

# Fibromyalgia & Small Fiber Polyneuropathy



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# What is fibromyalgia and how is it diagnosed?

- A chronic widespread pain syndrome with fatigue, cognitive difficulties, sleep disturbances and other associated symptoms
- After osteoarthritis, fibromyalgia (FM) is the 2<sup>nd</sup> most common rheumatologic disorder; it affects 2-8% of population globally
- 2011 modified American College of Rheumatology criteria
  - Number of painful body areas
  - Symptom severity (fatigue, sleep and cognitive difficulties)
  - No tender points required for diagnosis
- At least 3 months of symptoms with no other explanation

Figure. Example of a Patient Self-report Survey for the Assessment of Fibromyalgia Based on Criteria in the 2011 Modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia<sup>7</sup>

### Widespread Pain Index (1 point per check box; score range: 0-19 points)

① Please indicate if you have had pain or tenderness during the past 7 days in the areas shown below. Check the boxes in the diagram for each area in which you have had pain or tenderness.

### Symptom Severity (score range: 0-12 points)

② For each symptom listed below, use the following scale to indicate the severity of the symptom during the past 7 days.

- No problem
- Slight or mild problem: generally mild or intermittent
- Moderate problem: considerable problems; often present and/or at a moderate level
- Severe problem: continuous, life-disturbing problems

	No problem	Slight or mild problem	Moderate problem	Severe problem
<b>Points</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>
A. Fatigue	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
B. Trouble thinking or remembering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C. Waking up tired (unrefreshed)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

③ During the past 6 months have you had any of the following symptoms?

	0	1
A. Pain or cramps in lower abdomen	<input type="checkbox"/> No	<input type="checkbox"/> Yes
B. Depression	<input type="checkbox"/> No	<input type="checkbox"/> Yes
C. Headache	<input type="checkbox"/> No	<input type="checkbox"/> Yes

### Additional criteria (no score)

④ Have the symptoms in questions 2 and 3 and widespread pain been present at a similar level for at least 3 months?

No       Yes

⑤ Do you have a disorder that would otherwise explain the pain?

No       Yes

ACR indicates American College of Rheumatology. Scoring information is shown in blue. The possible score ranges from 0 to 31 points; a score  $\geq 13$  points is consistent with a diagnosis of fibromyalgia. Additional scoring information and a

printer-ready version of this survey that patients can complete are available online (eFigure 1 and eFigure 2 in the Supplement).

# **Fibromyalgia is a label for a symptom complex, does not meet criteria for a “disease”**

- The cause(s) of symptoms is unknown
- Unclear which organs, cells, molecules are involved
- Therefore, it is challenging to develop an objective test that can confirm if a patient has this or not
- Painful symptoms attributed to abnormal pain perception in the brain: “central sensitization” , but unclear what the cause of this might be

Recent research demonstrates objective evidence of small-fiber nerve abnormalities in up to half of FM patients



Anne Louise Oaklander, MD, PhD, Harvard Medical School and Massachusetts General Hospital

## Fibromyalgia: New Research Helps Unravel the Mystery

Bottom Line/Health | May 2014 |

**WHAT IMPORTANT NEW STUDIES HAVE UNCOVERED:** According to several studies published in 2013, one conducted by researchers at Massachusetts General Hospital, nearly half of people with fibromyalgia have evidence of a disease called *small-fiber polyneuropathy* (SFPN).

# An Unnerving Enigma

**NEW CLUES TO FIBROMYALGIA'S ORIGINS COULD CRACK THE CASE OF CHRONIC PAIN**  
BY STEPHANI SUTHERLAND

SCIENTIFIC AMERICAN MIND  
SEPTEMBER/OCTOBER 2014

## New research sheds light on mysterious fibromyalgia pain

Karen Weintraub, Special for USA TODAY 7:03 a.m. EST  
December 15, 2013

*This new understanding of fibromyalgia will hopefully lead to better treatments, doctors and researchers say.*

