

# Peripheral neuropathy and neuropathic pain management

## NW primary care virtual conference

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# OBJECTIVES AND DISCLOSURES

## OBJECTIVES:

- Understand possibly types of neuropathy and initiation of work up
- Learn about aspects of management of neuropathic pain
- Understand what forms of neuropathy require urgent referral/ evaluation

## DISCLOSURES:

None

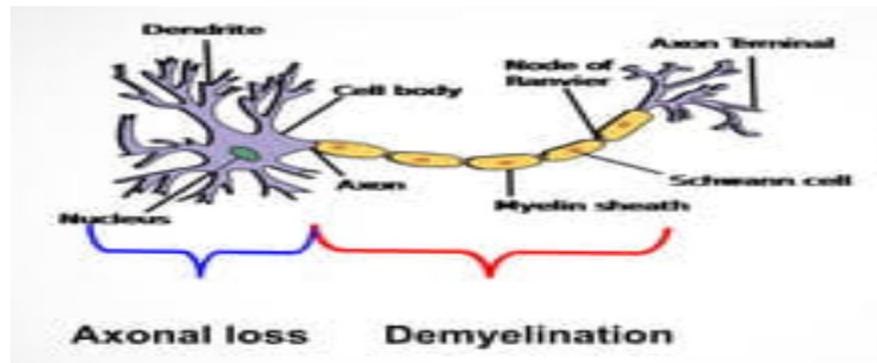
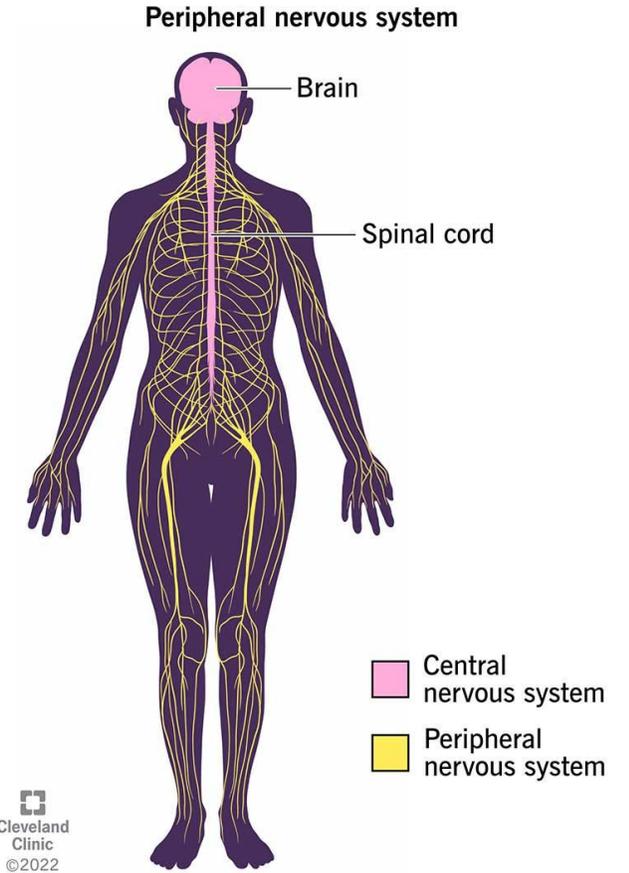
# ORGANIZATION OF TALK



# DEFINITION...

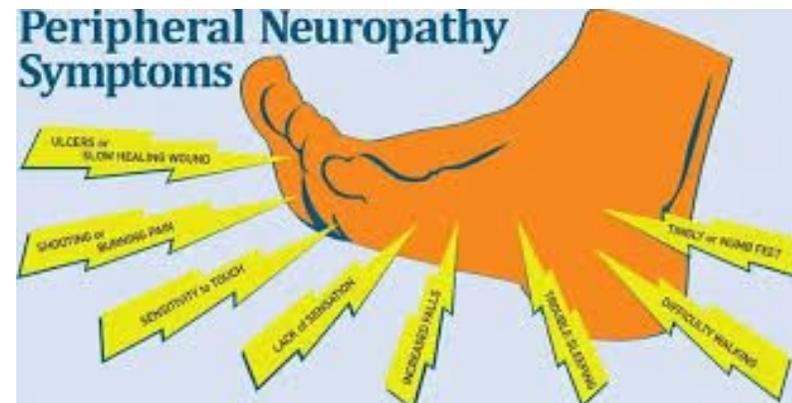
Peripheral neuropathy: disorders affecting the peripheral nerve endings and fibers

