Small-fiber neuropathy causes some ill-defined multisymptom illnesses

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http://NeuropathyCommons.org

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What are "small fibers"?

80% of peripheral axons are small-diameter fibers

They innervate and modulate organs and tissues

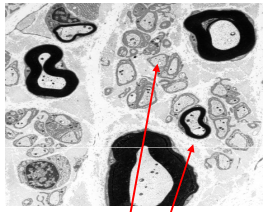
- skin, blood vessels, sweat glands, gut, bone, heart

They mediate multiple functions

- Sensations of pain and itch
- Autonomic functions
- Responses to injury and illness
- Tissue and body homeostasis

SFPN symptoms affect many organs and tissues

- Patients see different specialists for each symptom
  - Their underlying neuropathy remains unrecognized



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

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

SFPN can cause chronic widespread pain

Small fibers transmit pain signals, so widespread chronic pain is a common symptom

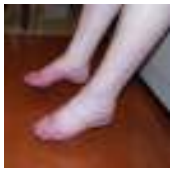
Length-dependent SFPN starts distally, spreads proximally

- **Distal axons are targeted**
  - 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.

Non-length dependent SFPN is proximal or patchy

- **Neuron cell bodies in trigeminal or spinal ganglia are targeted**

"Erythromelalgia" phenotype



A woman with red, burning feet and hands due to SFPN. She walked barefoot in snow to cool them.

This woman always carries a fan to cool her painful face. Her diagnosis is trigeminal ganglionitis from Sjögren's. Immunosuppression was effective.

from Oaklander AL. Immunotherapy prospects for painful small-fiber sensory neuropathies and ganglionopathies. *Neurotherapeutics*. 2015

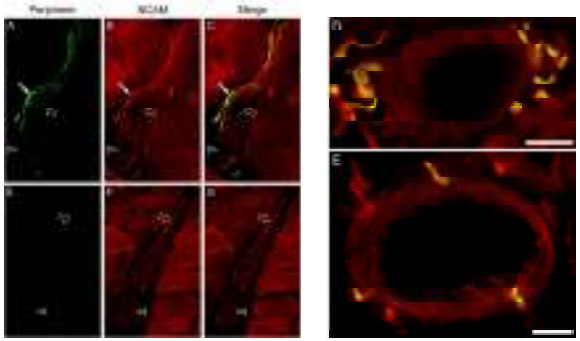
SFPN can cause cardiovascular symptoms

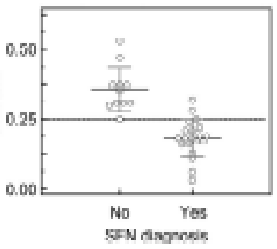
- Microvessels that lose nerve control can't open and close as needed
- Rapid heart beat is caused by cardiac denervation, hypotension, hypoxia
- More than 50% of POTS (postural orthostasis tachycardia syndrome) is caused by SFPN
  - Thieben, P. et al. Postural orthostatic tachycardia syndrome: The Mayo clinic experience. *Mayo Clin Proc, 2007*
- Small-fiber cardiovasculopathy can affect:
  - **Muscles**: fatigue, exercise intolerance, shortness of breath,
  - **Nerves**: dying back, impaired regeneration
  - **GI tract**: poor digestion, impaired nutrition
  - **Chronic headache?** Likely from impaired dural vascular responses

Systrom, Faria, Waxman, Oaklander
Exercise limit in small fiber axonopathy: An invasive cardiopulmonary exercise test study.
MDA Scientific Conference 2017

SFPN causes exercise intolerance -weakness, fatigue

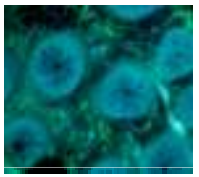
Top panels – normal control muscle
Bottom panels – muscle from SFPN patient





from: Dori, Lopate, Keeling, Pestronk. Myovascular innervation: axon loss in small-fiber neuropathies. *Muscle Nerve, 2015*

