Small-fiber polyneuropathy: A potential contributor to GW Illness?

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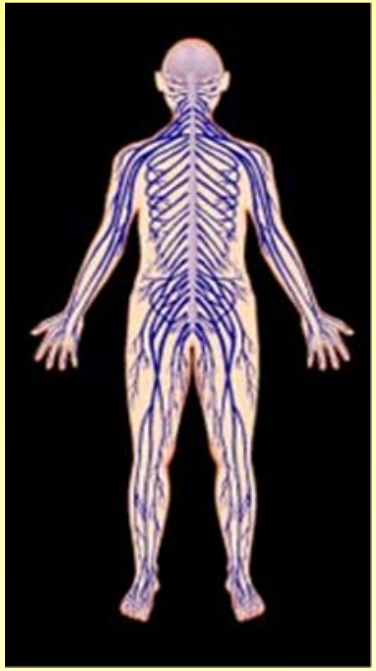
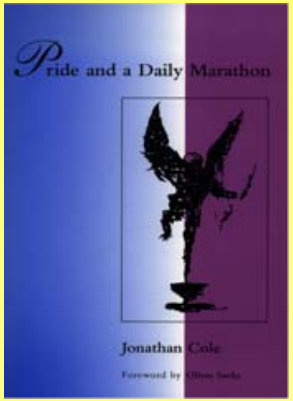
What is polyneuropathy?

- The peripheral nerves connect the central nervous system (brain and spinal cord) to the rest of the body.
- Nerves are cables made up of different kinds of wires (peripheral neurons) that connect very specifically to different cells in specific locations (motor, sensory, autonomic)
- Polyneuropathy means body-wide nerve damage, usually from a medical condition (e.g. diabetes) or toxic exposure (e.g. chemotherapy)
- Polyneuropathy symptoms often start in the feet at the ends of the longest axons (nerve fibers)



The symptoms of polyneuropathy depend on which type of axon (nerve fiber) is damaged



A healthy 19-year-old had sudden-onset, chronic, near-total immune-mediated large-fiber sensory neuronopathy.

He lost all touch and proprioception; pain and temperature were preserved.

He had no pain, only sensory hallucinations of “tingling”.

In diabetic polyneuropathy, the presence and severity of pain:

- Is independent of severity of demyelination
  Woltman et al, 1929
- Is independent of severity of large-fiber axonal degeneration
  Britland et al, 1990
- Correlates with severity of small unmyelinated fiber axonal degeneration
  Dyck et al, 1976

"Small-fibers" mediate pain

Small-diameter axons (small-fibers)

C-fibers

About 1 µm diameter, unmyelinated, conduct very slowly, convey various pain modalities

A-delta fibers

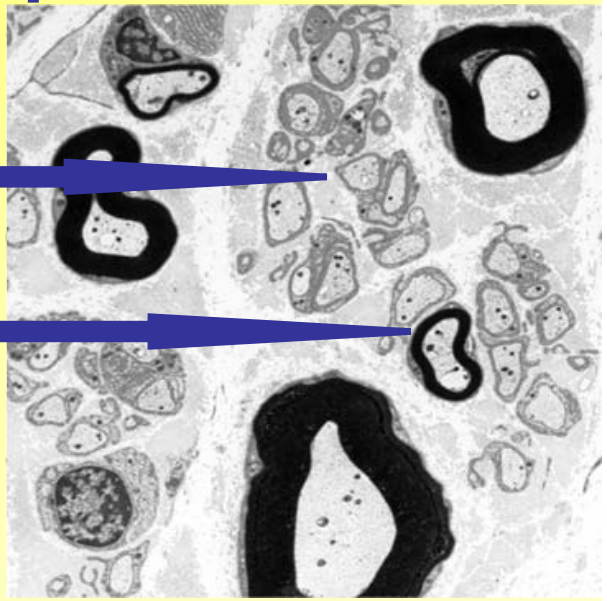
About 5 µm diameter, thinly myelinated, conduct slowly, localize pain

Post-ganglionic sympathetic axons

not morphologically distinguishable from C fibers

Not every pain fiber is small

Djouhri & Lawson, Abeta-fiber nociceptive primary afferent neurons: a review of incidence and properties in relation to other afferent A-fiber neurons in mammals. Brain Res Rev. 2004.



