Neuropathic Pain: Clinical Evaluation and Diagnostic Testing

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Teaching Goals:
To help neurologists order and interpret best tests for diagnosing neuropathic pain conditions

- Imaging
- Neurological tests
  - Electrophysiological tests (electromyography, nerve conductions)
  - Pathology - skin biopsy, nerve biopsy
  - Autonomic function testing (AFT)
  - Quantitative sensory testing
- Testing for underlying causes of neuropathy
  - Commonly available blood and urine tests
  - Genetic testing

Rationale:
Identifying the causes of pain permits offering disease-modifying treatments rather than just pain management

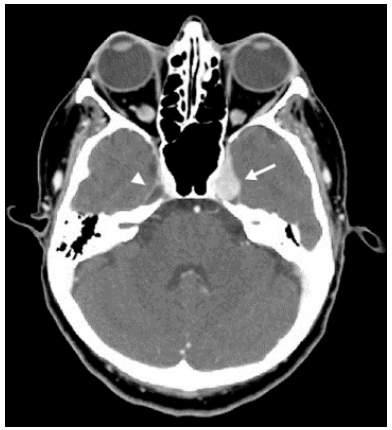
First try to localize the causal lesion

- Pain from the brain (encephalopathy)
- Pain from the V, VII, IX cranial ganglion
- Pain from the spinal cord (myelopathy)
- Pain from the spinal nerve roots (radiculopathy)
- Pain from the spinal ganglia (ganglionopathy/neuronopathy)
- Pain from the brachial or lumbosacral plexus (plexopathy)
- Pain from focal nerve injuries (mononeuropathy)
- Pain from generalized nerve lesions (polyneuropathy)

Than look for etiology
- try not to miss curable conditions

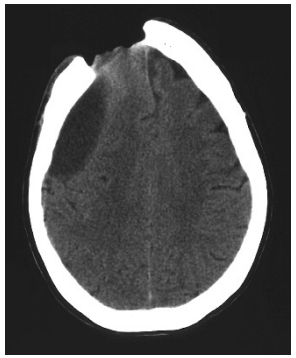
- Encephalopathy - Infarction, infection, trauma
- Cranial ganglion - Trigeminal neuralgia, zoster, multiple sclerosis, compression, inflammation
- Myelopathy - Trauma, compression, syrinx, tumor, infection
- Radiculopathy - Compression, Tarlov cysts
- spinal ganglionopathy/neuronopathy - Zoster, Sjogren's, zoster sine herpete
- Brachial or lumbosacral plexopathy - Diabetes, autoimmune
- Mononeuropathy - Trauma, compression, tumor, infarction
- Polyneuropathy - Multiple causes, mostly treatable

Imaging is key test for detecting brain, spinal cord, cranial ganglia lesions

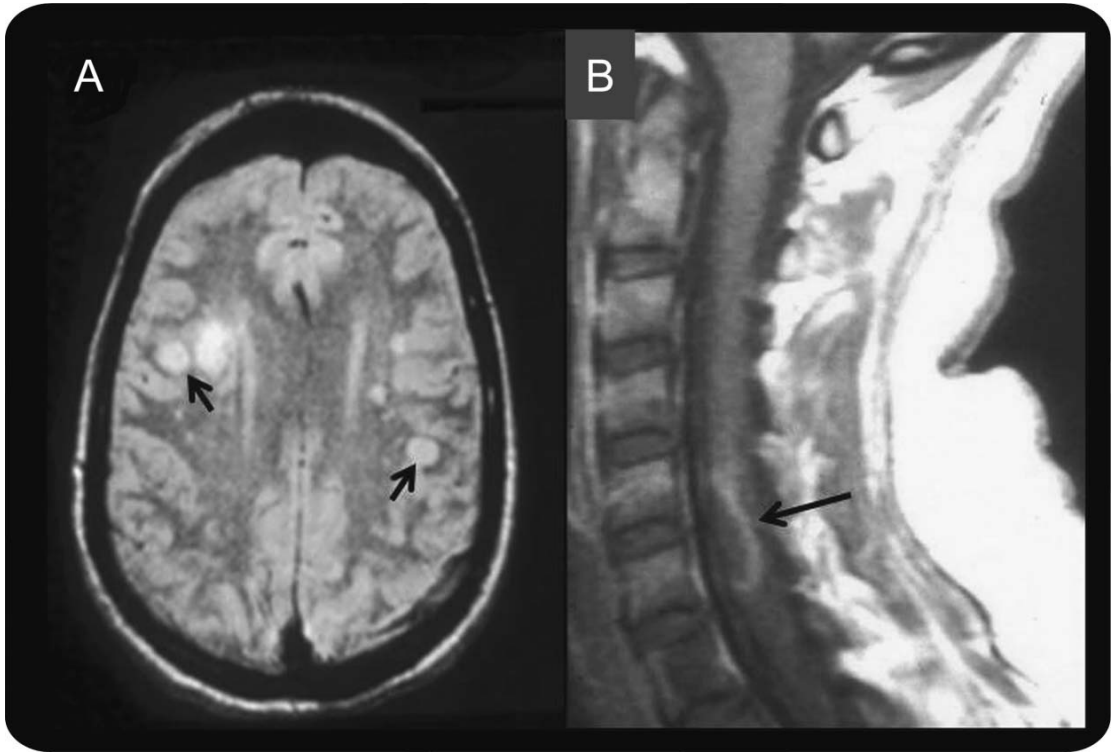


VZV infection of trigeminal ganglion

Hevner R, Vilela M, Rostomily R, et al. An unusual cause of trigeminal-distribution pain and tumour. Lancet Neurol. 2003; 2:567–571.