SFPN causes GI symptoms



Often labeled "irritable bowel syndrome" IBS
25% of Gulf War Veterans have GI symptoms

Upper GI symptoms of SFPN:
Nausea and vomiting after meals, reflux, esophageal erosions and strictures

Lower GI symptoms of SFPN:
Constipation, diarrhea, or both (irritable bowel)

Tests for gastrointestinal symptoms of SFPN:

- Gastric-emptying scintigraphy (below) shows slow emptying of stomach (arrows)
- Sitz marker study to measure colon transit time

Standing worsens cognitive functions in patients with neurogenic orthostatic hypotension. *Poda et al., Neurological Sciences, 2012*

SFPN affects the brain (who knew?)

Neurogenic orthostatic hypotension (POTS) can cause temporary impairment of

- **immediate memory**
- **working memory**
- **sustained attention**
- **visual search**
- **abstract thinking**

- Capsaicin-sensitive C- and A-fibre nociceptors control long-term potentiation-like pain amplification in humans. Henrich et al. *Brain*, 2015
- Imaging signatures of altered brain responses in small-fiber neuropathy: reduced functional connectivity of the limbic system after peripheral nerve degeneration. Hsieh et al. *PAIN*, 2015
- Increasing orthostatic stress impairs neurocognitive functioning in chronic fatigue syndrome with postural tachycardia syndrome. Ocon et al. *Clin Sci (Lond)*, 2012

Many SFPN symptoms improve when patients educated about neuropathy

For cardiovascular symptoms

- Stand slowly, compression garments
- Add salt and fluids to raise BP
- Regular exercise
- Elevate head of bed with bricks
- Improve oxygenation (no smoking), avoid hypoxia
- Medications include midodrine, fludrocortisone, rarely IV saline
- Pyridostigmine improves exercise capacity

For GI symptoms

- High-fiber diet, small meals, elevate head-of-bed, don't lie down after meals
- Anti-nausea medications can help, including marijuana
- Obstipation may require cecostomy tube to flush colon from externally

Objective confirmation of SFPN is difficult

Neuro exam is not sensitive
No muscle weakness, atrophy, fasciculations
Reflexes typically preserved
Large-fiber sensations (vibration, joint position, touch) typically OK
Small-fiber functions (pin, thermal, sweating) not entirely lost at onset

EMG/NCS does not detect SFPN
Electromyography only studies motor axons and muscle
Surface nerve conduction studies only large myelinated sensory and motor axons

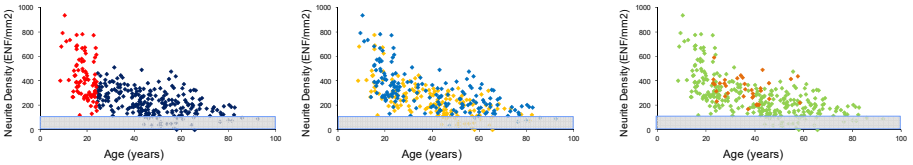
Quantitative sensory testing (QST)
NOT objective; relies on patient perception
R. Freeman, et al. Quantitative sensory testing cannot differentiate simulated sensory loss from sensory neuropathy. *Neurology, 2003.*

Surgical nerve biopsy
Used to be the "gold standard"
Still useful in rare patients
BUT, invasive, expensive, not widely available, leaves focal nerve damage
Can't repeat to follow course or treatment response

Current gold standard: Distal-leg skin biopsy

- 2-3 mm diameter skin punches removed from lower leg using local anesthesia
- Biopsies can be performed locally, put in Zamboni fixative, mailed to pathology lab
- 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 small fibers**
  - 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 ≤ 5th centile of predicted**
  - Predicted value is calculated from biopsying many normal volunteers (population sample)
  - Accurate diagnosis of SFPN depends on having accurate norms

MGH's multivariate regression normative model improves accuracy of skin-biopsy diagnosis down to age 7



