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

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All research (until very recently) sponsored by NIH (R01NS42866, R01NS052754, K24NS059892) and private foundations
No commercial sponsors, no conflicts of interest

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

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).

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


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.

- 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.

- 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
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)
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
- PGP9.5 visualizes all neurons, not a subset
- The neuronal localization of PGP9.5 has been verified by EM
- The epidermis contains almost exclusively TRPV1+ nociceptors
- ENF can be quantitated using LM

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
- Various painful sensory neuropathies
  - diabetes
  - HIV
  - idiopathic

Development of Painful Neuropathy is Associated with Loss of Nociceptive Nerve Endings in the epidermis

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

Dermal morphology is important as well

some patients have perivascular infiltrates

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

**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

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
  - 40 normal controls
  - 40 SFPN subjects
  - 40 osteoarthritis
- Establish best tests for SFPN

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.

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.


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

ENF density 290/mm²

ENF density 4/mm²

Laser Doppler Imaging

Laser Doppler blood flow monitoring

Case Report

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

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Conditions described as “erythromelalgia” and “erythromelalgia” are being formally specified by biological 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 intravenous infusion, and a prednisolone taper cured him. Similarities to other cases allowed us to tentatively characterize a new treatable cause of erythromelalgic acute adolescent autoimmune small-fiber axonopathy. In this report we evaluate various options for diagnosis and treatment.

[Arch Neurol. 2007;64:318-319]

Thank you for your invitation and for your attention

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