Oaklander et al., *PAIN*, 2002

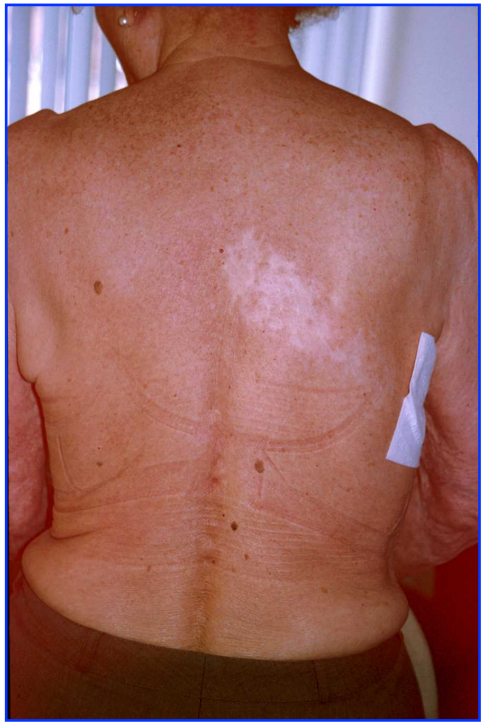


VZV infection of brain, spinal cord

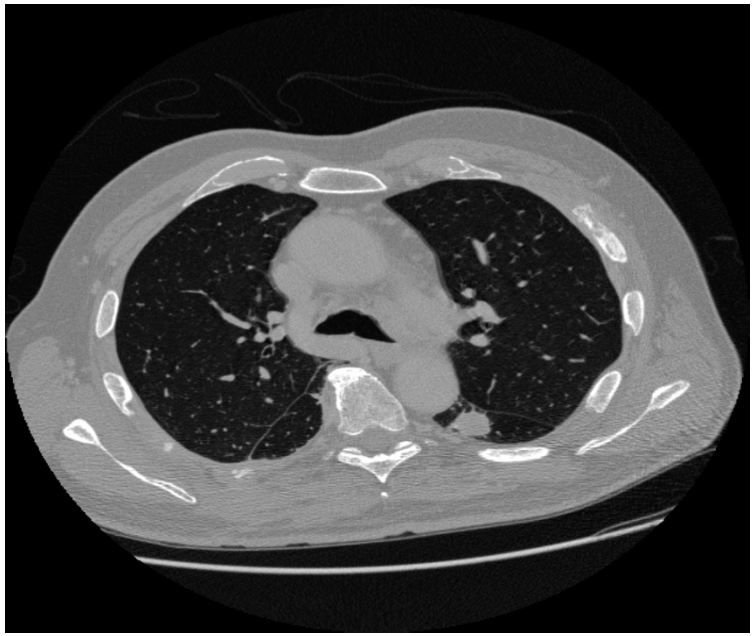
Nagel & Gilden, Neurology Clinical Practice, 2013

- Lumbar puncture can aid diagnosis of CNS infection
- For VZV, look for VZV antibodies (IgM, IgG) in CSF as well, may be more sensitive than VZV DNA
- Treat with IV acyclovir 10-15 mg/kg TID for 10-14 days

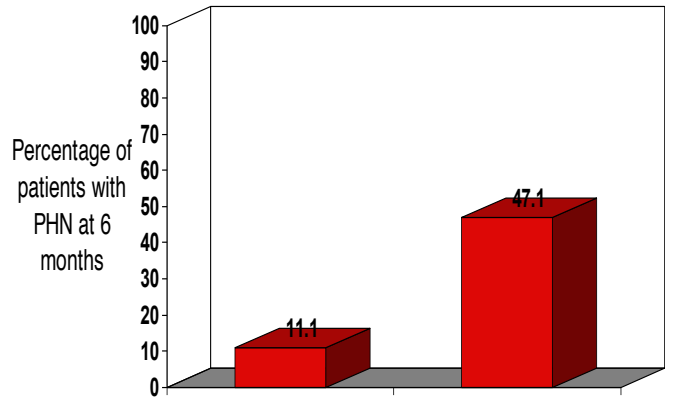
Diagnosing radiculopathy



- Diagnosis is obvious if history of zoster in same dermatome or visible zoster scars
- Diagnosis is challenging if:
  - rash not noticed or appreciated (subclinical)
  - zoster sine herpete (no rash)
- **Must** image such patients to rule out other causes of neuralgia
- Diabetes causes painful usually truncal radiculopathy/plexopathy
- Many treatable causes
  - infections, autoimmune, cancer
- Taking tricyclics during the months after shingles halves the risk of PHN lasting 6 months



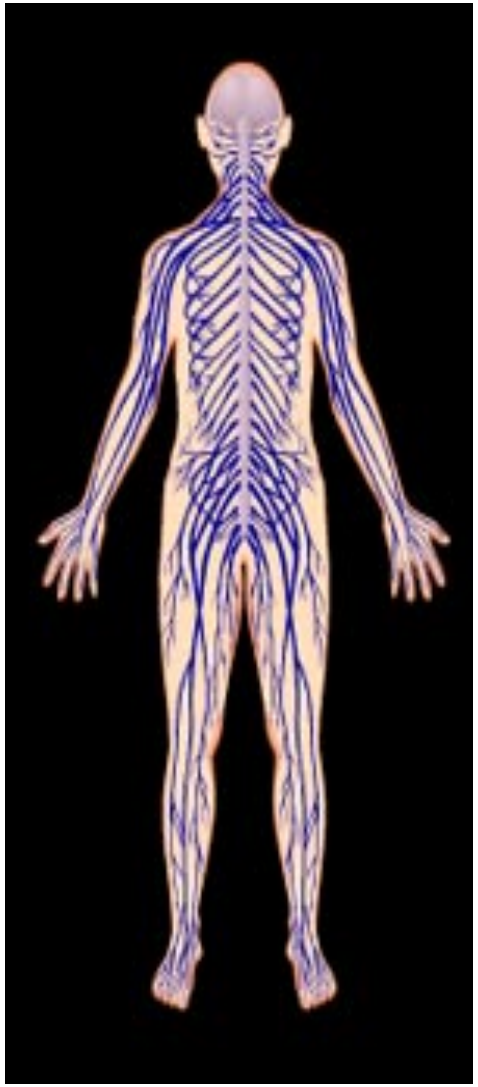
Chest CT from patient with self diagnosis of PHN after zoster sine herpete



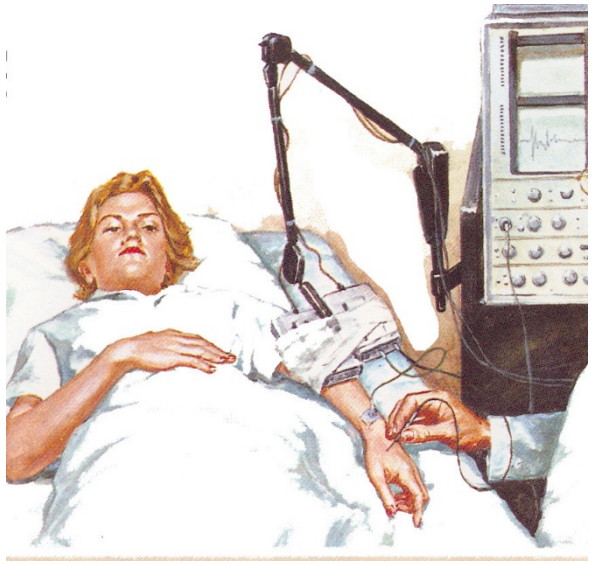
Dworkin RH. Prevention of postherpetic neuralgia. *Lancet*, 1999 (data reanalyzed from Bowsher, *J Pain and Symptom Management*, 1997)

Polyneuropathy is a common cause of widespread neuropathic pain

- Peripheral nerves contain different kinds of neurons (nerve fibers, axons) that connect to specific types of cells in specific locations (motor, sensory, autonomic)
- “Polyneuropathy” means generalized nerve damage, but symptoms usually start in the feet where the longest axons end
- Best known in older adults from medical conditions (e.g. diabetes) or toxic exposure (e.g. chemotherapy)
- “Large-fiber” polyneuropathy refers to diseases of myelinated fibers
- “Small-fiber” polyneuropathy refers to disease of unmyelinated and thinly myelinated fibers