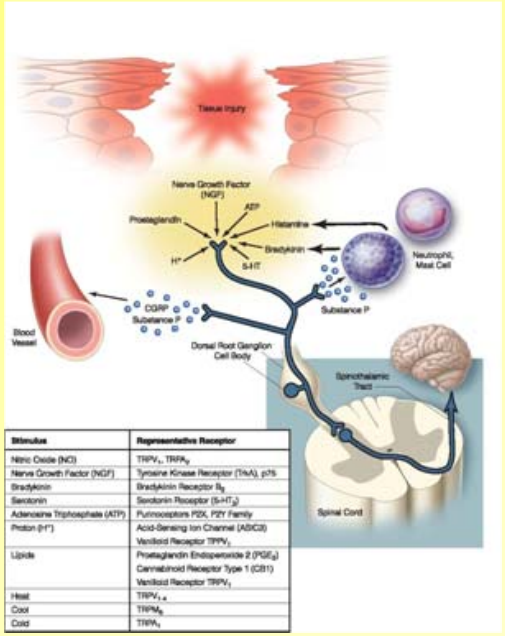
Cross-section of human sural nerve (EM)

What is neuropathic pain?

- Acute pain means pain caused by injury and illness
- It is a good thing, it makes us stop and seek help when injured or ill

- Chronic pain is pain lasting longer than 3 months (research definition).
- Most often it is caused by a known chronic disease
- It is severely disabling

- "Mystery pain" is chronic pain of unidentified cause.
- Examples include fibromyalgia, TMJ, complex regional pain disorder
- The cause of mystery pain is often neurological (neuropathic)



shingles, so get the vaccine already!

trigeminal neuralgia

amputation

cancer, and its treatments

HIV/AIDS and medicines to treat it

injuries and surgery

neurotoxins

diabetes, even pre-diabetes

Some symptoms of Gulf War Illness are consistent with small-fiber polyneuropathy (SFPN)

- Unexplained chronic pain – muscle, joint, headaches
- Skin complaints (rashes, hair loss)
- Cardiovascular symptoms (dizziness, palpitations, fainting)
- Gastrointestinal symptoms
- Poor sleep and chronic fatigue

Potential causes of polyneuropathy in GWI include toxic exposure (eg insecticides, chemical warfare agents), immunization, infectious disease, trauma

The previous studies of polyneuropathy in GWI have not tested for SFPN

- Jamal, et al. The "Gulf War syndrome". Is there evidence of dysfunction in the nervous system? *J Neurol Neurosurg Psychiatry* 60 (4):449-451, 1996.
- Haley, et al Evaluation of neurologic function in Gulf War veterans. A blinded case-control study. *JAMA* 277, 1997.
- Amato, et al. Evaluation of neuromuscular symptoms in veterans of the Persian Gulf War. *Neurology*, 1997.
- Rivera-Zayas, et al. Evaluation of Persian Gulf veterans with symptoms of peripheral neuropathy. *Mil.Med* 166 (5):449-451, 2001.
- Davis, et al. Clinical and laboratory assessment of distal peripheral nerves in Gulf War veterans and spouses. *Neurology*, 2004.
- Rose, et al. Evaluation of neuromuscular symptoms in UK Gulf War veterans: a controlled study. *Neurology* 63 (9):1681-1687, 2004.
- Joseph, et al. Decreased prevalence of peripheral nerve pathology by electrodiagnostic testing in Gulf War veterans. *Mil.Med*, 2004.