There are age differences

Normals ≤ 23 years (red; n=107) have more ENF than older normal subjects (blue; n=290). $p < 0.001$

There are sex differences

Normal females (blue; n=198) have more ENF than normal males (yellow; n=199) $p < 0.001$

There are ethnic differences

Asians (orange; n=38) have more ENF than age-matched non-Asians (green; n=206) $p = 0.01$

Many labs use a single threshold "cutoff" (76 ENF/mm²) to assess normality of distal-leg biopsies

Among all 105 abnormal MGH biopsies from patients under 40 in 2012-2013, the single "cutoff" (76 ENF/mm²) would have only detected SFPN in 26 (*75% false negative diagnosis rate*)

We developed a multivariate regression to calculate predicted norm for each patient's biopsy based on that person's age, sex, race

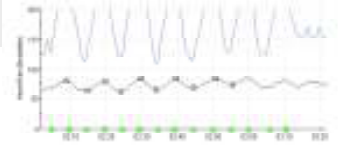
Our lab may be the only one in with norms for teens and kids (age 7 and above)

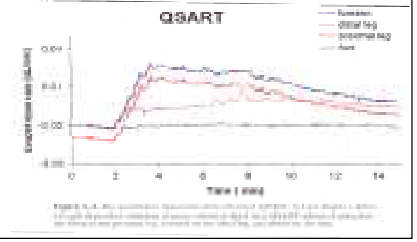
Composite autonomic function testing (AFT) is best test for physiology

Autonomic functions controlled by small fibers

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

AFT is noninvasive and repeatable, but expensive, not widely available, not specific for SFPN





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, 2009.

SFPN was considered a disease of midlife and older

- Few youngsters have the medical causes of polyneuropathy
- Very rare mendelian genetic polyneuropathies present in infants/toddlers
  - Familial dysautonomia/Riley-Day/HSAN III
  - Sodium channel NaV mutations

Paticoff et al. Defining a treatable cause of erythromelalgia: acute adolescent autoimmune small-fiber axonopathy. Anesth Analg, 2007

The index case that rocked my world

A healthy college student developed sudden burning pain in his hands and feet, tachycardia, nausea.
Skin biopsy showed SFPN, blood testing did not identify a cause
Corticosteroid treatment gave rapid pain relief and eventual cure
No recurrences in a decade off all medications

Isabelle Rapin MD

Verne Caviness MD DPhil

Are there kids and young adults with undiagnosed SFPN?

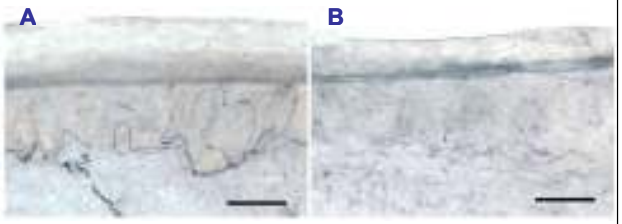
We extracted records of 41 consecutive patients with chronic widespread pain before age 21

Many called "juvenile fibromyalgia"

- 73% were female
- 68% were disabled from school or work
- 76% had pain onset in legs or feet
- 90% had cardiovascular symptoms (POTS, sinus tachycardia)
- 82% had GI symptoms (belly pain, nausea, vomiting, constipation, incontinence)
- 63% had sweating symptoms
- 34% had urological symptoms
- 63% had chronic severe headaches

59% of our young cohort had objective evidence of SFPN

- 30% (11/37) of skin biopsies interpreted as SFPN
- 53% (18/34) of Autonomic Function Tests (AFT) interpreted as SFPN
- 100% (2/2) of nerve/muscle biopsies interpreted as SFPN



Oaklander & Klein, Pediatrics 2013

Normal 18-year old white male has 675 axons/mm2

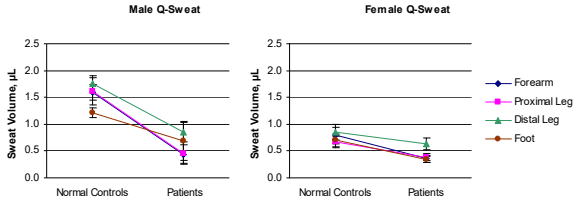
18-year old white male with chronic widespread pain has 155 axons/mm2