Considerable knowledge about large-fiber polyneuropathies



On neuro exam

- Muscle weakness, atrophy, fasciculations
- Reflexes are reduced distally
- Reduced large-fiber sensory modalities (vibration, joint position, touch)

LFPN diagnosis is confirmed with EMG/NCS

- EMG studies motor axons and muscle
- NCS studies large myelinated sensory and motor axons and myelin

Some LFPN are demyelinating:

Guillain-Barré, CIDP

Some LFPN are axonal:

Diabetes, ALS, MGUS

~ 80% of peripheral axons are "small fibers"

But 95% of publications concern large-fiber neuropathy

Small-fibers have multiple functions

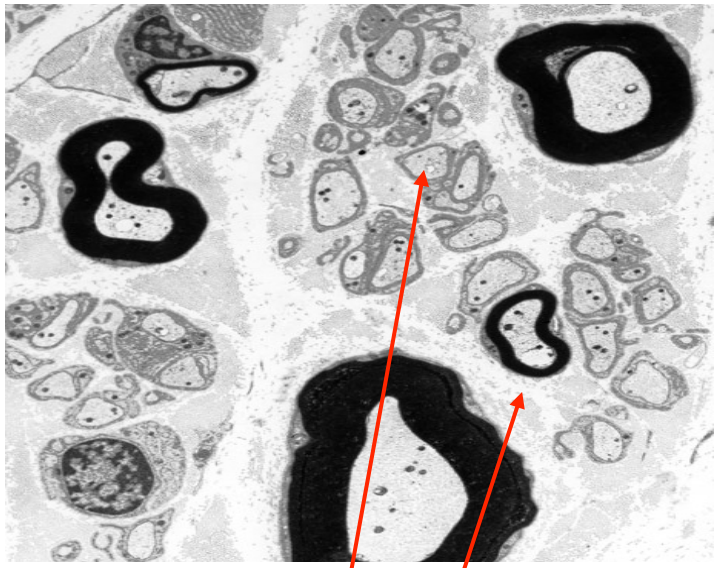
- They mediate various painful sensations
- They mediate post-ganglionic sympathetic functions
- They mediate responses to injury and illness
- They mediate "trophic" cellular responses

Small-fibers innervate multiple cells and organs

- They innervate blood vessels, sweat glands, periosteum and bone
- They innervate bone marrow

SFPN causes many non-neurological symptoms

- Each medical specialty pays attention mostly to symptoms in their own field



"Small-fibers" are the most common type of PNS axon

- C-fibers
- A-delta fibers
- autonomic axons

Small-fiber polyneuropathy is hard to diagnose

Limitations of neuro exam

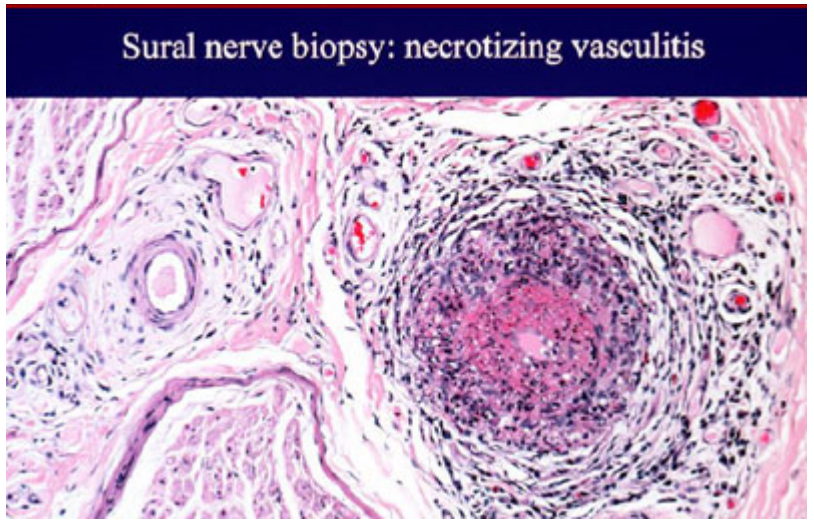
- No muscle weakness, atrophy, fasciculations
- Reflexes are preserved
- Partial injuries can cause chronic pain without sensory loss

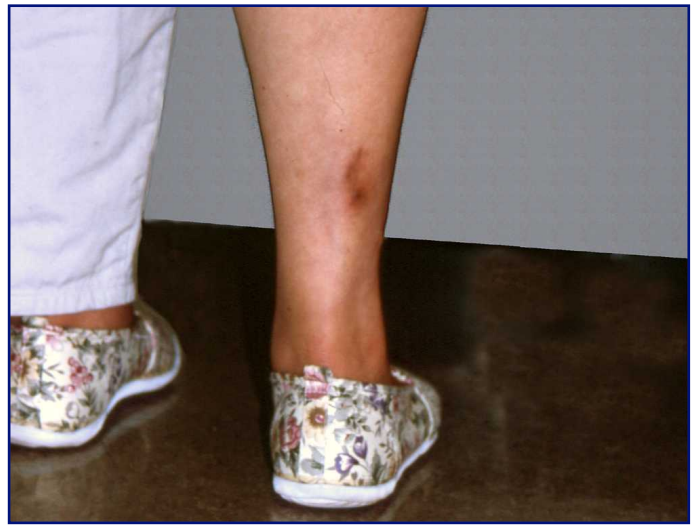
Sensory nerve biopsy was common in the past

Most often performed on sural nerve
Less sensitive than skin biopsy for detecting SFPN
Leaves numb area, can cause neuralgia
Can't be repeated to monitor treatment
Most useful for inflammation, infection, tumor

Limitations of standard nerve test (EMG/NCS)

- EMG only studies motor axons
- NCS only studies large myelinated axons





Quantitative Sensory Testing (QST)

- Not an objective test, relies on subject impression, can be fooled
  - R. Freeman, K. P. Chase, and M. R. Risk. Quantitative sensory testing cannot differentiate simulated sensory loss from sensory neuropathy. *Neurology 60 (3): 465-470, 2003.*
- Results not actionable, not specific for any one diagnosis
- Not currently reimbursed in the U.S.
- Very useful for research

M. M. Backonja, N. Attal, R. Baron, D. Bouhassira, M. Drangholt, P. J. Dyck, R. R. Edwards, R. Freeman, R. Gracely, M. H. Haanpaa, P. Hansson, S. M. Hatem, E. K. Krumova, T. S. Jensen, C. Maier, G. Mick, A. S. Rice, R. Rolke, R. D. Treede, J. Serra, T. Toelle, V. Tugnoli, D. Walk, M. S. Walalce, M. Ware, D. Yarnitsky, and D. Ziegler. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain 154 (9):1807-1819, 2013.*

