PERIPHERAL NEUROPATHIES –

DIAGNOSIS AND TREATMENT

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Financial disclosures

- Funding:
  - NIH
  - Thompson Family Foundation
  - ICTS

- Inventor on patent to use SARM1 dominant-negative to block axonal degeneration

Goals

- How to clinically stratify to determine who would benefit from specialty consultation
- How to treat symptoms of painful peripheral neuropathy

Patient 1

- 58 yo man
- **USOH** until 3 years ago: tingling in toes bilaterally and increased slowly involving more parts of his feet over the next two years
- About **6 months ago**:
  - Gait slower
  - Fell in the yard, because of ankle rolling
- **Current** symptoms:
  - Tingling to mid-shin bilaterally
  - Gait difficulties
  - Mild balance problems
- **Negative** for symptoms in arms/hands, pain, autonomic symptoms, weight changes

Patient 1

- **PMH:** HTN, anxiety
- **SH:** used to smoke 1 PPD for 20 yrs, stopped in 1999; drinks alcohol occasionally, no recreational drugs; no toxin exposure
- **FH**: mother: lung cancer, sister breast cancer
- **Examination**:
  - Normal VS
  - Normal general exam

Patient 1

- Normal cranial nerves
- **Motor:**
  - Muscle bulk normal
  - normal tone

	Right	Left
Deltoid	5/5	5/5
Biceps	5/5	5/5
Triceps	5/5	5/5
Wrist extension	5/5	5/5
Hand muscles	5/5	5/5
Iliopsoas	5/5	5/5
Quadriceps	5/5	5/5
Hamstrings	5/5	5/5
Tibialis anterior	**4/5**	**4/5**
Gastrocnemius	5/5	5/5
Toe extension	**4/5**	**4/5**

Patient 1

- **Sensation:**
- Light touch: intact
- Pinprick:
  - cannot feel PP on the right to his mid-foot afterwards pinprick gradient;
  - cannot feel PP on the left at the toes, afterwards gradient
- Vibration:

	Right	Left
Toe	**0/8**	**trace**
ankle	6/8	**3/8**
knee	6/8	**4.5/8**

- **Coordination** (Finger-Nose-Finger, Heel-Knee-Shin, Romberg)**:** intact

Patient 1

- **Reflexes:**

	Right	Left
Biceps	2+	2+
Triceps	2+	2+
Brachioradial	2+	2+
Patella	2+	2+
Ankle	**absent**	**absent**

- **Gait:** was able to get up on his toes briefly, could not walk on heels, could not tandem

Patient 1

- **Summary:** 58 year old man with 3 year history of tingling and 6 mo history of gait abnormalities and imbalance. On neurological examination, he has severely reduced vibration sense distally, a pin prick gradient in his legs, absent ankle reflexes and distal weakness of his feet.

- **Clinical diagnosis:** Sensorimotor peripheral polyneuropathy

Overview

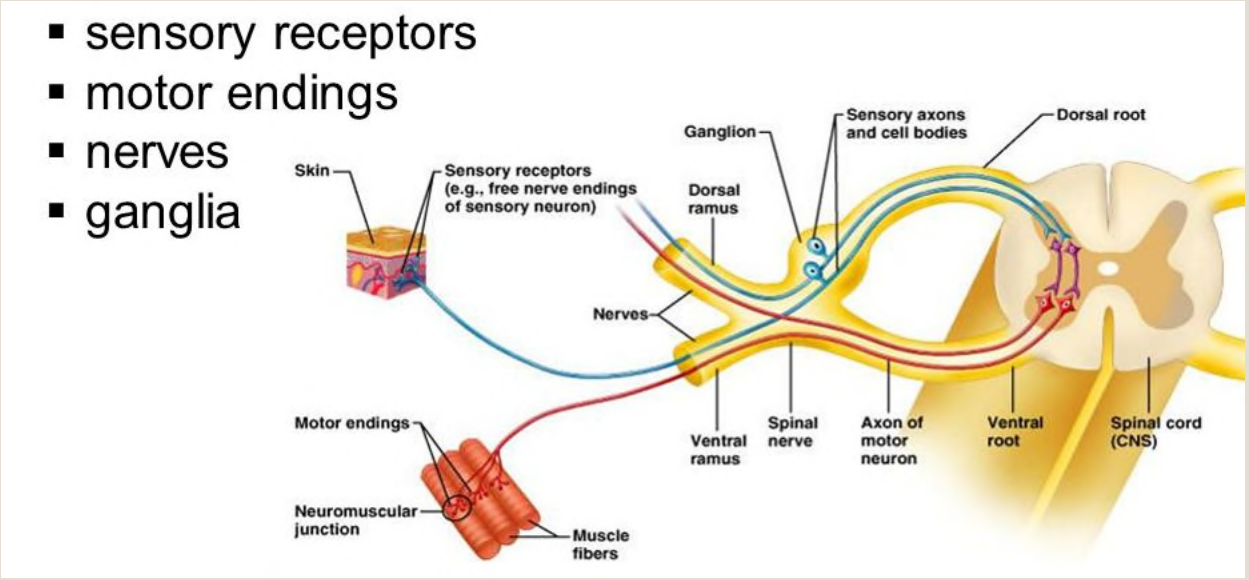
- Peripheral Neuropathy
  - Anatomy
  - Symptoms
  - Diagnosis
  - Symptomatic treatment

