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

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ABSTRACT

Fibromyalgia is a common, disabling syndrome that includes chronic widespread pain plus diverse additional symptoms. No specific objective abnormalities have been identified, which precludes definitive testing, disease-modifying treatments, and identification of causes. In contrast, small-fiber polyneuropathy (SFPN), despite causing similar symptoms, is definitionally a disease caused by the dysfunction and degeneration of peripheral small-fiber neurons. SFPN has established causes, some diagnosable and definitively treatable, eg, diabetes. To evaluate the hypothesis that some patients labeled as having fibromyalgia have unrecognized SFPN that is causing their illness symptoms, we analyzed SFPN-associated symptoms, neurological examinations, and pathological and physiological markers in 27 patients with fibromyalgia and in 30 matched normal controls. Patients with fibromyalgia had to satisfy the 2010 American College of Rheumatology criteria plus present evidence of a physician's actual diagnosis of fibromyalgia. The study's instruments comprised the Michigan Neuropathy Screening Instrument (MNSI), the Utah Early Neuropathy Scale (UENS), distal-leg neurodiagnostic skin biopsies, plus autonomic-function testing (AFT). We found that 41% of skin biopsies from subjects with fibromyalgia vs 3% of biopsies from control subjects were diagnostic for SFPN, and MNSI and UENS scores were higher in patients with fibromyalgia than in control subjects (all $P \leqslant 0.001$). Abnormal AFTs were equally prevalent, suggesting that fibromyalgia-associated SFPN is primarily somatic. Blood tests from subjects with fibromyalgia and SFPN-diagnostic skin biopsies provided insights into causes. All glucose tolerance tests were normal, but 8 subjects had dysimmune markers, 2 had hepatitis C serologies, and 1 family had apparent genetic causality. These findings suggest that some patients with chronic pain labeled as fibromyalgia have unrecognized SFPN, a distinct disease that can be tested for objectively and sometimes treated definitively.

1. Introduction

Fibromyalgia syndrome (FMS) is a collection of ill-defined symptoms that includes chronic widespread pain (CWP; defined as $\geqslant$3 months of axial, plus left- and right-side, plus upper- and lower-body pain [51]). FMS is common, having 1% to 5% prevalence in Western countries, affecting females 3 to 4 times more commonly than males, and conveying high health-care costs [29,49,50]. The American College of Rheumatology formulated and revised the diagnostic criteria that raised awareness of FMS and facilitated approval of medications to palliate symptoms [51,52], but the biological causes of FMS have remained unknown. Recent interpretations emphasize a biopsychosocial model in which "central sensitization" causes painful responses to stress and stimuli. However, the brain-imaging alterations in patients with FMS that engendered this hypothesis [17,22] were later reinterpreted as being nonspecific consequences rather than causal [21,40,47].

Small-fiber polyneuropathy (SFPN) is a neurological cause of CWP. Unlike FMS, SFPN has identifiable pathology, physiology and causes and thus is definitionally a disease. SFPN is caused by dysfunction and degeneration of the small-diameter unmyelinated (C-fibers) and thinly myelinated (A-delta) peripheral axons that mediate nociception. Symptoms usually begin distally with foot or leg pain, but advanced cases can spread proximally to involve the torso as well. Occasional patients begin with patchy, proximal or generalized (non–length-dependent) symptoms caused by attack directed at the neuronal cell bodies (ganglionopathy or neuronopathy) [16]. Many patients with SFPN also have

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cardiovascular, gastrointestinal, microvascular, or sweating complaints resulting from disturbed efferent effects of somatic and autonomic small-fibers on internal organs, blood vessels, and sweat glands [15,20].

