceration, and amputation

Diabete Metab. 1977 Dec;3(4):245-56.
Diabetes Care. 2013 Dec;36(12):3903-8.

EFFECT OF GLYCEMIC CONTROL IN DIABETIC POLYNEUROPATHY

- Type 1 diabetes
  - DCCT/EDIC trial
    - Intensive glycemic control resulted in 2 points lower HgbA1c versus conventional
    - Ameliorated onset of neuropathy and slowed progression based on electrophysiologic markers
- Type 2 diabetes
  - UKPDS trial
    - Most of the benefit driven by reduction in retinopathy; neuropathy trended toward statistical significance

Cochrane Database Syst Rev. 2012 Jun 13;(6):CD007543. doi: 10.1002/14651858.CD007543.pub2.

Enhanced glucose control for preventing and treating diabetic neuropathy.

Callaghan BC[1], Little AA, Feldman EL, Hughes RA.

AUTHORS' CONCLUSIONS: According to high-quality evidence, enhanced glucose control significantly prevents the development of clinical neuropathy and reduces nerve conduction and vibration threshold abnormalities in type 1 diabetes mellitus. In type 2 diabetes mellitus, enhanced glucose control reduces the incidence of clinical neuropathy, although this was not formally statistically significant (P = 0.06). However, enhanced glucose control does significantly reduce nerve conduction and vibration threshold abnormalities. Importantly, enhanced glucose control significantly increases the risk of severe hypoglycemic episodes, which needs to be taken into account when evaluating its risk/benefit ratio.

B12 DEFICIENCY-RELATED NEUROPATHY TREATMENT

- IM and oral therapy have equal efficacy.
- Oral therapy must be high enough to saturate intrinsic factor pathways allowing for absorption via passive diffusion (1000-2000 mcg daily).[1]
- MMA normalization is a useful biomarker to follow.
- Treatment will stop progression and provide some improvement in most patients, but complete resolution is rare.

[1] *Arch Internal Med*. 2005 May 23;165(10):1167-72.

MGUS

- Requires ongoing monitoring and/or referral to hematology with consideration of further testing based on likelihood / risk for hematologic malignancy such as multiple myeloma
- IgM gammopathy (MAG autoantibodies), lambda-restricted gammopathy (i.e., POEMS syndrome), and elevated lambda free light chains (AL amyloidosis) require special consideration.
- Causality of peripheral neuropathy in non-IgM gammopathies is unclear
  - In fact, IgA and IgG gammopathy with CIDP is clinically indistinguishable from classic CIDP
- Low threshold for neuromuscular consultation

CHRONIC IDIOPATHIC AXONAL POLYNEUROPATHY

- No proven disease-modifying therapy
- Advancing age is a major risk factor
  - Prevalence
    - General population: 1%
    - 65-79 years: 9%
    - > 80 years: 39%
- Overall benign course with good long-term prognosis with some mild insidious progression

Muscle Nerve. 2001 Nov;24(11):1476-81
J Neurol Neurosurg Psychiatry. 1994 Dec;57(12):1525-7.

ALCOHOLIC POLYNEUROPATHY

- Mainstay of treatment is cessation of alcohol.
- Should be supplemented empirically with thiamine.
- Prognosis is generally favorable with abstinence, but complete recovery may not occur.

CHEMOTHERAPY-INDUCED POLYNEUROPATHY

- In many cases, no effective treatment barring cessation of offending agent.
  - Significant research dedicated to prevention
- Some recovery is typical with cessation of therapy, but it may be incomplete.
- Coasting phenomenon.
- Evolving arena (e.g., immune checkpoint inhibitors).
- Unmasking of hereditary neuropathy has been reported.
- Low threshold for neuromuscular medicine consultation.