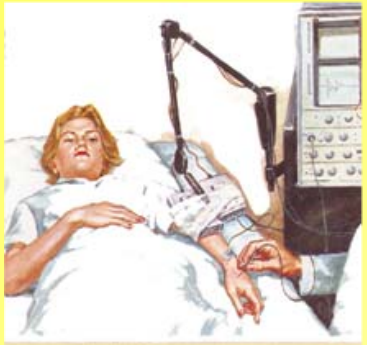
There is preliminary evidence of autonomic abnormalities in GWI that is consistent with SFPN

- 6 men and 5 women with GWI compared to 18 male and 18 female healthy controls for analysis of heart-rate variability. In women but not men with GWI, heart-rate variability was significantly lower than in controls.
  - Sex effects on heart rate variability in fibromyalgia and Gulf War illness. Stein, Domitrovich, Ambrose, Lyden, Fine, Gracely, Clauw. *Arthritis Rheum*, 2004.

- Tilt-table testing on 14 Gulf War veterans with chronic fatigue and 27 controls. More fatigued Gulf War veterans had neurally mediated hypotension than unfatigued control subjects, similar to observations in CFS.
  - Davis, Kator, Wonnett, Pappas, Sall. Neurally mediated hypotension in fatigued Gulf War veterans: a preliminary report. *Am J Med Sci*, 2000.

- 22 ill Gulf War veterans compared to 19 control veterans (heart rate variability, blood pressure, Valsalva ratio, sympathetic skin response, sweat imprint testing) found only blunted nocturnal heart-rate dip
  - Haley, et al. Blunted circadian variation in autonomic regulation of sinus node function in veterans with Gulf War syndrome. *Am J Med*, 2004.

Small-fibers are very hard to monitor



Limitations of neuro exam

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

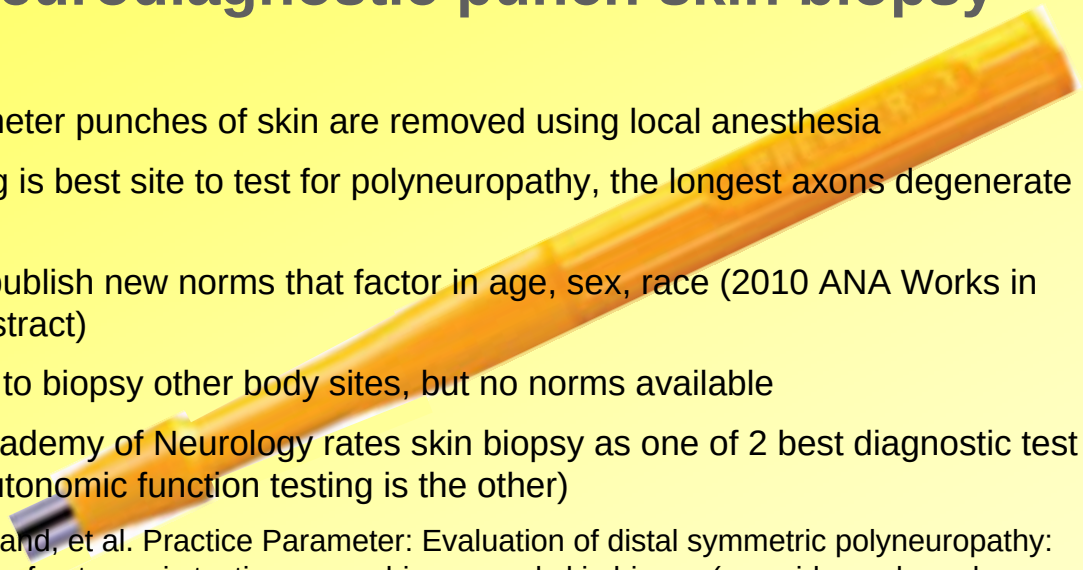
Limitations of standard nerve test (EMG/NCS)