SFPN often remains undiagnosed because complaints of CWP are subjective and nonspecific, and patients' strength and reflexes are usually preserved on examination. Diagnostic testing using surface electromyography and nerve-conduction studies is insensitive to SFPN. The best objective diagnostic tests for SFPN are distal-leg skin biopsy immunolabeled to reveal the density of small-fiber epidermal innervation (level C recommendation by the American Academy of Neurology; level A recommendation by the European Federation of Neurological Societies [8,28]), and autonomic function testing (AFT) of cardiovagal, adrenergic, and sudomotor small-fiber function (American Academy of Neurology level B recommendation [1,8]). Quantitative sensory testing is not recommended because it relies on subjective reports [12]. The best instruments for measuring the symptoms and signs of SFPN are those applied in this study. The value of diagnosing SFPN is that sometimes its causes can be identified and the disorder cured. Common causes of SFPN include diabetes, hematological malignancies, autoimmune conditions, infections, toxins (including medications), and genetic mutations [4,9].

SFPN and FMS have symptoms in common—not only multifocal CWP, but also Raynaud phenomena, dizziness, gastrointestinal and urological symptoms, fatigue, and headache [4], and many patients with SFPN report that their illness had been interpreted as FMS prior to diagnosis of SFPN. Electrodiagnostic testing of 58 patients labeled as having fibromyalgia for large-fiber demyelinating polyneuropathy found neuropathic abnormalities in 33% [6], and comparing sensory symptoms among 1434 patients with FMS and 1623 patients with painful diabetic polyneuropathy identified some commonalities [26]. Several recent abstracts suggest that SFPN and FMS may overlap [41,44,45]. Our discovery of objectively confirmed SFPN in 59% of patients with childhood-onset CWP [37], many originally labeled as having FMS, prompted this study.

2. Methods and subjects

2.1. Study design and subject recruitment

All procedures and protocols were approved by the institutional review board. Sample-size calculations assuming $\alpha = 0.05$ indicated that studying 33 subjects per group would have 90% power to detect a large effect size (0.8), and groups of 25 would have 80% power, so we planned for groups of 25 to 30. Recruitment strategies included print and e-mail advertising at Massachusetts General Hospital (MGH) and e-mail to MGH's Clinical Research database of $\geqslant$22,000 preregistered people interested in participation in clinical research (http://www.rsvpforhealth.partners.org/). No subjects were recruited from any neurology practice or clinic. We digitally searched MGH's medical records to identify patients with fibromyalgia, to whom we mailed a description of this study through their primary-care provider. We also recruited through fibromyalgia support groups on the social networking sites Facebook and Meetup.com. Respondents were telephone-screened for inclusion (see criteria below); medical records confirming prior FMS diagnoses were obtained; and all eligible respondents were invited for study (Fig. 1). Asymptomatic volunteers were selected on the basis of demographic characteristics that matched those of the cohort with FMS.

Inclusion criteria for all subjects were that they be at least 18 years old and have the ability to comprehend and execute the protocol. Exclusion criteria comprised inability to give informed consent and contraindication to AFT or skin biopsy. FMS subjects were additionally required to submit medical records that documented a prior independent physician's diagnosis of fibromyalgia, plus they were required to fulfill the American College of Rheumatology (ACR) 2010 diagnostic criteria for FMS as assessed by questionnaire [51]. These criteria require a score $\geqslant$7 on the widespread-pain inventory plus a score $\geqslant$5 on the symptom severity scale, or $\leqslant$3 on the widespread-pain inventory, or $\leqslant$6 if the symptom severity scale was $\geqslant$9 [51].

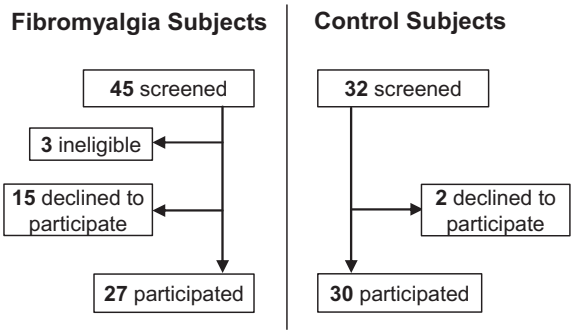

Fig. 1. Enrollment.