"In 2013 there's been this absolute explosion of papers," says neurologist Anne Louise Oaklander at Massachusetts General Hospital in Boston. "The whole view on this has shifted." Her lab published two studies in 2013 showing that roughly half of the cases of fibromyalgia are really a little-known condition affecting the nerves (neuropathy)

One of those neurologists, Anne Louise Oaklander of Massachusetts General Hospital, began seeking collaborators to investigate the link, but she could not find a rheumatologist willing to embark on such a speculative, interdisciplinary project. Finally, Oaklander took matters into her own hands. To search for signs of nerve damage in people with fibromyalgia, her team used several tests, including a skin biopsy, in which a clinician punches out a small sample from the skin of the hand or leg and examines the tiny nerves within the sample under a microscope. "No one had really looked appropriately before at nerves," Oaklander says.

# We analyzed records of 41 consecutive patients with chronic widespread pain that began before age 21

ARTICLE

- 73% were female
- 68% were disabled

## Evidence of Small-Fiber Polyneuropathy in Unexplained, Juvenile-Onset, Widespread Pain Syndromes

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### KEY WORDS

peripheral nervous system disease, widespread chronic pain, dysautonomia

### ABBREVIATIONS

AFT—autonomic function testing

CIDP—chronic inflammatory demyelinating polyneuropathy

CWP—chronic widespread pain

ENF—epidermal nerve fiber

ESR—erythrocyte sedimentation rate

GBS—Guillain-Barré syndrome, (acute inflammatory demyelinating polyneuropathy)

IVIg—intravenous immune globulin

POTS—postural orthostasis tachycardia syndrome

RR—reference range (of normal values for laboratory tests)

SFPN—small-fiber polyneuropathy

Dr Oaklander conceptualized and designed the study, obtained funding, extracted the data, participated in the data analysis, and drafted the initial manuscript and the rewrites. Dr Klein performed the autonomic function testing on the normal control subjects, participated in the data analysis, contributed to drafting and editing the figures, contributed to rewriting the manuscript, and approved the submitted and all revised versions of the manuscript.

This work was presented in abstract form to the American Neurologic Association (September 25–27, 2011; Manchester Grand Hyatt, San Diego, CA) and the Peripheral Nerve Society (June 25–29, 2011; Bolger Center, Potomac, MD).



**WHAT'S KNOWN ON THIS SUBJECT:** Acquired widespread pain syndromes of youth are prevalent, disabling, usually unexplained, and untreatable. Small-fiber polyneuropathy causes widespread pain and multisystem complaints in older adults. Some causes are treatable. Neurodiagnostic skin biopsy, autonomic function testing, and nerve biopsy permit objective diagnosis.



**WHAT THIS STUDY ADDS:** It identifies definite (in 59%) and probable (in 17%) small-fiber polyneuropathy among 41 young patients with otherwise-unexplained, childhood-onset widespread pain. It characterizes this new disease's clinical features, diagnostic, and treatment options. Some cases appeared immune mediated and responded to immunomodulatory therapies.

## abstract

**OBJECTIVE:** We tested the hypothesis that acquired small-fiber polyneuropathy (SFPN), previously uncharacterized in children, contributes to unexplained pediatric widespread pain syndromes.

**METHODS:** Forty-one consecutive patients evaluated for unexplained widespread pain beginning before age 21 had medical records comprehensively analyzed regarding objective diagnostic testing for SFPN (neurodiagnostic skin biopsy, nerve biopsy, and autonomic function testing), plus histories, symptoms, signs, other tests, and treatments. Healthy, demographically matched volunteers provided normal controls for SFPN tests.

**RESULTS:** Age at illness onset averaged  $12.3 \pm 5.7$  years; 73% among this

**59% of patients were diagnosed with definite SFPN**

Oaklander & Klein, Pediatrics 2012



# NIH Public Access

## Author Manuscript

*Pain*. Author manuscript; available in PMC 2014 November 01.

Published in final edited form as:

*Pain*. 2013 November ; 154(11): . doi:10.1016/j.pain.2013.06.001.

