PERIPHERAL NEUROPATHY: BASICS AND TREATMENT UPDATE

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- Nothing to disclose

LEARNING OBJECTIVES

- Discuss testing recommendations for distal symmetric polyneuropathy
- Update therapeutic options for peripheral neuropathies
- Review diagnosis and treatment of CIDP
- Review some atypical forms of neuropathy to improve recognition

CASE 1

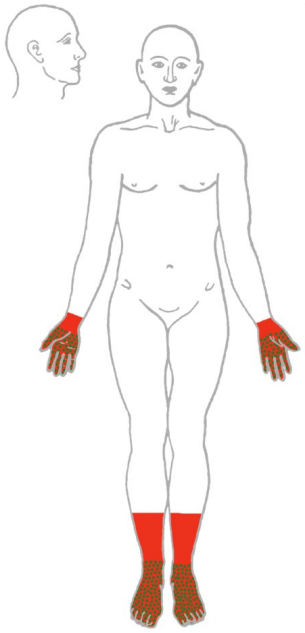
68-year-old woman with 6 months of:

- Foot burning and tingling
- Imbalance
- Tripping over feet

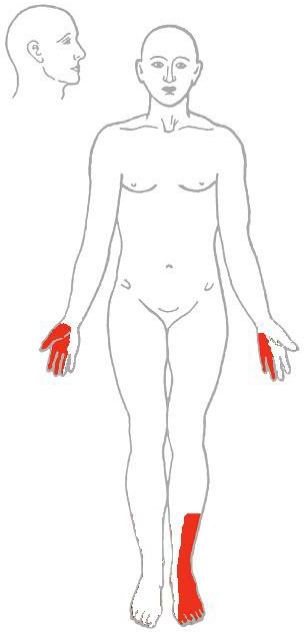
KEY NEUROPATHY QUESTIONS

Signs & Symptoms
Weakness (motor) Sensory (“positive” vs “negative”) Pain Autonomic Non-neurologic
Temporal Course
Days Weeks Months Years Continuous vs episodic

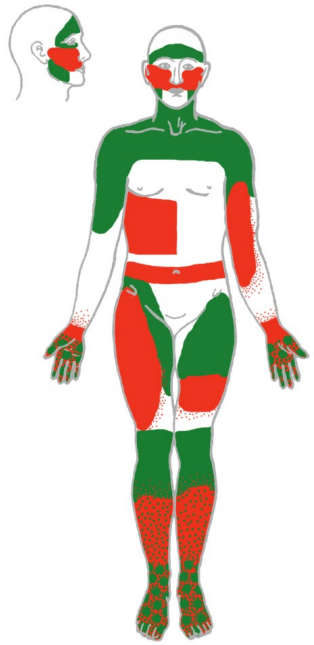
Anatomic distribution



Distal Symmetric



Focal Multifocal Asymmetric (1 or more mononeuropathies)



Proximal & Distal Symmetric or Asymmetric

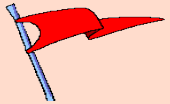
NOTHING BEATS A GOOD, CAREFUL NEUROMUSCULAR EXAMINATION !!!

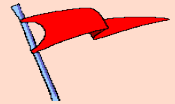
Video owned by Mayo Clinic

CLINICAL ASSESSMENT OF PERIPHERAL NEUROPATHIES

	Polyneuropathy	Poly-radiculopathy	Motor Neuron Disease	Multiple mononeuropathies	Myelopathy
Weakness	+	+	+	+	+
Atrophy	+/-	+/-	+	-	-
Distribution	Distal	Distal and proximal	Proximal or distal	Proximal > distal	Arm extensors Leg flexors
Bulbar	-	-/+	+/-	+	-
Symmetry	Symmetric	Symmetric or asymmetric	Asymmetric	Symmetric	Symmetric
Sensory	+	+	-	-	+
Pain	+/-	+/-	-	-	-
Reflexes	Reduced	Reduced	Increased	Normal (or reduced)	Increased

Atypical Features





Feature	Consider
Hands > Feet	Mononeuropathy (median, ulnar) Polyradiculopathy (CIDP) Cervical cord
Asymmetric	Mononeuropathy (fibular, ulnar) Radiculopathy (L5/S1, C8/T1) Polyradiculopathy
Motor without sensory	Motor neuron disease/motor neuropathy Distal myopathy LEMS Inherited motor neuropathy
Proximal (with distal) weakness	Polyradiculopathy Myopathy +/- neuropathy