2.2. Data acquisition

To quantitate symptoms, subjects consented to complete the Michigan Neuropathy Screening Instrument questionnaire (MNSI), which consists of 15 yes/no questions concerning foot sensation, including pain, numbness and sensitivity to temperature [11,34]. For diabetic small-fiber–predominant polyneuropathy, the sensitivity of the MNSI was 80%, specificity was 95%, positive predictive value was 97%, and negative predictive value was 74% [11]. All subjects also underwent targeted neurological examination, which was codified using the Utah Early Neuropathy Scale (UENS), a neurological examination of the lower legs and feet designed to detect small-fiber–predominant sensory neuropathy [43]. It focuses particularly on loss of small-fiber–mediated pin-evoked nociception. To provide additional information about the representativeness of the FMS and control samples, all subjects completed the Beck Depression Inventory (BDI-21) and the Medical Outcomes Study Short Form Health Survey (SF-36). These validated questionnaires have known profiles among patients with FMS and normal controls [2,3,23]. Subjects were compensated $100 plus parking expenses. Data were managed using the Harvard Clinical and Translational Science Center's secure online Research Electronic Data Capture (REDCap) platform [18], and the accuracy of data entry was verified.

Neurodiagnostic skin biopsies were processed and analyzed by our accredited clinical diagnostic laboratory according to consensus standards [8,27]. We removed 2 or 3 mm diameter skin punches from the anesthetized standard distal-leg site. Free-floating 50 μm vertical sections were immunohistochemically labeled against PGP9.5, a pan-neuronal marker (Chemicon, Temecula, CA) to reveal epidermal nerve fibers (ENFs) and permit standard measurements of their density (Fig. 2) [4,8,28]. Almost all PGP9.5-immunoreactive epidermal neurites are nociceptive small-fiber endings, and axonal localization of epidermal PGP9.5 immunolabeling has been verified ultrastructurally [42,48]. A single skilled morphometrist blinded to group allocation measured ENF density. Our laboratory reports ENF densities per mm^2 skin surface area to control for varying skin-section thickness between laboratories. Skin-biopsy corroboration of SFPN required meeting the standard clinical diagnostic criteria for SFPN diagnosis, namely ENF density <5th centile of predicted laboratory norm [28]. Our laboratory's sex-, age-, and race-specific norms are based on the multivariate analysis of 240 screened biopsies from normal volunteers [25].