## **Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia**

**Anne Louise Oaklander, MD, PhD<sup>1,2</sup>, Zeva Daniela Herzog, BA<sup>1</sup>, Heather Downs, BS<sup>1</sup>, and Max M. Klein, PhD<sup>1</sup>**

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41% of the skin biopsies from 27 FM patients and 3% of the skin biopsies from 30 normal subjects were diagnostic for SFPN

# Small fibre pathology in patients with fibromyalgia syndrome

Nurcan Üçeyler,<sup>1</sup> Daniel Zeller,<sup>1</sup> Ann-Kathrin Kahn,<sup>1</sup> Susanne Kewenig,<sup>1</sup> Sarah Kittel-Schneider,<sup>2</sup> Annina Schmid,<sup>1</sup> Jordi Casanova-Molla,<sup>1</sup> Karlheinz Reiners<sup>1</sup> and Claudia Sommer<sup>1</sup>

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doi:10.1093/brain/awt053

Brain 2013; 136; 1857–1867 | 1857

**BRAIN**  
A JOURNAL OF NEUROLOGY

In skin biopsies total and regenerating intraepidermal nerve fibers at the lower leg and upper thigh were reduced in 25 patients with fibromyalgia syndrome compared with control subjects.



# Evidence of Abnormal Epidermal Nerve Fiber Density in Fibromyalgia

Clinical and Immunologic Implications

Xavier J. Caro<sup>1</sup> and Earl F. Winter<sup>2</sup>

ARTHRITIS & RHEUMATOLOGY  
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DOI 10.1002/art.38662

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41 patients with FM and 47 control subjects  
underwent punch skin biopsy.

Epidermal fiber density was significantly  
diminished in FM patients.

# Reduction of Intraepidermal Nerve Fiber Density (IENFD) in the skin biopsies of patients with fibromyalgia: A controlled study<sup>☆</sup>

Michalis L. Kosmidis, Loukia Koutsogeorgopoulou, Harry Alexopoulos, Ioanna Mamali, Panagiotis G. Vlachoyiannopoulos, Michalis Voulgarelis, Haralampos M. Moutsopoulos, Athanasios G. Tzioufas, Marinos C. Dalakas \*

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15 of 46 (32.6%) FM patients had reduced IENFD compared to healthy controls