- By regional areas affected:
  - cranial neuropathy, compressive neuropathy (carpal tunnel), polyneuropathy,
- By affected parts of the nerve:
  - Axonal (90%) vs Demyelinating (10%) vs Mixed
  - Sensory, motor, mixed, small fiber neuropathy
- Number of nerves affected:
  - mononeuropathy, multifocal mononeuropathy,
  - polyneuropathy



# PREVALENCE AND SYMPTOMS

- Fairly common, 2.4% of population and 8% above 55 has a peripheral neuropathy
- **SYMPTOMS:**
  - Sensory: Burning, tingling, numbness, electric shock like pain, **imbalance (if severe or early in onset is a RED FLAG symptom)**
  - Motor: weakness, foot drop, tripping (**if severe, early, involving proximal muscles, fasciculations RED FLAG symptom**)
  - Autonomic: dry skin, loss of hair, dizziness and orthostatic lightheadedness, early satiety, altered sweating (**if severe, presenting symptom or early in diagnosis is a RED FLAG symptom**)



# SIGNS

## SENSORY:

- loss of pin prick, vibration, hyperalgesia, decreased light touch (monofilament light touch plus vibration higher sensitivity ~90% sensitivity and specificity)
- $\frac{1}{4}$  above 65 and  $\frac{1}{3}$  above 75 have some loss of distal vibration without neuropathy so single modality may not suffice
- Gait instability in proprioceptive loss / **sensory ataxia**

## MOTOR:

- weakness, atrophy, rarely **fasciculations** (grip, toe extension, distal foot strength), hammer toes, high arch

## AUTONOMIC:

- Hair loss sign, **orthostatic hypotension**



# APPROACH TO PERIPHERAL NEUROPATHY

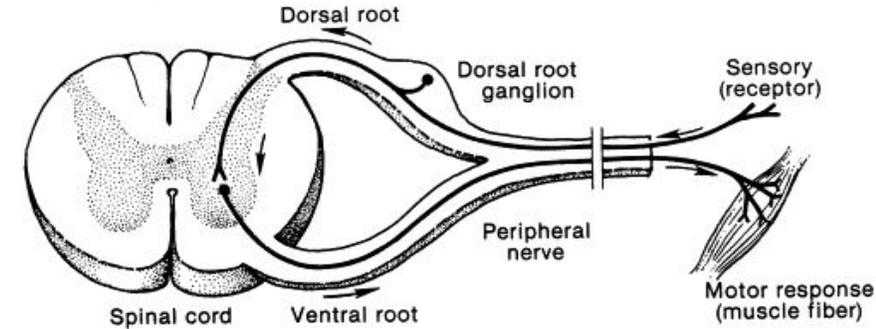
1. Are there symptoms referable to a nerve (numbness, tingling, weakness, cramping)

2. Is there mixed, motor, sensory or autonomic involvement

a. early autonomic involvement could suggest **amyloid neuropathy**,

b. pure motor could suggest a motor neuronopathy like **MND**

c. pure sensory could suggest a sensory ganglionopathy like **paraneoplastic disorders**



3. Distribution of symptoms: only distal, **distal plus proximal**, symmetric, vs **asymmetric/ patchy**

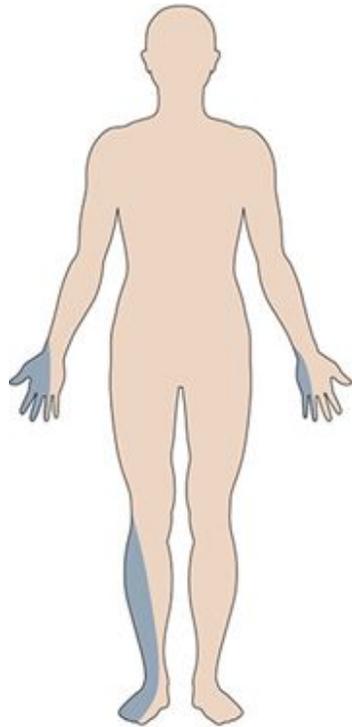
4. Is the sensory involvement associated with severe pain (**vasculitic neuropathies**) or severe proprioceptive loss (positive Romberg's early could suggest **sensory ganglionopathy**)