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

Surgical nerve biopsy common in the past

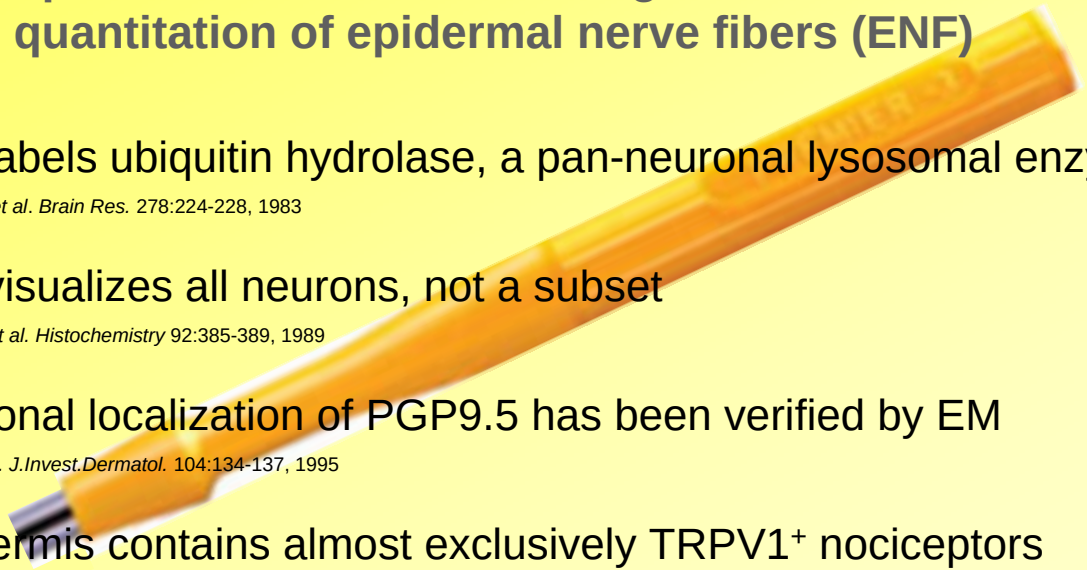
- Leaves numb area, can cause neuralgia
- Can't be repeated

Neurodiagnostic punch skin biopsy



- 2-3 mm diameter punches of skin are removed using local anesthesia
- The distal leg is best site to test for polyneuropathy, the longest axons degenerate first
- Our lab will publish new norms that factor in age, sex, race (2010 ANA Works in Progress abstract)
- It is possible to biopsy other body sites, but no norms available
- American Academy of Neurology rates skin biopsy as one of 2 best diagnostic test for SFPN (autonomic function testing is the other)
    - 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

Skin biopsies are immunolabeled against PGP9.5 to allow quantitation of epidermal nerve fibers (ENF)

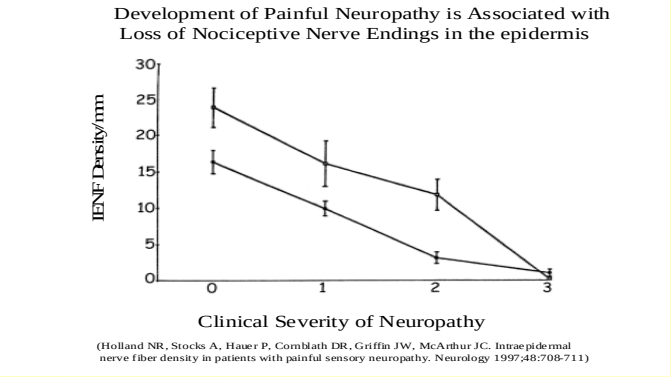


- PGP9.5 labels ubiquitin hydrolase, a pan-neuronal lysosomal enzyme
  - Thompson, *et al*. *Brain Res.* 278:224-228, 1983
- PGP9.5 visualizes all neurons, not a subset
  - Dalsgaard, *et al. Histochemistry* 92:385-389, 1989
- The neuronal localization of PGP9.5 has been verified by EM
  - Hilliges, *et al. J.Invest.Dermatol.* 104:134-137, 1995
- The epidermis contains almost exclusively TRPV1^{+} nociceptors
  - Simone, *et al. J Neurosci* 18 (21):8947-8959, 1998
- ENF can be quantitated using LM
  - McCarthy, *et al. Neurology* 45:1848-1855, 1995