# **SMALL NERVE FIBER INVOLVEMENT IN PATIENTS REFERRED FOR FIBROMYALGIA**

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MUSCLE & NERVE May 2014

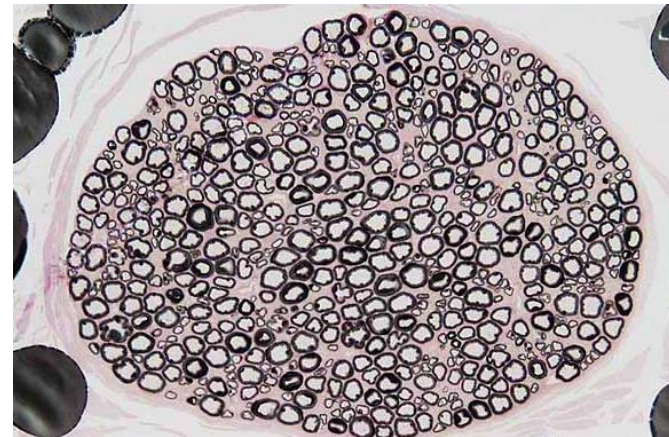
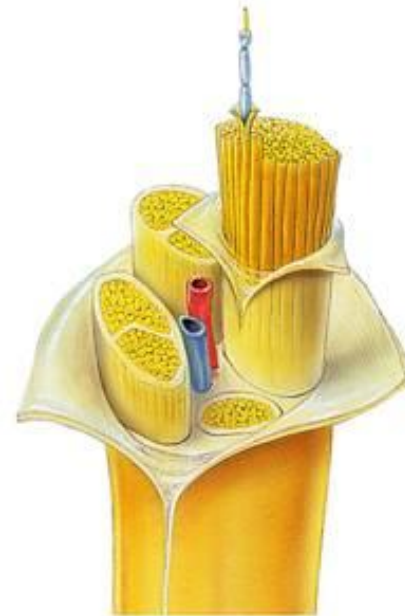
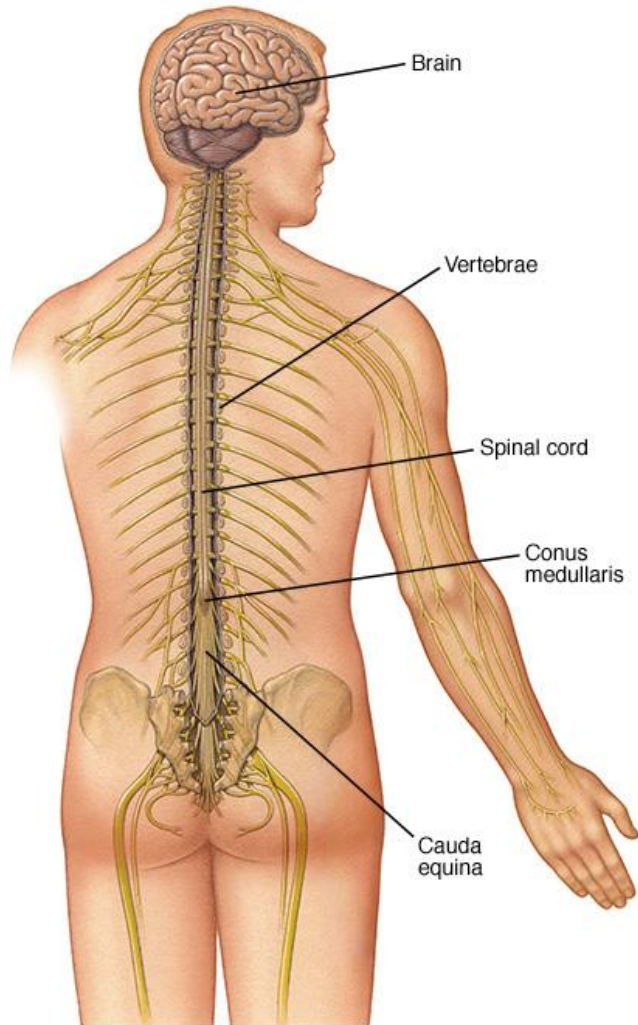
Twenty patients with fibromyalgia underwent neurological examination, nerve conduction studies, and skin biopsies from distal leg and thigh.

Results: Electrodiagnostic studies were normal in all patients. SFN was diagnosed in 6 patients by reduced epidermal nerve fiber density. These patients also showed abnormalities of both adrenergic and cholinergic fibers.

