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 2nd 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

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

<table>
<thead>
<tr>
<th>Points</th>
<th>No problem</th>
<th>Slight or mild problem</th>
<th>Moderate problem</th>
<th>Severe problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Trouble thinking or remembering</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Waking up tired (unrefreshed)</td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Points</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Pain or cramps in lower abdomen</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>B. Depression</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>C. Headache</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
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5. Do you have a disorder that would otherwise explain the pain?

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<thead>
<tr>
<th>No</th>
<th>Yes</th>
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</table>

ACR indicates American College of Rheumatology. Scoring information is shown in blue. The possible score ranges from 0 to 31 points; a score ≥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
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).
We analyzed records of 41 consecutive patients with chronic widespread pain that began before age 21

- 73% were female
- 68% were disabled

59% of patients were diagnosed with definite SFPN
Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia

Anne Louise Oaklander, MD, PhD\textsuperscript{1,2}, Zeva Daniela Herzog, BA\textsuperscript{1}, Heather Downs, BS\textsuperscript{1}, and Max M. Klein, PhD\textsuperscript{1}

\textsuperscript{1}Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, 02114

\textsuperscript{2}Department of Pathology (Neuropathology), Massachusetts General Hospital, Boston, Massachusetts, 02114

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,¹ Daniel Zeller,¹ Ann-Kathrin Kahn,¹ Susanne Kewenig,¹ Sarah Kittel-Schneider,² Annina Schmid,¹ Jordi Casanova-Molla,¹ Karlheinz Reiners¹ and Claudia Sommer¹

1 Department of Neurology, University of Würzburg, 97080 Würzburg, Germany
2 Department of Psychiatry, University of Würzburg, 97080 Würzburg, Germany

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. Caro¹ and Earl F. Winter²

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

Epidermal fiber density was significantly diminished in FM patients.
15 of 46 (32.6%) FM patients had reduced IENFD compared to healthy controls
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

Nerve conduction studies and EMG are normal in SFPN

SFPN can be difficult to detect by exam
- No muscle weakness
- Sensory abnormalities sometimes cannot be measured

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/mm²

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

(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”
# Tests for treatable causes of small-fiber polyneuropathy

| Date:        |  |  |

## BLOOD TESTS TO CONSIDER FOR ADULTS

- Complete blood count (if low, consider B12 or copper deficiency, lead arsenic toxicity)
- Chemistries (if high glucose test for DM, if renal dysfunction consider Fabry, mercury toxicity)
- AST, ALT (liver function; if abnormal consider hepatitis or alcohol)
- Hemoglobin A1c (if elevated strongly consider testing for diabetes)
- TSH thyroid screening
- Vitamin B12 levels (if 200-500 pg/dl consider testing for methylmalonic acid)
- ESR (sedimentation rate; if elevated, consider inflammatory/dysimmune conditions)
- ANA (antinuclear antibodies; higher titers suggest lupus or dysimmune conditions)
- Complement components C3 and C4 (if low, consider dysimmune conditions)
- Anti-Ro (SS-A) and anti-La (SS-B) (if present, consider Sjögren’s disease)
- CRP (C-reactive protein; if elevated, consider inflammatory/dysimmune conditions)
- Hepatitis C serology (if abnormal consider testing for cryoglobulins)
- Lyme antibodies by Western blot (for inhabitant or visitor to endemic area)
- SPEP/IFIX (immunofixation tests for lymphoproliferative disorders)
- Free κ/λ light chains (tests for less common lymphoproliferative disorders)
- IgA anti-IGG (transglutaminase antibodies; if present consider celiac sprue)
- ACE (angiotensin converting enzyme; if elevated consider sarcoidosis)

## TESTS TO CONSIDER IN SPECIFIC POPULATIONS

- 2 hour, 75 g fasting glucose-tolerance test (strongly consider for all at risk for DM)
- Methyleneal oxidase acid (consider if vitamin B12 level less than 500 pg/dl)
- Thiamine (if low, consider vitamin B1 deficiency)
- Pyridoxine (if elevated, consider vitamin B6 neurotoxicity)
- Anti- ds DNA, anti-Smith (consider if ANA present)
- Cryoglobulins, cryofibrinogens, viscosity (consider for myeloma, hsp C, RA, SLE)
- Fasting serum triglycerides (can worsen diabetic polyneuropathy)
- Urine protein electrophoresis to identify Bence Jones paraproteins
- 24 hour urine for arsenic, lead, mercury, cadmium (for artists, welders, miners)
- Phenotype-guided genetic sequencing esp. if family history (e.g., HBAN-1, SCN9A)
- Abdominal fat-pad biopsy for amyloid

Check medications e.g., therapy for cancer or HIV, statins, colchicine, isoniazid, dapsone, hydralazine, lithium, phenytin, vitamin B6, disulfiram, amiodarone, procainamide, perhexiline, streptokinase, nitrous oxide, metronidazole, nitrofurantoin, gold, thalidomide, TNF-antagonists, antimicrobials (chloramphenicol, fluoroquinolones, metronidazole, nitrofurantoin), history of GI surgery, malabsorption, alcoholism, work exposure to inorganic arsenic, thallium, mercury, industrial toxins, organophosphate insecticides.

## References


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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) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3–6 and SS scale score ≥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
   - Abdomen
   - Upper arm, right
   - Upper leg, right
   - Neck
   - Lower arm, left
   - Lower leg, left
   - Lower arm, right
   - Lower leg, right

2) SS scale score:
   - Fatigue
   - Waking unrefreshed
   - Cognitive symptoms
   For 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

<table>
<thead>
<tr>
<th>ordered today</th>
<th>not yet tested</th>
<th>abnormal value</th>
<th>normal value</th>
</tr>
</thead>
</table>

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- Chemistries (if high glucose test for DM; if renal dysfunction consider Fabry, mercury toxicity)
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- TSH thyroid screening
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**TESTS TO CONSIDER IN SPECIFIC POPULATIONS**

- 2 hour, 75 g fasting glucose-tolerance test (strongly consider for all at risk for DM)
- HIV (CDC recommends everyone ages 13-64 be tested ≥ once, high-risk more often)
- Methylmalonic acid (consider if vitamin B12 level less than 500 pg/dL)
- Thiamine (if low, consider vitamin B1 deficiency)
- Pyridoxine (if elevated, consider vitamin B6 neurotoxicity)
- Anti-ds DNA, anti-Smith (consider if ANA present)
- Cryoglobulins, cryofibrinogens, viscosity (consider for myeloma, hep C, RA, SLE)
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- Phenotype-guided genetic sequencing esp. if family history (e.g., HSAN-1, SCN9A)
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**OTHER TEST PERFORMED**