Polyneuropathies- all types

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Goals and Objectives

- Understand the approach to the evaluation of the patient with polyneuropathy
- Recognize the signs and symptoms associated with nerve disorders
- Know the basic pathological processes affecting peripheral nerves
- Understand how nerve disorders are classified and the common etiologies for nerve disease
- Be able to identify patients with small fiber polyneuropathy

Background

- Peripheral neuropathy is experienced by approximately 40 million people in the US
- Many peripheral neuropathies are mixed neuropathies with both large fiber and small fiber involvement
- Increasingly recognized is the demonstration of specific involvement of small myelinated or unmyelinated fibers, e.g. small fiber neuropathies

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200

Approach to Diagnosis in Nerve Disorders

- History
- Physical Examination
- Family History

- Investigations (not all are needed)
  - Bloodwork: severity/progress of neuropathy guides work-up. Especially to look for treatable causes of neuropathy
  - Electrodiagnostic: EMG/NCS; axonal versus demyelinating
    - Large (not small) fiber neuropathies
  - Lumbar puncture
  - Nerve biopsy
  - Genetic testing (for certain inherited neuropathies)

Often, no cause is determined (idiopathic)

Evaluating Nerve Disorders

Symptoms

- Negative
  - Weakness
  - Numbness
  - Unsteadiness
- Positive
  - Paresthesias, dysesthesias
  - Hyperpathia, allodynia
  - Restless legs

Examination

- Negative
  - Weakness*, clumsiness
  - Atrophy
  - Sensory loss*
    - Light touch, pinprick, temperature, vibration, joint position are tested
  - Diminished or absent reflexes*
- Positive
  - Fasciculations
  - Cramps

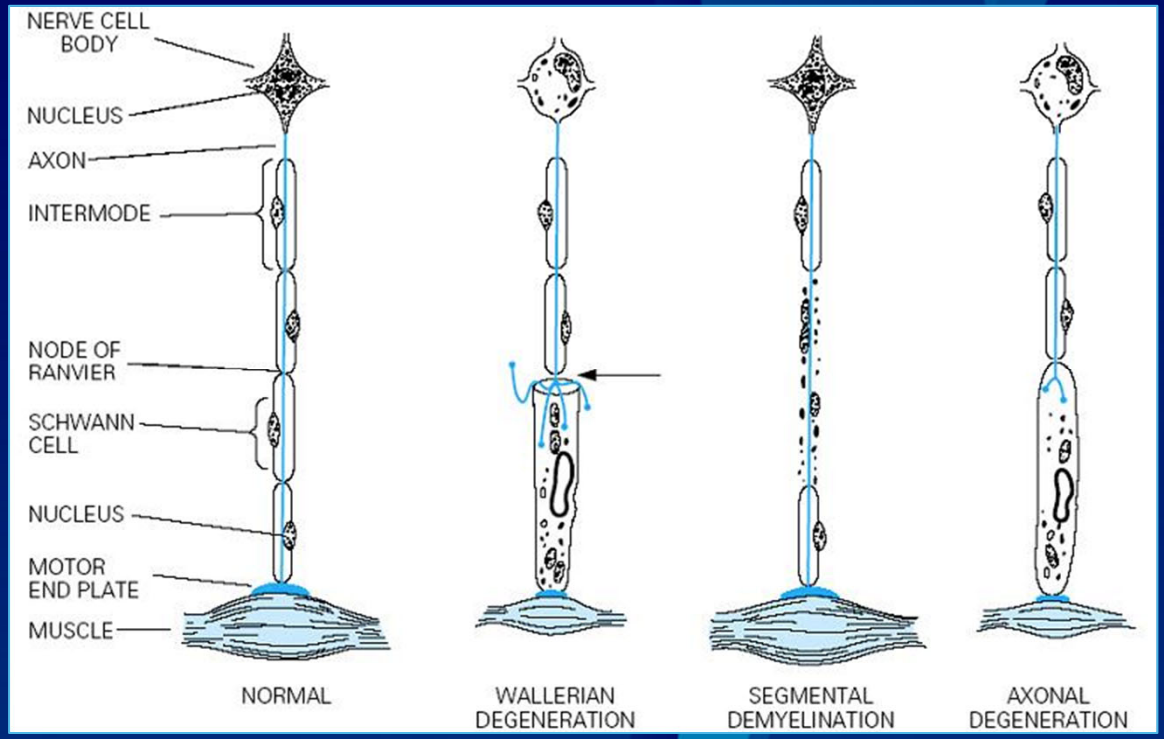
*In the distribution of the abnormal nerve(s)

Classification of Nerve Disorders

- **Tempo & Course**
  - Acute
  - Subacute
  - Chronic
  - Monophasic
  - Relapsing
  - Progressive
- **Nerve type**
  - Motor
  - Sensory
  - Autonomic
  - Mixed
- **Distribution**
  - Mononeuropathy
  - Mononeuropathy multiplex
  - Polyneuropathy
  - Radiculopathy
  - Polyradiculoneuropathy
  - Plexopathy
- **Pathology**
- **Etiology**

Pathologic Processes

- Wallerian degeneration (anterograde)
- “Dying-back” axonal degeneration
- Segmental demyelination
- Neuronopathy



Nerve Injury

- Neurapraxia
  - Focal demyelination
  - Anoxia/ischemia, mechanical factors
- Axonotmesis-loss of axon continuity
- Neurotmesis –connective tissue involved
  - I: perineurium, nerve sheath preserved
  - II:nerve sheath preserved only
  - III: complete separation of nerve

Etiology of Nerve Disorders

- Vascular
  - Systemic necrotizing vasculitis
  - Wegener granulomatosis
  - Giant cell arteritis
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Sjogren syndrome
  - Scleroderma
  - Mixed connective tissue disease
- Infectious/granulomatous
  - AIDS
  - Leprosy
  - Diphtheria
  - Sarcoidosis
  - Sepsis/multiorgan failure
  - Lyme disease
  - Herpes Zoster
  - Poliomyelitis
- Inflammatory
  - AIDP
  - CIDP
- Neoplastic
  - Compression/infiltration by tumor
  - Paraneoplastic syndromes
  - Paraproteinemias
  - Amyloidosis
- Toxic
  - Alcohol
  - Therapeutic drugs (extensive list; includes antibiotics (INH), AED's (phenytoin), platinum-containing chemotherapies)
  - Hexacarbons, organophosphates
  - Paralytic shellfish poisoning
  - Heavy metals
- Metabolic
  - Diabetes/other endocrinopathies
  - Uremia
  - Liver disease
  - Vitamin B12 deficiency
- Heredodegenerative
  - HMSN/HSAN
  - Familial amyloidosis
  - Friedreich Ataxia
  - HNPP
  - Porphyria
  - Metachromatic leukodystrophy
  - Krabbe disease
  - Abetalipoproteinemia
  - Tangier disease
  - Refsum disease
  - Fabry disease
- Entrapment

