Update in Diagnosis and Management of Peripheral Neuropathy

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Disclosures

- I have nothing to disclose

Learning Objectives

1. Discuss diagnostic approach to the patient with neuropathic symptoms
2. Identify red flags suggesting alternate diagnoses and treatable neuropathies
3. Discuss symptomatic management of patients with neuropathy

Overview

- The prevalence of polyneuropathy in the general population is around 4%
  - Up to 10% in patients >40
  - Up to 50% of patients with diabetes
- Diagnostic evaluation focuses on identifying possible immune neuropathies, reversible risk factors
  - Diabetes, amyloidosis, B12 deficiency, toxin exposure
- Management is largely symptomatic (pain)

Diagnostic Approach- History

- Aim to distinguish
  - Pattern of symptoms (e.g. length-dependent, symmetry)
  - Temporal progression of symptoms
  - Identify associated symptoms that distinguish involvement of specific fiber types
- Differentiate between
  - Distal symmetric polyneuropathy
  - Small fiber neuropathy
  - Radiculopathy
  - Plexopathy
  - Myelopathy
  - Motor neuropathy

Diagnostic Approach- History

- Positive Symptoms
  - Motor: cramps, twitching
  - Sensory: Burning pain, “buzzing”, “vibrating”, tingling, allodynia, hyperesthesia
- Negative Symptoms
  - Motor: Weakness, fatigue, wasting
  - Sensory: Numbness, imbalance, difficulty feeling temperature
- Autonomic symptoms
  - Orthostasis, cold feet with changes in skin color, dyshidrosis, incontinence, erectile dysfunction, early satiety, bloating/constipation/diarrhea.

Diagnostic Approach- History

- Temporal profile and pattern
  - Location of initial symptoms
  - Asymmetry
  - Tempo of progression
    - Monophasic, slowly progressive, fluctuating, stepwise

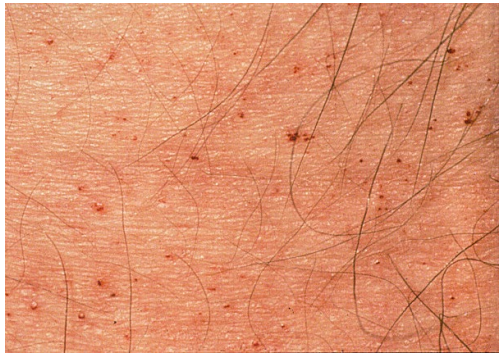
Diagnostic Approach- History

- Alcohol use
- Tobacco use
- Diet or history of gastric bypass
- Exposures
- Medications
  - Chemotherapies (platins, vincristine, bortezomib- Multiple Myeloma)
  - HIV-related treatment
  - Vitamin B6 (doses exceeding 50-100mg daily)
  - Phenytoin, amiodarone
- Family History

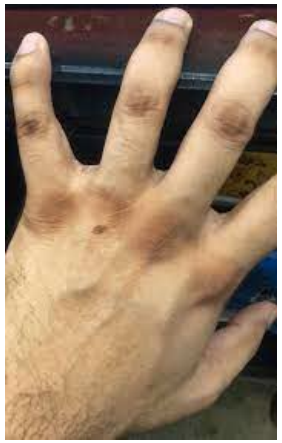
Diagnostic Approach- Exam

- Skin:
  - POEMS: Acrocyanosis, clubbing
  - Dependent erythema (autonomic involvement)
  - Purpura (vasculitic neuropathies)
  - Angiokeratomas (Fabry's)
  - Hyperpigmentation, glossitis (B12 deficiency)
- Feet:
  - Hammer toes, pes cavus
  - Intrinsic muscle atrophy

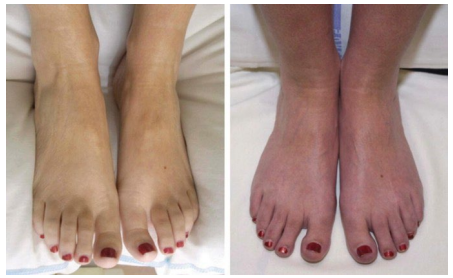
Acrocyanosis, clubbing



Angiokeratomas



Hyperpigmentation



Diagnostic Approach- Exam

- Cranial nerves:
  - Anosmia (B12 deficiency)
  - Pupillary response (dysautonomia)
  - Facial sensory loss (Sjogrens)
- Motor:
  - Visual observation for atrophy, fasciculations
  - Toe extensors
  - Ability to spread toes
  - Distal contractures