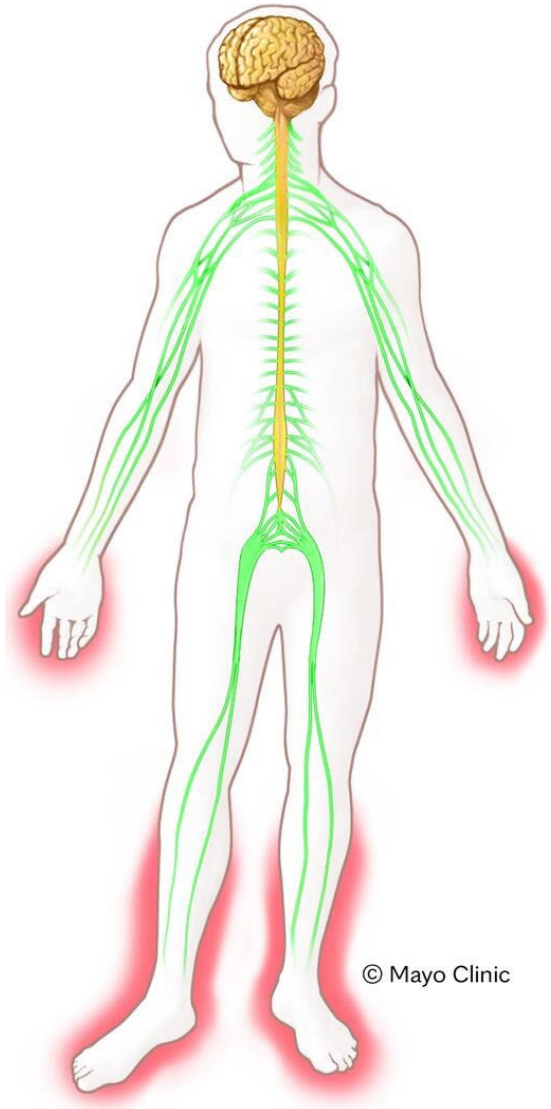
CONDITIONS CAUSING ATYPICAL PATTERNS

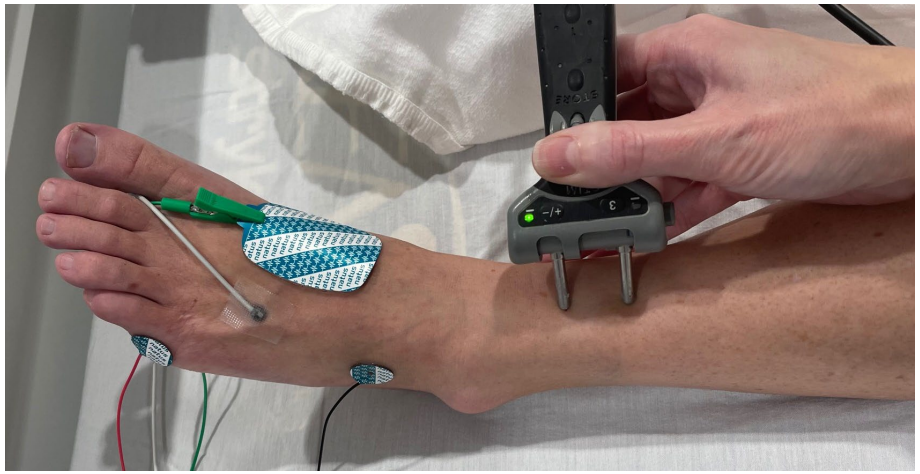
Sensory Neuropathy / Ganglionopathy	Motor predominant neuropathy	Multiple mononeuropathies ("mononeuritis multiplex")	Demyelinating neuropathies	Subacute polyradiculopathy
• Sjogren's • Lyme • Syphilis • Sarcoid • HIV, HTLVI • Paraneoplastic (small cell lung) • B6 toxicity • B12 deficiency • Vitamin E deficiency • Cisplatinum, thalidomide • Spinocerebellar ataxia • Friedreich's ataxia	• CIDP / Guillain-Barre syndrome • Multifocal motor neuropathy with conduction block • Porphyria • Lead intoxication • Diphtheria • Dapsone, Vincristine • Hereditary (CMT) *Motor Neuron Diseases* *ALS (hyperreflexia)* *Spinal muscular atrophy* *Kennedy's disease* *Distal Myopathies* *Inclusion body myositis* *Distal muscular dystrophies* *NMJ disorders* *LEMS*	• Vasculitis • Hepatitis C (Cryoglobulinemia) • Diabetes • Sarcoidosis • Amyloidosis • Hereditary neuropathy with liability to pressure palsies	Uniform • CMT type 1 • Adrenomyeloneuropathy • Metachromatic leukodystrophy • Krabbe's disease • Cerebrotendinous xanthomatosis • CIDP (AIDP) Non-uniform • MGUS (esp IgM) • Anti-MAG neuropathy • Osteosclerotic myeloma • Toxic (amiodarone, perhexiline, arsenic, hexane) • Hereditary neuropathy with pressure palsy (HNPP)	• Inflammatory (GBS, CIDP) • Vasculitis • Diabetes • Infectious (HIV, CMV, Lyme) • Sarcoid • Paraproteinemia • Infiltrative (amyloid, neoplastic) • Vascular malformation (dural AVF)

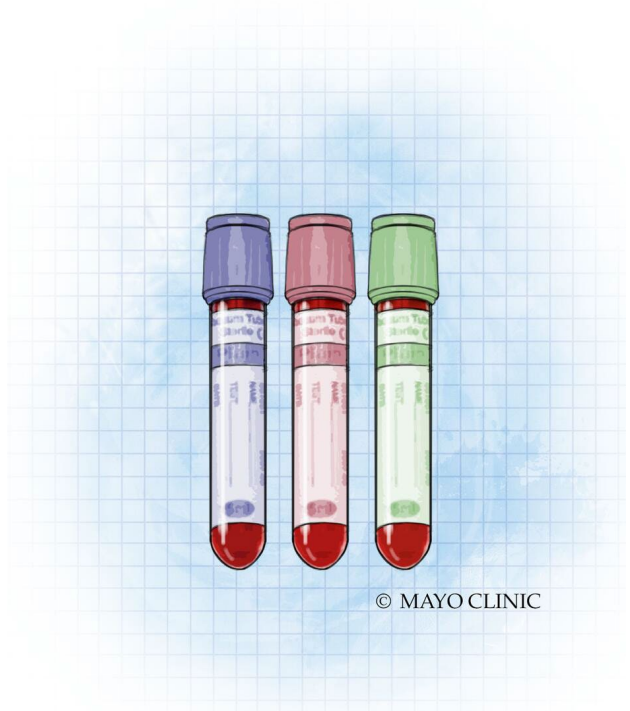
CASE 1

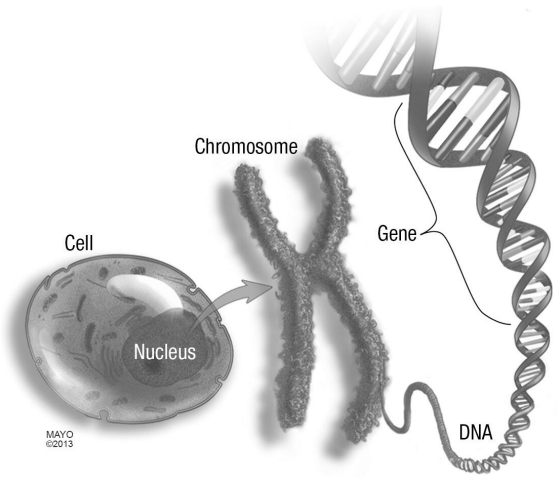
- 68-year-old woman with 6 months of foot burning and tingling, tripping over feet
- Examination:
  - Distal, symmetric leg toe extensor and foot dorsiflexor weakness
  - Areflexia
  - Loss of sensation (all modalities) to ankles

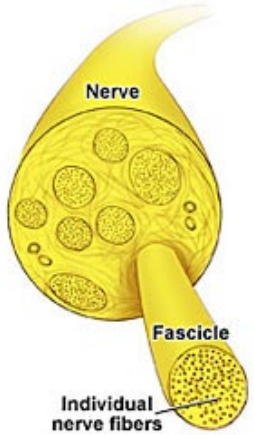
DISTAL SYMMETRIC POLYNEUROPATHY WORKUP









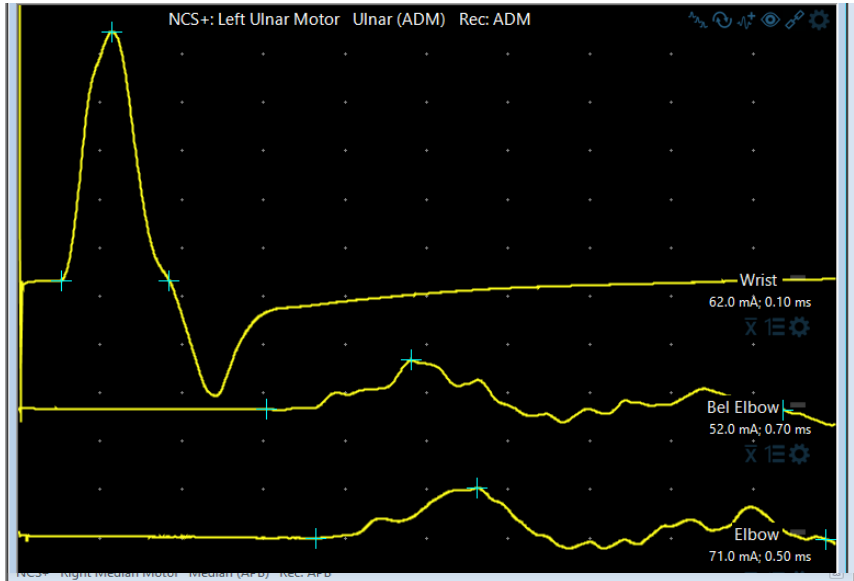


The yield of screening laboratory tests is 37% - 58%.