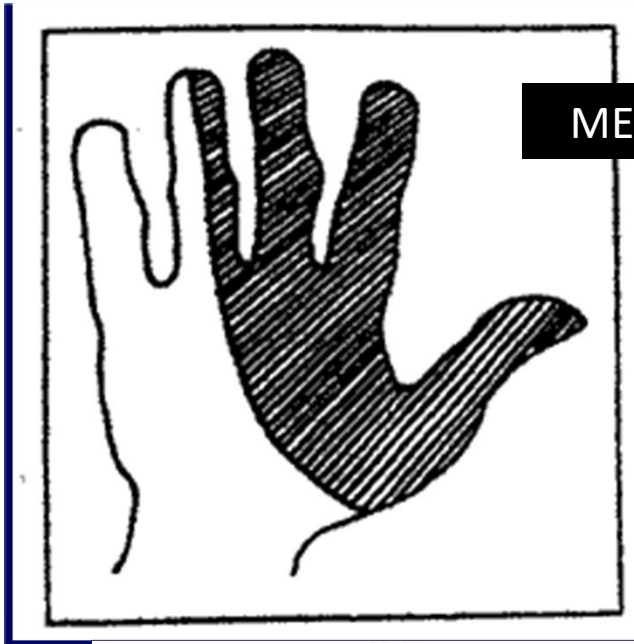
Mononeuropathies

- Isolated nerve lesions with deficits restricted to the nerve in question
- Commonly related to entrapment, trauma
- Frequently encountered mononeuropathies in clinical practice include:
  - Median
  - Ulnar
  - Radial
  - Peroneal
  - Lateral femoral cutaneous

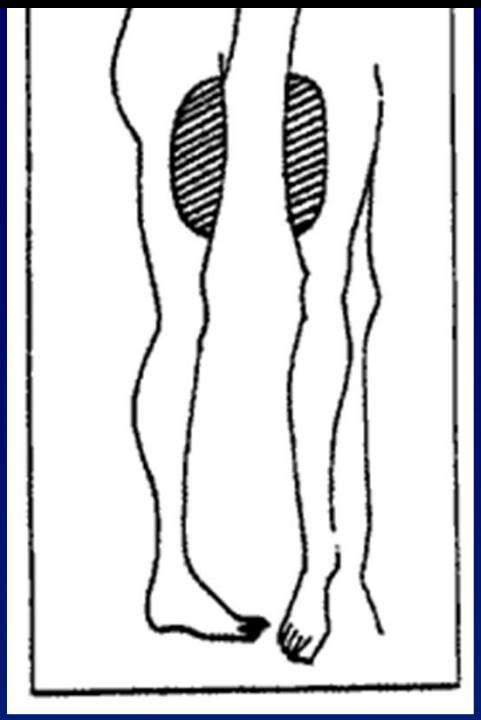
Entrapment Neuropathy

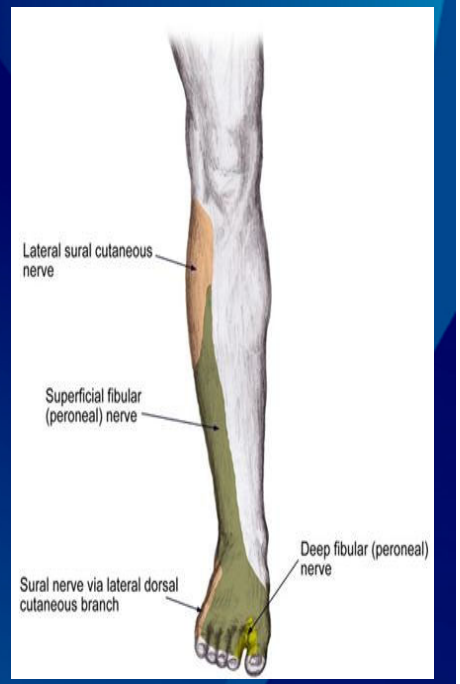
- Nerves at risk pass through tight fibrous or fibro-osseous channels
- Mechanical distortion leads to focal demyelination and possibly axonal injury
- Most Common: Median nerve at wrist (carpal tunnel), Ulnar nerve at elbow, peroneal nerve at fibular head

MEDIAN



LATERAL FEMORAL CUTANEOUS





Fibular (Peroneal)

ULNAR

RADIAL

Mononeuropathy Multiplex

- Several individual nerves are affected
  - Usually at random and non-contiguously
- Examination reveals deficits attributable to the involvement of one or more isolated peripheral nerves
- Often related to vasculitis or other inflammatory/autoimmune conditions.
- Diabetes

Polyneuropathies

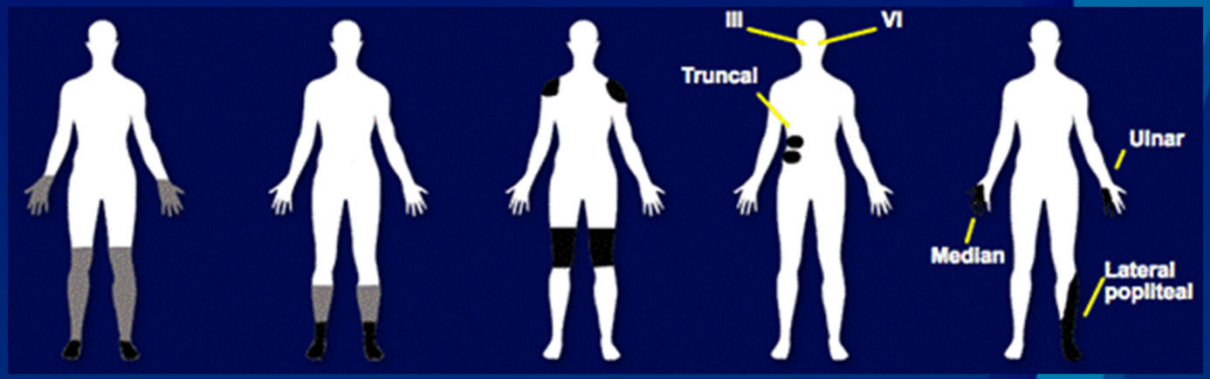
- Refers to a disorder of numerous peripheral nerves at a given time
- Often characterized by a distal, symmetric sensory deficit (“glove and stocking” distribution)
- Can be further subclassified as primarily axonal or demyelinating in nature

Polyneuropathies
common considerations by pathology

- Axonal
  - Metabolic
  - Inherited
  - Nutritional, toxins
  - Vasculitis
- Demyelinating
  - Immune mediated/inflammatory
  - Inherited
  - nutritional, toxins

Axonal Polyneuropathies

- **Diabetic Neuropathy**
  - Most often a distal symmetric polyneuropathy
    - Large or small fiber; autonomic neuropathy may coexist
  - Asymmetric neuropathy may involve cranial nerves, thoracic or limb nerves
    - Result from ischemia (vasa nervosa); entrapments
  - Proximal motor neuropathy (diabetic amyotrophy) with severe proximal limb pain and weakness
    - Believed to result from immune-mediated epineural microvasculitis



Axonal Polyneuropathy
Select other causes

- Renal Failure
- Alcohol
  - Probably multifactorial
  - Nutrition important
  - Painful sensory/”Stocking-glove” type