Skin biopsies are used clinically to diagnose small-fiber polyneuropathy

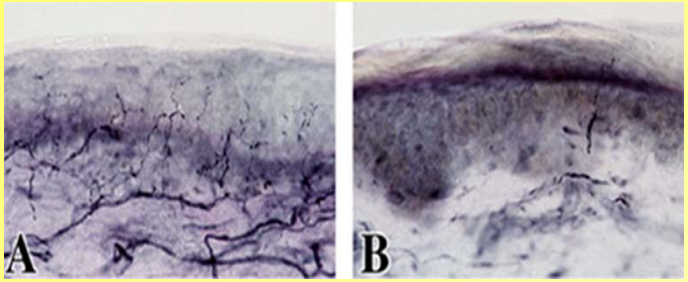
- "essentially no remaining fibers innervating the epidermis" in the legs of patients with Fabry disease
  - Scott *et al*. Quantitative analysis of epidermal innervation in Fabry disease. *Neurology*, 1999

- Various painful sensory neuropathies
  - diabetes
  - HIV
  - idiopathic

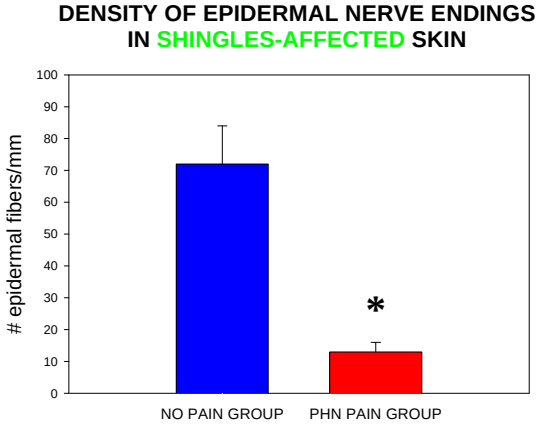


Skin biopsies provide a powerful research tool to study pain

After shingles, patients with post-herpetic neuralgia (PHN) have fewer nerve endings left than patients without PHN

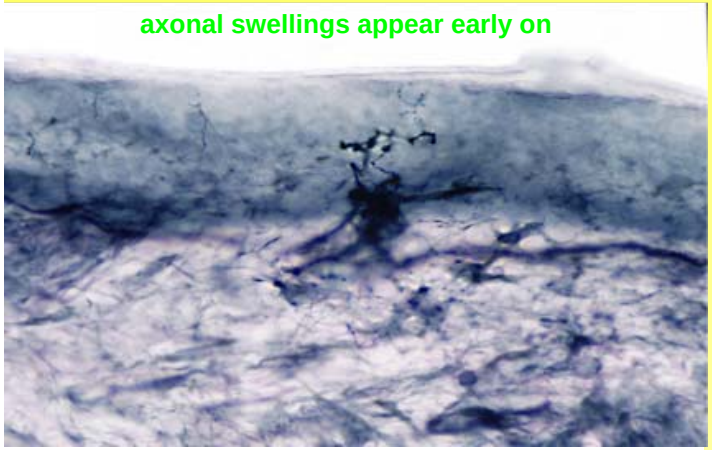


PGP-immunolabeled skin biopsies from torso of age-matched women without (A), and with PHN (B) after prior shingles