Peripheral Neuropathy

- Estimated 20 million people in USA alone suffer from peripheral neuropathy

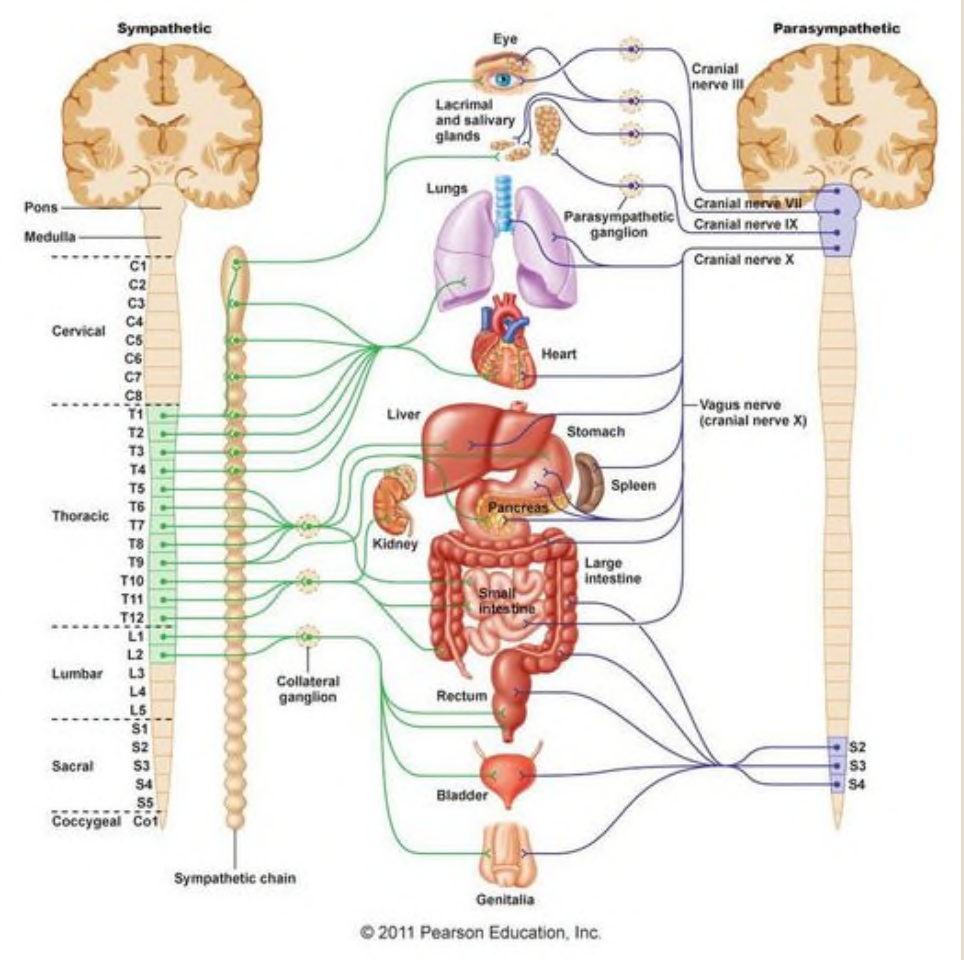
Peripheral nervous system - Anatomy

- Motor
- Sensory

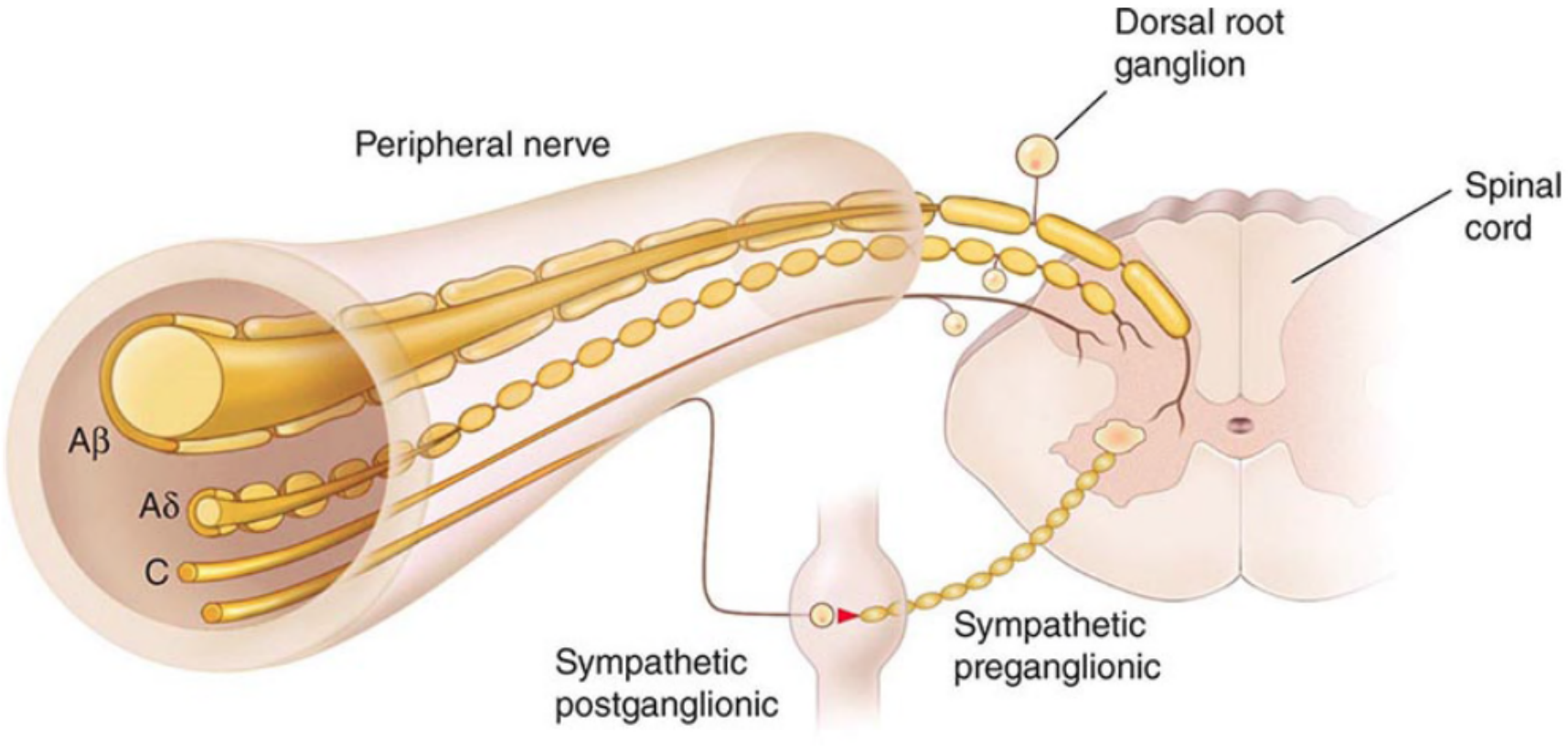


Peripheral nervous system

- Autonomic



Peripheral Nerve



Peripheral Nerve

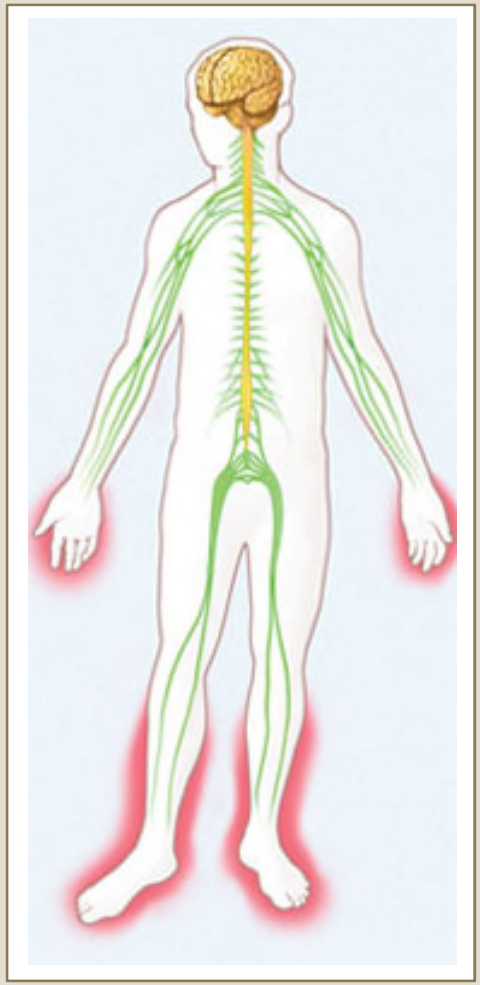
Fiber Type	CV m/s			Neuro exam
A alpha	100	Muscle afferent, efferent; Sensory		Muscle reflexes Light touch Vibration Proprioception
A beta	50	Muscle afferent; Sensory		
A gamma	40	Muscle efferent; Sensory		
A delta	20	Free nerve endings of touch and pressure Nociceptors Cold thermoceptors Preganglionic autonomic function	Pain Light touch Temperature	Pin prick Temperature
C fibers	2	Nociceptors Warmth receptors Postganglionic autonomic function	Pain Light touch temperature	