Diagnostic Approach- Exam

- Sensory exam
  - Large fiber- vibration, joint position sense, Romberg
  - Small fiber- pin/temperature
  - Distal vs proximal, symmetry
- Reflexes
  - Usually down unless small fiber only
  - Preserved reflexes may prompt concern for concurrent CNS lesion
- Gait
  - Ability to stand without use of hands (?proximal weakness)
  - Ability to walk on toes/heels to assess for subtle weakness
  - Wide based gait or difficulty with tandem?

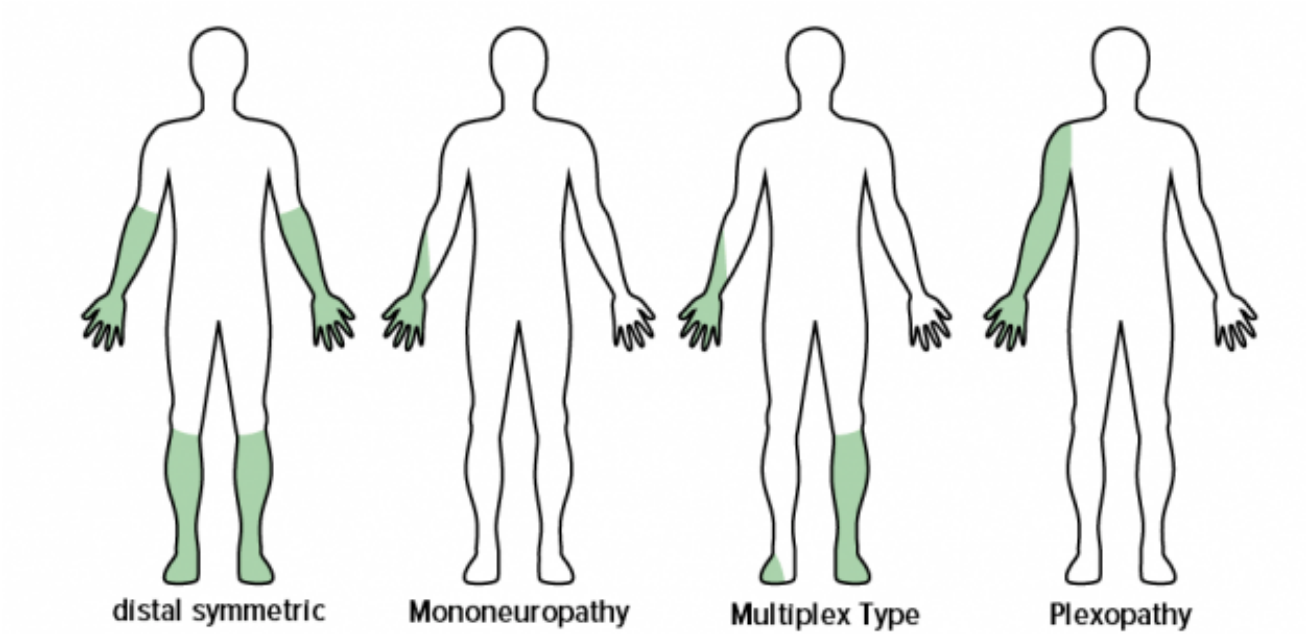
Diagnostic Approach- Patterns

- Fiber type classification: motor predominant
  - Multifocal Motor neuropathy
  - Motor Neuron Disease
  - GBS, CIDP
  - Lead Toxicity
  - Hereditary neuropathies
- Fiber type classification: Sensory
  - Diabetes mellitus
  - B12 deficiency
  - Amyloidosis
  - Sjogren's
  - Alcohol use
  - Hereditary