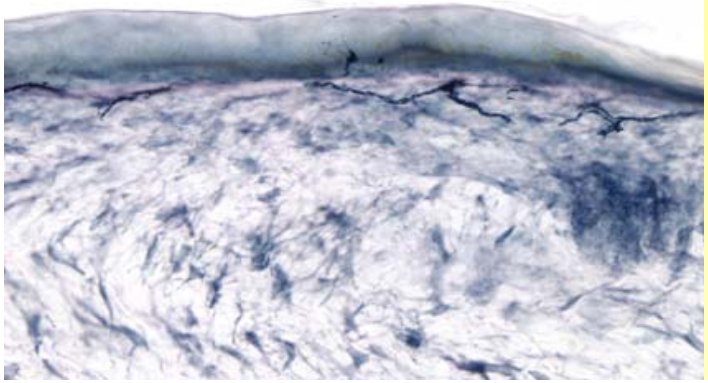


Oaklander et al. *Annals of Neurology* 1998

axonal swellings appear early on

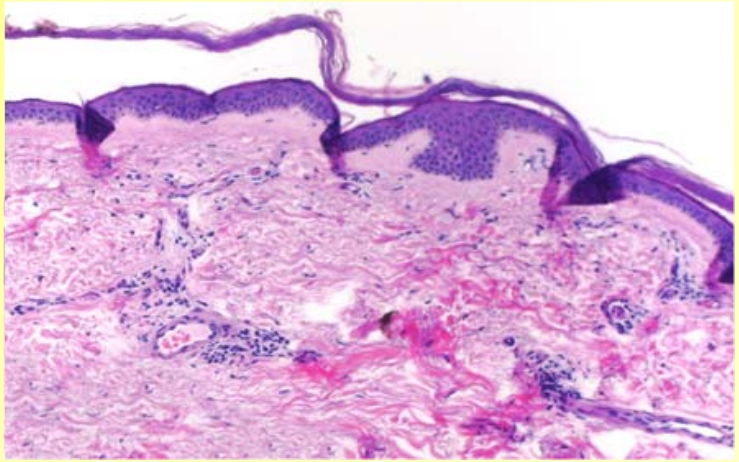


epidermal denervation appears later



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 n... NEJM, 2004

Amato and Oaklander, NEJM (2004)

But additional diagnostic tools are needed

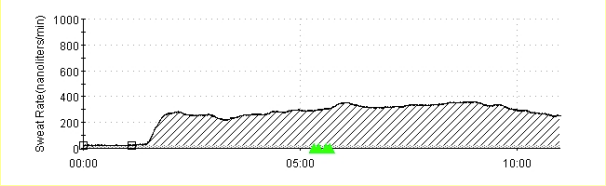
- Not all small-fibers go to the skin
- Loss of skin innervation occurs late in SFPN
- Physiological tools may offer earlier detection

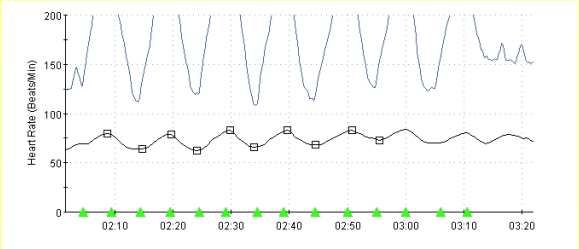
- The American Academy of Neurology also recommends autonomic function testing (AFT) for diagnosis of SFPN
  - England, et al. Practice Parameter: Evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology*, 2009.

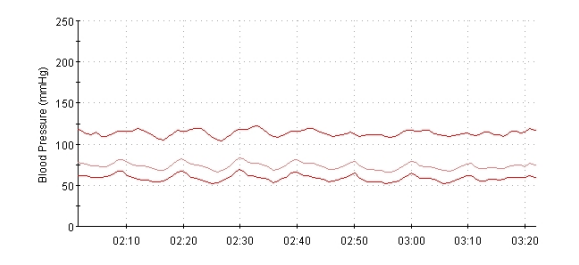
Autonomic Function Test (AFT)

Set of tests of autonomic functions controlled by small fibers – consists of four tests:

- QSART (quantitative sudomotor axon reflex test) – “sweat measurement”
- Heart-rate response to deep breathing
- Heart-rate and blood-pressure responses during Valsalva maneuver
- Heart-rate and blood-pressure responses to tilt