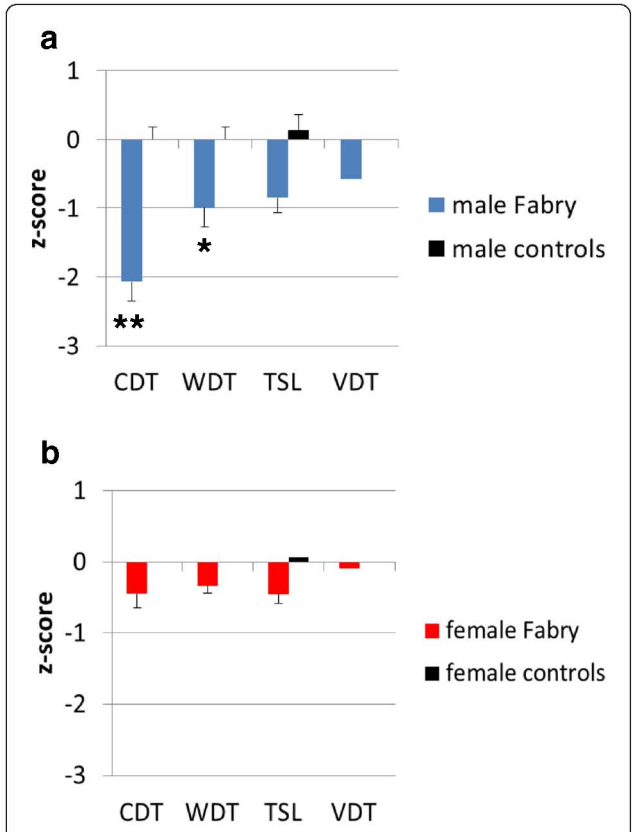
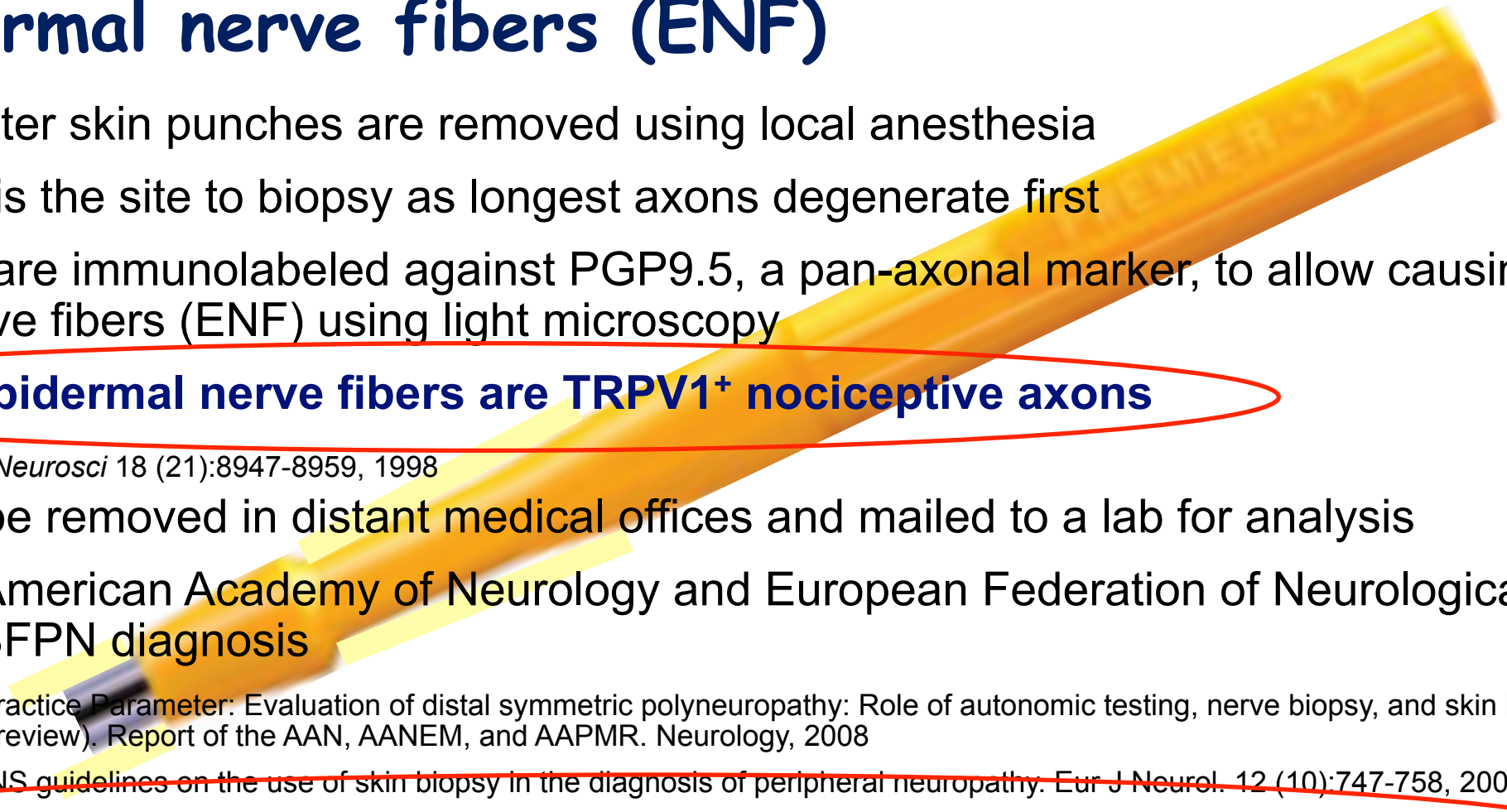


Figure 1 Sensory profile of Fabry patients. The bar graphs show the z-score sensory profiles of quantitative sensory testing (QST) at the left dorsal foot in Fabry patients compared to healthy controls. Healthy controls are represented by the black zero line. Z-scores < 0 display loss of function, z-scores >0 show gain of function. **a**) Male Fabry patients have elevated detection thresholds for cold and warm (CDT, WDT), while the thermal sensory limen (TSL) for changing temperatures and the vibration detection threshold (VDT) was not different from controls. **b**) Female Fabry patients do not differ from female controls except for slightly elevated WDT. *$p < 0.05$, **$p < 0.01$.