Diagnostic Approach- Patterns

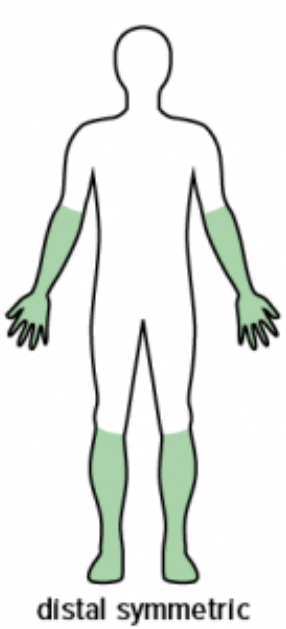
- Autonomic- acute
  - GBS
  - Autoimmune autonomic ganglionopathy
  - Acute porphyria
- Chronic
  - Diabetes mellitus
  - Amyloidosis
  - HSAN
  - Fabry's
  - Sjogren's

Patterns


distal symmetric
Mononeuropathy
Multiplex Type
Plexopathy

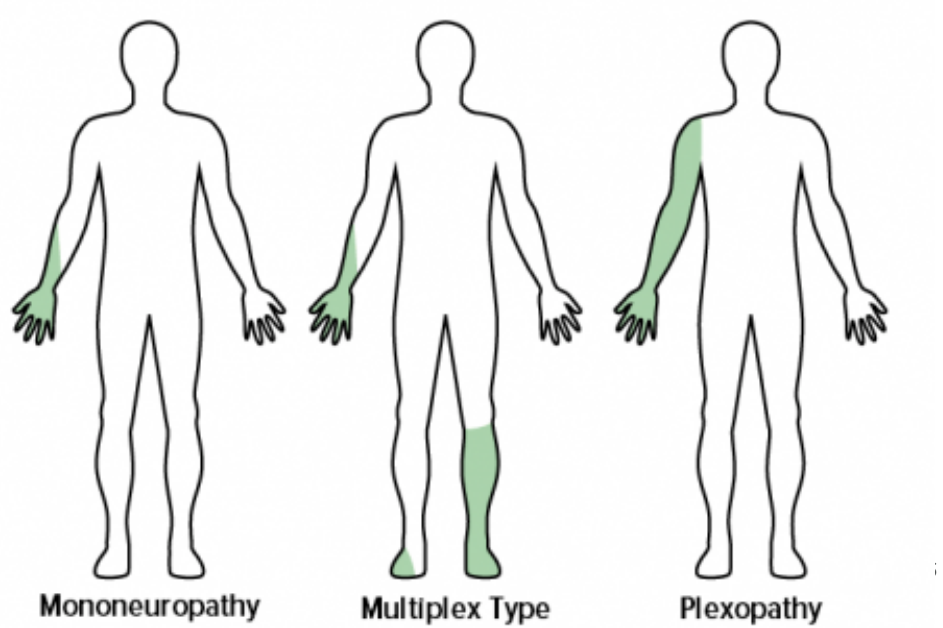
Distal symmetric polyneuropathy

- Most common
- Metabolic
  - Diabetes mellitus
  - Obesity
- Toxic- chemotherapy
- Inherited
- Idiopathic (30%)



Non-length dependent

- Immune-mediated neuropathies
  - Sarcoidosis
  - Sjogrens
- Infectious (lyme, HIV, leprosy)
- Demyelinating
  - CIDP
  - MADSAM
  - MAG



Sensory neuronopathy/ganglionopathy

- Paraneoplastic (Hu)
- Para-infectious
- Sjogren
- HIV
- B6 (pyridoxine toxicity)
- Idiopathic

Red Flags

- Proximal muscle weakness
  - Can occur with CIDP, polyradiculopathies (paraneoplastic syndromes)
- Rapid progression
- Asymmetry
- Sensory ataxia early in course
- Weakness
- Concurrent unexplained cardiomyopathy

Diagnostic-labs

- Distal symmetric polyneuropathy
  - Fasting glucose, 2 hr glucose tolerance test, A1c
  - Vitamin B12 (+/- MMA)
  - Immunofixation
  - CBC, CMP
- Mononeuritis Multiplex
  - ESR, CRP, ANA dsDNA, ANCA (PR3/MPO), RF, C3,C4, SSA/SSB, Hepatitis B/C, cryoglobulin