# Fibromyalgia and Small Fiber Polyneuropathy

**What is “small fiber polyneuropathy”?**

# Peripheral Nervous System



# Small Fiber Polyneuropathy (SFPN) Symptoms

**Small nerve function:** Sensation of pain, light touch, temperature and itching

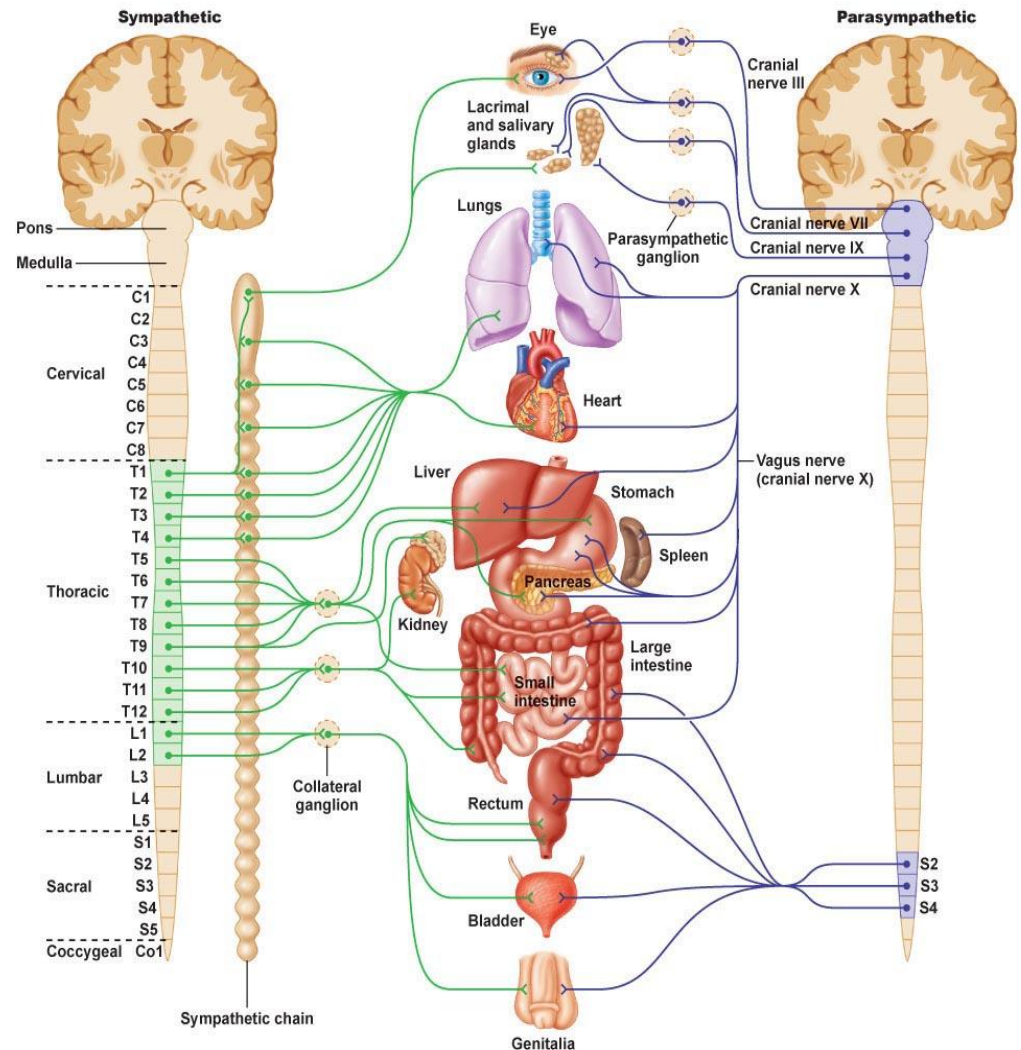
- Widespread pain (or itching) and sensory loss (numbness)
- Disturbances of sensation on the skin:
  - Tingling, pins and needles
  - Electric shock–like pain
  - Cold-like pain, burning sensation
  - Feeling of a wrinkle in a sock that cannot be removed
  - Small pebbles or sand in the shoe
  - Uncomfortable and painful feeling of the skin with touch (Allodynia)

*“The bed sheets are painful, and therefore, they wear socks or use “foot tents” to keep the sheets from making physical contact with the feet.”*

# Dysautonomia in SFPN

## Small nerve function: Performance of Autonomic Nervous System

- Dry eyes and dry mouth
- Blurry vision
- Cardiovascular dysfunction
  - Dizziness on standing, syncope, POTS, headache, “brain fog”
- Gastrointestinal symptoms
  - Bloating, nausea, feeling of “fullness”, diarrhea, constipation
- Bladder dysfunction
  - Frequent voiding, urinary urgency, difficulty to initiate urine stream
- Sexual dysfunction
- Abnormal sweating