AAN Practice Parameter. Neurology 2009; 72: 185-192. (reaffirmed 1/2022)

ROLE OF EDX TESTING IN NEUROPATHIES

- Localize (length-dependent, polyradiculopathy, multiple mononeuropathies)
- Assess motor and sensory fibers (not small fibers)
- Determine **axonal** vs **demyelinating**



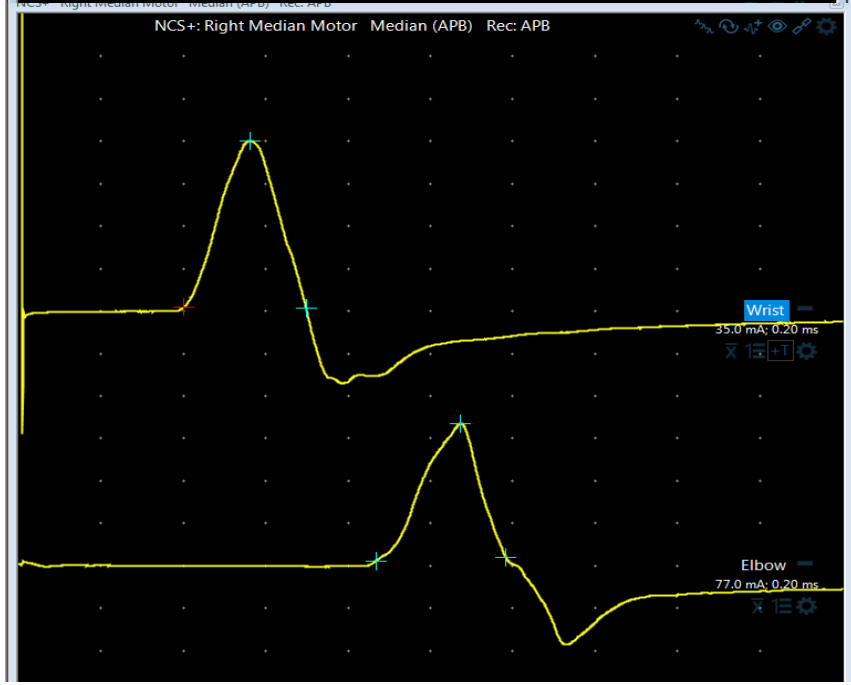
Tables | L/R Compare | Notepad | Graphs

Motor Sites

Site	Latency (ms)	Neg. Amp (mV)	Neg. Dur (ms)	Neg Area (ms*mV)	Temp °C
Left Ulnar (ADM)					
Wrist	2.6	10.3	6.6	34.2	33
Bel Elbow	15.2	2.1	31.6	17.4	32.5
Elbow	18.2	**2.1**	31.2	20.1	32.7
Wrist (M)	**NR**	**NR**	**NR**	**NR**	32
Elbow (M)	**NR**	**NR**	**NR**	**NR**	32.3

Motor Segments

Segment	Distance (mm)	Lat Diff (ms)	CV (m/s)
Left Ulnar (ADM)			
Wrist-ADM	66		
Bel Elbow-Wrist	238	12.6	19
Elbow-Wrist	358	15.6	**23**



Tables | L/R Compare | Notepad | Graphs

Motor Sites

Site	Latency (ms)	Neg. Amp (mV)	Neg. Dur (ms)	Neg Area (ms*mV)	Temp °C
Right Median (APB)					
Wrist	**10.0**	3.9	7.4	15.6	29.8
Elbow	21.7	**3.2**	7.9	12.5	30

Motor Segments

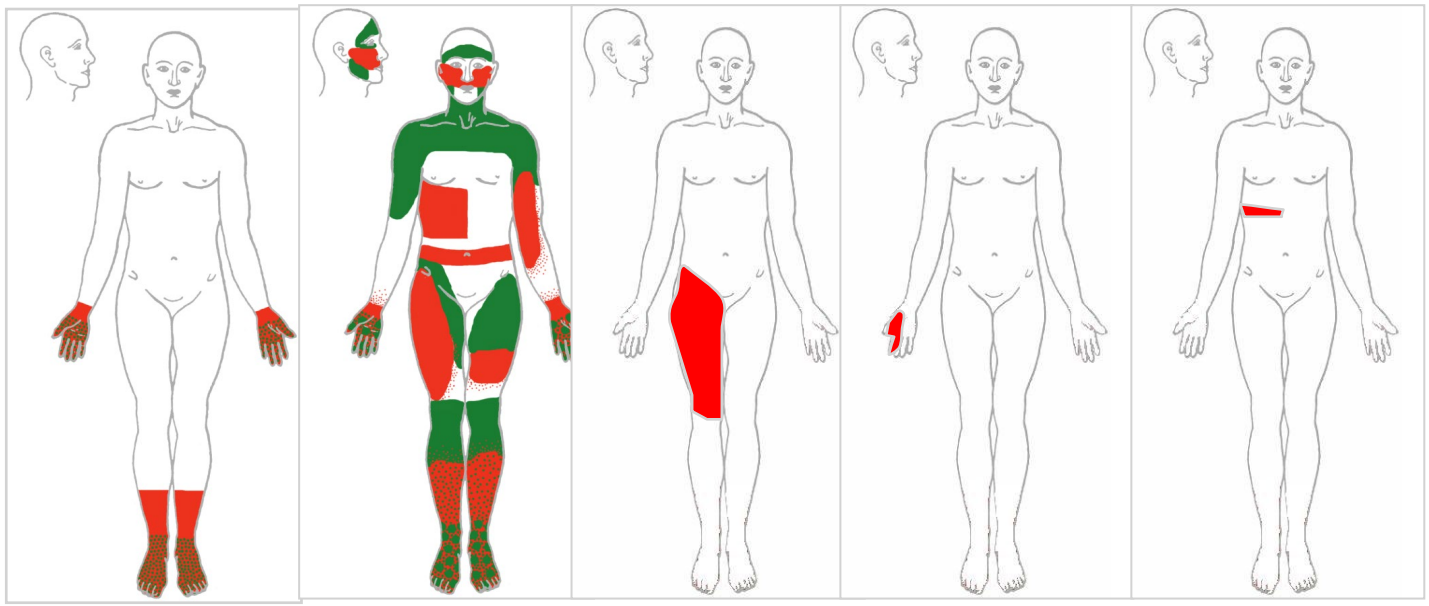
Segment	Distance (mm)	Lat Diff (ms)	CV (m/s)
Right Median (APB)			
Wrist-APB	67		
Elbow-Wrist	228	11.7	**19**

DISTAL SYMMETRIC POLYNEUROPATHY LABORATORY TESTING

OGTT	61%
Hgb A1C	26%
Fasting glucose	11%
ANA	3%
SPEP	3%
Vit B12	2%
TSH	0%
ESR	0%

(n=138 Smith AG 2004)

TYPES OF NEUROPATHY ASSOCIATED WITH DIABETES



CBC	Anemia, myeloproliferative
AST, ALT, creatinine	Hepatic or renal disease
Fasting glucose, Hgb A1C **OGTT**	Diabetes Impaired glucose tolerance
B12, Methylmalonic acid **(Vitamin E, copper if myelopathy)**	Vitamin deficiencies
SPEP **Monoclonal protein study** **Metastatic bone survey** **Fat aspirate**	Paraproteinemia Osteosclerotic myeloma Amyloidosis
TSH	Hypo-, Hyperthyroidism
ESR, ANA, ENA, ds-DNA	Vasculitis, connective tissue disease