Length dependent sensorimotor peripheral neuropathies

- 74% to 82% of cases are length dependent, sensory predominant
- At least 1/3 idiopathic
- Progress slowly
- Unlikely to cause severe physical disability

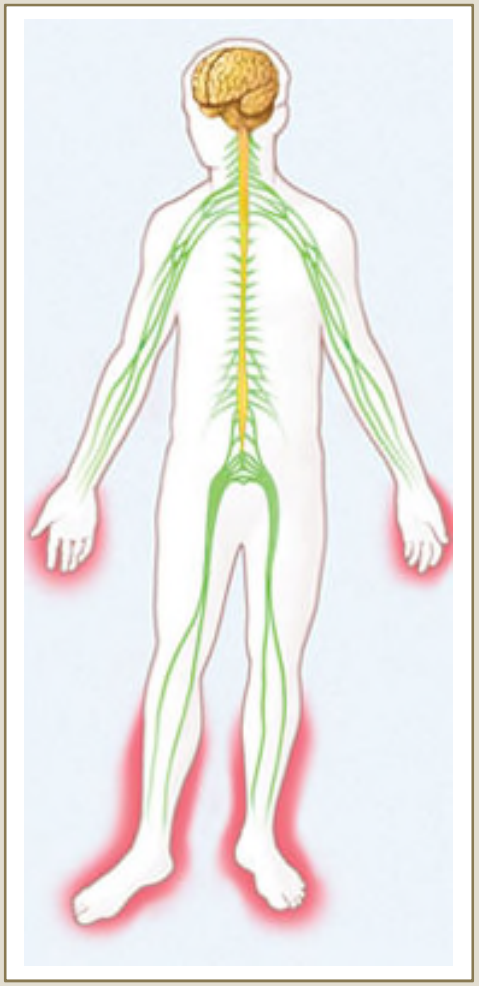
Length-dependent sensorimotor peripheral neuropathy

- **Characteristics:**
  - From distal to proximal:
    - Feet first, when leg symptoms approach knee, hand involvement
  - Ascending
  - Symmetric
  - Slowly progressive
  - Sensory symptoms usually precede motor weakness



Length-dependent sensorimotor peripheral neuropathy

- **Symptoms:**
  - A) Positive symptoms
    - Tingling
    - Abnormal sensation
    - Pain – burning, lanciating
    - Allodynia
  - B) Negative symptoms
    - Numbness