-Nutritional- eg vitamin B12

-Inherited neuropathies (eg CMT type 2)

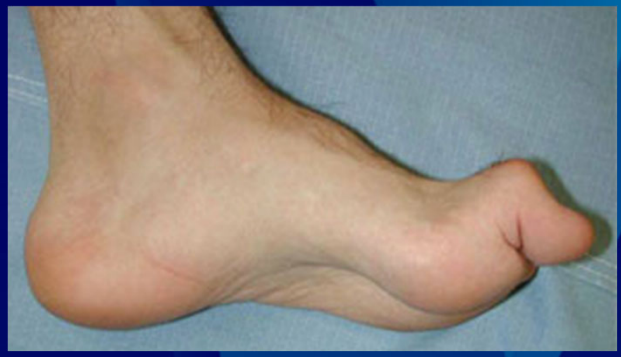
Toxic Neuropathies

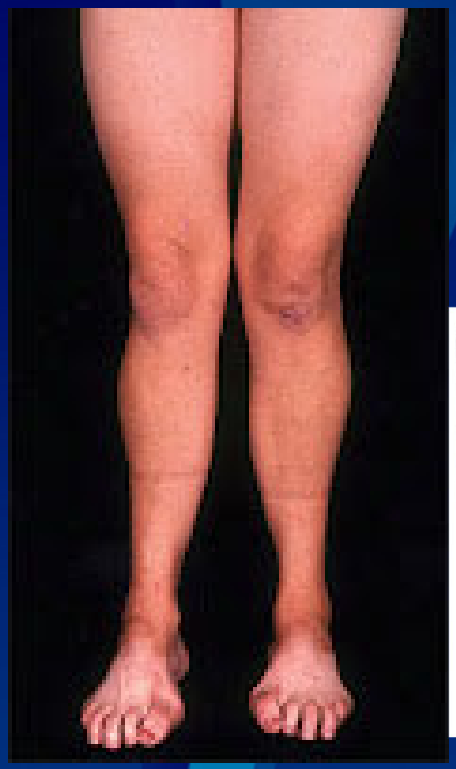
may be axonal or demyelinating

- Arsenic
- Heavy Metals (lead, mercury)
- Antibiotics (eg INH)
- Chemotherapy (eg taxol, cis-platinum)
- Thallium
- Hexacarbons
- Seizure Medicines (Phenytoin)
- Many More……the list is long!

Demyelinating Polyneuropathies

- **Charcot-Marie-Tooth hereditary motor and sensory neuropathy, type 1 (CMT-1)**
  - Most common demyelinating polyneuropathy
  - Distal weakness and atrophy
  - Musculoskeletal deformities (pes cavus, hammer toes, "inverted champagne bottle" legs)
  - Sensory symptoms less common
  - EMG/NCS useful in determining demyelinating from axonal variants
  - Genetic testing available
  - Type 2 CMT/HMSN is axonal but similar phenotype





Hereditary (HMSN)- classification

- HMSN1- autosomal dominant/demyelinating
  - Types 1A-1D
- HNPP
- HMSN 2-autosomal Dominant/axonal
  - 2A-2F
- HMSN3 (Dejerine sottas)
- HMSN 4 (A-F)
  - Recessive (both axonal and demyelinating)
- HMSN X

Demyelinating Polyneuropathies

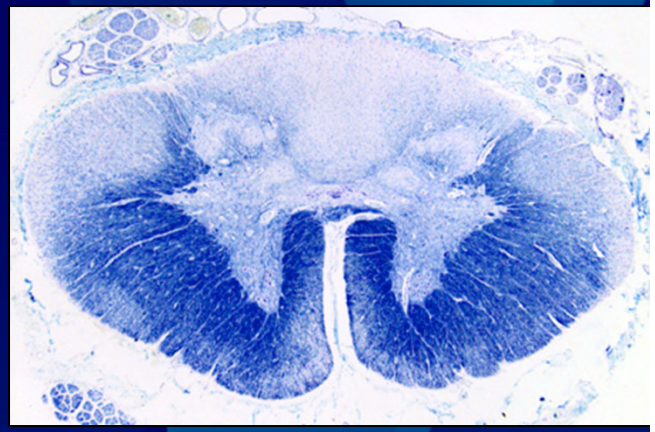
- **Acute Inflammatory Polyradiculoneuropathy (AIDP; Guillain-Barre syndrome)**
  - Most common **acquired** demyelinating polyneuropathy
  - Autoimmune segmental demyelination of motor > sensory nerves
  - Molecular mimicry (i.e. Campylobacter jejuni)
  - Ascending weakness and respiratory compromise occurring over days-weeks
  - Areflexia
  - Facial weakness common
  - Autonomic dysfunction common
  - Usually monophasic; complete recovery is possible
  - CSF finding: albumino-cytologic dissociation (elevated protein with normal or low white blood cell count)
  - EMG/NCS useful in diagnosis (variants, mimics)
  - Acute treatment: IVIG, plasmapheresis

Infectious

- Leprosy
  - Common worldwide in past, still to be considered
- Diphtheria
  - Oculobulbar involvement
- Lyme Disease
- Herpes Zoster
- HIV
- Poliomyelitis, other enteroviruses, West Nile

Neuropathy with myelopathy

- **Friedreich's ataxia**
  - Most common autosomal recessive ataxia
  - Results from an expanded GAA trinucleotide repeat in a noncoding region of the gene for frataxin on chromosome 9 (loss of function)
  - Signs include progressive limb and gait ataxia, dysarthria, loss of joint position and vibration senses, absent deep tendon reflexes in legs, extensor plantar responses
  - Usually presents by 8-15 years; loss of ambulation by 15 years after onset; >95% wheelchair bound by age 45
  - Associated features include kyphoscoliosis with restrictive lung disease, cardiomyopathy with arrhythmias and heart failure, optic atrophy, and diabetes mellitus
  - Characterized degeneration of dorsal root ganglia and axons, beginning in the periphery, with ultimate loss of neurons and secondary gliosis. Degeneration of corticospinal tracts, dorsal columns, spinocerebellar tracts.



cerebellar ataxia

Amyotrophic Lateral Sclerosis (ALS)

- Disorder of upper and lower motor nerves
- Usually death 2-6 years after diagnosis
- Lower motor nerve – atrophy, weakness, fasciculations
- Upper motor nerve- “long tract signs”- brisk deep tendon reflexes, pathologic reflexes (eg Babinski)