5. What is the temporal evolution **acute (days to 4 wks)**, **subacute 4 to 8 weeks** chronic months to years,

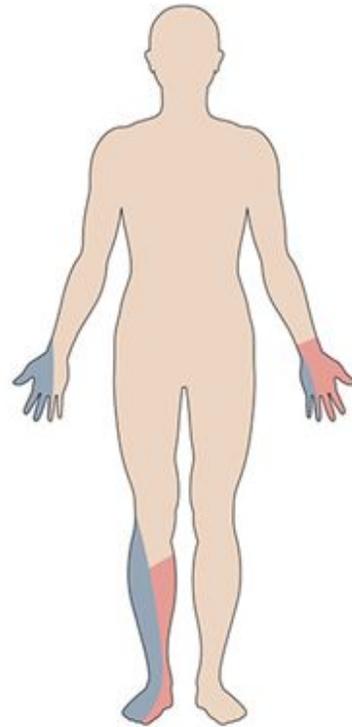
association with meds/ vaccines (coasting)

# PATTERN RECOGNITION

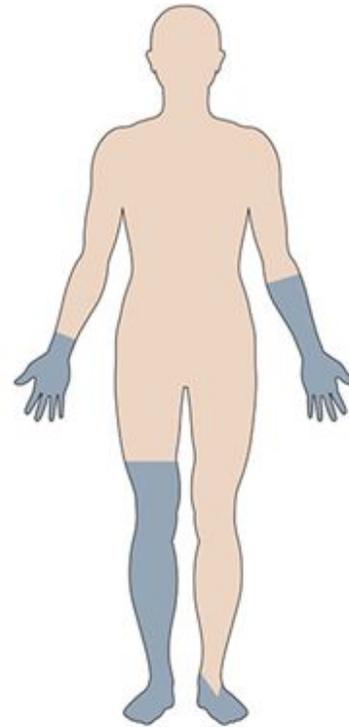
MOST COMMON



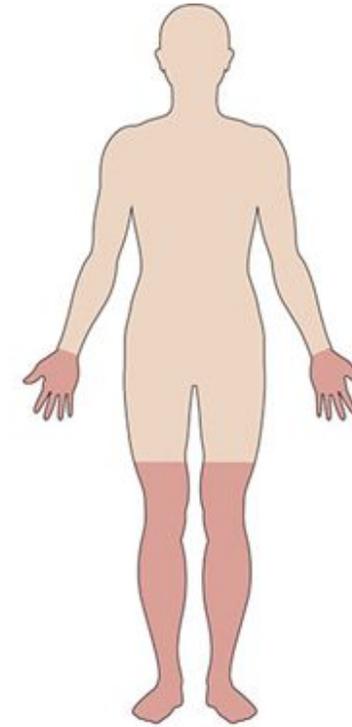
Multifocal neuropathy



Early overlapping multifocal neuropathy



Late overlapping multifocal neuropathy (asymmetric polyneuropathy)



Distal symmetric polyneuropathy

Nature Reviews | Neurology

# PATTERN RECOGNITION

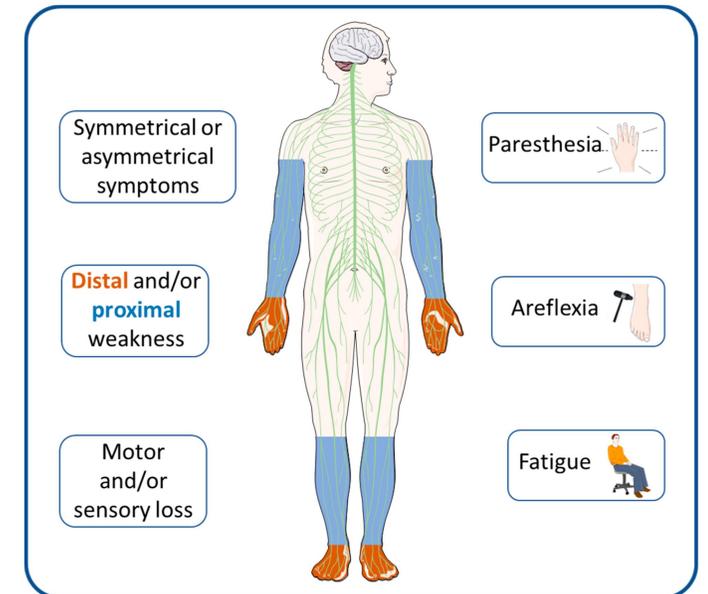
## SYMMETRIC DISTAL SENSORY LOSS WITH/ WITHOUT WEAKNESS (MOST COMMON)

Characteristic features:

- Distal (tip of toes/ bottom of foot) progressing proximally, the longer the axon, the more likely affected
- Arms don't get affected until later and again tip of fingers first, reflexes lost distal first
- Can be associated with pain
  - if severe pain and asymmetric (one foot then another) think vasculitic neuropathy
- Often slow progressive over years (diabetic, alcohol related toxic neuropathies)
- Pattern seen with toxic/ metabolic causes