Length-dependent sensorimotor peripheral neuropathy

- Imbalance
- Distal muscle weakness (tripping, falling, difficulties opening bottles, turning door knobs)
- Autonomic symptoms:
  - Dry eyes/mouth
  - Constipation/diarrhea
  - Early satiety
  - Lightheadedness/orthostasis
  - Erectile dysfunction
  - Urinary incontinence
  - Abnormalities in sweating (hyper/hypohidrosis)

Peripheral Sensorimotor Neuropathy – Stratifying

- Length dependent
- Length independent
- Multifocal

- Red flags:
  - Significant weakness
  - Length independent (symptoms in hands first or hands and feet at same time)
  - Multifocal
  - Prominent autonomic symptoms (e.g., anhidrosis)

Examination

- Cranial nerves
- Motor:
    - tone
    - strength: especially distally
- Sensation:
    - light touch, vibration, proprioception
    - Pin prick, temperature
- Romberg
- Reflexes
- Gait

Stratifying
- Specialty consultation

- Multifocal neuropathy (hand drop and foot drop)
- Pure motor or autonomic symptoms
- Severe or diffuse sensory neuropathies causing gait ataxia and proprioceptive dysfunction
- Acute onset
- Fast progressive
- Clinical uncertainty

Length dependent sensorimotor peripheral neuropathy

- **Causes:**
  - Diabetes mellitus
  - Chemotherapy
  - Dysproteinemia
  - HIV
  - Metabolic
  - Endocrine
  - Toxins
  - Small vessel disease
  - alcohol

SPECIAL ARTICLE

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 72 January 13, 2009

-Highest yield serological testing:

- Screen for diabetes melllitus (11%)
- Vitamin B12 with methylmalonic acid (3.6%)
- Serum and urine immunofixation (10%)

Others:

-CBC, CMP, TSH, ESR

Rare:

- Lyme, Celiac (anti tissue transglutaminase), copper (bariatric surgery), Vitamin E, toxic (heavy metals), autoimmune (ANA, ANCA, ENA, cryoglobulin)

Evaluation – Nerve conduction studies/EMG

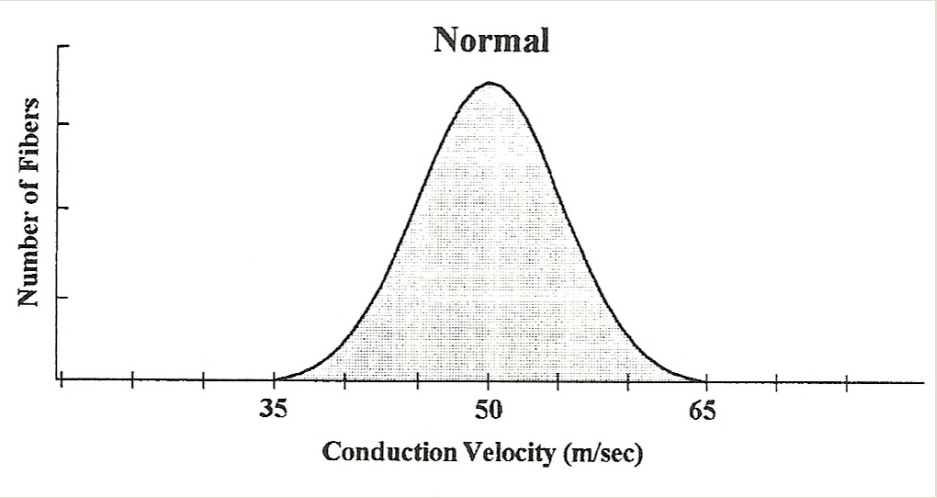
- Confirm diagnosis
- Localize
- Affected modalities (sensory/motor)
- Axonal/demyelinating
- Severity

- Decrease of SNAP amplitude first (sural, superficial peroneal), followed by reduced CMAP amplitude

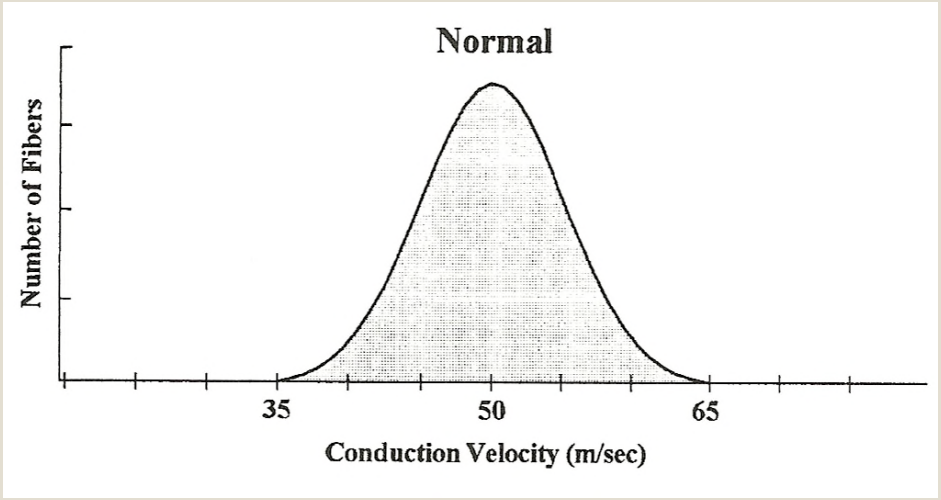
Length-dependent sensorimotor peripheral neuropathy - Nerve conduction studies/EMG