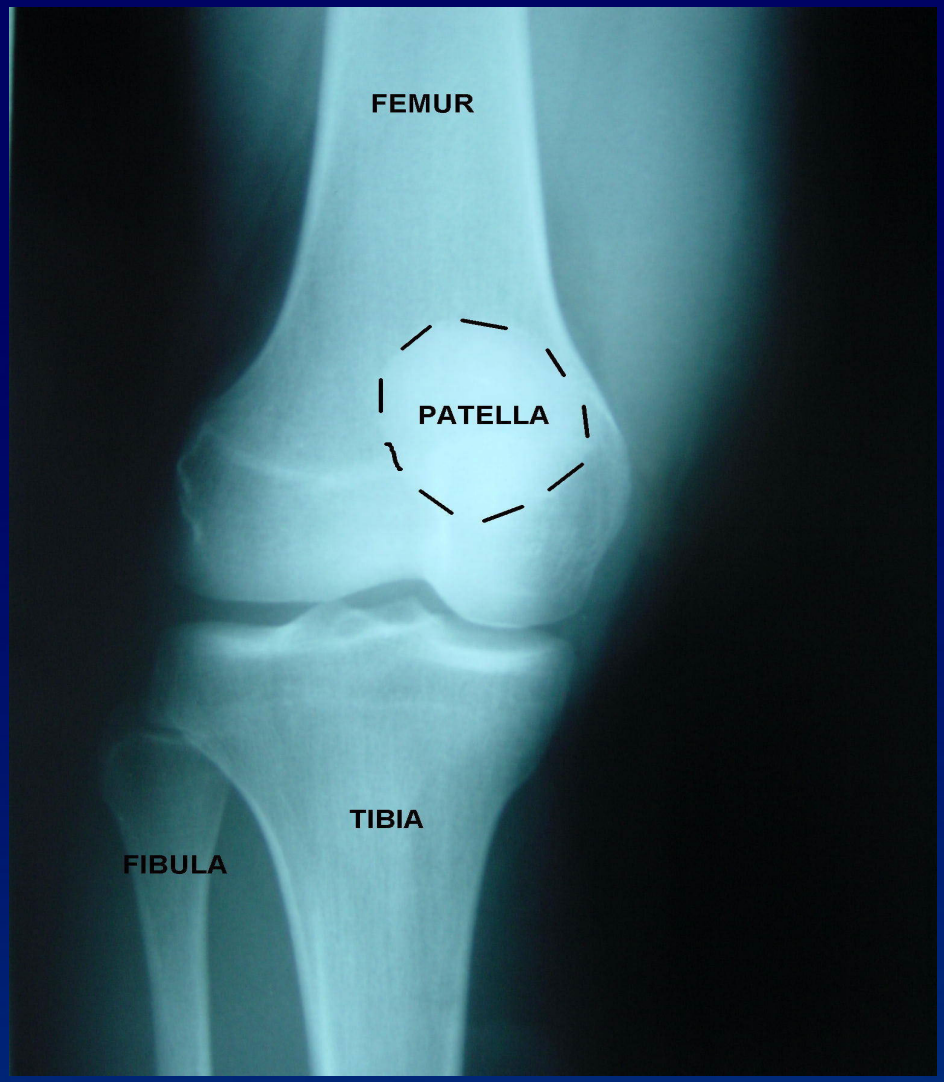
ALS

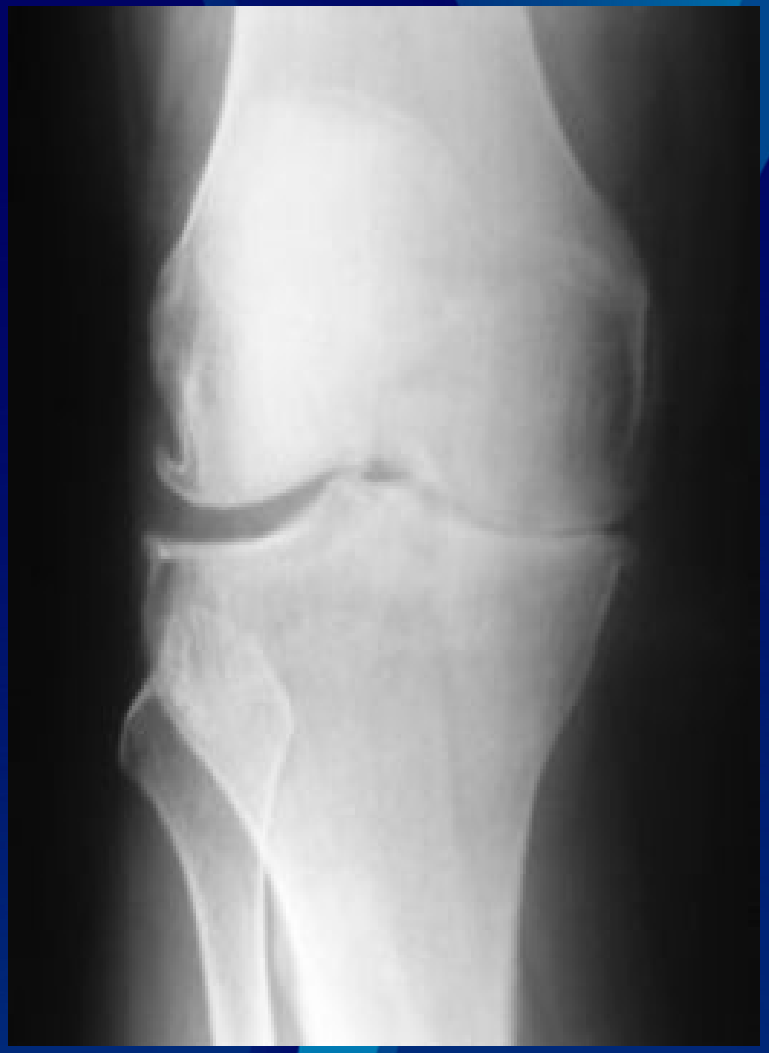
- 2 most common forms of presentation- limb onset & bulbar onset
- Widespread denervation of muscle in body
- Affects motor nerves (minimal sensory involvement)
- Respiratory failure
- Dysphagia
- Loss of independence, may become non-ambulatory

What is Neuropathic Pain?

- Pain arising as a direct consequence of diseases affecting the somatosensory system.
  - Grading system: definite, probable, possible
    - R-D Treede et al. *Neurology* 2008, Proposed by IASP Neuropathic Pain Special Interest Group.
- In Plain English: Pain from the nerves, spinal cord, or brain. Not originating in the bones, muscles, organs.

Which person has pain?





Differential diagnosis- Widespread or Difficult to Diagnose Localized Pain

- Rheumatic
  - Arthritis (OA, RA)
  - Polymyalgia Rheumatica
  - Osteomalacia
  - Myopathy
  - Spondyloarthropathies
  - Systemic Lupus Erythematosus
- Endocrine
  - Hypothyroidism
  - Diabetes
- Neurologic
  - Multiple sclerosis
  - Chiari malformation
  - Spinal stenosis
  - Radiculopathy
  - Polyeuropathy
  - Fibromyalgia
- Other
  - SMALL FIBER POLYNEUROPATHY?