Autonomic Function Testing detected SFPN in 53%

There are no normative data from children, so we recruited and studied demographically matched normal young control subjects

- **27%** of young patients vs. **3%** of controls had low heart-rate variability with respiration
- **42%** of young patients vs. **0%** of controls had abnormal cardiovascular response to Valsalva
- **75%** of young patients vs. **18%** of controls had abnormal heart-rate and/or BP during tilt-table testing
- **82%** of young patients vs. **34%** of controls had reduced sweat production on the arms and legs

work of Max Klein PhD



What causes early-onset SFPN?

0% of patients had family history of neuropathy

0% of patients had history of major psychiatric illness

34% of patients had history of autoimmune illness; mostly autoantibody mediated:

- 6 autoimmune thyroiditis
- 2 systemic (juvenile Sjögren's, juvenile SICCA)
- 2 Henoch-Schönlein purpura
- 1 each brachial plexitis, type-I diabetes, post-viral arthritis, immune thrombocytopenic purpura, Crohn's, and trochleitis, one Hashimoto's encephalopathy

Oaklander & Klein, Pediatrics 2013

Blood tests identify underlying causes of SFPN

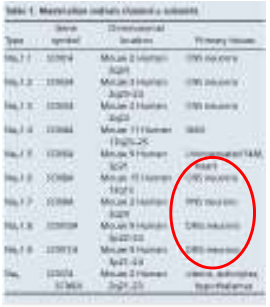
Only useful tests in our young cohort

Elevated ESR (≥ 15 mm/hr)	37%
ANA (≥ 1:80 dilution)	45%
Low complement 3 (< 85 mg/dl)	21%
Low complement 4 (< 20 mg/dl)	46%

Oaklander & Klein, Pediatrics 2013

Don't bother with these

CSF	Always normal
Blood tests:	Complete blood count, electrolytes including glucose, renal, liver, and thyroid function, hemoglobin A1c, lipids, vitamins, immunoglobulins, serum protein immunofixation
Urine tests:	Heavy metals, protein immunofixation, porphyrins, amino and organic acids
Infectious tests:	Hepatitis C, syphilis, HIV, Lyme, babesiosis, ehrlichiosis
Immune tests:	Rheumatoid factor antibody, lupus autoantibodies, ANCA, total complement
Genetic tests:	CMT, Fabry, transthyretin, HNPP, familial hemiplegic migraine, cystic fibrosis



We sequence NaV genes as a 2nd line testing option

Sebastian is a 9 year old with years of painful burning feet, itchy legs and painless foot ulcers. He cried from pain every day, missed school

Mom has similar, milder, symptoms since age 7
Skin biopsies in the family showed small-fiber loss
Na_v sequencing showed pathogenic G856D variant in SCN9A voltage-gated sodium channel.

NaV polymorphisms change action potentials of small fibers, they fire too much then degenerate

His pain did not respond to opioids but mexiletine completely stops it

Sebastian was on television to educate about small-fiber neuropathy

http://www.wcvb.com/health/doctors-finally-able-to-help-boy-suffering-with-chronic-pain-for-years/39849148

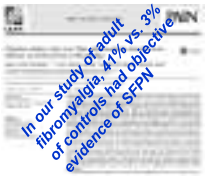
Some older adults with unexplained multi-symptom illnesses have early-onset SFPN

- Some cases develop in older adults during their 30's and 40's.
  - Dabby, Acute steroid responsive small-fiber sensory neuropathy: a new entity? *J PNS*, 2006
- Many cases develop in youth but persist undiagnosed for decades
  - DoD grant GW140169 funds us to develop ways to diagnose SFPN present for 25 years
- Preliminary clinical evidence suggests that some patients still respond to treatment even decades after onset