# Small Fiber Polyneuropathy (SFPN) Diagnosis



## SFPN can be difficult to detect by exam

- ❖ No muscle weakness
- ❖ Sensory abnormalities sometimes cannot be measured

## Nerve conduction studies and EMG are normal in SFPN



## Sural nerve biopsy is an older test

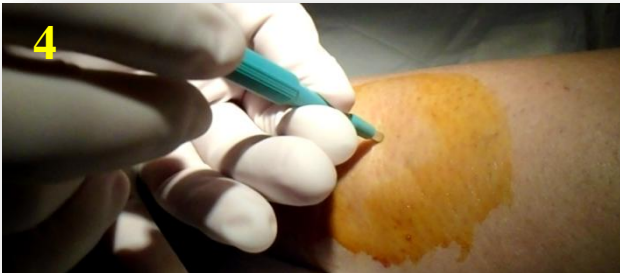
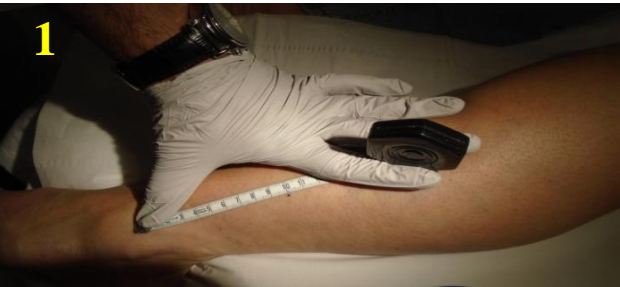
- ❖ Leaves a numb area
- ❖ Can cause neuralgia
- ❖ Can't be repeated