Common Neuropathic Pain Diagnoses

- Diabetic Peripheral Neuropathy*
- Post Herpetic Neuralgia*
- Radicular Pain (neuropathic low back pain)
- Traumatic Peripheral Nerve Injury
- Complex Regional Pain Syndrome
- Chronic Postop Pain
- Phantom Limb Pain
- HIV related neuropathy
- Spinal Cord Injury*
- Post-stroke pain
- Trigeminal Neuralgia*
- Small Fiber Polyneuropathy

* FDA approved medications available

Polyneuropathies may involve small and large nerve fibers

	Large-fiber neuropathy	Small-fiber neuropathy
Symptoms	Numbness, pins and needles, tingling, poor balance	Pain: burning, electric shocks, stabbing pain, numbness
Exam Findings	Reflexes, proprioception Vibration, +/- motor	Thermal, pin-prick sensation, allodynia
Functional changes	Pressure, balance, fall risk	Nociception; protective sensation
Diagnostic test	EMG/NCV, sural nerve biopsy	QST, nerve biopsy, Intraepidermal nerve fiber density (skin biopsy)

Small Fiber Polyneuropathy Definition and Key Facts

- Small fiber neuropathies (SFN) result from damage to the peripheral nerves affecting small myelinated A-Delta and unmyelinated C fibers.
- The fibers affected include both small somatic as well as autonomic fibers
- Thermal perception and nociception are subserved by small fibers
- Enteric function is also subserved by small fibers
- LARGE fibers are heavily myelinated and involved in muscle control, as well as touch, vibration adn position sense

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200

Small Fiber Polyneuropathy Definition and Key Facts-2

- Most SFNs occur in a length-dependent fashion – first stocking distribution changes and then later glove distribution
- Less common but no longer rare, non-length dependent SFN can results in symptoms involving the face, trunk, proximal limbs, or other more localized areas
- The pathogenesis of injury to small fibers is not well understood

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200

Small Fiber Polyneuropathy Definition and Key Facts-3

- SFN can progress to involve large fibers as well
- Muscle cramps may be one of the presenting complaints of SFN
- Epidemiologic data from the Netherlands suggest a minimum incidence of 12/100,000 people
- Children also can experience SFN- the diagnosis may be more challenging in adults as will be discussed later

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200;Peters MJ, et al. Incidence and prevalence of small-fiber neuropathy: a survey in the Netherlands. Neurology 20133;81:1356-60; Oaklander AL, Klein MM. Evidence of small-fiber polyneuropathy in unexplained, juvenile-onset, widespread pain syndromes. Pediatrics 2013;131:e1091-1100.)

Small Fiber Polyneuropathy: BIG impact on quality of life

- In one study that measured the impact specifically on SFPN on quality of life, 265 patients enrolled
- SFN-SIQ, VAS, 36 item short form health survey evaluated
- SFPN patients demonstrated a marked overall reduction in quality of life
- Physical and mental measures were decreased
- Other reported data suggests significant direct and indirect healthcare costs with increasing levels of pain in idiopathic SFN

Chan AC, Wilder-Smith EP. Small fiber neuropathy: getting bigger! Muscle Nerve 53:671-682, 2016 , Schaefer C, et al. Journal of Medical Economics. 2014;17:394-407)

Disorders Associated with SFN

- Diabetes
- Impaired Glucose Tolerance
- Metabolic Syndrome
- Sarcoidosis
- Thyroid Dysfunction
- HIV
- Vitamin B12 Deficiency
- Vitamin B1 Deficiency
- Chemotherapy drugs
- Antiviral Agents
- Celiac Disease
- Sjogren's Syndrome
- Paraneoplastic Syndromes
- Paraprotenemia
- Rheumatoid Arthritis
- Idiopathic (up to 50%!)

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200

Disorders Associated with SFN-2

- Guillain-Barre Syndrome
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Restless Leg Syndrome
- Hepatitis C
- Systemic Lupus Erythematosus
- Amylodosis
- Fabry's Disease
- Ehlers Danlos Syndrome
- Hereditary Sensory Neuropathies
- Hereditary Autonomic Neuropathies
- Central post stroke pain

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200

Disorders associated with SFN-3

- Alcohol use
- Rabies, varicella or Lyme vaccine
- Anti-TNF inhibitors
- Metonidazole
- Linezolid
- Statins
- Sodium channelopathies
- Parkinson disease
- Pompe disease
- Wilson disease
- ALS
- Fragile X
- X linked adrenoleukodystrophy
- Chronic renal disease

Chan AC, Wilder-Smith EP. Small fiber neuropathy: getting bigger! Muscle Nerve 53:671-682, 2016

SFN Pathophsyiology- Possible role of Sodium Channel mutations

- Genetic variants in the structure/function of sodium channels may lead to either loss of pain sensitivity or enhanced pain
- Inactivating mutations in SCN9A, which encodes Nav 1.7 is associated with congenital insensitivity to pain
- Gain of function mutations in SCN9A may result in SFN
- Various mutations in TRPA 1 or NAv1.8(SCN10A) and Nav 1.9 (SCN11A) also may lead to SFN
- Might this information lead to new treatments?

Bennett DL, Woods CG. Painful and painless channelopathies. Lancet Neurol 2014 Jun;13(6):587-99.

SFN Symptoms

- Symptoms vary widely in severity
- Often affected individuals describe a gradual onset of vague distal sensory disturbances
- Examples include feeling like there is sand in the person's shoe, a sock feeling as if it has pebbles in it, pins and needle sensations, cold painful sensations or tingling.

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200

SFN Symptoms-2

- Burning pain in the extremities, sometimes severe
- Allodynia and hyperesthesia
- Socks or bedsheets may be painful
- Symptoms are often worse at night

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200

SFN Symptoms-3

- Autonomic and enteric dysfunction including: dry eyes, dry mouth, lightheadedness with changes in posture, syncope, abnormalities of sweating, erectile dysfunction, GI symptoms such as nausea and emesis, constipation, diarrhea, changes in urinary frequency including nocturia.

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200

SFN- Diagnosis

- Normal or practically normal basic physical and neurological examination!!!
- However, possible findings include decreased pin prick, diminished thermal sensation, hyperalgesia, dry skin
- A detailed history is vital to making the diagnosis
- Ancillary testing may be helpful as well

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200

Common Diagnostic Studies and Limitations

Studies

- Blood studies
- X-ray, CT, MRI
- Electromyography (EMG)
- Nerve conduction velocity (NCV)
- ***Quantitative sensory testing (QST)***
- ***Skin biopsy***

Limitations of EMG/NCV

- Insensitive in acute injury
- Normal result does not rule out neuropathic pain
- Cannot assess function of small-fiber nerves involved in most neuropathic pain

Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. McGraw-Hill Companies; 2000.