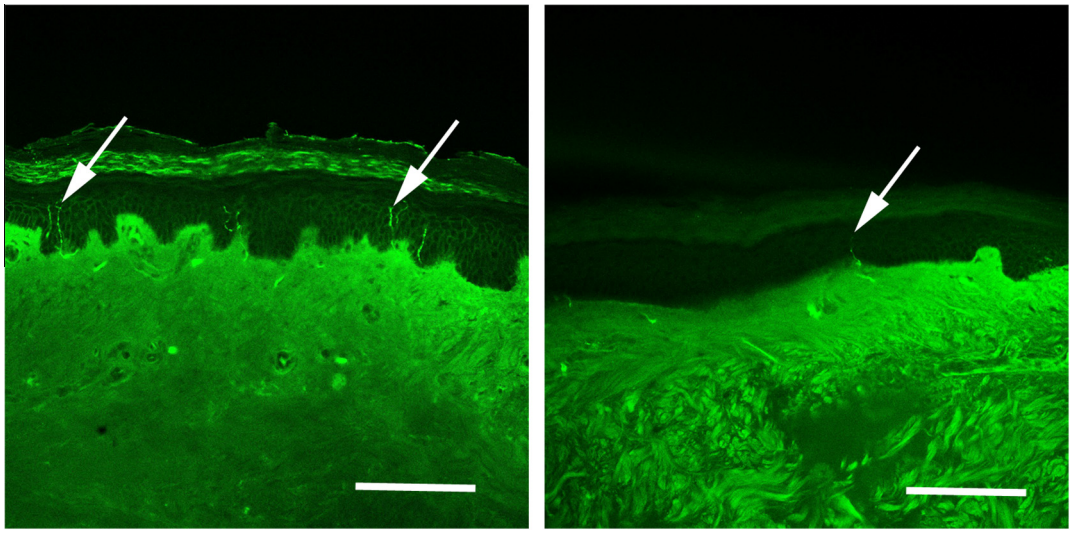

Fig. 2. Immunohistochemical visualization of sensory nerve endings in distal-leg skin biopsy by anti-PGP9.5-immunoreactivity. Arrows depict labeled axons. (A) Biopsy from 44-year-old Caucasian female, control subject with normal density of epidermal innervation (337 neurites/mm^2 skin surface area; at the 76th centile of predicted value). (B) Biopsy from 47-year-old Caucasian female, fibromyalgia subject with reduced density of epidermal innervation diagnostic for small-fiber polyneuropathy (135 neurites/mm^2 skin surface area; at the 3rd centile of predicted value). Bars represent 50 μm.

AFT was also performed using standard clinical diagnostic methods, equipment (WR Medical Electronics, Stillwater, MN), and interpretations recommended for SFPN diagnosis [1,8]. Subjects were directed to avoid wearing compressive clothing and to not smoke, eat or consume alcohol or caffeine for 4 h preceding testing. Their medications were reviewed, and potentially interfering medications were held for 24 to 48 h before testing (including all medications with anticholinergic effects, pain medications, antidepressants, antihistamines, cough and cold remedies, and cardiovascular modulators, including adrenergics, diuretics, antihypotensive agents, and attention-deficit medications [9,33]). We measured heart-rate variability to deep breathing (6/m while supine) and the Valsalva maneuver, hemodynamic responses to 80 degrees head-up tilt for 10 m, and acetylcholine-evoked sweat production. We applied the sole validated quantitative scoring system (Composite Autonomic Scoring Scale) [30] and later modifications [33,35,36], incorporating equipment-specific reference ranges. Corroboration of SFPN by AFT required at least 2 of 4 abnormal AFT subtest results. Standard sex- and age-adjusted definitions of abnormality were used: abnormal heart-rate response to deep breathing comprised <2.5th centile of predicted norm, and abnormal response to the Valsalva maneuver comprised no change in phase II, or Valsalva ratio <2.5th centile [33]. Abnormal tilt-table responses comprised change in heart rate $\geqslant$30, reductions in systolic blood-pressure $\geqslant$20 or reductions in diastolic blood-pressure $\geqslant$10 [13,33]. Abnormal sweat production comprised at least 2 sites with <50% of the 5th centile of norm for sex and age [33]. Because we used a Q-Sweat machine but published diagnostic norms use quantitative sudomotor axon reflex testing (QSART) units [32], we converted our measurements to QSART.

2.3. Outcome variables and data analysis

We followed consensus diagnostic criteria for SFPN in adults or children [7], and standard clinical practice in accepting any one or more objective-test results consistent with SFPN as confirming the diagnosis in a person who had sought medical help for otherwise unexplained symptoms consistent with SFPN [8,28]. Summary statistics comprised group means ± standard errors. Proportions of abnormal results were compared between groups by χ^2analysis.

3. Results

3.1. Validation of study groups

Table 1 demonstrates that the patients with fibromyalgia and control subjects were demographically similar, and that the patients with FMS were similar in age, sex and race to larger cohorts of patients with FMS, including those used to define the syndrome [39,51]. The mean age at onset of FMS in the current cohort was 28.8 ± 3.0 yr, and illness duration averaged 19.1 ± 2.7 yr. Scores on the BDI identified control subjects as not depressed and FMS subjects as mildly depressed on average, consistent with prior FMS cohorts [3,23]. The physical and mental component scores of the SF-36 identified control subjects as being at or near the population mean of 50, whereas patients with FMS had significantly lower scores, consistent with illness (both $P < 0.001$; Table 1). The mean mental component scores score in patients with FMS (40.2) was very similar to the mental component scores reported in larger FMS cohorts (38.6, 43.1), but their physical component scores (35.6) were less abnormal (28.0, 29.6), suggesting that the current sample may have had slightly less physical disability than historical FMS cohorts (as reviewed in [19]).