Fibromyalgia affects 1-5% of population; 75% are female

We prospectively tested whether SFPN causes some fibromyalgia cases

- **Inclusion:** must meeting American College of Rheumatology 2010 diagnostic criteria plus have a clinical fibromyalgia diagnosis
- Based on power analysis, we studied 27 fibromyalgia patients, 30 matched controls
- **Outcomes:**
  - **Symptoms** were measured by Michigan Neuropathy Screening Instrument
  - **Signs** were measured by the Utah Early Neuropathy Scale
  - **Pathology** was measured by PGP9.5-immunolabeled skin biopsy
  - **Pathophysiology** was measured by autonomic function testing
- **Results:**
  - 41% of fibromyalgia subjects vs. 3% of controls had SFPN by skin biopsy
  - Fibromyalgia group but not controls had symptoms and signs of SPPN



SFPN may underlie almost half of cases of fibromyalgia

Kim, Kim, Oh, Clauw. **Characteristic electron microscopic findings in the skin of patients with fibromyalgia-preliminary study.** Clin.Rheumatol, 2008.

Üçeyler, et al. **Small fibre pathology in patients with fibromyalgia syndrome.** *Brain*, 2013

Albrecht, et al. **Excessive peptidergic sensory innervation of cutaneous arteriole-venule shunts (AVS) in the palmar glabrous skin of fibromyalgia patients: Implications for widespread deep tissue pain and fatigue.** *Pain Med* 14 (6):895-915, 2013.

Serra, et al. **Hyperexcitable C nociceptors in fibromyalgia.** *Annals of Neurology*, 2013.

Giannoccaro, et al. **Small nerve fiber involvement in patients referred for fibromyalgia.** Muscle Nerve, 2013.

Caro & Winter. **Evidence of abnormal epidermal nerve fiber density in fibromyalgia: Clinical and immunologic implications.** Arthritis Rheumatol, 2014.

de Tommaso, et al. **Update on laser-evoked potential findings in fibromyalgia patients in light of clinical and skin biopsy features.** J Neurol, 2014.

Kosmidis, et al. **Reduction of intraepidermal nerve fiber density (IENFD) in the skin biopsies of patients with fibromyalgia: A controlled study.** J.Neurol Sci, 2014.

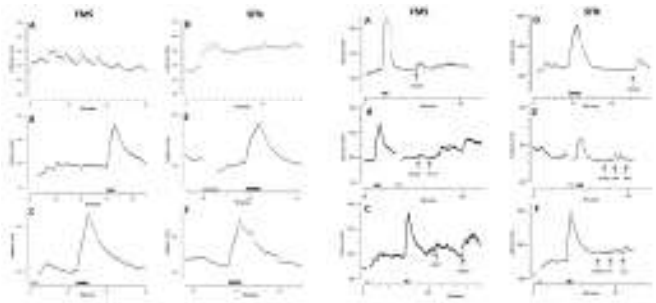
Ramirez, et al. **Small fiber neuropathy in women with fibromyalgia. An in vivo assessment using corneal confocal bio-microscopy.** Sem Arthritis Rheumat, 2015

Doppler et al. **Reduced dermal nerve fiber diameter in skin biopsies of patients with fibromyalgia.** Pain, 2015

Group	n
Fibromyalgia	30
Small fiber neuropathy	17
Normal controls	9

Microneurography shows fibromyalgia and SFPN feature similar C-fiber abnormalities

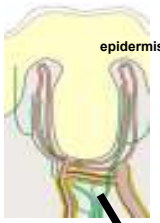
Spontaneous activity | **Peripheral sensitization**



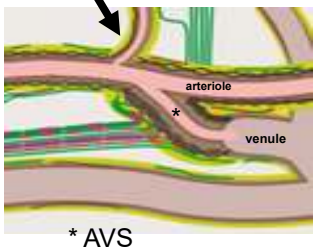
Hyperexcitable C nociceptors in fibromyalgia. Serra et al. Annals of Neurology 2014;75:196-208.