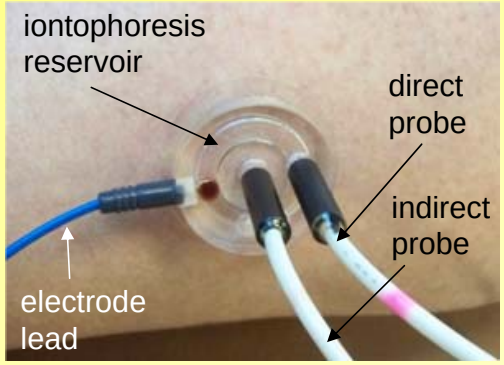






Measuring axon flare is a potential biomarker of SFPN

- Vasodilating chemical is introduced via iontophoresis
- Increase in skin blood flow (“axon flare”) is measured in response to vasodilator
- Laser Doppler flowmetry provides images of flare area and time-resolved flare intensity



Laser Doppler Imager

Laser Doppler perfusion and temperature monitor

Our project plan

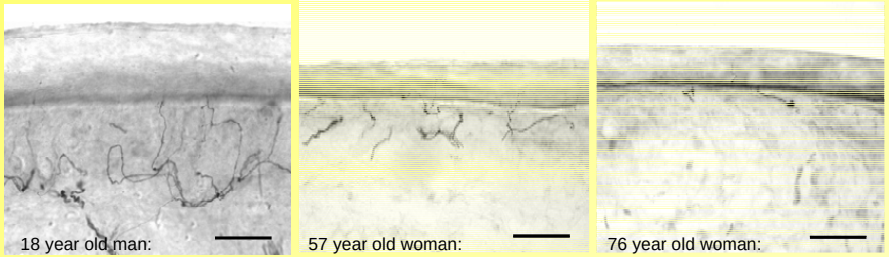
Aim I. To determine which specific measurements of skin innervation, autonomic function, and skin blood flow provide the most sensitive, specific, and practical objective test for SFPN.

- **Establish demographically correct skin biopsy norms** → 120 normal controls
- **Establish best tests for SFPN** → 40 normal controls, 40 SFPN subjects, 40 osteoarthritis

Aim II. To use the best of these tests to determine the prevalence of SFPN among GW-ill veterans and to compare SFPN prevalence to the prevalence in unaffected Gulf-War veterans and civilian controls.

- **Determine prevalence of SFPN in Gulf War-ill veterans** → 150 healthy Gulf War veterans, 150 Gulf War-ill veterans

Skin biopsy diagnosis of SFPN depends entirely upon comparison with accurate normative data



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 far more dermal and epidermal innervation than the middle-aged and elderly adults

- **Our preliminary results from screened normal subjects show that skin innervation reduces with age**
- **Normative values used for clinical diagnosis around the world need to be corrected for age, as we will propose**

Presented at the 135th Annual Meeting of the American Neurological Association, San Francisco, 2010.

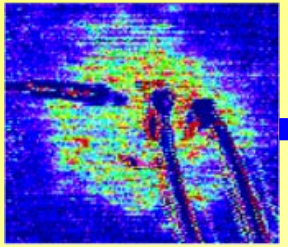
Autonomic Function

- Studies of 10 screened normal subjects on clinical equipment finds no abnormalities other than interference with sweat testing in one subject with lots of leg hair
- We have been collecting data from SFPN patients tested for clinical diagnosis
- Thank you to DoD for our new research AFT equipment – installation is Nov 15!!!

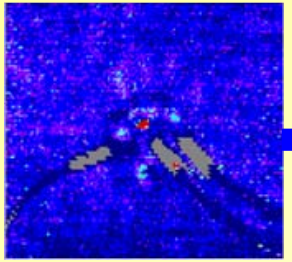
Preliminary results – axon flare

- Age-matched normal subject (upper) and SFPN patient (below)
- Iontophoresis of 0.1% histamine for 60 seconds
- Laser Doppler Images are at 12 minutes post-iontophoresis