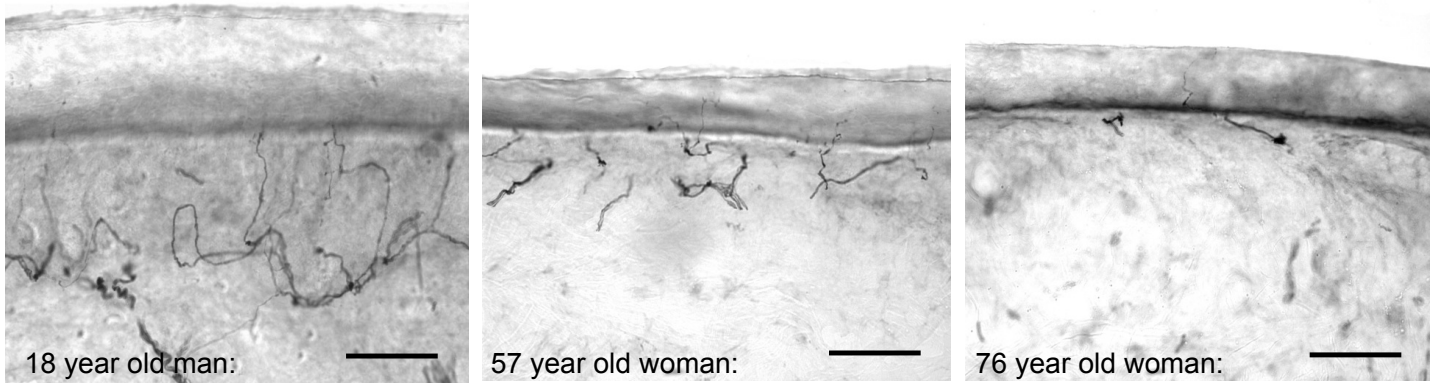
Üçeyler *et al. BMC Neurology* 2013 **13**:47
doi:10.1186/1471-2377-13-4

Objective diagnosis of SFPN is made by counting epidermal nerve fibers (ENF)



- 2-3 mm diameter skin punches are removed using local anesthesia
- The distal leg is the site to biopsy as longest axons degenerate first
- Skin biopsies are immunolabeled against PGP9.5, a pan-axonal marker, to allow causing of epidermal nerve fibers (ENF) using light microscopy
- **Virtually all epidermal nerve fibers are TRPV1^{+} nociceptive axons**
  - Simone, *et al. J Neurosci* 18 (21):8947-8959, 1998
- Biopsies can be removed in distant medical offices and mailed to a lab for analysis
- Endorsed by American Academy of Neurology and European Federation of Neurological Societies for SFPN diagnosis
  - England, et al. Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the AAN, AANEM, and AAPMR. Neurology, 2008
  - Lauria, et al. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. Eur J Neurol. 12 (10):747-758, 2005.
- **SFPN is diagnosed if patient's ENF density is below 5th centile of predicted value**
  - Predicted value is calculated from biopsying many normal volunteers (population sample)
  - Accurate diagnosis of SFPN depends on having accurate norms

Accurate normative data provide the basis of skin-biopsy testing for SFPN



18 year old man:
675 ENF/mm2 skin surface area

57 year old woman:
240 ENF/mm2 skin surface area

76 year old woman:
125 ENF/mm2 skin surface area

Bar represents 50 microns

PGP9.5 immunolabeled vertical skin sections from normal Caucasian subjects of different ages

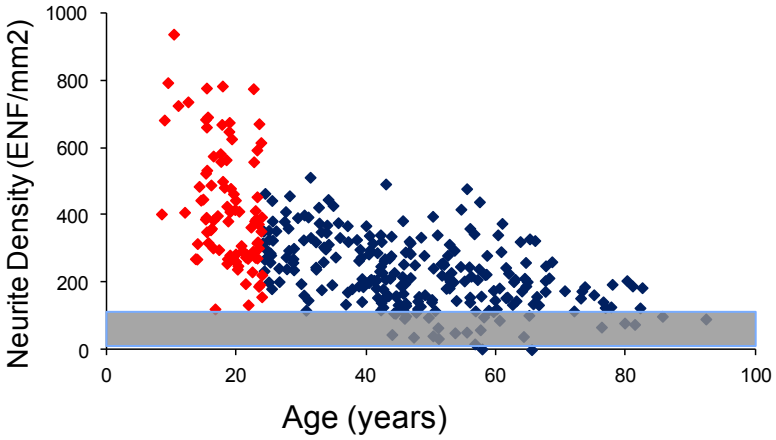
The teenager (left) has much more dermal and epidermal innervation than the middle-aged and elderly adults

Results from normal subjects show that skin innervation regresses with age

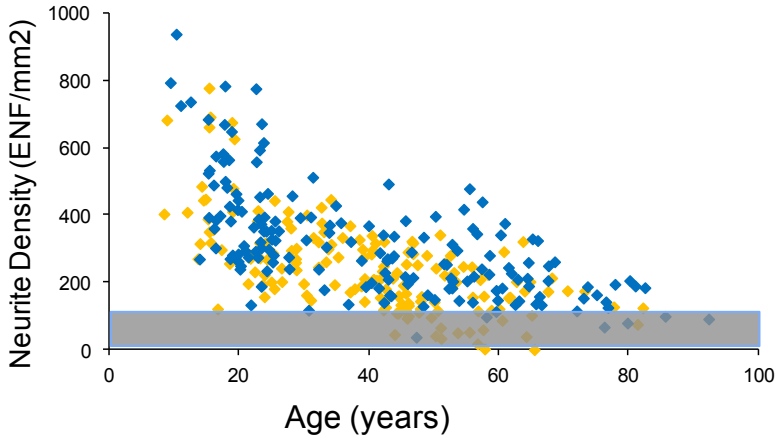
Normative values used for clinical diagnosis around the world need to be corrected for age, as we will propose

M. Klein et al; presented at the 135th Annual Meeting of the American Neurological Association

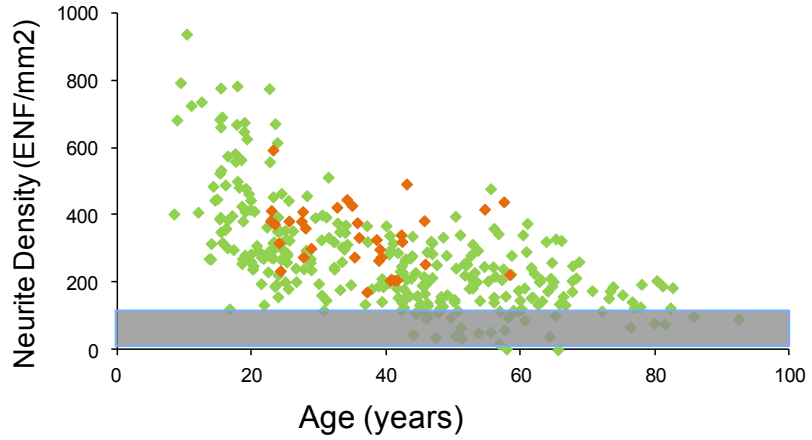
The MGH normative series (n=373) shows that better norms improve accuracy of skin-biopsy diagnosis of SFPN