## SYMMETRIC DISTAL AND PROXIMAL WEAKNESS WITH SENSORY LOSS

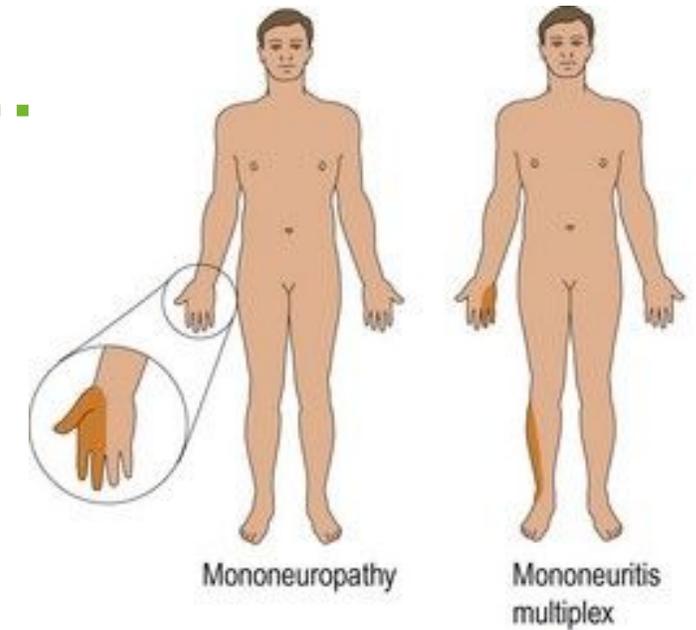
- Proximal and distal weakness and or sensory loss
- \*\*\*\* EARLY loss of reflexes all over
- Acute to subacute progression
- Pattern in AIDP/ Guillan Barre or CIDP, **ER/ Urgent eval**



# PATTERN RECOGNITION...

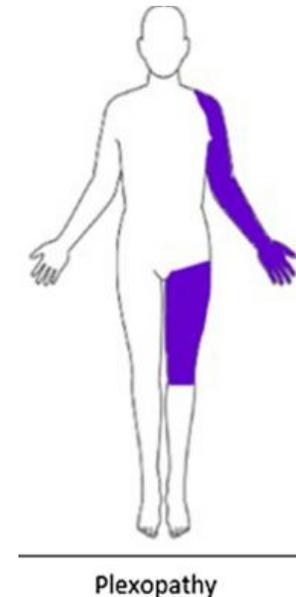
## ASYMMETRIC DISTAL WEAKNESS WITH SENSORY LOSS:

- Single nerve/root (carpal tunnel or radiculopathy)
- Multiple nerves or roots (needs eval)
  - Vasculitis, infectious causes (leprosy/ HIV/ Sarcoid)
  - MADSAM (Lewis Sumner disease)



## ASYMMETRIC PROXIMAL AND DISTAL WEAKNESS WITH SENSORY LOSS

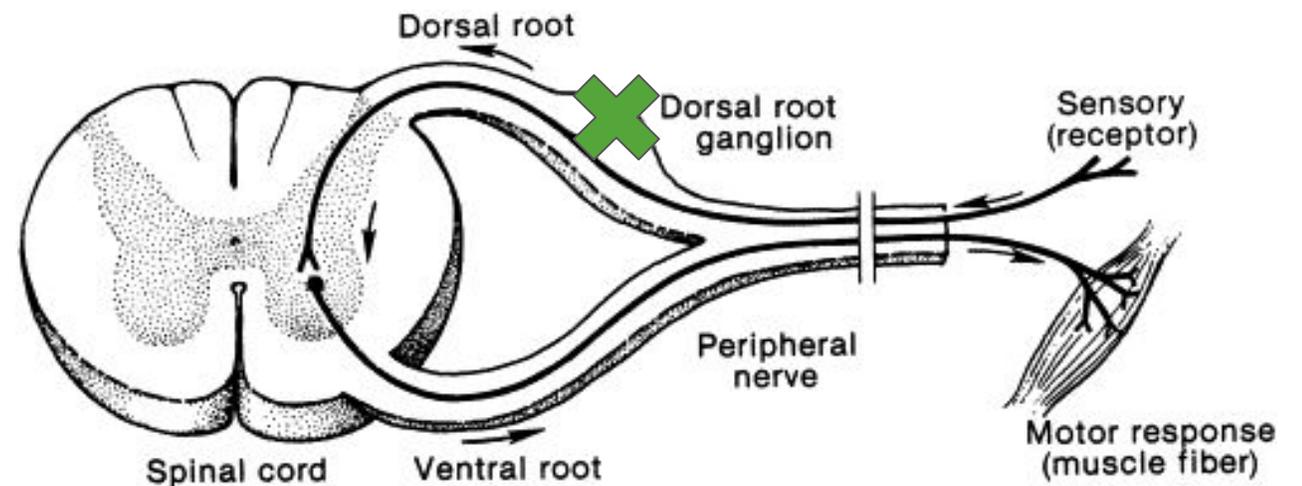
- Diabetic poly radiculoplexopathy
- Hereditary plexopathies
- Neoplastic/ infiltrative plexopathies