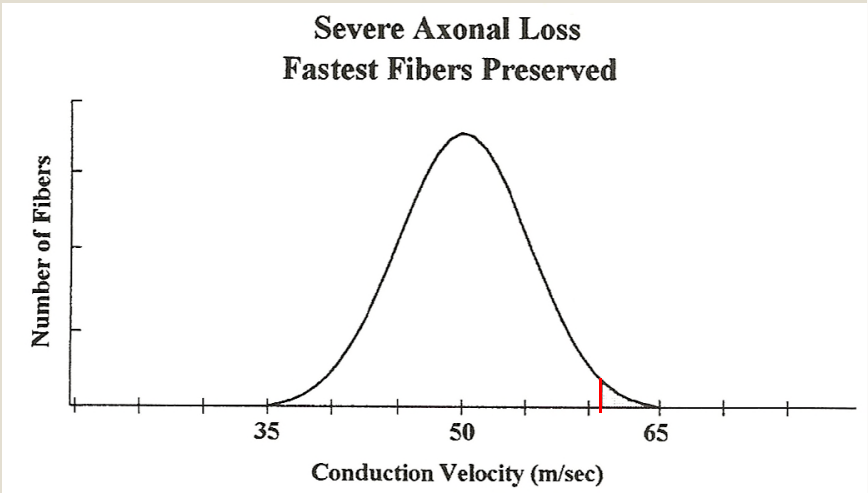
- Decrease of sensory nerve action potential (SNAP) amplitude first (sural, superficial peroneal),
- followed by reduced compound muscle action potential (CMAP) amplitude
- Nerve conduction velocity can be normal or mildly slowed (>70% LLN)
- EMG with signs of distal denervation (foot muscles)