Diagnostic-labs

- With myelopathy
  - B12, Copper, Vitamin E
- Demyelinating
  - MAG, GM1a, GQ1b, GD1a
  - Contactin, CASPR1, neurofascin antibodies
  - Usually does not require LP unless there is diagnostic uncertainty
  - Consider genetic testing if longstanding

Diagnostics: Electrodiagnostics

- Always get if red flags
- Distinguish radiculopathy from neuropathy
- Identify concurrent entrapment neuropathy
- Aid in small fiber neuropathy evaluation
- Identify demyelination
  - Certain features on NCS can indicate the presence of an inherited demyelinating neuropathy
    - Uniformly prolonged latencies
    - Diffusely (and very) slow velocities
    - No temporal dispersion

Diagnostics: Autonomic testing

- QSART:
  - Assess postganglionic sudomotor nerve fibers
  - 75-90% sensitivity in SFN
- Sympathetic sweat response
  - Assess change in skin resistance in response to arousal stimulus
  - No clearly established quantitative criteria
- Heart rate variability
  - HR increases with inspiration, decreases with expiration
  - Assesses variability with RR intervals with normal and deep breathing.

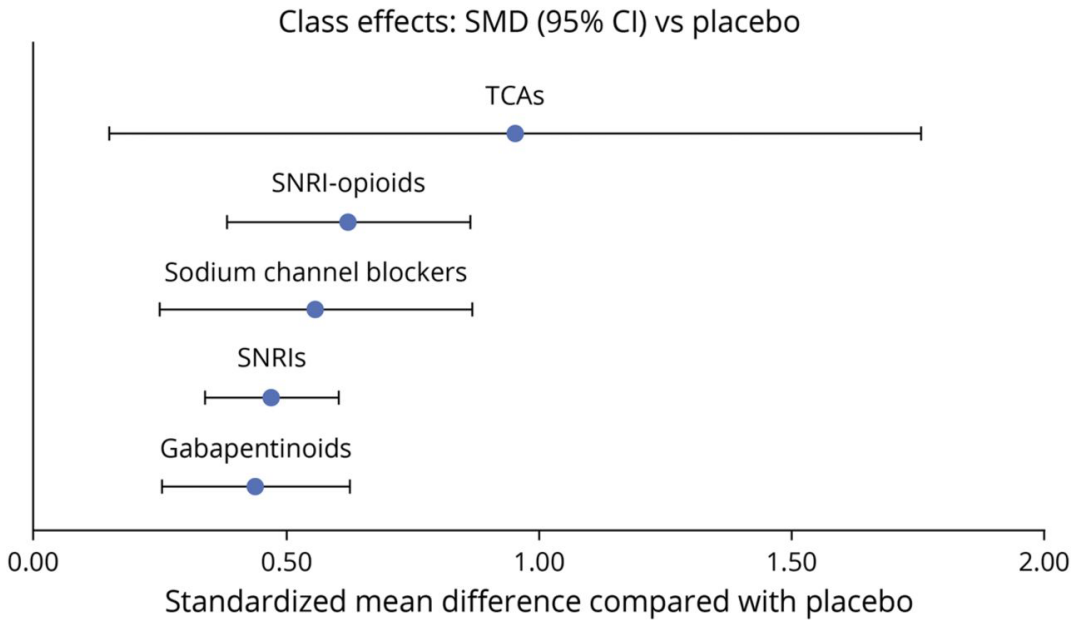
Diagnostics: Biopsy

- Skin Biopsy for small fiber neuropathy
  - Ankle, distal leg, proximal thigh- standard sites with normative reference values
  - Evaluate intraepidermal nerve fiber density
- Nerve Biopsy Indications
  - Acute nondemyelinating neuropathies
  - Suspected vasculitis/Mononeuritis Multiplex
  - Weakness

Symptomatic management- pain
AAN recommendations for first line agents

	Dosage (mg/d)	Duration (wk)
Duloxetine	40-60	12
Venlafaxine	150-225	6
Desvenlafaxine	200	13
Gabapentin	900-3600	4-8
Pregabalin	300-600	5-12
Microgabalin	15-30	5
Oxcarbazepine	1400-1800	16
Lamotrigine	200-400	6
Lacosamide	400	12
Valproic acid	1000-1200 (20mg/kg/d)	4-12
Amitriptyline	75-150	6