There are age differences



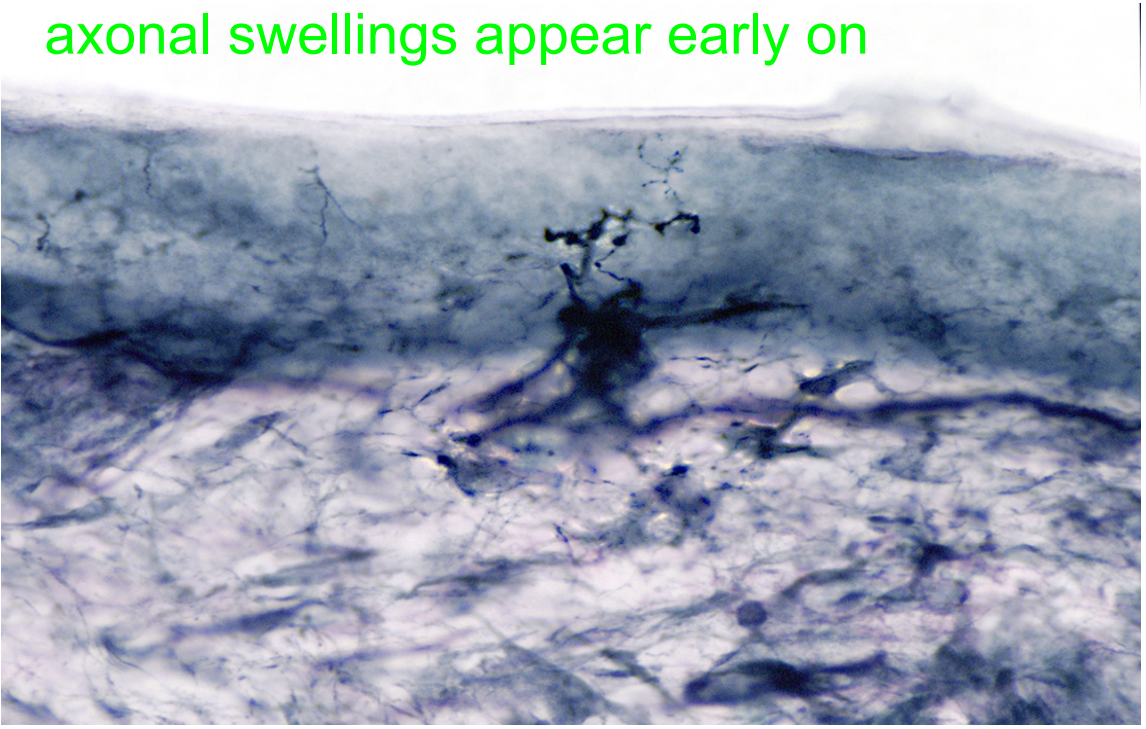
There are sex differences



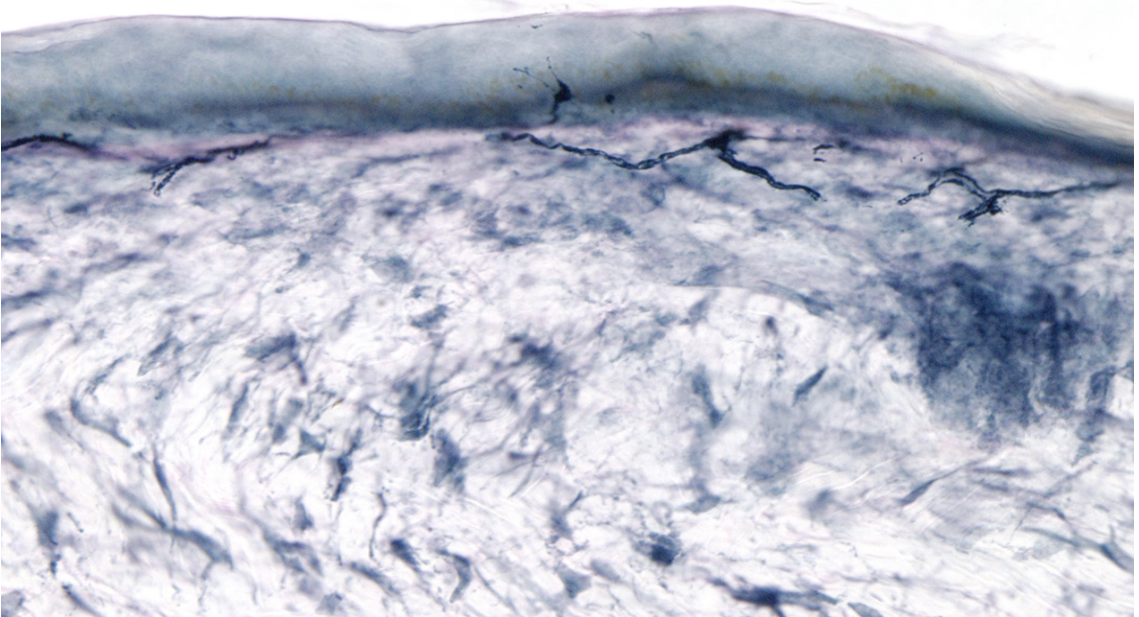
There are ethnic differences

- Most diagnostic laboratories use a single threshold "cutoff" (76 ENF/mm^2) to assess normality of submitted biopsies.
- We developed a multivariate regression to calculate an age-, sex-, race-specific predicted norms for each individual biopsy.
- Among all 105 biopsies from patients ≤ age 40 that our lab diagnosed with SFPN in 2012-2013, applying the most common commercial threshold would have only detected SFPN in 26 (***75% false negative diagnosis***).