3.2. Symptoms and neurological-examination signs consistent with SFPN

The MNSI has a range of possible scores between 0 and 15, in which abnormal was previously defined as >2 [34]. The MNSI scores of 28 control subjects were, on average, in the normal range (1.3 ± 0.3), whereas scores of the 23 FMS subjects were, on average, abnormal and consistent with polyneuropathy (5.8 ± 0.6, $P \leqslant 0.001$; Table 1). Results of the UENS standardized neurological examination were available from 27 patients with FMS and 26 control subjects. UENS scores can range between 0 and 42, with the ideal score being 0. There is no established cutoff between normal and abnormal UENS scores, but the scores of patients with FMS were significantly higher than the scores of control subjects (3.1 ± 0.7 vs 0.5 ± 0.2, $P \leqslant 0.001$; Table 1), providing evidence that the FMS group but not the control group had examination findings consistent with SFPN. Fig. 3 depicts the differing categories of

Table 1
Summary statistics for all study participants.

Characteristic	Fibromyalgia subjects, n = 27	Control subjects, n = 30	*P* value
Demographic variables			
Age, mean yr (± SEM)	46.5 (2.3)	44.8 (1.9)	0.576
Age range, yr	26–68	25–65	–
Female sex, no.(%)	20 (74.1%)	24 (80.0%)	0.460
White race, no. (%)	21 (77.8%)	22 (73.3%)	0.361
Duration of fibromyalgia symptoms, mean yr (±SEM)	19.1 (2.7)		
Objective test results			
ENF density < 5%, no. (%)[a]	11 (40.7%)	1 (3.4%)	1.14×10^{-24}
Abnormal AFT, no. (%)[b]	5 (19.2%)	4 (13.3%)	0.271
One or more of the above, no. (%)[c]	13 (50.0%)	5 (17.2%)	2.40×10^{-5}
Signs and symptoms (range, healthy → ill)			
MNSI, mean ± SEM (range, 0–15; abnormal >2)	5.8 ± 0.6	1.3 ± 0.3	2.11×10^{-9}
UENS ± SEM (range, 0–42; ideal = 0)	3.1 ± 0.7	0.5 ± 0.2	6.21×10^{-4}
BDI, mean ± SEM (range, 0–63; ideal = 0)	14.4 ± 1.8	3.3 ± 0.8	4.35×10^{-7}
SF-36 PCS ± SEM (range, 100–0, μ = 50, SD = 10)	35.6 ± 2.1	52.5 ± 1.4	8.07×10^{-9}
SF-36 MCS ± SEM (range, 100–0, μ = 50, SD = 10)	40.2 ± 2.4	54.7 ± 1.2	1.26×10^{-6}

AFT, autonomic function test; BDI, Beck Depression Inventory; ENF, epidermal nerve fiber; MCS, mental component summary; MNSI, Michigan Neuropathy Screening Instrument; PCS, physical component summary; SEM, standard error of the mean; SF-36, Medical Outcomes Study Short Form Health Survey; SFPN, small-fiber polyneuropathy; UENS, Utah Early Neuropathy Scale.
[a] One control subject declined biopsy.
[b] One fibromyalgia subject withdrew from sweat test.
[c] Three FMS subjects had both abnormal ENF density and abnormal AFT results.