30% reduction in pain is considered a success in clinical trials



Symptomatic management- pain

- Best evidence:
  - Gabapentin, pregabalin, Venlafaxine
- Topical lidocaine
  - Helpful when pain is well-localized to the distal extremities
- Capsaicin cream
  - Transient receptor potential cation channel subfamily V member 1 (TRPV1) agonist
  - With high dose or repeat exposure causes epidermal axonal degeneration
- Capsaicin patch (Qutenza)
  - Some evidence of benefit- ELEVATE trial demonstrated noninferiority to pregabalin

Symptomatic management-pain

- Alpha-Lipoic Acid
  - Questionable benefit from large studies
- Cannabidiol and Cannabis-derived treatments
  - Multiple MOA
  - Generally poor quality studies suggesting mild benefit
- Exercise/activity
  - Moderate aerobic exercise and strength training
- Spinal cord stimulation

Symptomatic management- Cramping

Normalize metabolic abnormalities

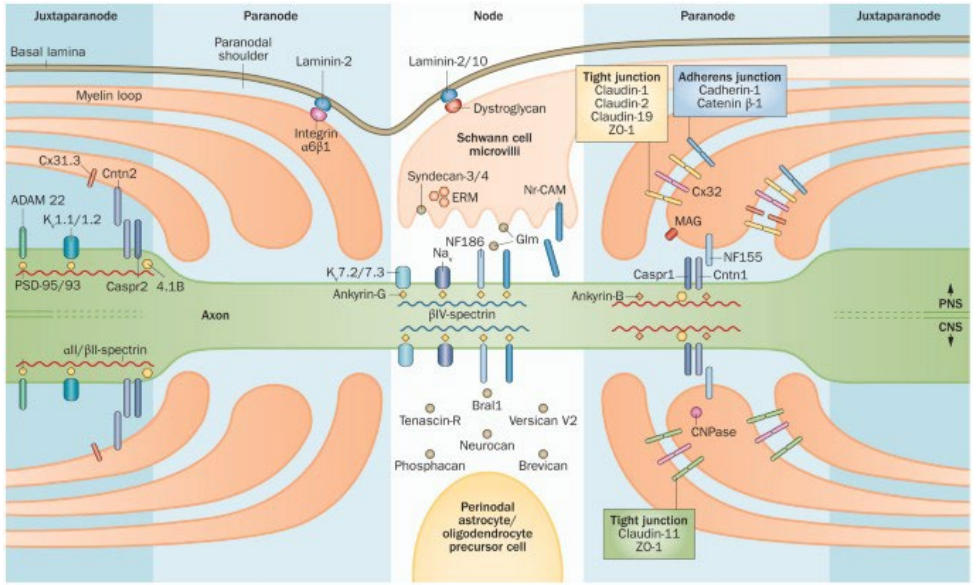
- Carbamazepine: 200 mg bid or tid
- Amitriptyline: 25 to 100 mg qhs
- Verapamil: 120 mg qd
- Phenytoin: 300 mg qd
- Vitamin E: 400 IU qd
- Riboflavin: 100 mg qd
- Quinine sulfate: 260 mg qhs or bid

Treatment: CIDP

- IVIg
  - 2g/kg load followed by 1 g/kg q3 weeks
  - Reassess need and taper
- SCIg
  - 0.4g/kg 20% SCIg weekly
- Corticosteroids
  - Oral prednisolone 1-1.5g/kg/d
  - IV methylprednisolone 0.5g weekly
  - Dexamethasone 40mg/d x 4 days q4 weeks
- PLEX
  - Usually if refractory to the above