Hereditary Clues

- "Negative" sensory symptoms (loss of feeling)
- Motor > sensory
- "Always clumsy", childhood/young adult onset
- Foot deformities (high arches/hammertoes), gait difficulties, podiatrist consultations
- Examine accompanying family members

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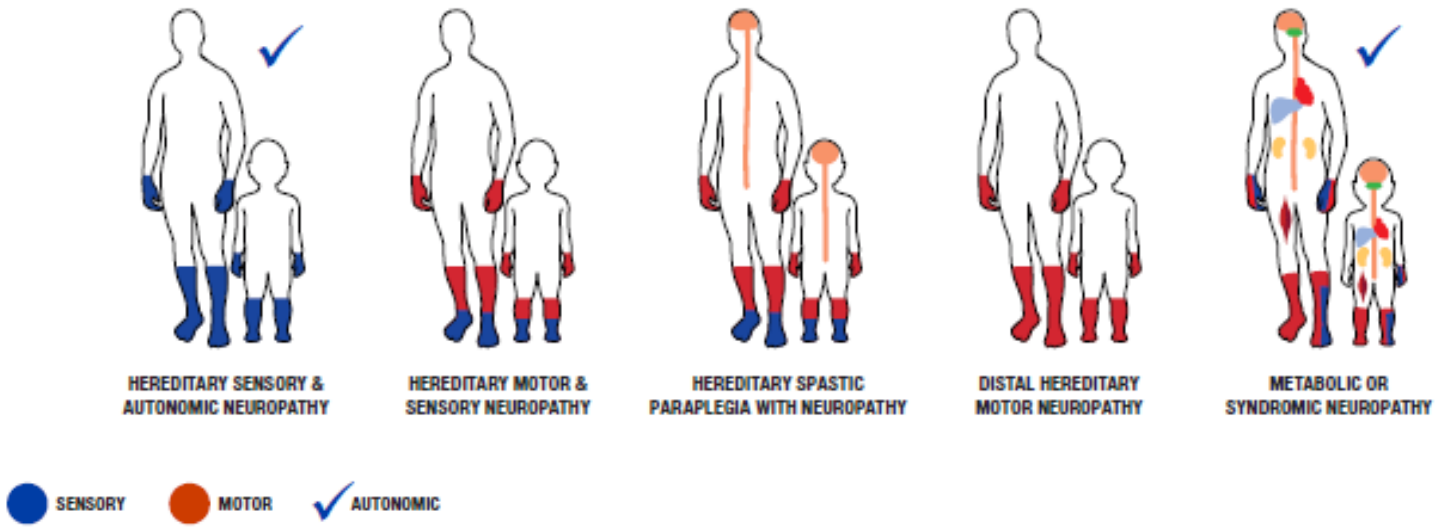
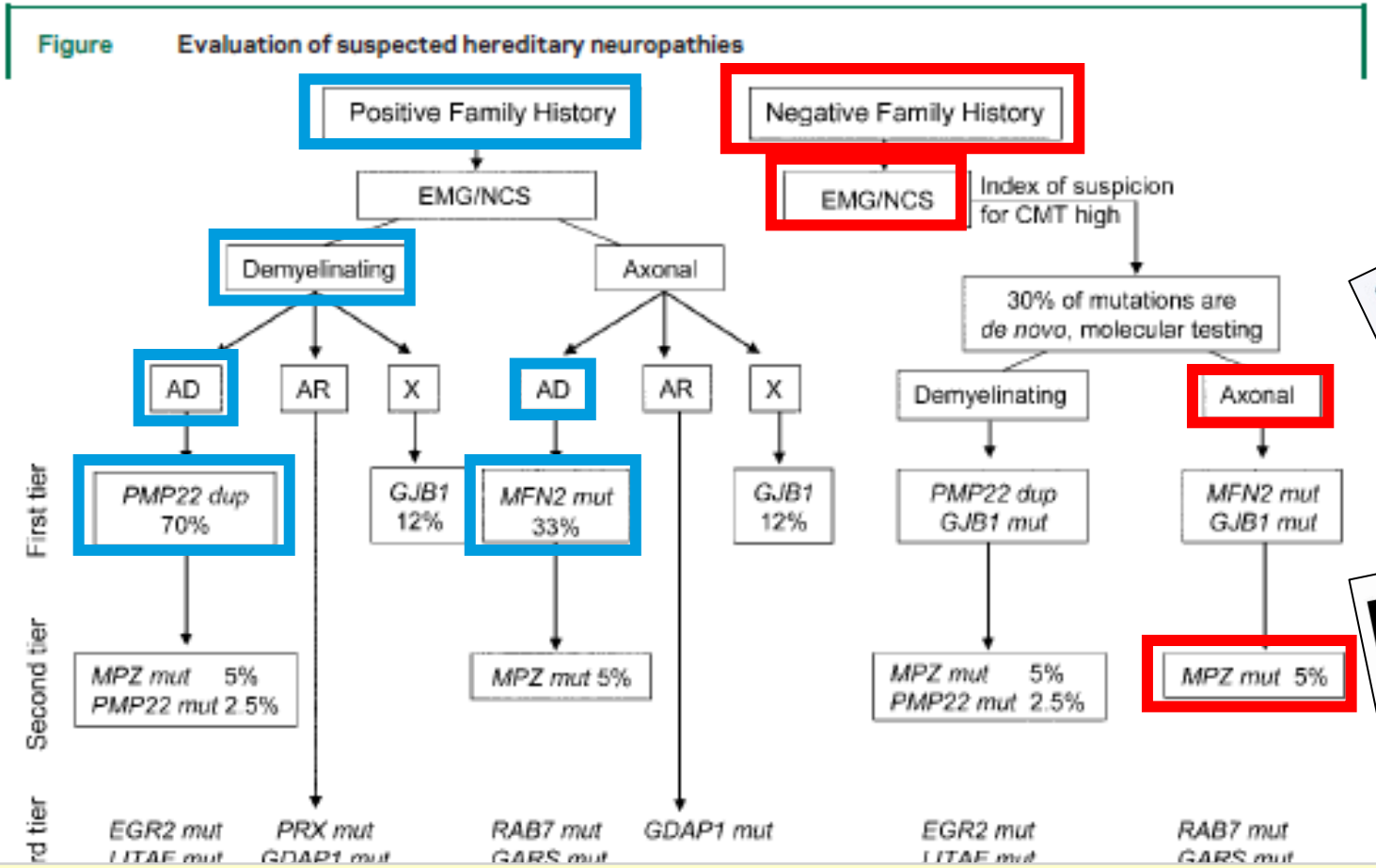
CATEGORICAL
NEUROMUSCULAR EVALUATIONS