SFN-Diagnosis-additional information

- Various written tools such as the Neuropathic Pain Symptom Inventory may be helpful
- Quantitative Sensory Testing- this can detect thresholds of thermal pain, thermal sensation and vibration for example. Contact Heat Evoked Potentials attempts to link peripheral activation to central.
- Quantitative Sudomotor Axon Reflex testing (QSART)

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200

SFN-Diagnosis-Skin Biopsy

- Skin Biopsy- this has become widely accepted as a technique to evaluate the structure of small nerve fibers.
- The standard is a 3-mm skin punch biopsy that can be taken from anywhere over the body.
- Due to the need to compare to normal values the lower extremity is most commonly assessed (also length dependent SFN more common than non-length dependent)
- The results are expressed as the number of intraepidermal fibers per mm
- The sensitivity (78-92%) and specificity (65-90%) is fairly high for this technique

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200

SFN-Skin Biopsy- 2

- Intraepidermal nerve fibers (IENF) are unmyelinated sensory endings that arise from the sub-papillary dermis
- They widely express the TRPV1 receptor- this means they are distal nociceptors
- One of the more common areas to perform a skin biopsy for diagnostic purposes is 10cm proximal from the lateral malleolus
- Using antibodies against the protein gene product (PGP 9.5), a cytoplasmic ubiquitin carboxyl-terminal hydrolase, the number of fibers crossing the dermal-epidermal junction can be quantified – measured as IENF/millimeter

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200 , Lauria G, et al. J Peripher Nerve Syst 2010;15:202-207)

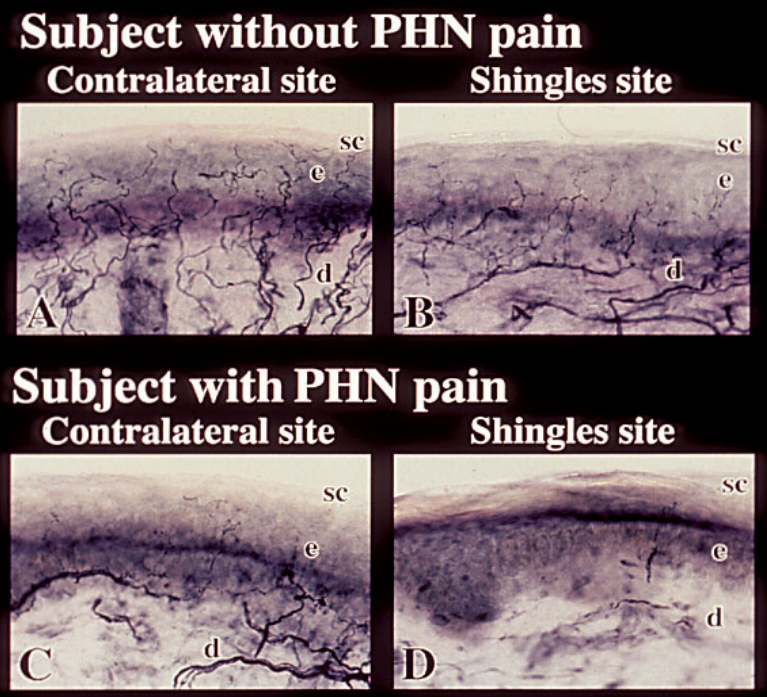
SFN-Skin Biopsy- 3

- Studies have demonstrated stability of IENFD in normal controls as well as in patients with idiopathic SFN when re-biopsied in the same sensory territory after 3 weeks
- IEFND decreases with age in SNF associated with various etiologies
- IEFND has been found to be decreased in non-painful disorders such as Parkinson's disease, ALS, critical illness and periperhal arterial disease- more to be discussed!

Lauria G, et al. J Peripher Nerve Syst 2010;15:202-207);Lauria et al. Neurology 2015;84:2368-2371

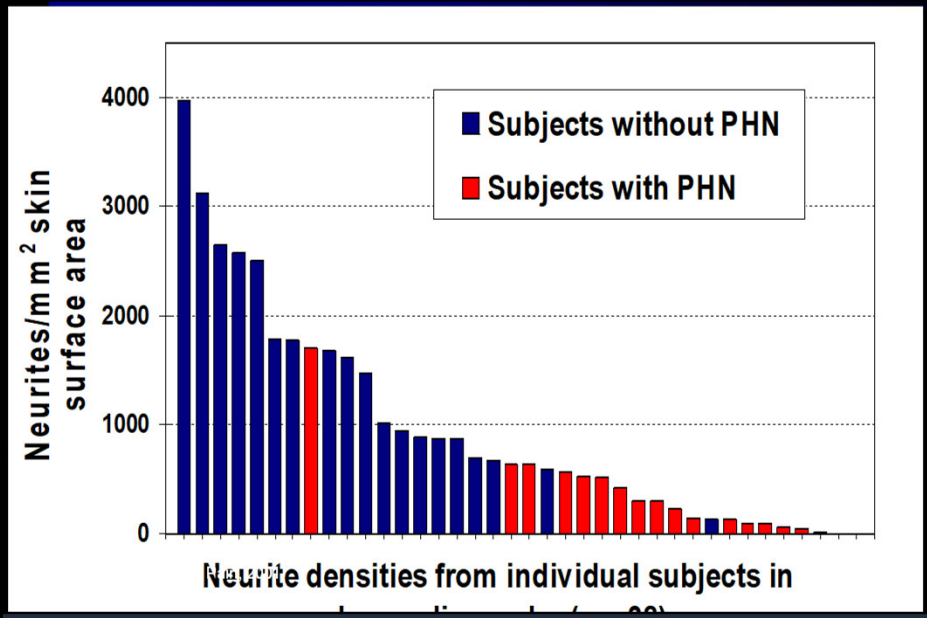
Loss of skin nerve fibers in PHN

PGP 9.5 Immunolabeling of Sensory Nerve Endings in Skin Biopsies



A.L. Oaklander et al., 1998

The density of epidermal nerve endings in previously shingles-affected skin



Oaklander AL, et al *Ann Neurol* 1998;
Oaklander AL, et al *Pain* 2001

SFN- Diagnosis-Corneal Confocal Microscopy (CCM)

- CCM visualizes the C-fibers originating from the trigeminal nerve that travel to the Bowman's membrane of the cornea
- CCM software can quantify: corneal nerve fiber density (CNFD), corneal nerve fiber tortuosity, corneal nerve branch density, corneal nerve fiber length
- Studies support that patients with both non-length dependent as well as length dependent SFN demonstrate a decrease in CNFD

Tavakoli M, et al. Diabets Care 2015;38:838-843; Gemignani F et al. J Peripher Nerv Syst 2010;15:57-62; Tavakoli M et al. Exp Neruolo 2010;223:245-250.

Functional and Imaging Assessment of Small Nerves

- Quantative Sensory Testing
- Microneurography
- Nociceptive Evoked Potentials
- Peripheral Nerve Ultrasound
- Magnetic Resonance Imaging

Devigili G, et al. Brain 2008;131:1912-1925; Serra J Neuroscience Letters 2010;470:155-157; Mobascher A et al. Neuroimage 2009;45: 917-926; Persson AK et al. Ann Neuro 2013;140-145;Tseng MT et al. Hum Brain Mapp 2013;34:2733-2746.