Laser Doppler Imaging

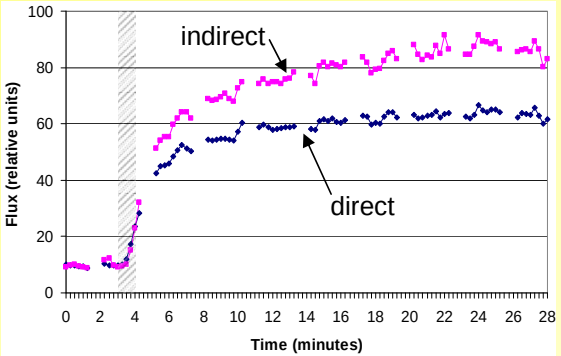


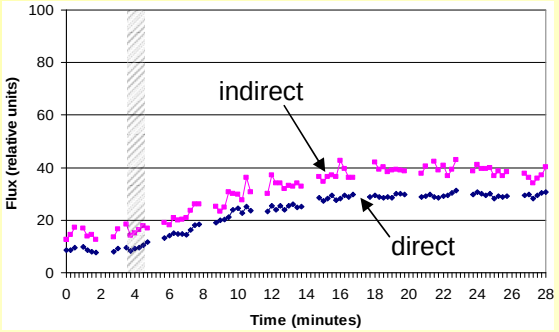
ENF density 290/mm²

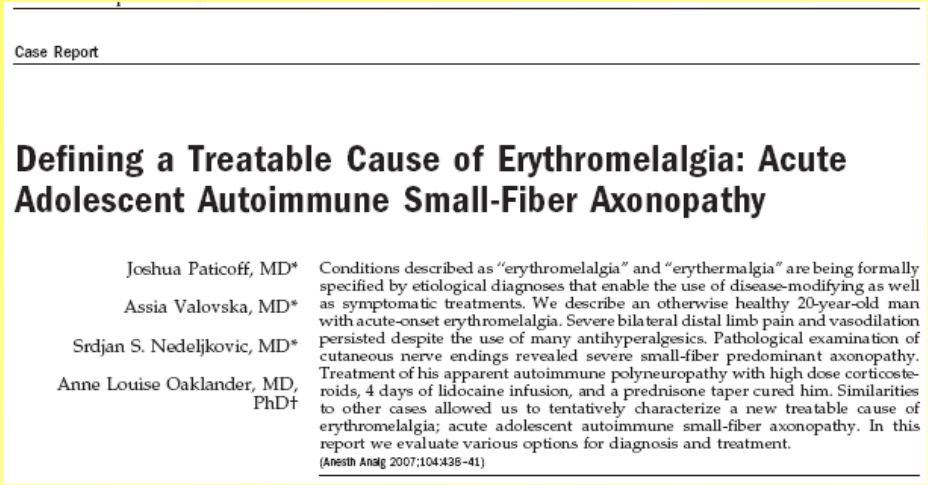


ENF density 4/mm²

Laser Doppler blood flow monitoring







Case Report

Defining a Treatable Cause of Erythromelalgia: Acute Adolescent Autoimmune Small-Fiber Axonopathy

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Srdjan S. Nedeljkovic, MD*
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Conditions described as "erythromelalgia" and "erythermalgia" are being formally specified by etiological diagnoses that enable the use of disease-modifying as well as symptomatic treatments. We describe an otherwise healthy 20-year-old man with acute-onset erythromelalgia. Severe bilateral distal limb pain and vasodilation persisted despite the use of many antihyperalgesics. Pathological examination of cutaneous nerve endings revealed severe small-fiber predominant axonopathy. Treatment of his apparent autoimmune polyneuropathy with high dose corticosteroids, 4 days of lidocaine infusion, and a prednisone taper cured him. Similarities to other cases allowed us to tentatively characterize a new treatable cause of erythromelalgia; acute adolescent autoimmune small-fiber axonopathy. In this report we evaluate various options for diagnosis and treatment.

(Anesth Analg 2007;104:438–41)

- J. L. Chamberlain, S. J. Pittock, A. M. Oprescu, C. Dege, M. Apiwattanakul, T. J. Kryzer, and V. A. Lennon. Peripherin-IgG association with neurologic and endocrine autoimmunity. *J. Autoimmunity*, 2010.

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- Thank you for your invitation and for your attention
- We have clinical and research openings for fellows and faculty; spread the word!