AUTONOMIC NEUROPATHY

- Diabetic autonomic neuropathy
  - Cardiac autonomic neuropathy: relative risk of silent myocardial ischemia and death is doubled with symptomatic reduced heart rate variability.
- Amyloidosis
- Autoimmune
  - Ganglionic acetylcholine receptor (gAChR) antibodies
- *Postural orthostatic tachycardia syndrome*

MEDICATIONS FOR NEUROPATHIC PAIN

- Pregabalin 300 – 600 mg daily (Level A, effective)
- Gabapentin 900 – 3600 mg daily, venlafaxine 75 – 225 mg daily, duloxetine 60 – 120 mg daily, amitriptyline 25 – 100 mg daily, valproate 500 – 1200 mg daily, opioids (morphine sulfate, tramadol 210 mg, oxycodone controlled release), dextromethorphan 400 mg daily, capsaicin, and percutaneous electrical nerve stimulation (Level B, probably effective)
- Lidocaine patch (Level C, possibly effective)
- Oxcarbazepine, lamotrigine, lacosamide, mexilitene, pentoxifyline, and clonidine (Level B, probably not effective)
- Topiramate, alpha-lipoic acid (Level U, insufficient evidence)

Neurology. 2011 May 17;76(20):1758-65.

ALGORITHMIC APPROACH TO NEUROPATHIC PAIN

- Lidocaine patch on feet (3 patches maximum at once up to 12 hours per day)
  - Pregabalin 50 mg tid (or gabapentin 300 mg tid) uptitrated to 100 mg tid (or 1200 mg tid) as tolerated and effective
    - Add SNRI (duloxetine 30 – 60[120] mg daily; venlafaxine 37.5 – 225 mg daily) or amitriptyline 25 mg – 100 mg qHS
      - Add Tramadol 50 mg q6h prn for breakthrough pain
        - Add oxycodone, morphine, or dextromethorphan (limited to nighttime dosing if able to promote sleep, minimize opioid exposure, and minimize tachyphylaxis) or consider pain management referral

Amato A, Russell J. In: *Neuromuscular disorders 2nd Edition*. McGraw-Hill Education; 2016.

CONDITIONS REQUIRING NEUROMUSCULAR MEDICINE REFERRAL

- Vasculitic neuropathy (mononeuropathy multiplex)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Amyloid neuropathy
- Hereditary motor and sensory neuropathy (Charcot-Marie-Tooth [CMT] disease)
- Sensory ganglionopathy
- Paraneoplastic neuropathy

SENSORY GANGLIONOPATHY

- Chemotherapy
  - History of exposure (particularly platinum-based chemotherapy such as cisplatin)
- B6 toxicity
  - B6 level
- Sjogren's syndrome
  - SSA / SSB, consider referral to rheumatology / lip (labial salivary gland) biopsy
- Paraneoplastic (anti-Hu, -CRMP5, -amphyphysin)
  - Axonal Neuropathy, Autoimmune/Paraneoplastic Evaluation, Serum (Mayo clinic, TEST ID: AIAES)
- Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS)
  - RFC1 repeat expansion testing

VASCULITIC NEUROPATHY

- Systemic vasculitides
  - CBC, CMP, UA
  - ESR, CRP, ANA, RF
  - ANCA (myeloperoxidase [MPO], proteinase 3 [PR3]) antibodies
  - Acute hepatitis panel, cryoglobulins
  - Complement levels
- Restricted to peripheral nervous system
  - Isolated peripheral nervous system vasculitic neuropathy, neuralgic amyotrophy, diabetic lumbosacral radiculoplexus neuropathy (diabetic amyotrophy), non-diabetic lumbosacral radiculoplexus neuropathy

AMYLOID NEUROPATHY

- AL amyloidosis
  - Proteinuria, unexplained heart failure, hepatosplenomegaly, bilateral carpal tunnel syndrome, peripheral neuropathy (small fiber sensory and autonomic fibers)
  - Aggressive disease with prognosis reflective of extent of organ involvement
- Hereditary transthyretin (hATTR) amyloidosis
  - Variable penetrance, age of onset, and clinical course
  - Length-dependent polyneuropathy starting with loss of temperature and pain sensations in the feet, along with life-threatening autonomic dysfunction leading to cachexia and death within 10 years on average[1]
- Wild-type transthyretin (ATTRwt) amyloidosis
  - Not a cause of peripheral neuropathy
  - Manifests with bilateral carpal tunnel syndrome (often initially) and cardiomyopathy (not typically as severe as AL amyloid cardiomyopathy)

[1] *Lancet Neurol.* 2011 Dec;10(12):1086-97.

WHAT TO DEFER FOR NEUROMUSCULAR MEDICINE EVALUATION

- Nerve biopsy (usually sural nerve)
- Lumbar puncture (outpatient)
- Genetic testing
- Initiating treatment for CIDP

THANK YOU