When to Consider Genetic Testing

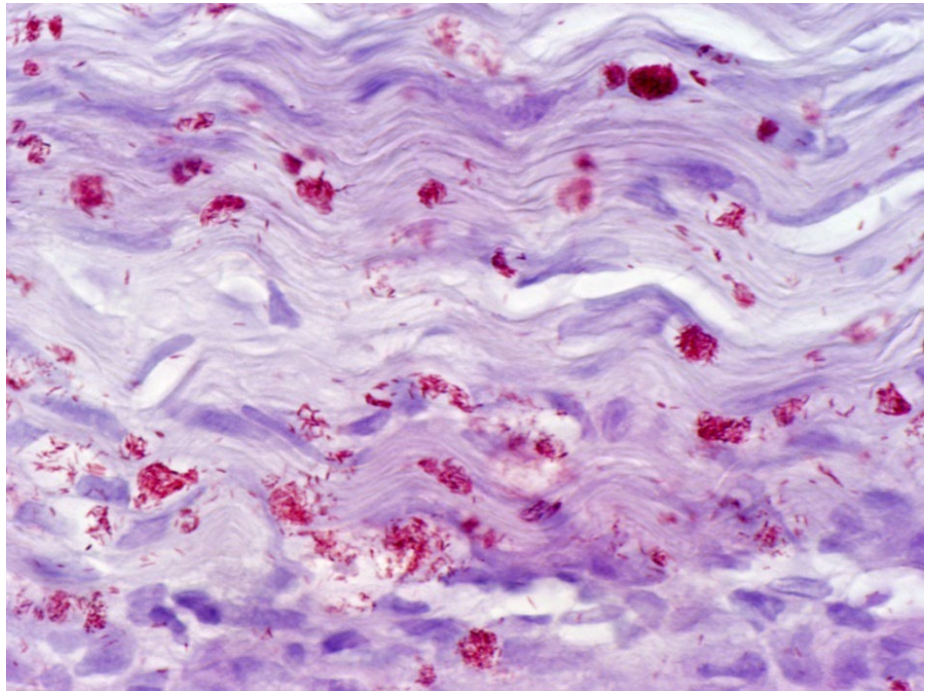


Useful for patients who exhibit a classic hereditary neuropathy phenotype.
(+ Family History, Early onset, Demyelinating)

Insufficient evidence in idiopathic PN without hereditary phenotype.

AAN Practice Parameter. Neurology 2009; 72: 185-192. (reaffirmed 1/2022)

(SURAL) NERVE BIOPSY



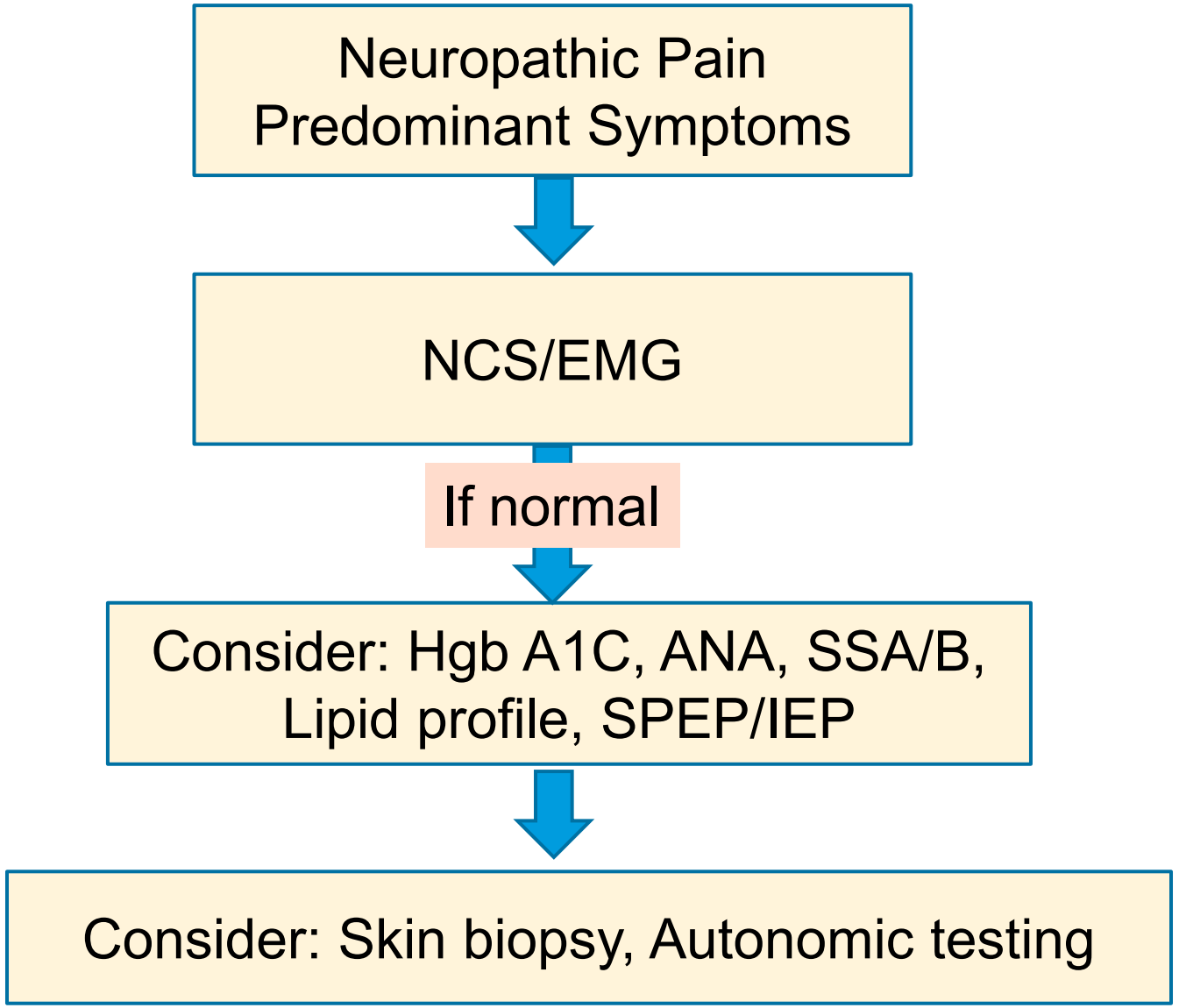
Conditions Identified by Nerve Biopsy
Vasculitis (diabetic, systemic)
Amyloidosis
Sarcoidosis
Lymphoma
Nerve sheath tumors
Leprosy

When to order?

Subacute
Severe
Rapidly progressive
Atypical

***AAN Practice Parameter 2009**

SMALL FIBER NEUROPATHY APPROACH



Skin biopsy: Validated, reproducible marker of small fiber sensory pathology

AAN Practice Parameter: "Possibly useful"

Adapted from Gwathmey KG, Pearson KT. Diagnosis and management of sensory polyneuropathy. BMJ 2019; 365:1108.