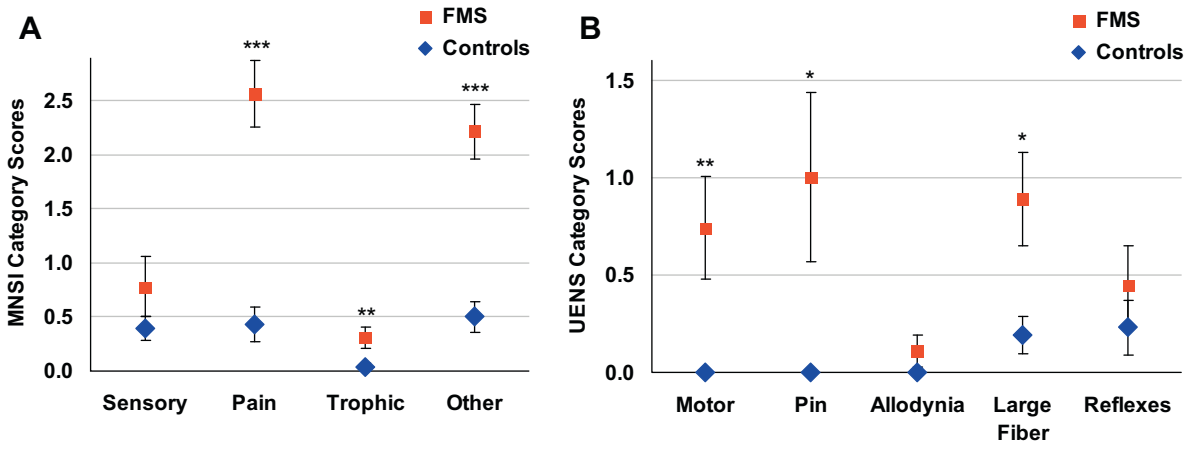

Fig. 3. Evidence of SFPN from neuropathy symptom scales. (A) Comparison of Michigan Neuropathy Screening Instrument scores for subjects with FMS and control subjects by questionnaire category. Sensory comprised MNSI questions 1, 7 and 13; pain comprised questions 2, 3, 5, 6, and 12; trophic comprised questions 8, 14 and 15; other comprised questions 4, 9, 10, and 11. (B) Comparison of Utah Early Neuropathy Scale scores for subjects with FMS and control subjects by examination category: motor (great-toe extension); pin (absent and reduced sensation); allodynia (in toes and foot); large fiber sensation (vibration and great-toe position); and reflexes (deep tendon at the ankle). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

results from the MNSI and UENS. The lack of allodynia among patients with FMS on both the UENS and the sensory category of the MNSI was of interest.

3.3. Objective tests corroborative of SFPN diagnosis

Overall, 50% of subjects with fibromyalgia as opposed to 17% of controls had one or more objective test results consistent with SFPN ($P \leqslant 0.001$; Table 1). Skin-biopsy results (Fig. 2) drove this difference, with 41% of biopsies from FMS patients vs 3% of biopsies from control subjects having ENF densities <5th centile of predicted laboratory norm ($P \leqslant 0.001$; Table 1). One control subject met skin-biopsy criteria for SFPN without having corresponding symptoms or signs (ENF <1st centile; MNSI score ⩽2; UENS score, 0). This was tentatively attributed to a concurrent diagnosis of multiple endocrine neoplasia-2, including thyroid cancer, which has been associated with axonopathy [5]. In contrast, AFT results were similar overall between patients with fibromyalgia and control subjects ($P = 0.27$; Table 1). One subject from each group had abnormally reduced heart-rate changes during deep breathing ($P = 0.46$); 7 FMS subjects vs 3 controls had abnormal responses to Valsalva ($P = 0.0006$); 9 subjects in each group had abnormal responses to tilt ($P = 0.50$); and 4 FMS subjects vs 0 controls had low sweat production at more than 1 site (P undefined).

3.4. Comparing results from fibromyalgia subjects with vs. without skin biopsies corroborative of SFPN

Given the highly significant differences in skin-biopsy results and the lack of differences in AFT results between FMS and control subjects, we performed a secondary analysis to compare the other test results between FMS subjects who did or did not meet skin-biopsy criteria for SFPN. Table 2 demonstrates that FMS subjects with SFPN-diagnostic skin biopsies were similar in sex and age

Table 2
Summary statistics comparing FMS subjects with or without objective evidence of SFPN.