axonal swellings appear early on

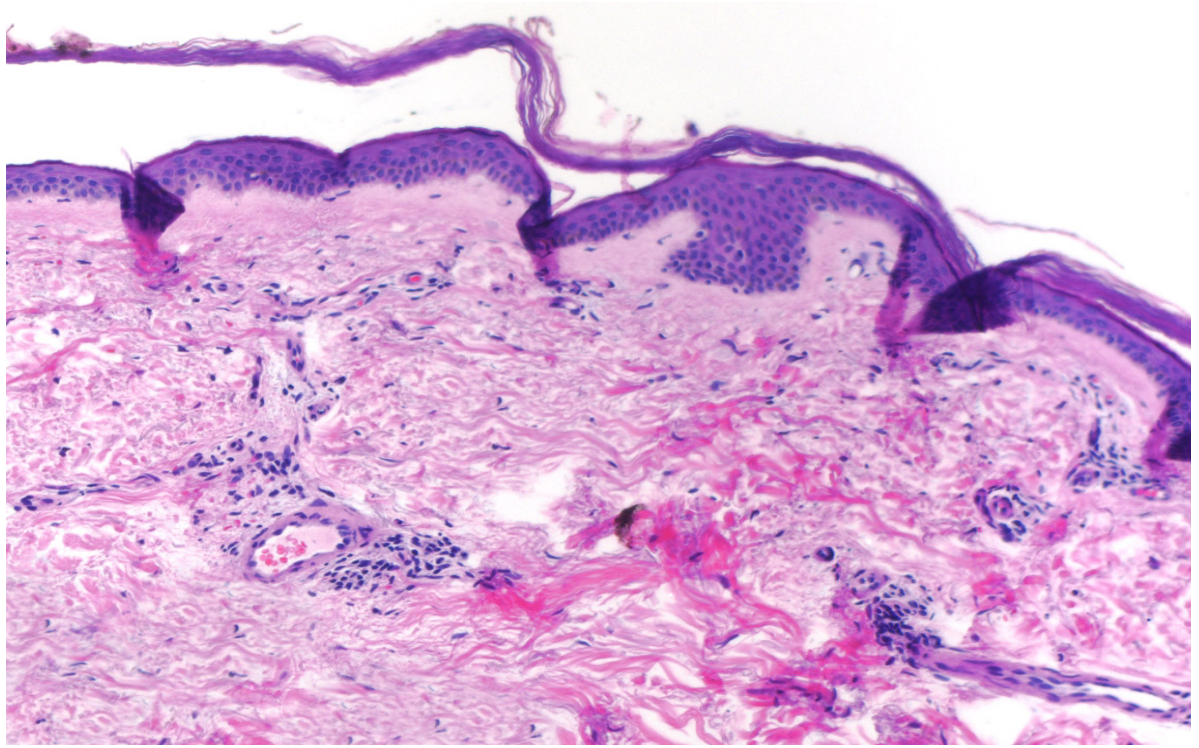


epidermal denervation appears later



Dermal morphology is important as well

some patients have perivascular infiltrates



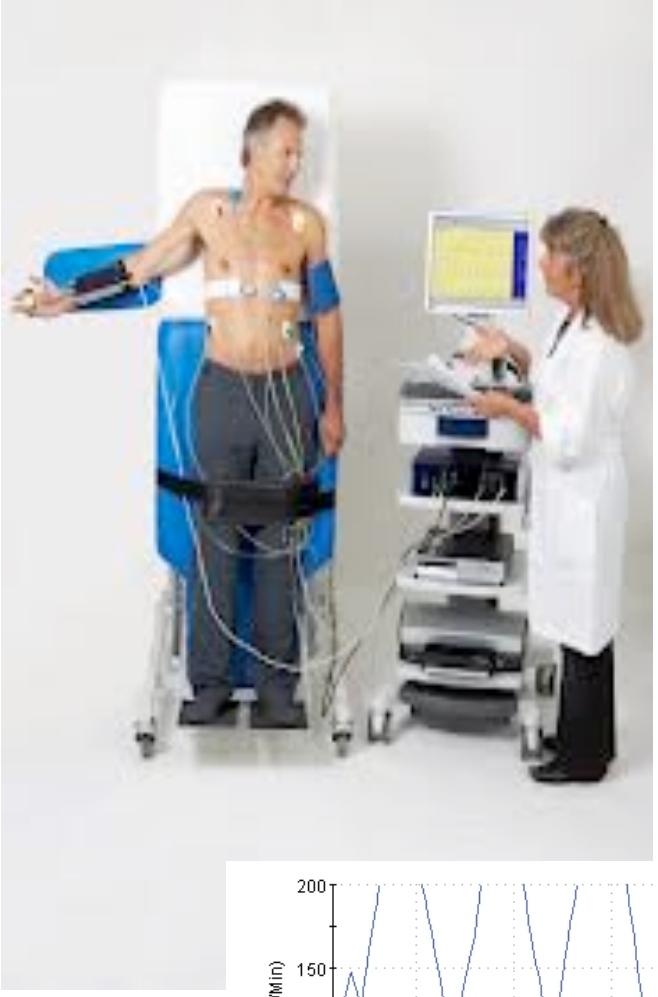
Amato & Oaklander. Case records of the MGH. A 76-year-old woman with pain and numbness in the legs and feet NEJM, 2004

Physiological diagnostic tests for SFPN

The American Academy of Neurology also recommends autonomic function testing (AFT) for diagnosis of SFPN

- Physiologic changes happen earlier than pathologic changes
- Noninvasive
- More easily repeated

J. D. England, G. S. Gronseth, G. Franklin, G. T. Carter, L. J. Kinsella, J. A. Cohen, A. K. Asbury, K. Szigeti, J. R. Lupski, N. Latov, R. A. Lewis, P. A. Low, M. A. Fisher, D. N. Herrmann, J. F. Howard, Jr., G. Lauria, R. G. Miller, M. Polydefkis, and A. J. Sumner. Practice Parameter: Evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (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* 72:177-184, 2009.

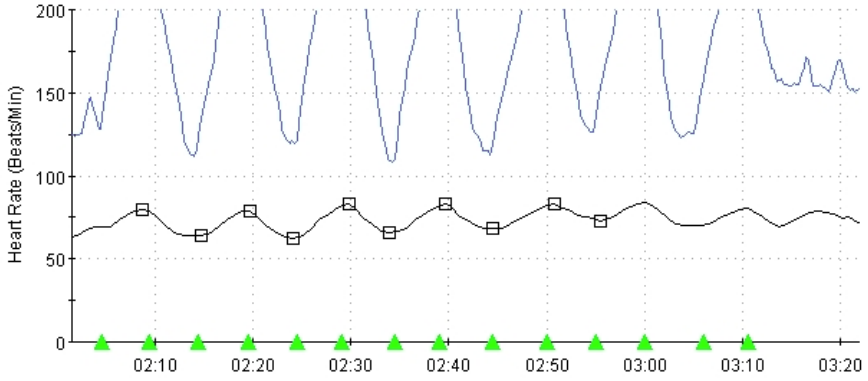


Autonomic Function Testing (AFT) is endorsed for SFPN diagnosis

- Physiologic changes happen earlier than pathologic changes
- Noninvasive and more easily repeated

Autonomic functions are controlled by small fibers

- Heart-rate response to deep breathing
- Heart-rate and blood-pressure responses during Valsalva maneuver
- Heart-rate and blood-pressure responses to tilt
- Sudomotor response (sweat production)