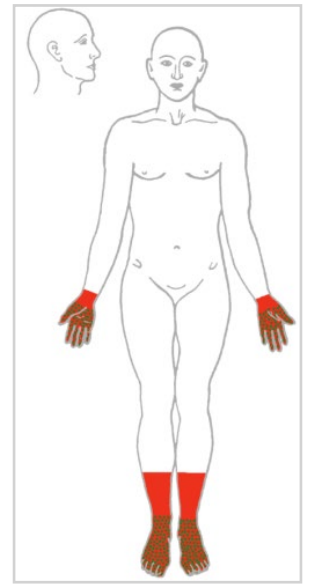
DIABETES & NEUROPATHY

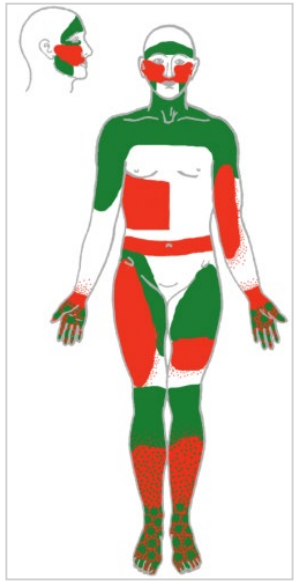
Accounts for 30-50% of causes of PN
Present (including subclinically) in ~45% of pts with DM

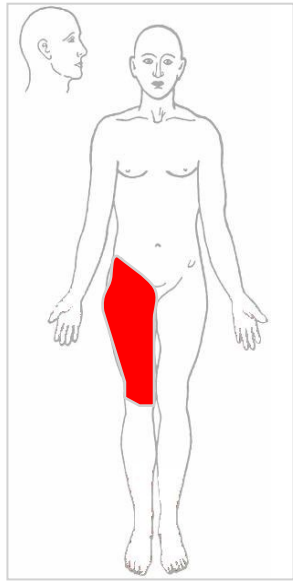
Does not necessarily correlate with degree of diabetic control (may precede diagnosis)

Optimizing glycemic control may delay PN
(non-significant trend in meta-analysis)

? Optimal treatment and outcome ?







*** Vincent AM et al. J Periph Nerve Sys 2009*
****Kassardjian et al. J Neurol Sci 2015*

TRANSTHYRETIN (TTR) HEREDITARY AMYLOIDOSIS POLYNEUROPATHY

59 yo man with hx of cardiomyopathy.
1 year of numbness in feet
6 months of bilateral hand numbness.

EMG: axonal polyneuropathy and moderate bilateral CTS

Consider when symmetric PN and:
Family history of neuropathy
Autonomic dysfunction
Cardiac involvement (arrhythmia, AV block, cardiomyopathy)
Gastrointestinal dysmotility
Renal impairment
Bilateral carpal tunnel syndrome

- TTR Stabilizers
  - Diflunisal (NSAID) – inhibits TTR amyloid fibril formation
  - Tafamidis – po; stabilizes tetramers, delays progression of neuropathy (2019 meta-analysis of 6 trials)*
- Gene modifying therapies
  - Inotersen (antisense oligonucleotide) – reduces serum levels of TTR; thrombocytopenia/renal dysfunction/glomerulonephritis – 284 mg SQ 1x/week
  - Patisiran (small interfering RNA targets TTR mRNA) – 0.3 mg/kg IV q3weeks
  - Vutrisiran - SQ

* Zhao Y, et al. J Clin Neurol 2019

SOME MEDICATIONS ASSOCIATED WITH NEUROPATHY

Drug Category	Sensorimotor	Sensory Neuropathy
Cardiovascular	• Amiodarone *	• Statins ?? • Perhexiline*
Chemotherapeutics	• Bortezomib • Thalidomide • Taxanes (paclitaxel, docetaxel)	• Vincristine (Vinca alkaloids) • Cisplatinum • Oxaliplatin
Antibiotics & Nucleoside reverse transcriptase inhibitors	• Metronidazole • Nitrofurantoin	• Isoniazid • Linezolid • Zalcitabine, didanosine
Immunosuppressive agents	• Biologicals (adalimumab, infliximab, etanercept)* – polyradiculopathies (GBS), multiple mononeuropathies • Leflunomide • Tacrolimus	
Others	• Colchicine • Phenytoin	• B6 toxicity • Hexane

*Demyelinating

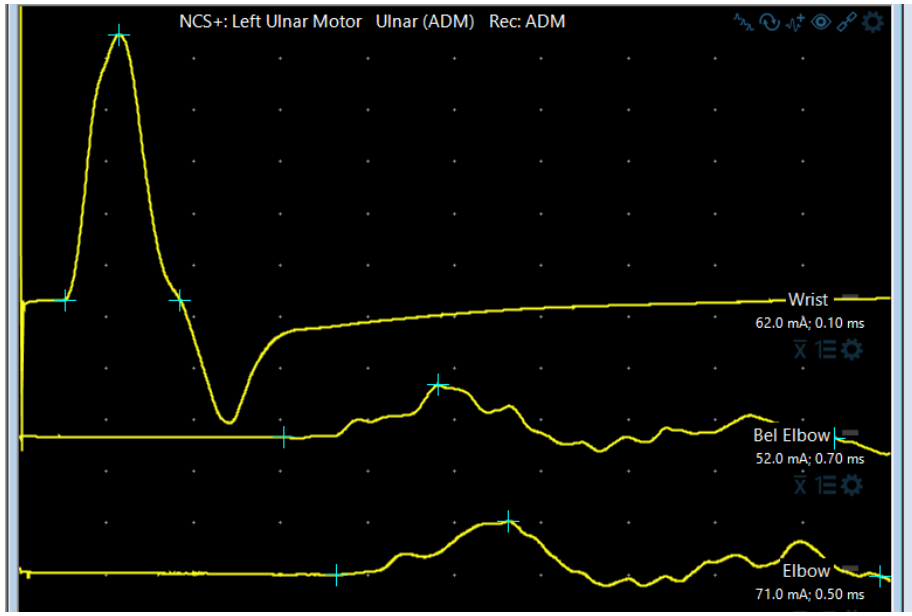
SYMPTOMATIC TREATMENT
NEUROPATHIC PAIN (STRONGEST EVIDENCE)

Drug	Dose	Adverse Effects
Pregabalin	150 – 600 mg (3 doses)	Weight gain, dizziness, sedation, edema
Gabapentin	300 – 3600 mg (3 doses)	Weight gain, dizziness, sedation, edema
Venlafaxine	75 – 225 mg (2-3 doses)	N/V, dizziness
Duloxetine	60 – 120 mg (2 doses)	N/V, dizziness
TCAs (amitriptyline, nortriptyline)	25 – 150 mg	Weight gain, sedation, anticholinergic effects
Tramadol	100 – 400 mg (4 doses)	N/V, constipation, sedation

Treat with maximal (tolerated) dose; adequate length (4-6 weeks)

Gwathmey KG, Pearson KT. Diagnosis and management of sensory polyneuropathy. BMJ 2019; 365:1108.

