Small-fiber neuropathy causes some ill-defined multisymptom illnesses

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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

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 vasomotor neuritis 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 foot 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.

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
- 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

Axons Schwann cells merge merge

% of Schwann cell profiles with axons


**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

**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


**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

EMG/NCS does not detect SFPN
Electromyography only studies motor axons and muscle
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

Quantitative sensory testing (QST)
NOT objective; relies on patient perception

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
- 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
- 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

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

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

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.

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

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
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 Sjogren's, juvenile SICCA)
- 2 Henoch-Schonlein purpura
- 1 each brachial plexitis, type-I diabetes, post-viral arthritis, immune thrombocytopenic purpura, Crohn's, and trocheitis, one Hashimoto's encephalopathy

Oaklander & Klein. Pediatrics 2013

Blood tests identify underlying causes of SFPN

Only useful tests in our young cohort

<table>
<thead>
<tr>
<th>Test</th>
<th>Extent</th>
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<tbody>
<tr>
<td>Elevated ESR (≥ 15 mm/hr)</td>
<td>37%</td>
</tr>
<tr>
<td>ANA (≥ 1:80 dilution)</td>
<td>45%</td>
</tr>
<tr>
<td>Low complement 3 (&lt; 85 mg/dl)</td>
<td>21%</td>
</tr>
<tr>
<td>Low complement 4 (&lt; 20 mg/dl)</td>
<td>46%</td>
</tr>
</tbody>
</table>

Don't bother with these

<table>
<thead>
<tr>
<th>Test</th>
<th>Extent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>Always normal</td>
</tr>
<tr>
<td>Blood tests</td>
<td></td>
</tr>
<tr>
<td>Complete blood count, electrolytes</td>
<td>Complete blood count, electrolytes including glucose, renal, liver, and thyroid function, hemoglobin A1C, lipids, vitamins, immunoglobulins, serum protein immunofixation</td>
</tr>
<tr>
<td>ANA</td>
<td></td>
</tr>
<tr>
<td>Infectious tests</td>
<td></td>
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<tr>
<td>Hepatitis C, syphilis, HIV, Lyme, babesiosis, ehrlichiosis</td>
<td></td>
</tr>
<tr>
<td>Immune tests</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid factor antibody, lupus autoantibodies, ANCA, total complement</td>
<td></td>
</tr>
<tr>
<td>Genetic tests</td>
<td></td>
</tr>
<tr>
<td>CMT, Fabry, transthyretin, HNPP, familial hemiplegic migraine, cystic fibrosis</td>
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Oaklander & Klein. Pediatrics 2013

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
- NaV 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

Oaklander & Klein. Pediatrics 2013

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.
- 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

Sebastian was on television to educate about small-fiber neuropathy

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 SFPN

Fibromyalgia patients also have myovascular denervation

- Albrecht et al., Pain Medicine, 2013

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
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<tbody>
<tr>
<td>Fibromyalgia</td>
<td>30</td>
</tr>
<tr>
<td>Small fiber neuropathy</td>
<td>17</td>
</tr>
<tr>
<td>Normal controls</td>
<td>9</td>
</tr>
</tbody>
</table>

SFPN may underlie almost half of cases of fibromyalgia


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


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

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

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.

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.

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.

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

Bars are mean scores.

P = 0.0027

P = 0.0050
### Similarities between FMS and GWI

<table>
<thead>
<tr>
<th>SF-36 Physical and Mental Component Scores</th>
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<tbody>
<tr>
<td>Symptomatic GW Veterans</td>
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<tr>
<td>SF36: PCS Scores</td>
</tr>
<tr>
<td>Symptomatic veterans</td>
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<tr>
<td>SF36: MCS Scores</td>
</tr>
<tr>
<td>Symptomatic veterans</td>
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</tbody>
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#### Is dysimmunity a newly recognized cause of SFPN?

- 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?

- 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)

**In our young cohort, immunotherapies helped 80%**

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

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

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

Recent MGH Contributors
Heather Downs BS
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Fana Sanjana

The EOVA WRIISC visits MGH

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