Fibromyalgia patients also have myovascular denervation

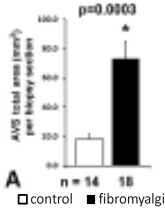
- Albrecht et al., Pain Medicine, 2013

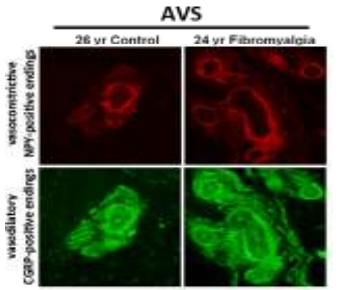


- Arteriovenous shunts (AVS) shift blood away from the muscles to the skin for heat regulation
- Small-fiber innervation of AVS controls if they open or shut
- Dilated AVS in fibromyalgia may contribute to muscle ischemia, aches and exercise intolerance



* AVS





We surveyed blood tests to find causes of "initially idiopathic" SFPN

We studied 195 patients of all ages with confirmed SFPN
Blood tests identified potential causes in 57%

Hyperglycemia is not a major cause of iiSFPN in New England
2% had diabetes; below population prevalence
22% had pre-diabetes; below population prevalence (37%)

42% had at least one marker of dysimmunity
Most common blood test abnormalities:
high ESR (28%), ANA ≥ 1:160; (27%), low C4 (16%)


Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy


M. Lang MD

Our commitment to the DoD and the VA:

GW093049 Undiagnosed small-fiber polyneuropathy - Is it a component of GWI?
To measure the prevalence of SFPN among Gulf War Ill Veterans

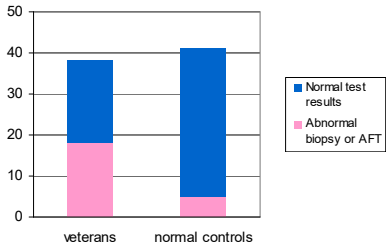
GW130109 Characterizing Treatable Causes of Small Fiber Polyneuropathy in Gulf War Veterans
Develop Case Definition of SFPN
Apply validated tests to Veterans
Look at serum and tissues for treatable causes of SFPN

GW140169 Diagnosis of Late-Stage, Early-Onset, Small-Fiber Polyneuropathy
Develop simplified screening instruments (e.g., questionnaires, exams)
Develop and evaluate simple diagnostic devices (e.g., pupillometry)
Identify genetic markers of predisposition to SFPN


Max Klein PhD


Co-PI
Jorge Serrador PhD
EOVA WRIISC

SFPN appears prevalent among all GW Veterans



Diagnostic Tests: skin biopsy and/or autonomic function testing

47% (18/38) among our GW veterans had abnormal results vs.12% of nonveteran controls (5/41)

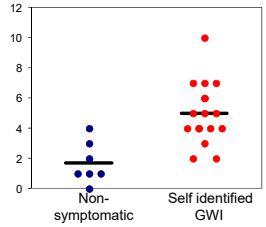
P = 0.0010

Total N so far = 79

work of Max Klein PhD

Neuropathy symptoms in GWI-symptomatic vs. healthy GW Veterans

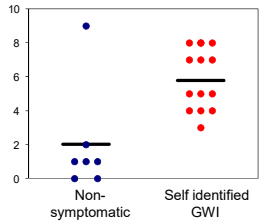
Scores from Michigan Neuropathy Screening Instrument (MNSI) from non-symptomatic, symptomatic, and certified Gulf War ill Veterans.



Bars are mean scores.
P = 0.0027

3 with VA GWI diagnosis + 23 with GWI symptoms vs 12 healthy Veterans

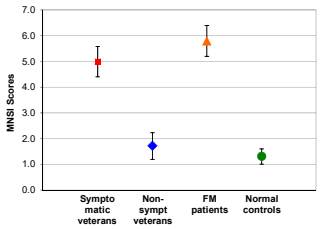
Pain scores (0-10) from non-symptomatic, symptomatic, and certified Gulf War ill Veterans.