# PATTERN RECOGNITION

## ASYMMETRIC LARGE FIBER/ PROPRIOCEPTIVE LOSS WITHOUT WEAKNESS (needs urgent eval)

- Often an indication of a sensory ganglionopathy
- Disproportionate level of imbalance/ unsteadiness for duration of neuropathy, early falls
- Balance worse in darkness/ night
- Causes
  - Paraneoplastic neuropathy
  - Sjogrens
  - Cisplatin associated neuropathy
  - HIV
  - Vit E deficiency/ B6 toxicity



# PATTERN RECOGNITION.....

## ASYMMETRIC DISTAL WEAKNESS WITHOUT SENSORY LOSS or SEGMENTAL WEAKNESS:

- If accompanied by upper motor neuron signs (hyper reflexia despite weakness, elevated tone, upgoing toes)- ALS/ Motor neuron disease
- Without upper motor neuron findings
  - Progressive muscular atrophy, early ALS prior to UMN involvement
  - Multifocal motor neuropathy
  - Subacute/ post infectious: ENTEROVIRUS 68 in children/ WEST NILE

## SYMMETRIC SENSORY LOSS WITH UPPER MOTOR NEURON SIGNS (MYELONEUROPATHY):

- May or may not have weakness
- Always consider subacute combined degeneration of cord from B12 deficiency
- Copper deficiency can mimic this (seen in patients with gastric bypass or on zinc supplements)
- Rarely spinal cord lesions/ tumors can present like this

# A FEW OTHER PATTERNS TO CONSIDER

## 1. SMALL FIBER NEUROPATHIES

- a. Often associated with large fiber distal symmetric neuropathies
- b. Can be small fiber only so negative on EMG, Sjogrens/ Diabetic neuropathy
- c. Can be length dependant symmetric or patchy, work up similar to large fiber

## 2. AUTONOMIC NEUROPATHIES:

- a. isolated autonomic dysfunction
- b. often associated with a small and sometimes large fiber neuropathy
  - i. Diabetic, hereditary amyloid neuropathy, HIV associated neuropathy, autoimmune autonomic neuropathy

# DRUG INDUCED NEUROPATHY/ TOXIC pattern

- B6 deficiency and excess: B6 deficiency causes a length dependant neuropathy, excess causes a ganglionopathy
- Isoniazid: secondary to B6 deficiency
- Phenytoin: distal symmetric length dependant
- HIV Rx: mainly older nucleotide reverse transcriptase inhibitors, uncommon now from current drugs
- Leflunomide in RA treatment, distal pattern
- Amiodarone: mixed demyelinating plus axonal neuropathy, can be associated with tremor, imbalance
- Metronidazole: distal sensory painful neuropathy