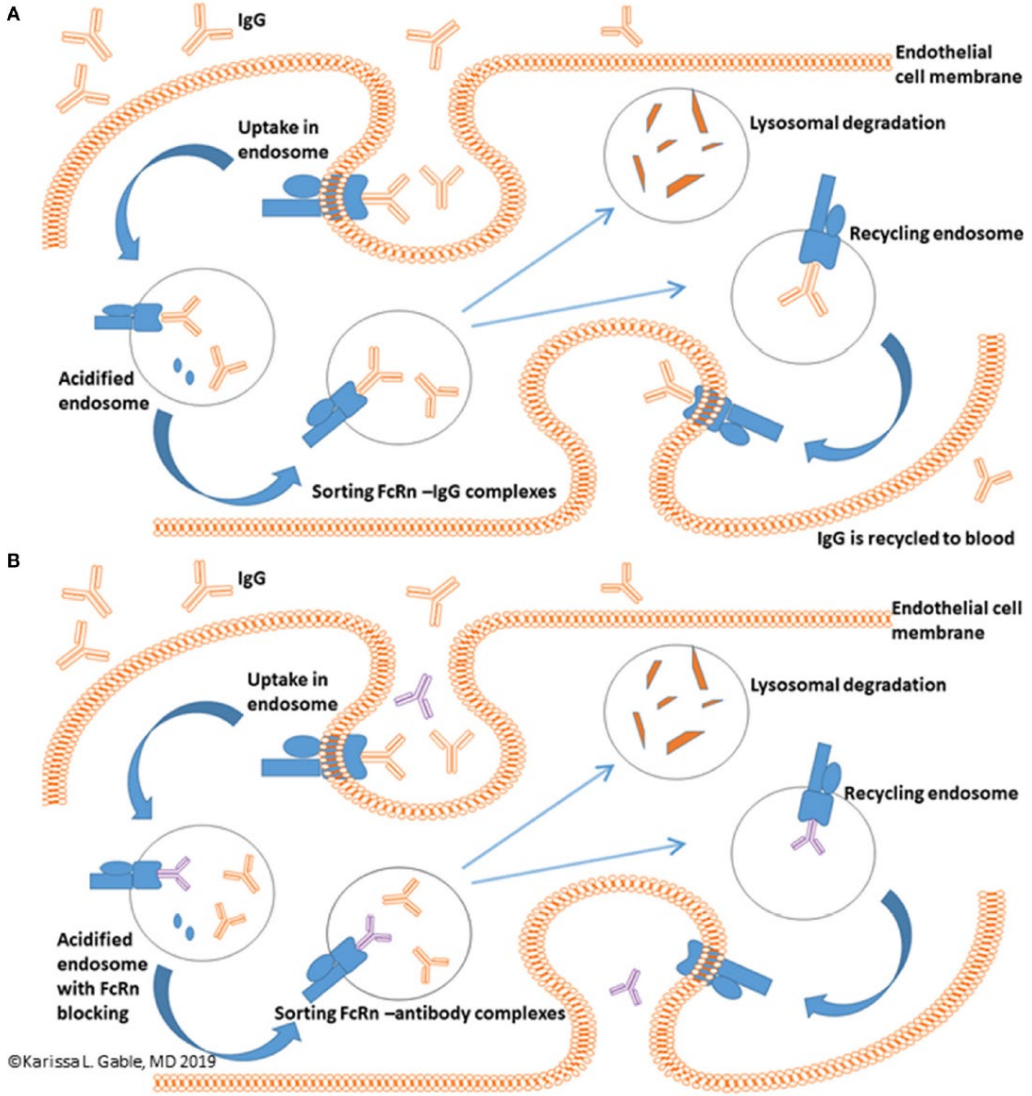
Treatment: CIDP

- Rituximab- consider in select cases
  - ?Refractory MMN
  - MAG
  - Nodo-paranodopathies- Neurofascin 155, Neurofascin 140, Contactin-1, CASPR1
  - IgG4 antibodies



CIDP: Future therapeut

- Efgartigamod: Phase 2 clinical trial, currently enrolling
  - 18 or older
  - Probable or definite CIDP (EFNS/PNS 2010 criteria)
  - Currently treated with steroids or IVIG, previously treated with steroids or IVIG, or treatment naïve
  - Excluding MMN, MAG, patients with IgM antibodies, POEMS