Nerve conduction velocity – Axon loss

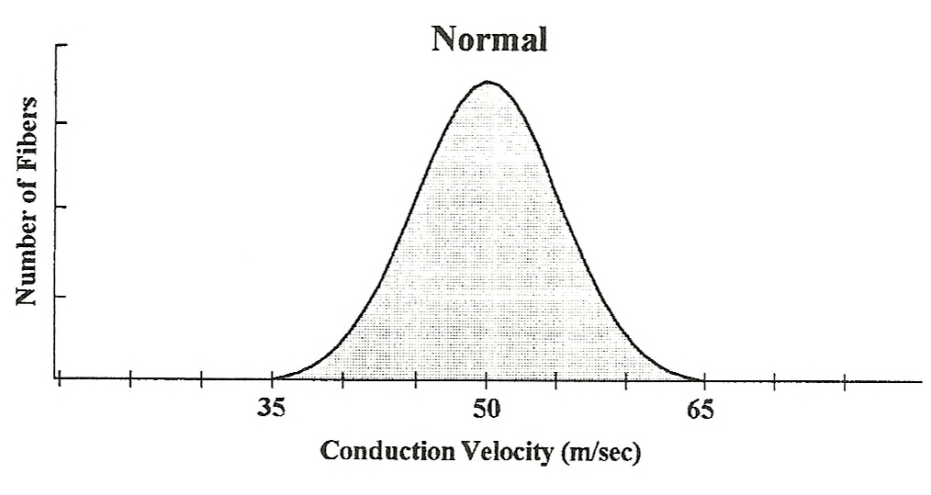


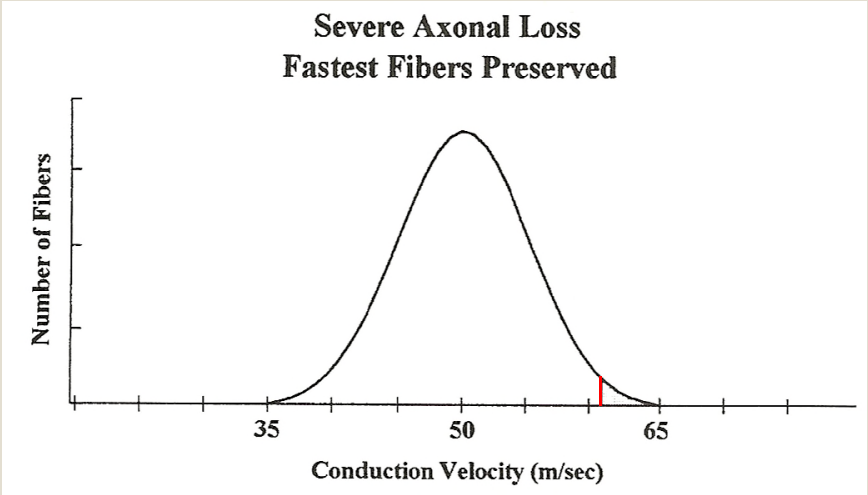
Nerve conduction velocity – Axon loss

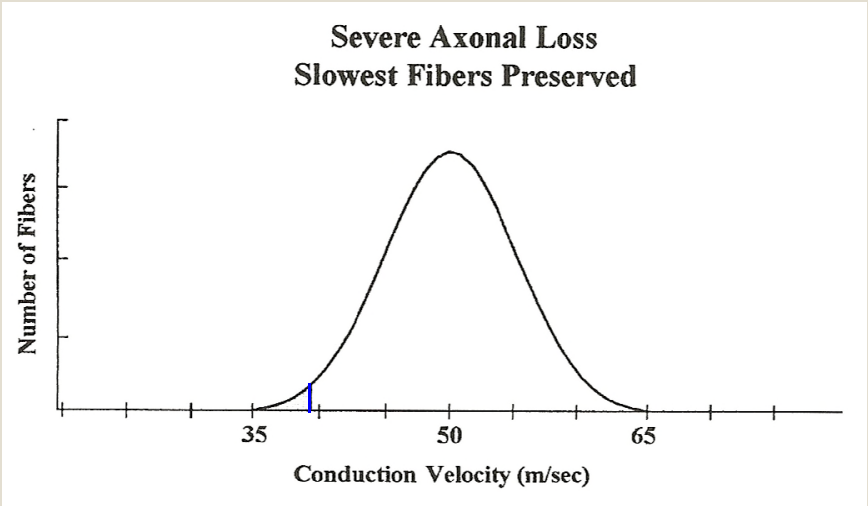




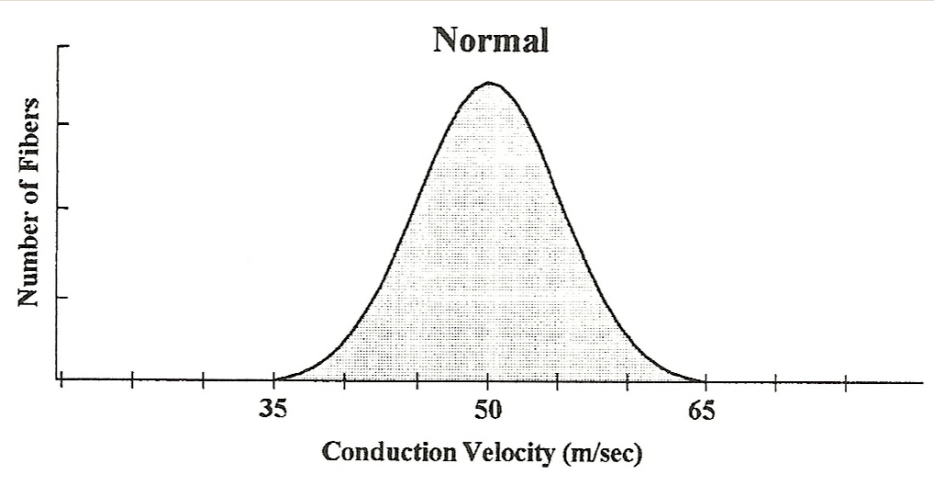
Nerve conduction velocity – Axon loss

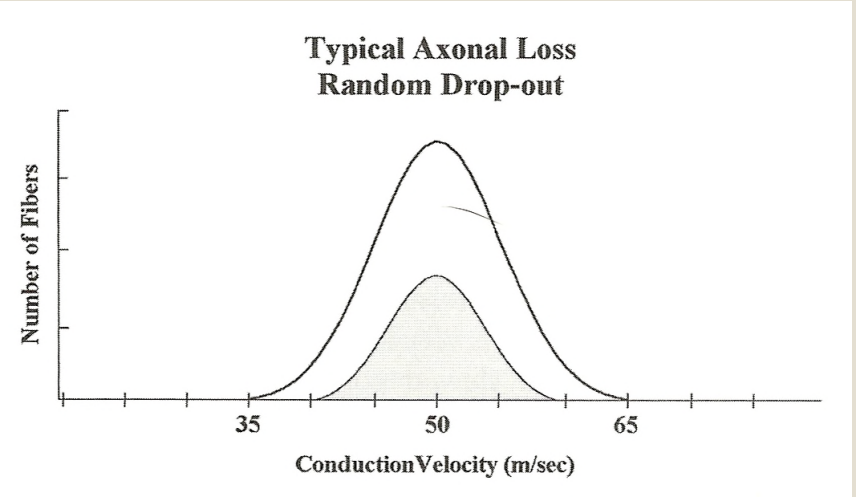






Nerve conduction velocity – Axon loss





Length-dependent sensorimotor peripheral neuropathy – Symptomatic management

- Foot care, properly fitted footwear, monitor feet

- Neuropathic pain (burning, pins and needles, electrical, allodynia):
  - Gabapentin
    - 300 mg PO TID; max: 3600 mg/day
  - Pregabalin (Lyrica)
    - 75 mg PO BID; max: 300 mg PO BID
  - Tricyclic antidepressants:
    - Amitriptyline
      - 100 mg PO qpm; max: 150 mg/d
    - Nortriptyline
  - Duloxetine (Cymbalta)
    - 60 mg PO daily
  - Venlafaxine (Effexor)
  - Topicals:
    - Lidocaine (5%) cream or ointment

Patient 1

Laboratory testing:

- Serum IF:
  - IgG kappa monoclonal protein, free kappa light chain monoclonal protein
- Low IgG, IgA, IgM levels
- Kappa free light chain: 242 (0.33-1.94);
- kappa/lambda ratio: 190.55 (0.26-1.65)
- No lytic lesions on skeletal survey
- Bone Marrow biopsy:

- Diagnosis: Multiple Myeloma

Patient 2

- 66 yo man
- USOH until 6 months ago (Octoboer) could walk about 2 miles, was physically active
- End of October: Numbness around his left ankle
- 2-3 weeks later numbness 3 fingers L hand
- 3 weeks later right ankle numbness and L foot weakness
- Increasingly balance problems, starts to walk with a cane
- 2 weeks later difficulties getting up from his seated position
- Noticed muscles in lower legs were "gone", had great difficulties walking, started to use a walker for walking
- Over time, numbness increased to his calves
- One month ago: weakness in his hands (difficulties cutting food eating, handwriting)

Stratification

- 1. Is it a length dependent neuropathy?
- 2. Is it symmetrical?
- 3. Red flags?