# CHEMOTHERAPY ASSOCIATED NEUROPATHY

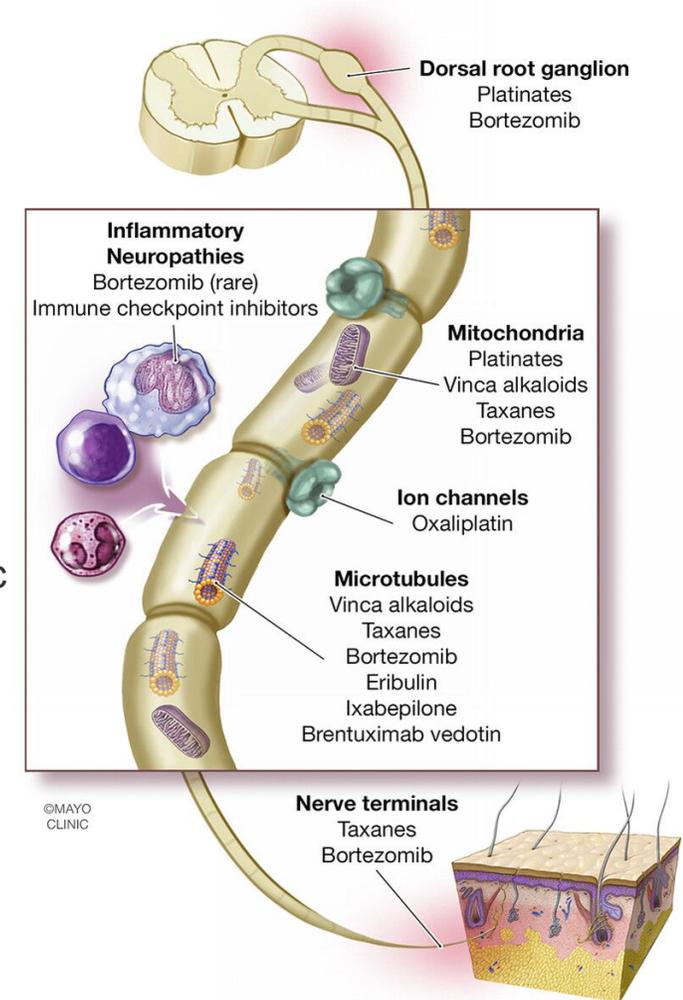
Onset: subacute, progressive, phenomenon of coasting (progression for 4 to 6 mo post exposure)

Patterns:

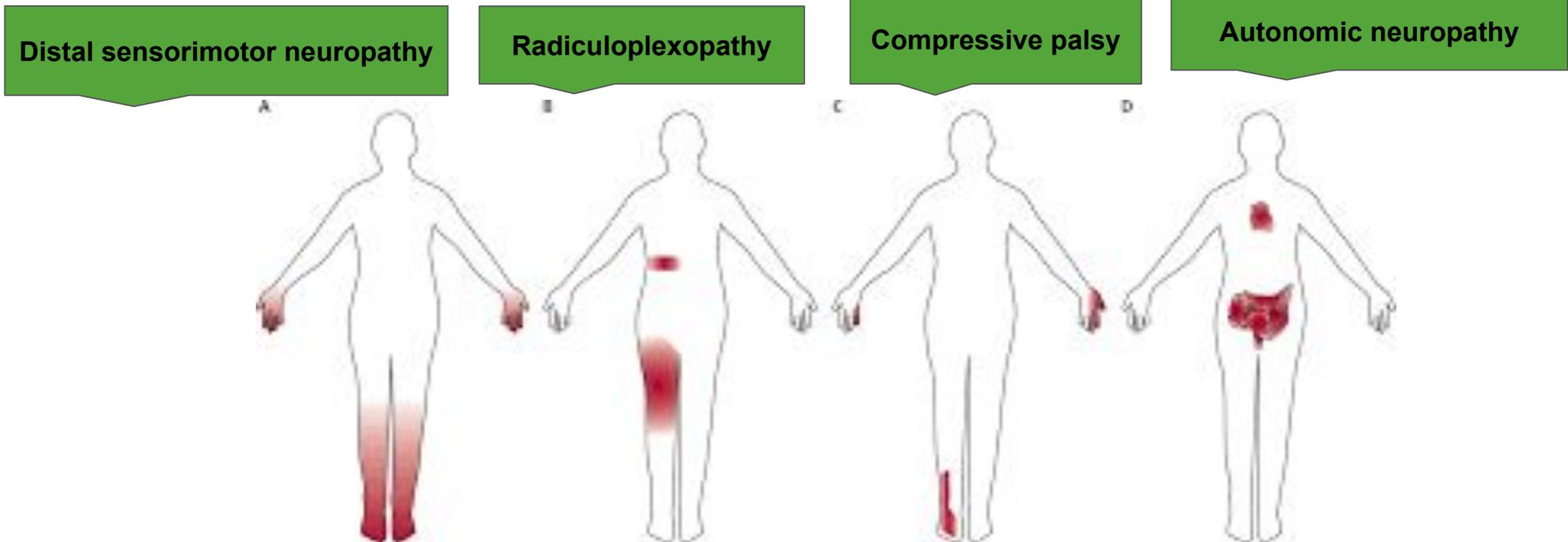
- Length dependant sensory more than motor (taxanes)
- Sensory predominant (neuronopathy/ ganglionopathy) (platin)
- Length dependant motor more than sensory (vinca alkaloids) +/- autonomic issues
- Length dependant sensory or sensory neuronopathy: Proteosome inhibitors
  - Bortezomib