Treatment: Vasculitic neuropathy

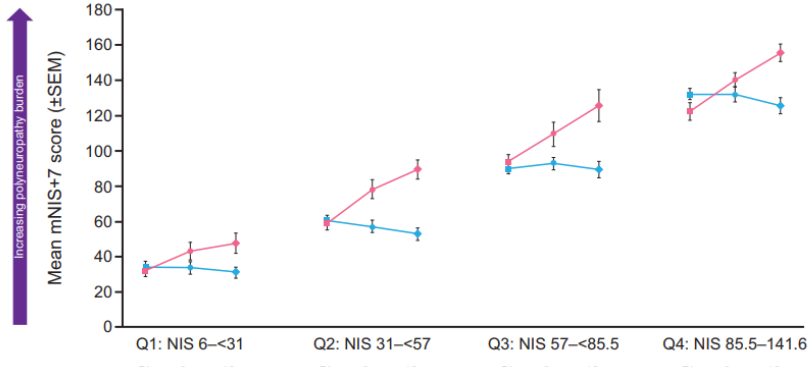
- Vasculitic neuropathy
  - ANCA vasculitis:
    - Induction with steroids and cyclophosphamide or Rituximab
    - Maintenance with azathioprine, methotrexate, MMF, or rituximab

Treatment: hTTR Amyloidosis: siRNAs

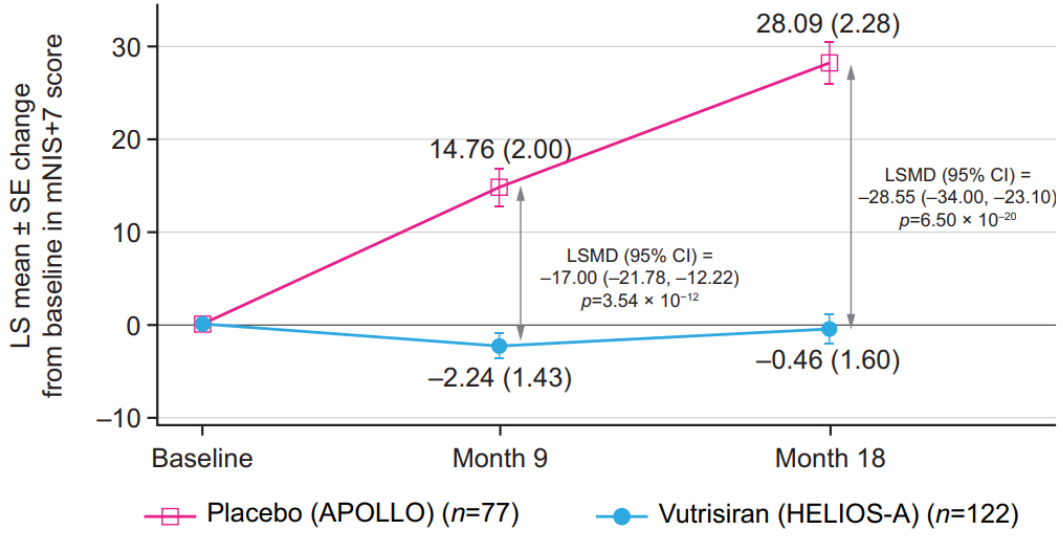
- Patisiran (Onpattro)
  - APOLLO trial
  - IV q3weeks

Vutisieran (Amvutra)
HELIOS trial
SQ q3 months

Supplement with Vitamin A



		Q1: NIS 6–<31			Q2: NIS 31–<57			Q3: NIS 57–<85.5			Q4: NIS 85.5–141.6		
		BL	9 m	18 m	BL	9 m	18 m	BL	9 m	18 m	BL	9 m	18 m
Patisiran	*n*	37	36	36	34	32	32	36	35	33	41	38	36
	Mean (±SEM) change from baseline	—	−0.7 (2.0)	−3.2 (2.1)	—	−2.4 (2.8)	−6.4 (3.3)	—	2.4 (2.8)	−1.9 (3.4)	—	0.3 (2.8)	−5.4 (3.6)
Placebo	*n*	19	17	13	22	17	14	20	19	15	16	14	9
	Mean (±SEM) change from baseline	—	11.4 (4.3)	18.4 (5.7)	—	16.4 (3.4)	29.5 (5.0)	—	15.6 (4.6)	31.9 (7.0)	—	17.9 (4.6)	32.5 (6.7)



Conclusion

- Key elements of the history and physical can identify red flags warranting more thorough workup
  - Weakness, rapid progression, asymmetry
- Set expectations for management of pain
- Optimize dosing of neuropathic pain agents and consider using dual therapy
- Novel therapeutics continue to emerge for immune neuropathies and amyloidosis.

Questions