Patient 2

- PMH: HTN, GERD
- Meds: NC
- SH: does not drink alcohol, no drugs, no toxin exposure
- FH: PD and dementia

Patient 2
Exam

- VS nml, General exam nml
- Neuro:
  - CN normal
  - Motor:
    - Normal tone

Patient 2 Exam

	Right	Left
deltoids	5/5	5/5
biceps	5/5	5/5
triceps	5/5	5/5
wrist extension	5/5	5/5
FDI	**4/5**	**4/5**
APB	5/5	**4/5**
iliopsoas	5/5	5/5
quadriceps	5/5	5/5
hamstrings	5/5	5/5
tibialis anterior	**2/5**	**2/5**
gastrocnemius	**4-/5**	**5-/5**
foot eversion	**0/5**	**0/5**
foot inversion	**0/5**	**0/5**

Patient 2
Exam

- Sensation:
  - Light touch: intact
  - Pinprick: intact
  - Proprioception intact on the right, moderately impaired on the left

  - Vibration sense:

  -

	Right	Left
Toes	**trace**	**1/8**
Ankle	**2/8**	**1/8**
Knee	5/8	5/8
Finger	5/8	5/8
Elbow	5.5/8	7/8

Patient 2 - Exam

- Coordination:
  - No Romberg testing possible

- Reflexes

	Right	Left
Biceps	0	1+
Triceps	0	0
Brachioradial	0	0
Patella	0	0
Ankle	0	0

Patient 2 - Exam

- Gait:
  - Requires a walker to walk
  - High steppage gait

Patient 2 - Summary

- Six month history of progressive, asymmetrical, distal predominant weakness and numbness
- On neurological examination he has severe weakness in his feet and mild to moderate weakness in his hands. In addition he has decreased reflexes throughout and decreased vibration sense with no changes in pinprick sensation

Patient 2

- Differential diagnosis?
- What to do next diagnostically?

Patient 2 - NCS/EMG

- Absent tibial and peroneal CMAPs
- Absent sural, median and ulnar SNAPs
- Conduction velocities: between 19.9 to 35.6 m/s

Patient 2 - NCS/EMG

- Absent tibial and peroneal CMAPs
- Absent sural, median and ulnar SNAPs
- Conduction velocities: between 19.9 to 35.6 m/s

- Diagnosis: acquired, mixed axonal and demyelinating sensorimotor peripheral neuropathy.

Chronic inflammatory demyelinating plyradiculopathy (CIDP)

- Symptoms and signs of neuropathy progressive for at least 2 months
- Progressive, symmetric proximal and distal **weakness** of arms and legs (increasing difficulty rising from a chair, going upstairs, opening jars
- Sensory-motor
- Exam:
  - Particularly large fiber modalities involved (**vibration**)
  - Hypo or **areflexia** (4 limbs)
  - Sensory ataxia, gait imbalance

Chronic inflammatory demyelinating plyradiculopathy (CIDP)

- Can be pure sensory (MAG)
- Cranial neuropathy
  - Mild facial weakness
  - Ophthalmoparesis
  - Dysarthria
  - Dysphagia
  - Hearing loss
  - vertigo

CIDP – electrophysiological testing

3 out of 4 criteria must be met:

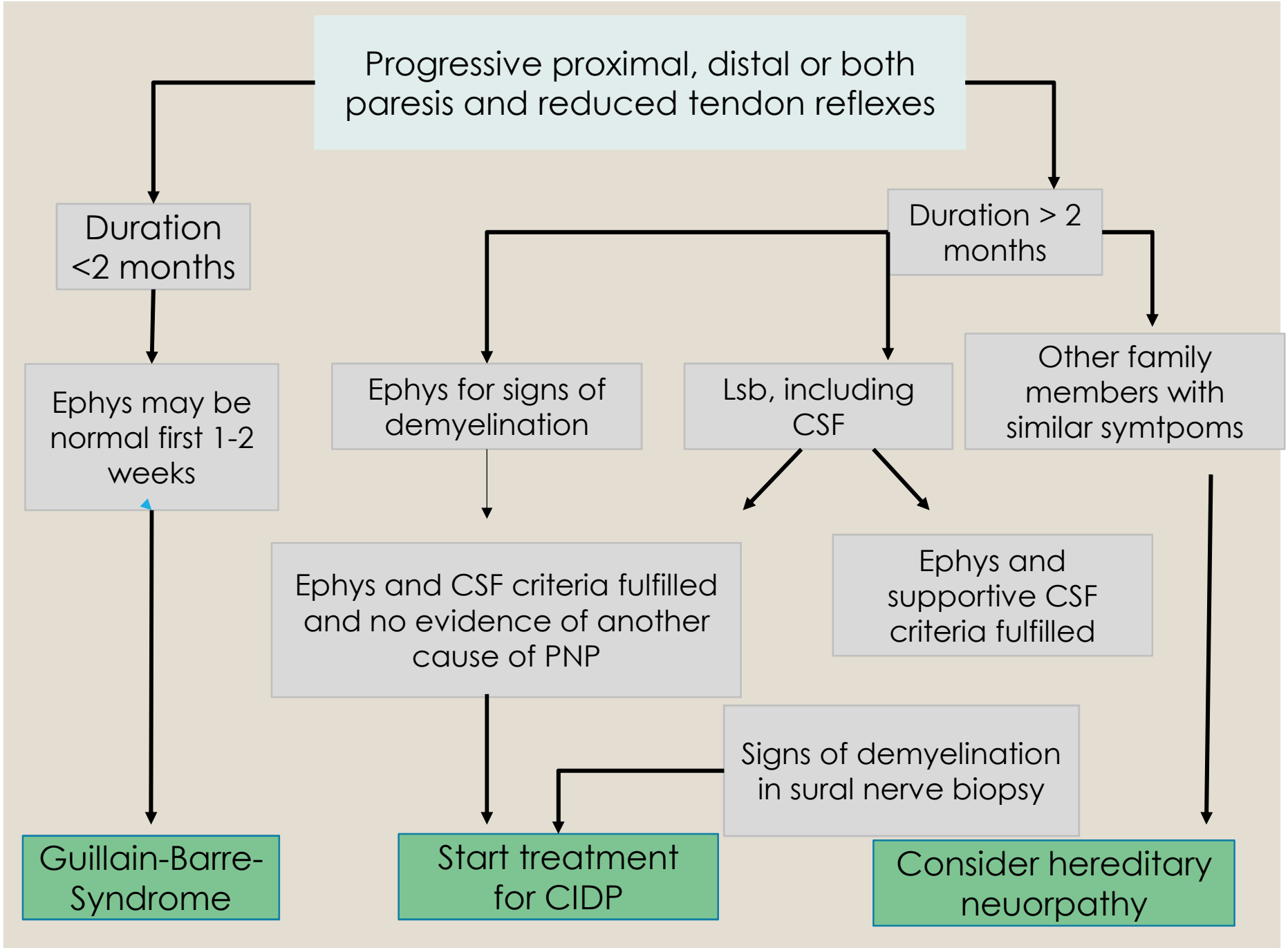
- Reduction in conduction velocity in two or more motor nerves:
  - <80% of lower limit of normal if amplitude is >80% of LLN
  - <70% of lower limit of normal if amplitude is <80% of LLN
  - (generally <30 m/s in legs, and <36 m/s in arms)
- Conduction block
- Prolonged distal latencies
- Absent F waves in two or more nerves