CASE 2



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Wrist (M)	**NR**	**NR**	**NR**	**NR**	32
Elbow (M)	**NR**	**NR**	**NR**	**NR**	32.3

Motor Segments

Segment	Distance (mm)	Lat Diff (ms)	CV (m/s)
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Wrist-ADM	66		
Bel Elbow-Wrist	238	12.6	19
Elbow-Wrist	358	15.6	**23**

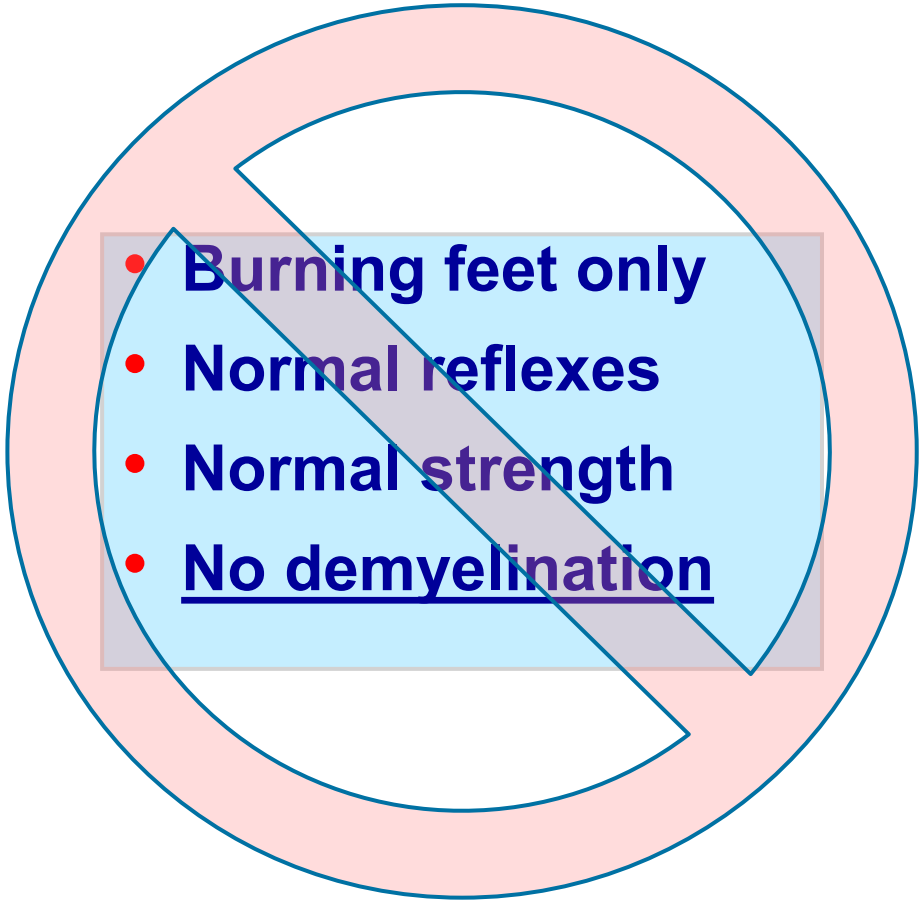
- 58-year-old man with 6 months of leg and hand weakness and numbness
- Tripping over feet, difficulty rising
- Loss of sensation in hands and feet
- Examination:
  - Distal and **proximal** leg and arm weakness, **left worse than right**
  - **Areflexia**
  - Loss of vibration and proprioception to ankles and fingers

CLINICAL MANIFESTATIONS

Symptoms/ Signs	Motor Neuron Diseases	Polyradiculopathy	Polyneuropathy	Neuromuscular Junction Disorders	Myopathy
Weakness	+	+	+	+	+
Atrophy	+	+/-	+/-	-	+/-
Distribution	Proximal or distal	Distal and proximal	Distal	Proximal > distal	Proximal
Bulbar	+/-	-	-	+	+/-
Symmetry	Asymmetric	Symmetric or asymmetric	Symmetric	Symmetric	Symmetric
Sensory	-	+	+	-	-
Pain	-	+/-	+/-	-	-
Reflexes	Increased	Reduced	Reduced	Normal (or reduced)	Normal

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULOPATHY (CIDP)

EAN-PNS Guideline on Dx and Rx of CIDP: Report of a Joint Task Force – Second Revision
Progressive or relapsing motor and sensory (>2 months)
Symmetric
Distal and proximal weakness
Sensory involvement
Absent or reduced DTRs
EDX: Demyelinating features (≥ 2 nerves)
CSF: elevated protein (*not necessary if diagnostic criteria met)
Test for monoclonal proteins Consider testing for nodal and paranodal antibodies MAG antibodies IF IgM paraprotein (esp. distal CIDP)