Small fiber polyneuropathy-blood/other tests

- Metabolic: thyroid functions, HbA1C, FBS
- Nutritional: CBC, Hepatic Profile, Vitamin B1 and B12
- Infectious: CRP, HIV, Lyme, HBV, HCV
- Autoimmune: ESR, ANA, Anti-ENA, ANCA, anti-gliadin, RF, serum ACE, ? CXR
- Paraneoplastic: Tumor markers, LDH, Myeloma screen, SPE, anti-Hu and anti-CV2/CRMP-5 ab

Chan AC, Wilder-Smith EP. Small fiber neuropathy: getting bigger! Muscle Nerve 53:671-682, 2016

Small fiber polyneuropathy- blood/other tests(continued)

- Neurotoxins: urine and blood toxicology, review drug history
- Herditary: alpha-galactosidase A, globotriaosylceramide levels, renal panel, urine protein, genetic testing for SCN9A or SCN10A
- Lumbar puncture: if you suspect inflammatory, auto-immune or paraneoplastic etiologies

Chan AC, Wilder-Smith EP. Small fiber neuropathy: getting bigger! Muscle Nerve 53:671-682, 2016

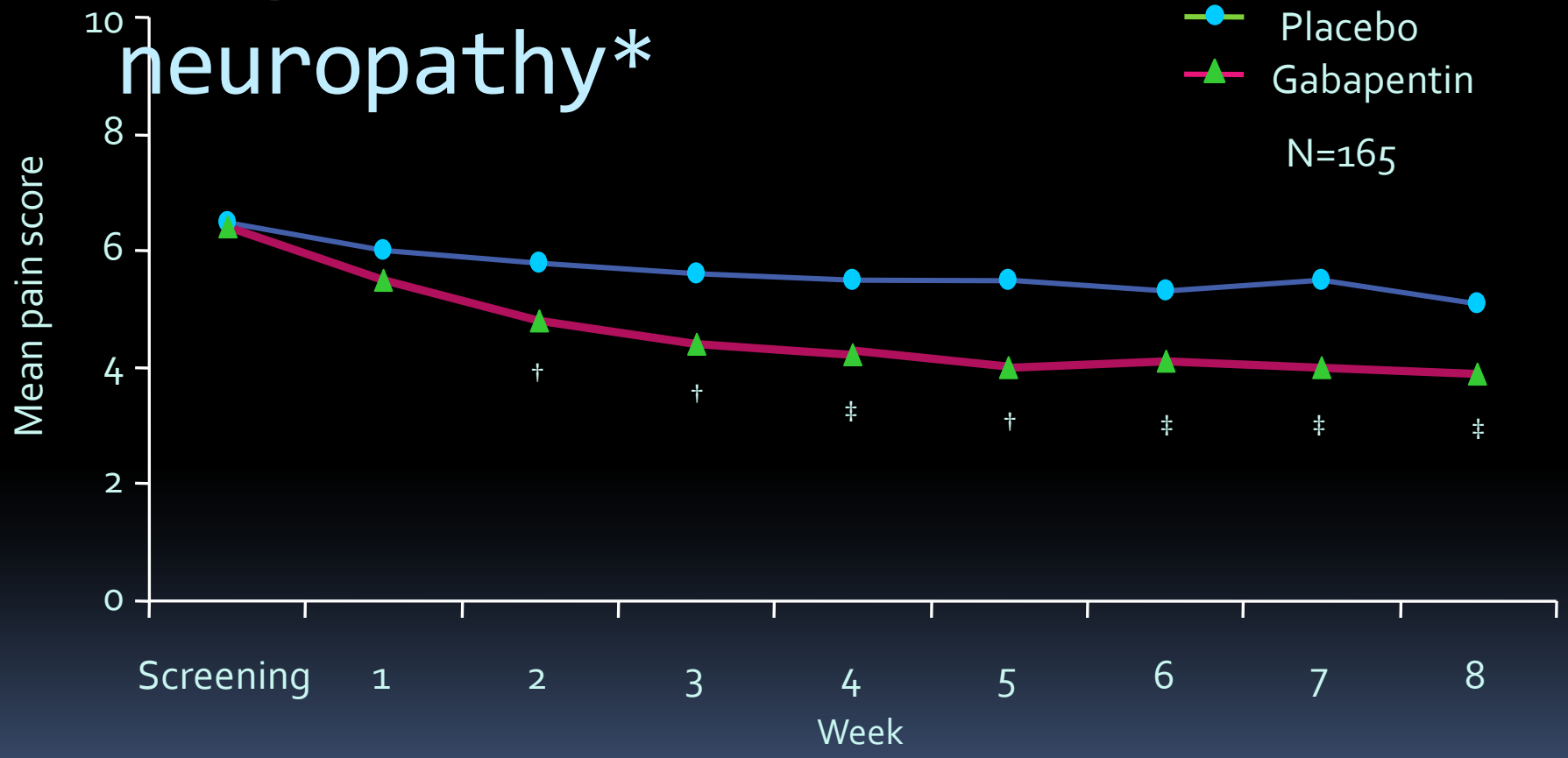
More about voltage gated sodium channelopathies

- $Na_v1.7$ and $Na_v1.8$ gain of function mutations in inherited erythromelagia
- $Na_v1.7$ in paroxysmal extreme pain disorder- paroxysmal rectal, ocular or submandibular pain with flushing with possible autonomic dysfunction- 10 gain of function mutations have been identified
- $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ gain of function mutations in SFN

McDonnell A et al. Brain 2016;139:1052-1065;Faber CG et al. Ann Neurol 2012;71:26-39; Faber CG et al. PNAS 2012;109:19444-19449;Huang J et al. J Clin Invest 2017;127:2805-2814.

"Discouraging Data on the Antidepressant (AS WELL AS MANY OTHER TREATMENTS)"

Gabapentin in the treatment of painful diabetic neuropathy*



*Not approved by FDA for this use

† *P* <0.01; ‡ *P* <0.05

Adapted from Backonja M, et al. *JAMA*. 1998;280(21):1831-1836.

SFN- Treatment

- Treat the treatable! If an underlying cause of SFN can be determined, optimal treatment of the causative condition may lessen the symptoms of SFN
- Few studies and no guidelines have examined the pharmacologic treatment of the pain associated with SFN
- In one such study, both gabapentin and tramadol were found to be effective for SFN

Hovaguimian A, Gibbons CH. Diagnosis and Treatment of Pain in Small-fiber Neuropathy Curr Pain Headache Rep (2011) 15:193-200

Neuropathic pain recommendations of various societies

	EFNS, Europe Neurology	Canadian Pain Society	IASP NeuPSIG
First line	TCA GBP/PGB Lidocaine 5% plaster	TCA GBP/PGB	TCA, SNRI GBP/PGB Lidocaine 5% Opioid (specific circumstances)
Second line	SNRI (Opioid)	SNRI Lidocaine 5%	Opioid Tramadol
Third line	Opioid Lamotrigine Capsaicin	Opioid (except methadone)	Paroxetine Bupropion NMDA antagonist
Fourth line		Methadone	

EFNS, European Federation of Neurological Societies; IASP, International Association for the Study of Pain; NeuPSIG, Neuropathic Pain Special Interest Group

Attal N, et al. *Eur J Neurol*. 2006;13(11):1153-1169. Dworkin RH, et al. *Pain*. 2007;132(3):237-251.
Moulin DE, et al. *Pain Res Manag*. 2007;12(1):13-21.