## NOTE ON CHECK POINT INHIBITORS:

1. programmed cell death protein-1 (PD-1) inhibitors, ligand of PD-1 (PD-L1) inhibitors and cytotoxic 4 (CTLA-4) inhibitors.
2. MABs affect immune recognition of self and foreign antigens, increases immune surveillance
- 3 **Neuropathy can be of any kind:** demyelinating, cranial, acute axonal, sensory neuronopathy, acute or subacute demyelinating neuropathy (25%), cranial neuropathies (25%), acute axonal neuropathy, mononeuritis multiplex..., Consider this possibility when evaluating



# PATTERNS OF DIABETIC NEUROPATHY



# DIAGNOSTIC WORK UP

- With a combination of clinical exam, history, family history and screening labs, etiology for around 70% of DISTAL LENGTH DEPENDANT SYMMETRIC neuropathies diagnosed, 20 to 30% may be idiopathic (possibly genetic)
- AAN practice parameters for screening of DISTAL LENGTH DEPENDANT NEUROPATHY
  - HbA1c/ fasting glucose, B12 with MMA and homocysteine, Serum immunofixation would be the highest yield
  - Serum immunofixation over SPEP as IgM MGUS can be missed sometimes on SPEP alone, we do SIFE and SPEP together
- Other ancillary labs that can be considered CBC, CMP, TSH, Glucose tolerance test (controversial), copper levels, Vit E levels in proprioceptive loss, celiac screen (if with GI symptoms), CRP if concerned for vasculitic process, autoimmune screening if concerned about inflammatory/ autoimmune process
- Always screen for excessive alcohol use (third most common cause of neuropathy, and around 50% of chronic alcoholics have neuropathy on clinical exam,

## DIAGNOSTIC WORK UP continued....

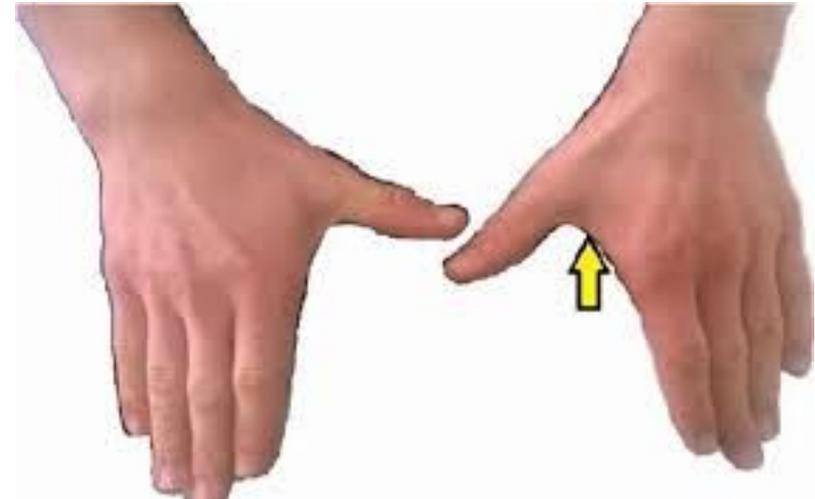
- EMG/ NCS: helpful in documenting type of neuropathy (axonal vs demyelinating) and progression, also for compressive neuropathies (CTS/ ulnar neuropathy), and looking at motor neuron disease/ sensory neuropathies
  - EMG/ NCS maybe negative in small fiber neuropathy and cryptogenic inflammatory sensory polyradiculopathy (CISP) (root involvement)
- Small fiber nerve biopsy can help in pure small fiber neuropathies
- Limited role for LP or nerve biopsy unless any of the less common types

# QUIZ ON PATTERN.....

**CASE 1:** 40 year old male with remote history of left elbow fracture in childhood, presenting with **1 yr history of left hand weakness,**

- On exam has first interosseous atrophy, finger abduction weakness,
- pin loss in little and ring finger,

1. What is the pattern?
2. What is the next step in evaluation?



# QUIZ ON PATTERN.....

**CASE 2:** 45 year old female with **6 month history of toe tingling on both sides, 3 months of hand tingling and now weakness in hands and feet (symmetric)**

- shoulder abductors are weak, as are her triceps and finger abductors, she has bilateral hip flexor weakness and foot drop
- Is Areflexic and loss of pin and vibration in feet till mid thigh and hands

1. What is the pattern?
2. What is the next step in evaluation?

# QUIZ ON PATTERN.....

**CASE 3:** 65 year old male with 8 year history of diabetes with **slow progressive numbness and tingling in feet with burning pain at night for the past 3 years**, is on metformin