CIDP – Laboratory Features

- CSF:
  - Mandatory: normal cell count (<10),
  - supportive: elevated protein (>45 mg/dl)
    - 80-95% of patients
- Up 25% monoclonal gammopathy
- MRI: enhancement of nerve roots

Medical conditions associated with CIDP

- HIV
- DM
- Inflammatory bowel disease
- MGUS
- Paraneoplastic
  - POEMS
  - Lymphoma
  - Small cell carcinoma of the lung
  - Carcinoma of pancreas, colon
- BM and organ transplantation


Progressive proximal, distal or both paresis and reduced tendon reflexes
Duration <2 months
Duration > 2 months
Ephys may be normal first 1-2 weeks
Ephys for signs of demyelination
Lsb, including CSF
Other family members with similar symtpoms
Ephys and CSF criteria fulfilled and no evidence of another cause of PNP
Ephys and supportive CSF criteria fulfilled
Signs of demyelination in sural nerve biopsy
Guillain-Barre-Syndrome
Start treatment for CIDP
Consider hereditary neuorpathy

CIDP - Treatment

- Corticosteroids
  - Oral or IV
  - IV: 1000 mg/day Solu-Medrol IV for 3-5 days
  - 1000 mg IV weekly for 1-2 months, then slowly down-titrate
- IVIG
  - 2g/kg over 2-5 days (e.g., 0.4 g/kg/d)
  - 1g/kg q 2 weeks to 6 weeks
- Referral to Neurology
- Plasma exchange
- Immune modulators

Patient 3

- 67 yo woman with DM and diabetes-associated neuorpathy
- Noticed sudden onset of numbness of digits 4 and 5 of right hand
- Over next two months numbness increased
- Weakness and atrophy ulnar
- 3 months later tripping over her left toes
- Left wrist drop and numbness
- One week later acute onset left foot drop

Stratification

- Length dependent?
- Symmetric?

Patient 3

- Exam: asymmetric weakness:
  - hand right(0/5) > left 4/5)
  - Foot: left (0/5) > right (5/5)

  - Decreased sensation to PP, LT entire right hand, thereafter normal
  - Patchy decrease of all modalities L arm, and both legs

  - DTRs: 2+ upper extremities and patella, absent ankle reflexes

Patient 3

- Red flags

Patient 3

- Further testing:
  - Positive ANCA
  - Vasculitis on skin biopsy
  - Immune features on biopsy of posterior cutaneous radial nerve
  - Diagnosis: Mononeuritis multiplex
  - Treatment: IV steroids and Azathioprine
  - Outcome: got strength back in feet (5/5), walks unaided; full strength left hand, weakness right thumb

Patient 4

- 47 yo man in his USOH until 5 yrs ago
- Avid runner
- Decreased sweating while running (none over legs and his socks remain dry)
- Overheating while running – core body temperature up to 101F

- Other symptoms:
  - Dry eyes (Restasis)
  - Dry mouth (chews gum)
  - Constipation and diarrhea
  - Early satiety

- No numbness, tingling, weakness

Patient 4

- Normal VS, normal general exam
- Normal cranial nerves
- Normal motor exam
- Sensation:
  - Intact to LT, PP, vibration
- Coordination: intact
- Gait normal

- Autonomic testing:
- RR interval
  - Sympathetic skin response
  - Sweat test

- Skin biopsy

Patient 4

- Sweat test abnormal in patchy distribution
- Decreased intra-epidermal nerve fibers
- Diagnosis: Autonomic neuropathy

Autonomic neuropathy

- Diabetes mellitus
- Hereditary
- Amyloidosis (+weakness)
- GBS (+weakness)
- Paraneoplastic
- Idiopathic
- Immune mediated

Patient 4

- Despite extensive and repeated work-up no cause identified
- Treatment with steroids and IVIG was unsuccessful
- Symptomatic treatment

Summary

- Length-dependent, symmetric sensorimotor peripheral neuropathy
  - typically slowly progressive
  - Unlikely to cause severe physical disability
  - Highest yield laboratory testing: DM, VitB12 (with MMA), serum immunofixation

- Red flags (referral to Neurology)
  - Weakness
  - Asymmetry
  - Length independent/multifocal
  - Rapidly progressive
  - Severe sensory
  - Clinical uncertainty

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