SFN- Is IVIG (intravenous immunoglobulin) an Emerging Treatment?

- A recent report described 3 patients with sarcoidosis and SFN who were experiencing severe pain as well as dysautonomia
- Each patient had biopsy proven SFN
- Each patient had failed to response to "conventional" analgesic/symptomatic approaches
- Each patient received an initial dose of IVIG 2g/kg followed by 1g/kg doses at regular intervals- each with dramatic resolution of pain and autonomic symptoms
- Further larger studies are warranted

Parambi JG, Tavee JD, Zhou L, et al. Efficacy of intravenous immunoglobulin for small-fiber neuropathy associated with sarcoidosis. Resp Med 2011 Jan;105(1):101-5.

SFN- Is IVIG (intravenous immunoglobulin) an Emerging Treatment?-2

- Limited data for Sjogren's syndrome- IVIG 2g/kg
- Juvenile onset unexplained widespread pain treated with IVIG in 15 patients by Oaklander et al- treated at 2g/kg/month at least 3 times- 62% demonstrated significant improvement
- In another study, 46 patients with SFPN associated with dysautonomia were treated with one or more IVIG treatment- for patients with pain intensity levels ≥ 3 or with significant dysautonomia, the treatment was helpful

Oaklander A, Immunotherapy Prospects for Painful Small-fiber Sensory Neuroapthies and Ganglionopathies. Neurotherapeutics 2015

SFN- Is IVIG (intravenous immunoglobulin) an Emerging Treatment?-3

- 55 patients with "apparently autoimmune" small-fiber polyneuropathy treated with IVIG
- IVIG treatment duration averaged 28 +/- 25 months
- Improvements were noted in autonomic function testing, pain reduction, sweat production
- 16% of patients were considered in remission after multiple treatments

Liu X et al. IVIG for apparently autoimmune small-fiber polyneuropathy:first analysis of efficacy and safety The Adv Neurol Disord 2018 Jan 8

SFPN and Fibromyalgia

- Approximately 50% of patients who have been diagnosed with Fibromyalgia in several published studies have demonstrated findings consistent with SFPN on diagnostic biopsies- studies to be reviewed on subsequent slides
- What does that mean?
- What does that mean about interpreting FM studies that have already been published?

CWP, SFPN and Fibromyalgia I

- 27 patients with fibromyalgia who satisfied the 2010 ACR criteria were compared to 30 matched controls
- 41% of skin biopsies from fibromyalgia subjects compared to 3% from controls were diagnostic for SFPN
- The Michigan Neuropathy Screening Instrument and Utah Early Neuropathy Scale scores were higher in fibromyalgia patients

Oaklander AL, et al. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia Pain 2013 Nov;154(11):2310-6.

CWP, SFPN and Fibromyalgia II

- 25 patients with fibromyalgia were compared to 10 depressed patients and controls
- Small fiber evaluation included QST, pain-related evoked potentials and quantified intraepidermal nerve fiber density and regenerating IENF of the lower leg and upper thigh
- Compared with control subjects fibromyalgia patients BUT not depressed patients had impaired small fiber function

Uceyler N, et al. Small fibre pathology in patients with fibromyalgia syndrome. Brain 2013 Jun;136(Pt6):1865-67.

CWP, SFPN and Fibromyalgia II (continued)

- Skin biopsy findings demonstrated that total and regenerating IENFs at the lower leg and upper thigh were reduced in patients with fibromyalgia compared with controls
- A reduction in unmyelinated nerve fiber bundles was seen in patients with fibromyalgia compared with depressed and control subjects
- The authors concluded that the results point towards a neuropathic nature of fibromyalgia.

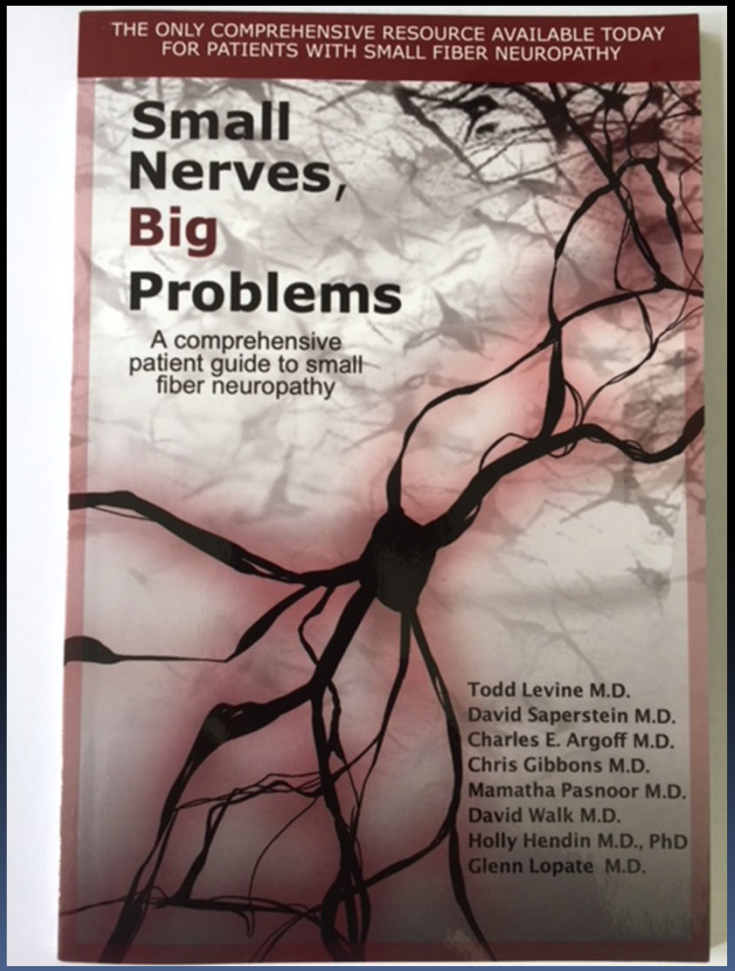
Uceyler N, et al. Small fibre pathology in patients with fibromyalgia syndrome. Brain 2013 Jun;136(Pt6):1865-67.

Complex chronic pelvic pain and SFN

- Retrospective study with objective to demonstrate the prevalence of SFN in patients with refractory chronic pelvic pain
- 25/39 patients (64%) demonstrated skin biopsy findings consistent with SFN
- Co-morbid conditions noted included GERD (46%), migraine (38%), IBS (33%), fibromyalgia (38%), endometriosis (15%), interstitial cystitis (18%), vulvodynia (5%), other chronic pain syndromes (36%)

Chen A, De E, Argoff C. Pain Med 2018 Feb 13

Patient Education



Levine T, et al. Small Nerves Big Problems: A comprehensive guide to small fiber neuropathy. Hilton Press. Chicago, IL (2017)

Summary

- There are many (!) types of polyneuropathy
- Treatment varies depending upon the type
- Multiple medical conditions are associated with SFN including many considered common
- Recognizing SFN and its existence in perhaps more conditions than previously recognized may lead to improved treatment approaches