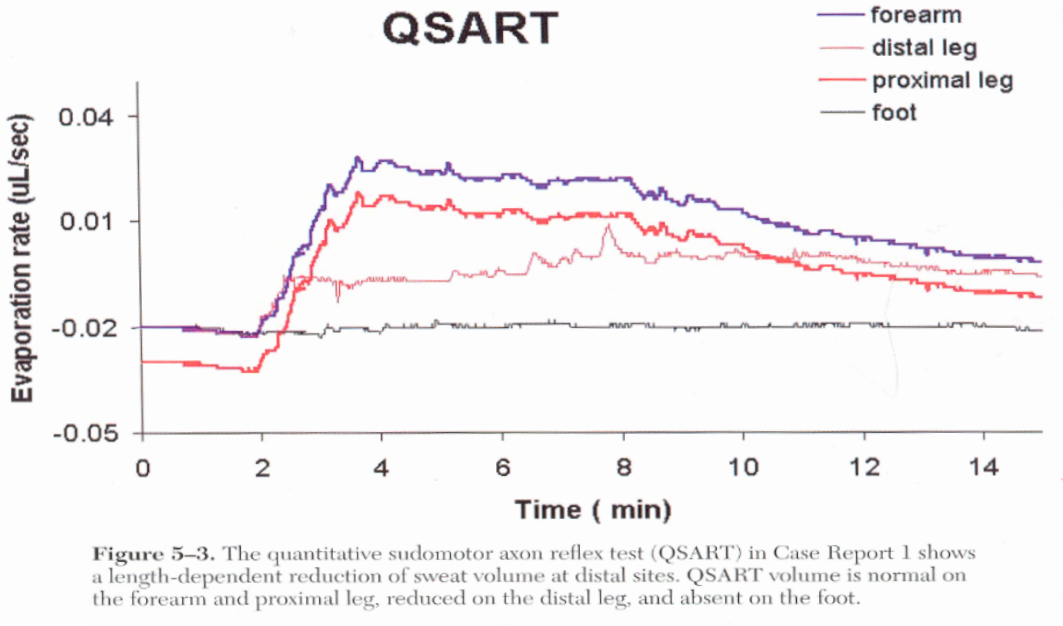


Figure 5–3. The quantitative sudomotor axon reflex test (QSART) in Case Report 1 shows a length-dependent reduction of sweat volume at distal sites. QSART volume is normal on the forearm and proximal leg, reduced on the distal leg, and absent on the foot.

J. D. England, et al. Practice Parameter: Evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (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* 72:177-184, 2009.

Tests for treatable causes of small-fiber polyneuropathy

Patient name
Medical record number
Date of birth

Date: _____/_____/_____

ordered today	not yet tested	abnormal value	normal value	BLOOD TESTS TO CONSIDER FOR ADULTS
☐	☐	☐	☐	Complete blood count (if low, consider B12 or copper deficiency, lead/arsenic toxicity)
☐	☐	☐	☐	Chemistries (if high glucose test for DM; if renal dysfunction consider Fabry, mercury toxicity)
☐	☐	☐	☐	AST, ALT (liver function; if abnormal consider hepatitis or alcohol)
☐	☐	☐	☐	Hemoglobin A1c (if elevated strongly consider testing for diabetes)
☐	☐	☐	☐	TSH thyroid screening
☐	☐	☐	☐	Vitamin B12 levels (if 200-500pg/dl consider testing for methylmalonic acid)
☐	☐	☐	☐	ESR (sedimentation rate; if elevated, consider inflammatory/dysimmune conditions)
☐	☐	☐	☐	ANA (antinuclear antibodies; higher titers suggest lupus or dysimmune conditions)
☐	☐	☐	☐	Complement components C3 and C4 (if low, consider dysimmune conditions)
☐	☐	☐	☐	Anti-Ro (SS-A) and anti-La (SS-B) (if present, consider Sjögren's disease)
☐	☐	☐	☐	CRP (C-reactive protein; if elevated, consider inflammatory/dysimmune conditions)
☐	☐	☐	☐	Hepatitis C serology (if abnormal consider testing for cryoglobulins)
☐	☐	☐	☐	Lyme antibodies by Western blot (for inhabitant or visitor to endemic area)
☐	☐	☐	☐	SPEP/IFIX (immunofixation tests for lymphoproliferative disorders)
☐	☐	☐	☐	Free κ/λ light chains (tests for less common lymphoproliferative disorders)
☐	☐	☐	☐	IgA anti-TTG (transglutaminase antibodies; if present consider celiac sprue)
				TESTS TO CONSIDER IN SPECIFIC POPULATIONS
☐	☐	☐	☐	2 hour, 75 g fasting glucose-tolerance test (strongly consider for all at risk for DM)
☐	☐	☐	☐	HIV (CDC recommends everyone ages 13-64 be tested ≥ once, high-risk more often)
☐	☐	☐	☐	Methylmalonic acid (consider if vitamin B12 level less than 500 pg/dL)
☐	☐	☐	☐	Thiamine (if low, consider vitamin B1 deficiency)
☐	☐	☐	☐	Pyridoxine (if elevated, consider vitamin B6 neurotoxicity)
☐	☐	☐	☐	Anti-ds DNA, anti-Smith (consider if ANA present)
☐	☐	☐	☐	Cryoglobulins, cryofibrinogens, viscosity (consider for myeloma, hep C, RA, SLE)
☐	☐	☐	☐	Fasting serum triglycerides (can worsen diabetic polyneuropathy)
☐	☐	☐	☐	Urine protein electrophoresis to identify Bence Jones paraproteins
☐	☐	☐	☐	24 hour urine for arsenic, lead, mercury, cadmium (for artists, welders, miners)
☐	☐	☐	☐	ACE (angiotensin converting enzyme; for sarcoidosis in patients with lung symptoms)
☐	☐	☐	☐	Phenotype-guided genetic sequencing esp. if family history (e.g., HSAN-1, SCN9A)
☐	☐	☐	☐	Abdominal fat-pad biopsy for amyloid
☐	☐	☐	☐	OTHER TEST PERFORMED_____

Check medications e.g., therapy for cancer or HIV, statins, colchicine, isoniazid, dapsone, hydralazine, lithium, phenytoin, vitamin B6, disulfiram, amiodarone, procainamide, perhexiline, streptokinase, nitrous oxide, metronidazole, nitrofurantoin, gold, thalidomide, TNF-antagonists, antimicrobials (chloramphenicol, fluoroquinolones, metronidazole, nitrofurantoin), fluoroquinolones, history of GI surgery, malabsorption, alcoholism, exposure to inorganic arsenic, thallium, mercury, industrial toxins, organophosphate insecticides.

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Author: A.L. Oaklander MD PhD 07/21/15

Once SFPN diagnosis is established, test for treatable causes

- Consider exposure to industrial toxins
  - Heavy metal toxicity requires 24-hour urine sample
- Consider exposure to toxic medications
- Treating medical causes is more effective than managing symptoms (eg pain meds)

Consider genetic testing in select patients with no evidence of cause from history or blood testing

Erythromelalgia and Reynaud's feature microvascular dysregulation, usually in the distal limbs

S. W. Mitchell. On a rare vaso-motor neurosis of the extremities, and on the maladies with which it may be confounded. *Am J Med Sci*, 1878

Both are strongly linked to SFPN

C. B. Bunker, et al. Deficiency of calcitonin gene-related peptide in Raynaud's phenomenon. *Lancet*, 1990

M. D. Davis, et al. Erythromelalgia: vasculopathy, neuropathy, or both? A prospective study of vascular and neurophysiologic studies in erythromelalgia. *Arch.Dermatol.*, 2003

A.L. Oaklander. Erythromelalgia: small-fiber neuropathy by any other name? *Pediatrics*, 2005.

Erythromelalgia is well-recognized in children; early-onset forms are linked to mutations in NaV1.7, 1.8, 1.9 sodium channels

NaV polymorphisms change electrophysiological function of small fibers, can make them hyperexcitable and/or more likely to degenerate

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