- On exam has no weakness, ankle reflexes are lost, rest are preserved
- sensory loss to pin, light touch and vibration in toes, mildly unsteady at night but no falls

1. What is the pattern?
2. What is the next step in evaluation?

# QUIZ ON PATTERN.....

**CASE 4:** 56 year old female with 3 year history of diabetes, started on semaglutide, lost around 20 lb over 4 months, A1c dropped by 2.4 from 9.4 to 7. **Noted over last 2 months,** severe pain over left thigh and weakness in the thigh and leg, and now left foot drop and tingling in foot, severe pain, unable to sleep,

- On exam has quadriceps atrophy, weakness hip flexion and knee extension on left side, left foot drop
- loss of vibration in toes and distal sensory loss in foot, absent ankle reflexes and left knee reflex is lost

1. What is the pattern?

2. What is the next step in evaluation?

# QUIZ ON PATTERN.....

**CASE 5:** 52 year old female with a remote history of gastric bypass, **presenting with numbness and tingling in toes for 6 months and then hands for 3 months**, very unsteady, needed a walker in the last 2 months and now in wheelchair

- exam motor strength looks fine, maybe slightly weak hip flexors,
- distal loss of sensations till thigh and absent proprioception in legs
- absent ankle reflexes but knee reflexes are very brisk and has spread

1. What is the pattern?
2. What is the next step in evaluation?

# QUIZ ON PATTERN.....

**CASE 6:** 68 year old male without any major past medical history, **noted 8 months ago some weakness in right hand**, decreased grip, then fatigue, came back from trip, quite short of breath in last 4 months, cant lay flat at night, has lost 20 lbs in last 3 months

- On exam has diffuse muscle atrophy, fasciculations in biceps, triceps, pectorals
- weak thumb abductors, biceps, triceps and deltoid, short of breath at rest
- Preserved and brisk reflexes in upper extremities as well as lower extremities

1. What is the pattern?
2. What is the next step in evaluation?

# PHARMACOLOGIC MANAGEMENT

- For all of the distal symmetric polyneuropathies focus would be on management of symptoms unless a cause is identified and managed (deficiency, stopping a toxic cause etc)
- **NEUROPATHIC PAIN MEDICATIONS**
  - Gabapentinoids: similar side effect profile (grogginess, weight gain/ edema, mood changes, cognitive effects controversial)
    - Gabapentin: 300 to 1200 mg tid, titrate slow , above 600mg at a time absorption maybe limited
    - Pregabalin: 50 to 100 mg tid
    - Number needed to treat 7-8

# PHARMACOLOGIC MANAGEMENT

## NEUROPATHIC PAIN MEDICATIONS:

- **TRICYCLICS:** SE: dry mouth, cardiac side effects, grogginess, anticholinergic side effects a concern in elderly
  - Amitriptyline: 10-20 mg titrating further
  - Nortriptyline: similar doses
- **SNRI: better tolerated usually**
  - Duloxetine: 30 titrate to 60 mg, rarely 90 mg
  - Venlafaxine: 37.5 mg titrated up
  - Monitor for SNRI withdrawal when tapering off

# PHARMACOLOGIC MANAGEMENT....

## NEUROPATHIC PAIN MEDICATIONS:

- In refractory cases can consider carbamazepine/ oxcarb
  - Screen HLA-B\*15:02 in ALL ASIANS due to higher risk for Steven Johnsons
  - monitor side effects: hyponatremia, drop in blood counts, imbalance/ double vision
- Topical options
  - Lidocaine cream/ patch
  - Capsacin patch/ cream

# NON PHARMACOLOGIC/ ALTERNATIVE OPTIONS

## CANNABINOIDS

- Oral cannabinoids (THC/ CBD) limited data from a smaller study
- May have some role for topical cannabinoids

## ALPHA LIPOIC ACID:

- Earlier studies in iv alpha lipoic acid showed some symptomatic benefit in Diabetic sensorimotor polyneuropathy,
- Oral alpha lipoic acid at 600 mg a day could have similar benefits though a Cochrane review suggested little no benefit, limited however by attrition

# NON PHARMACOLOGIC/ ALTERNATIVE OPTIONS

- Acupuncture: some limited data, meta analysis in diabetic neuropathy suggested reduction in symptom burden
- TENS unit may have some limited benefit more in longer term ongoing use
- NO evidence for laser / LED light etc
- Some role for CBT in pain management
- Evidence for lifestyle medicine helping symptom management in DM
  - Low fat/ carb, high fiber plant based diet with exercise
  - Manage other risk factors like alcohol use, potential medications that can worsen neuropathy

Thank you.  
QUESTIONS?