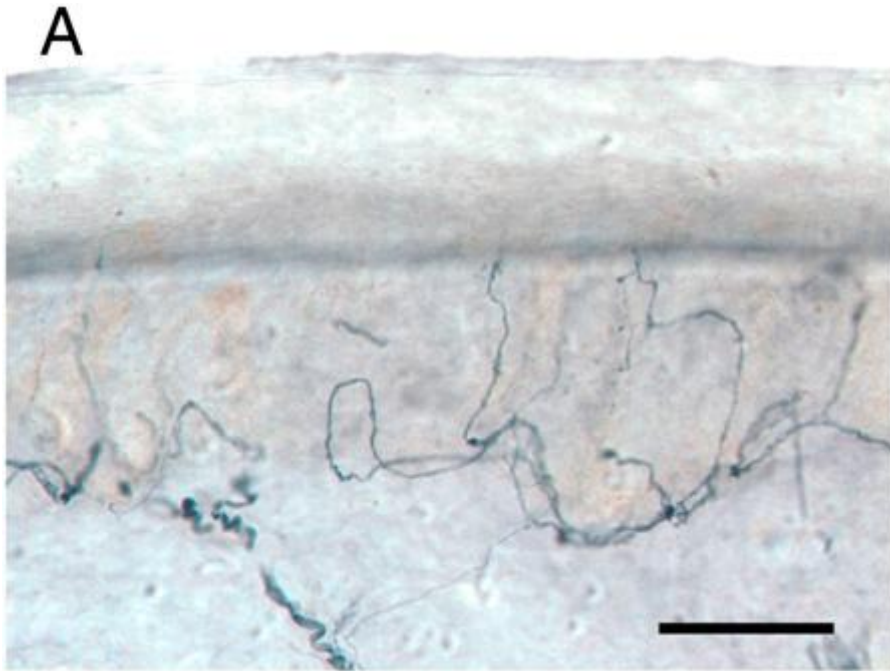


# Objective diagnosis of SFPN is made by Skin Biopsy

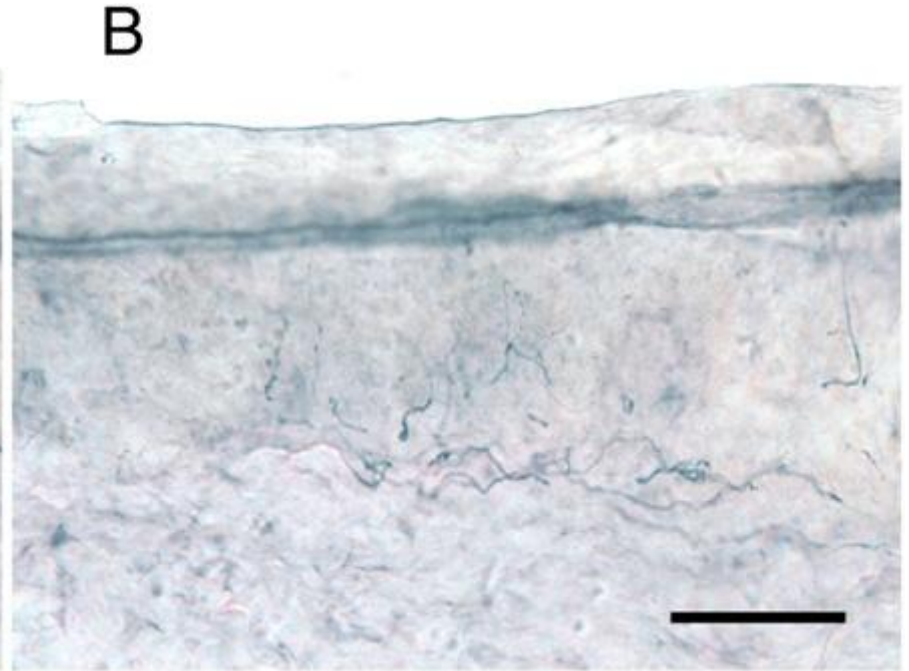
- 3 mm skin punch is removed from the lower leg using local anesthesia
- Samples are stained for a nerve marker (PGP9.5) to allow skin nerve fibers to be counted with light microscopy



# Epidermal Nerve Fiber Density



*Normal 18-year old white male  
has 675 axons/mm<sup>2</sup>*



*18-year old white male with chronic  
widespread pain has 155 axons/mm<sup>2</sup>*

(Oaklander and Klein, Pediatrics 2013)

# Autonomic Function Testing (AFT) is also endorsed for SFPN diagnosis



## Autonomic functions are controlled by small fibers

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

# Causes of Small Fiber Polyneuropathy

- **Metabolic:** Diabetes, Borderline diabetes, Thyroid dysfunction
- **Autoimmune diseases:** Sjögren's syndrome, Sarcoidosis, RA, SLE
- **Nutritional:** B12 & B6 deficiencies, B6 toxicity , Alcohol, Celiac disease
- **Infections:** HIV, Lyme, Hepatitis C, Hepatitis B
- **Medications:** chemotherapy, certain antibiotics, anti HIV medications
- **Paraproteinemias** (monoclonal proteins)
- **Amyloidosis**
- **Paraneoplastic** (cancer related)
- **Genetic**
- Despite extensive testing, in some patients the cause of neuropathy remains unknown: “idiopathic”



# How can SFPN be treated?

- Best is to treat the underlying cause of neuropathy
- Neuropathic pain medications can be used:
  - **Antidepressants** (Nortriptyline, Duloxetine, Milnacipran), **Antiepileptics** (Gabapentin, Pregabalin, Oxcarbazepine, Lamotrigine), **opioids** and **topical agents**
- Immunotherapy in selected patients with autoimmune causes that are not improving with symptomatic treatment

# Non-drug strategies to treat low blood pressure and high heart rate

- **Stand up slowly**, particularly after eating, urination, bowel movement
- **Increase salt and fluid intake**, to increase blood volume
- **Elevate head of the bed**
- **Compression stockings**, abdominal binders
- **Maximize tissue oxygenation**: no smoking, aerobic exercise
- **Avoid deconditioning and low-oxygen environments** : flying, high altitude
- **Treat anemia or low albumin**
  
- Referral to subspecialists with expertise on treating dysautonomia
  - Cardiologist: Dr Nancy Gracin at MGH
  - GI specialist: Dr Braden Kuo at MGH

# Conclusion

- Evaluating patients with chronic widespread pain/fibromyalgia for small fiber polyneuropathy may open avenues to treatment
- Skin biopsy is a simple and safe office test, but accurate interpretation requires an experienced lab with a large normative data set
- Mass General is the only hospital with normative data for young adults, teenagers and children
- Any doctor can order skin biopsy at MGH or other local providers
- Order forms on line at <https://NeuropathyCommons.org>
- Blood tests may identify causes of SFPN and permit definitive treatment for some patients



Thank you for your attention

**Table 4. Fibromyalgia diagnostic criteria**

**Criteria**

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

- 1) Widespread pain index (WPI)  $\geq 7$  and symptom severity (SS) scale score  $\geq 5$  or WPI 3–6 and SS scale score  $\geq 9$ .
- 2) Symptoms have been present at a similar level for at least 3 months.
- 3) The patient does not have a disorder that would otherwise explain the pain.