Bars are mean scores.
P = 0.0050

Similarities between FMS and GWI

Comparing neuropathy symptoms



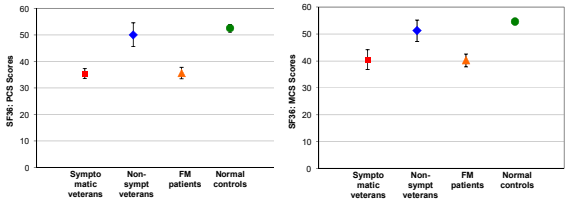
Symptomatic GW Veterans

Healthy GW Veterans

Fibromyalgia patients

Healthy non-Veteran controls

SF-36 Physical and Mental Component Scores



Is dysimmunity a newly recognized cause of SFPN?

Evidence so far suggests autoantibodies

- Cell infiltrates in some nerve and skin biopsies are sparse
- Bland CSF
- Low C4 in 46% c/w autoantibody-mediated immunity; more likely classic or lectin than alternative complement pathway
- Comorbid autoimmune conditions are predominantly antibody-associated
- Cellularity at onset cannot be excluded because biopsies performed late in course

Could immunotherapies help patients with "apparently autoimmune" SFPN?

In our young cohort, immunotherapies helped 80%

- **Our preliminary criteria for considering immunotherapies:**
  - Objectively confirmed SFPN
  - Disabling symptoms not improving on their own
  - History and/or lab tests excluding other causes
  - History and/or lab tests consistent with dysimmunity
- **Corticosteroids were effective in 67% (10/15)**
  - Inpatients got IV methylprednisolone 1 g/day x 3-5 days
  - Outpatients got prednisone 1 mg/kg/day x 4 weeks followed by brief taper
- **Immunoglobulin (IVIG) was effective in 63% (5/8)**
- **Rep**

Oaklander & Klein, Pediatrics 2013

MGH Nerve Unit database tracks SFPN patients to prepare for treatment studies


Immunotherapy Prospects for Painful Small-Fiber Sensory Neuropathies and Ganglionopathies

As of 4/14/17, 3852 patients/subjects
155 kids under 18
535 young adults between 18 and 35
3000 skin biopsy results
350 DNA and sera

Moving to web-based recruitment and external collaborations/links
First contributions last week from NJ WRIISC

Improving readiness for multicenter clinical trials of immunotherapies for apparently autoimmune small-fiber polyneuropathy

NIH U01 NS128093 submitted Feb 17 2017

This grant would fund readiness studies to prepare for FDA-quality clinical trials of immunotherapies for apparently autoimmune small-fiber neuropathy

We are developing and validating tools for tracking SFPN symptoms and signs

Roi Treister PhD

Gary Zirpoli PhD

Treister, Lodahl, Lang, Tworoger, Sawilowsky, Oaklander. Initial development and validation of a patient-reported symptom survey for small-fiber polyneuropathy. Journal of Pain, in press.

Summary:

- There are approved objective biomarkers for SFPN diagnosis and study
- Children and young adults do develop SFPN that is rarely treated
- 1/3-1/2 of adults with unexplained chronic widespread pain and multi-organ symptoms (fibromyalgia, Gulf War illness) have undiagnosed SFPN
- Blood tests suggest medical cause in ~60% of patients with "initially idiopathic" SFPN
- Dysimmunity appears to be major cause of early-onset SFPN "aaSFPN"

- *Have we discovered small-fiber analogs of Guillain-Barré and chronic inflammatory demyelinating polyneuropathy (CIDP)?*
- *Should we be treating "aaSFPN" with immunotherapies rather than opioids?*

Thanks to our contributors and funders

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Thanks to mentors Steve Hauser, Drew Helmer

http://NeuropathyCommons.org