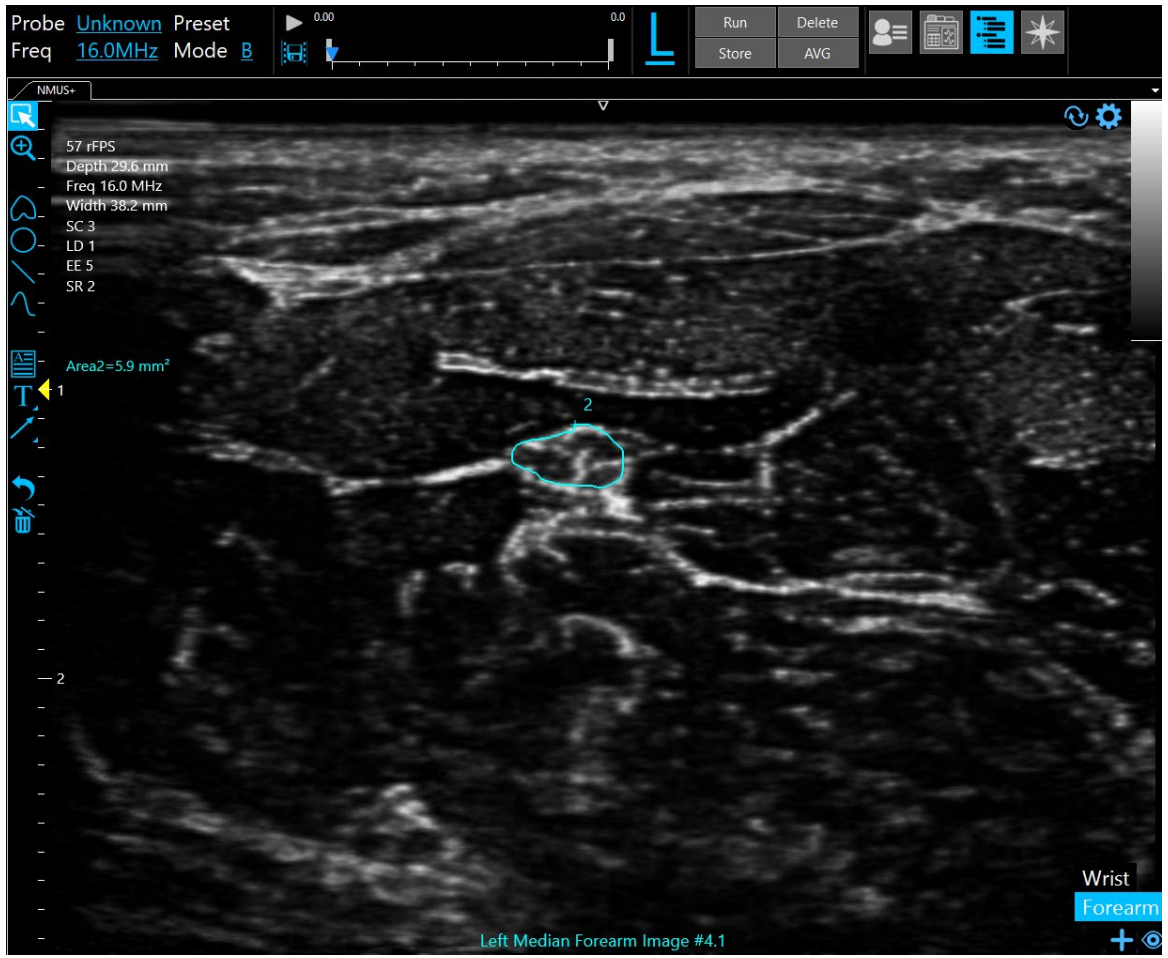


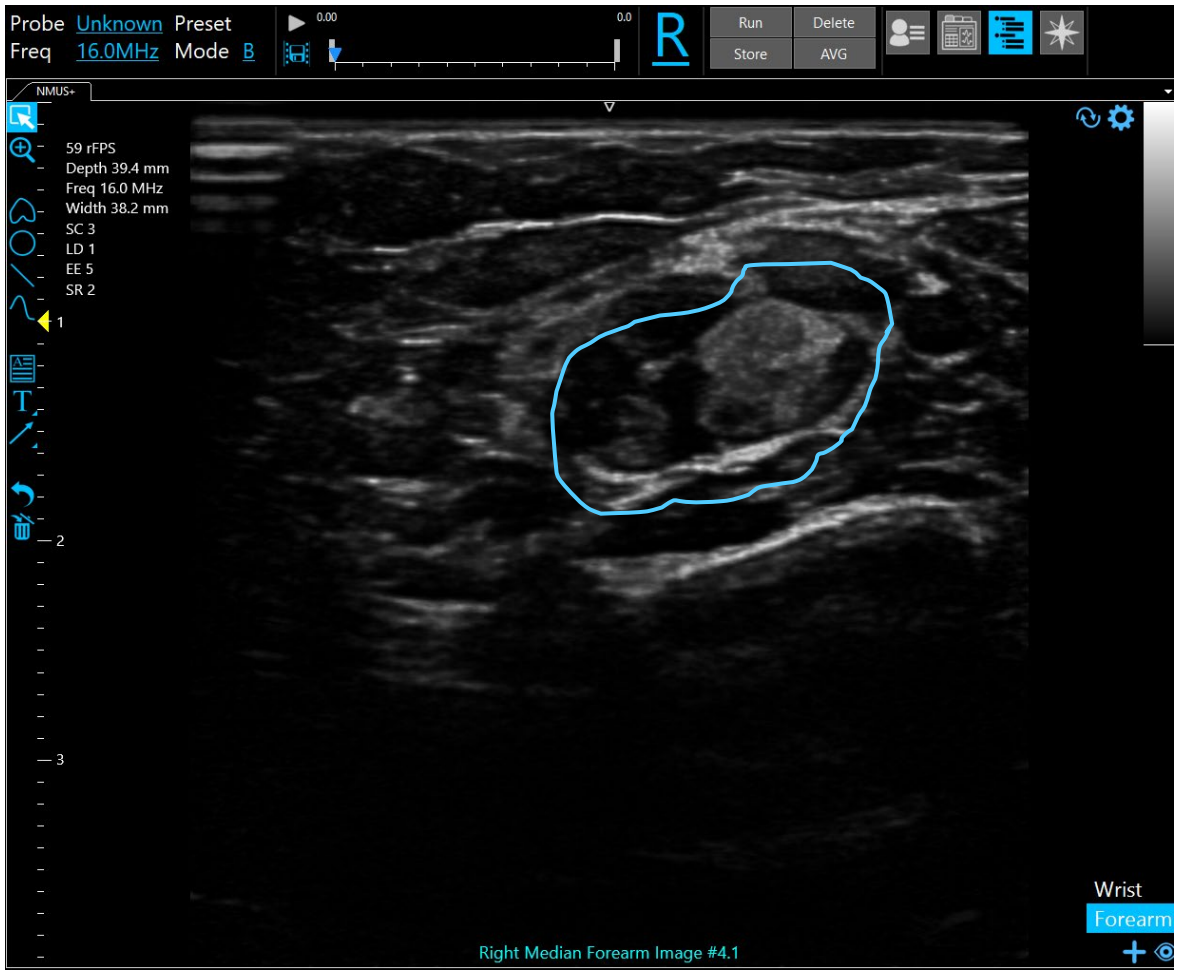
Van den Bergh PYK et al. J Peripher Nerve Syst 2021;26:242-268.
History, Diagnosis, and Management of Chronic Inflammatory Demyelinating Polyradiculoneuropathy
Dyck PJB, Tracy JA. Mayo Clinic Proceedings, June 2018

NEUROMUSCULAR ULTRASOUND

MAY BE USEFUL IN PTS WITH “POSSIBLE” CIDP

ENLARGEMENT OF CSA IN AT LEAST 2 SITES IN PROXIMAL MEDIAN NERVE OR BRACHIAL PLEXUS





Van den Bergh PYK et al. J Peripher Nerve Syst 2021;26:242-268.

CIDP TREATMENT

Treatment	Administration	Side effects/Cost
IVIG	IV (0.4 grams/kg daily for 5 days; weekly x 1-3 months, then increase interval *(Lancet Neurol 2008 Feb;7:136-144)* *SC Ig - possibly similar efficacy for maintenance*	HA, flu-like illness, HTN Expensive
Corticosteroids (prednisone)	Oral (60 mg daily, gradual taper to lowest effective dose) Pulse dose IV methylprednisolone: option *Positive response in up to 87%. Viala et al, 2010	Glucose impairment, Osteopenia, Avascular necrosis, Weight gain, pneumocystis pneumonia, dermatologic, sleep disturbance Cost: $15/month
PLEX	Every other day for 5 treatments; weekly x 1-3 months, then increase intervals	

- **Possibly effective** if failure of proven treatment (low evidence): azathioprine, cyclophosphamide, cyclosporin, mycophenolate mofetil, rituximab
- **Not recommended**: Methotrexate, Interferon β 1a, fingolimod, alemtuzumab, bortexomib, etanercept, fludarabine, natalizumab, tacrolimus†

† No statistically significant benefit

CIDP VARIANTS

	Typical	Distal CIDP (DADS) (2/3 with IgM)	Multifocal CIDP (MADSAM)	Focal CIDP	Motor CIDP	Sensory CIDP
Distribution	Proximal & distal	Distal (Legs > arms)	Distal (Arms > legs)	Proximal & distal (Arm or leg)	Proximal & distal	Distal & proximal
Symmetric	+	+	-	-	+	+

Autoimmune Nodopathies (5-10%)*	Features
Neurofascin-155 (NF-155)	Younger age Distal weakness, ataxia, tremor
Contactin-1 (CNTN1)	Weakness, ataxia
Contactin-associated protein 1 (Caspr1)	Ataxia, neuropathic pain, cranial nerve
* Demyelinating features on EMG, lack of inflammation on biopsy, poor response to IVIg (Rituximab)	

Van den Bergh PYK et al. J Peripher Nerve Syst 2021;26:242-268.

TAKE HOME POINTS

- Use clinical exam to guide localization and differential diagnosis of neuropathies
- Understand the testing performed and limitations to identify potential etiologies of neuropathies
- Recognize diagnostic criteria and treatment options for immune mediated neuropathies

QUESTIONS & DISCUSSION