**Ascertainment**

- 1) WPI: note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.

Shoulder girdle, left	Hip (buttock, trochanter), left	Jaw, left	Upper back
Shoulder girdle, right	Hip (buttock, trochanter), right	Jaw, right	Lower back
Upper arm, left	Upper leg, left	Chest	Neck
Upper arm, right	Upper leg, right	Abdomen	
Lower arm, left	Lower leg, left		
Lower arm, right	Lower leg, right		

- 2) SS scale score:

Fatigue

Waking unrefreshed

Cognitive symptoms

For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:

0 = no problem

1 = slight or mild problems, generally mild or intermittent

2 = moderate, considerable problems, often present and/or at a moderate level

3 = severe: pervasive, continuous, life-disturbing problems

Considering somatic symptoms in general, indicate whether the patient has:\*

0 = no symptoms

1 = few symptoms

2 = a moderate number of symptoms

3 = a great deal of symptoms

The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.

\* Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

# Tests for treatable causes of small-fiber polyneuropathy

Patient name  
 Medical record number  
 Date of birth

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

## BLOOD TESTS TO CONSIDER FOR ADULTS

ordered today	not yet tested	abnormal value	normal value	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Complete blood count (if low, consider B12 or copper deficiency, lead/arsenic toxicity)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Chemistries (if high glucose test for DM; if renal dysfunction consider Fabry, mercury toxicity)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	AST, ALT (liver function; if abnormal consider hepatitis or alcohol)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Hemoglobin A1c (if elevated strongly consider testing for diabetes)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	TSH thyroid screening
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Vitamin B12 levels (if 200-500pg/dl consider testing for methylmalonic acid)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	ESR (sedimentation rate; if elevated, consider inflammatory/dysimmune conditions)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	ANA (antinuclear antibodies; higher titers suggest lupus or dysimmune conditions)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Complement components C3 and C4 (if low, consider dysimmune conditions)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Anti-Ro (SS-A) and anti-La (SS-B) (if present, consider Sjögren's disease)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CRP (C-reactive protein; if elevated, consider inflammatory/dysimmune conditions)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Hepatitis C serology (if abnormal consider testing for cryoglobulins)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Lyme antibodies by Western blot (for inhabitant or visitor to endemic area)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	SPEP/IFIX (immunofixation tests for lymphoproliferative disorders)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Free $\kappa/\lambda$ light chains (tests for less common lymphoproliferative disorders)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	IgA anti-TTG (transglutaminase antibodies; if present consider celiac sprue)

## TESTS TO CONSIDER IN SPECIFIC POPULATIONS

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2 hour, 75 g fasting glucose-tolerance test (strongly consider for all at risk for DM)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	HIV (CDC recommends everyone ages 13-64 be tested $\geq$ once, high-risk more often)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Methylmalonic acid (consider if vitamin B12 level less than 500 pg/dL)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Thiamine (if low, consider vitamin B1 deficiency)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Pyridoxine (if elevated, consider vitamin B6 neurotoxicity)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Anti-ds DNA, anti-Smith (consider if ANA present)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Cryoglobulins, cryofibrinogens, viscosity (consider for myeloma, hep C, RA, SLE)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Fasting serum triglycerides (can worsen diabetic polyneuropathy)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Urine protein electrophoresis to identify Bence Jones paraproteins
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	24 hour urine for arsenic, lead, mercury, cadmium (for artists, welders, miners)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	ACE (angiotensin converting enzyme; for sarcoidosis in patients with lung symptoms)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Phenotype-guided genetic sequencing esp. if family history (e.g., HSAN-1, SCN9A)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Abdominal fat-pad biopsy for amyloid
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OTHER TEST PERFORMED _____