Characteristic	FMS subjects with objective evidence of SFPN, n = 13	FMS subjects without objective evidence of SFPN, n = 14	*P* value
Demographic variables			
Age, mean yr (± SEM)	46.4 (2.8)	46.7 (3.7)	0.951
Age range, yr	26–63	28–68	–
Female sex, no. (%)	9 (69.2%)	11 (78.6%)[a]	0.404
White race, no. (%)	13 (100.0%)	8 (57.1%)	0.003
Outcomes (range, normal → abnormal)			
ENF, mean centile (± SEM)	3.8 (1.9)	48.2 (7.2)	0.00001
ENF density <5%, no. (%)[b]	11 (84.6%)	0 (0.0%)	
Abnormal AFT, no. (%)	5 (38.5%)	0 (0.0%)	
MNSI, mean ± SEM (range, 0–15; abnormal >2)	6.6 ± 0.6	4.7 ± 0.9	0.085
UENS ± SEM (range, 0–42; ideal, 0)	3.8 ± 1.2	2.5 ± 0.8	0.340
BDI, mean ± SEM (range, 0–63; ideal, 0)	18.5 ± 2.5	10.7 ± 2.2	0.028
SF-36 PCS ± SEM (range, 100–0, μ, 50, SD, 10)	35.5 ± 3.6	35.7 ± 2.3	0.963
SF-36 MCS ± SEM (range, 100–0, μ, 50, SD, 10)	35.1 ± 2.8	44.9 ± 3.4	0.038

AFT, autonomic function test; BDI, Beck Depression Inventory; ENF, epidermal nerve fiber; MCS, mental component summary; MNSI, Michigan Neuropathy Screening Instrument; PCS, physical component summary; SEM, standard error of the mean; SF-36, Medical Outcomes Study Short Form Health Survey; SFPN, small-fiber polyneuropathy; UENS, Utah Early Neuropathy Scale.
[a] 6 of 11 women were white.
[b] 3 FMS subjects had ENF density <5% plus abnormal AFT.

(70% female, mean age 46.4 ± 2.8 yr) to FMS subjects with nondiagnostic skin biopsies (77% female, mean age 46.7 ± 3.7 yr). However, all FMS/SFPN subjects were Caucasian, compared to only 57% of non-SFPN/FMS subjects ($P = 0.003$). The mean ENF centile value among FMS/SFPN subjects was 3.8 ± 1.9, whereas it was at the population mean (48.2 ± 7.2) among non-SFPN/FMS subjects ($P < 0.001$). Additionally, 39% of SFPN/FMS subjects had abnormal AFT results, whereas 0 non-SFPN/FMS subjects had such results. On the MNSI, UENS, BDI, and SF-36, both groups had largely similar results (Table 2).

3.5. Underlying causes of SFPN in patients with fibromyalgia

Testing for known causes of SFPN in FMS/SFPN subjects had not been planned, but it was requested by so many subjects with skin biopsies diagnostic for SFPN that we offered the recommended blood tests to all of them [9]. All 13 FMS/SFPN subjects had hemoglobin A_{1C} <6.0 mg/dL. For 2-h glucose-tolerance tests (75 g load) 8 of 11 subjects were normal according the current criteria of the American Diabetes Association. Two subjects had barely impaired fasting glucose levels (100 mg/dL and 102 mg/dL), one accompanied by marginal glucose intolerance (2 h = 140 mg/dL). The 2 FMS/SFPN subjects who did not undergo glucose-tolerance tests had normal random glucose levels (90 and 100 mg/dL). In contrast, 2 of 11 patients tested positive for hepatitis C, 1 a known case, the other a new diagnosis. All 13 subjects had noncontributory serum chemistries, blood counts, thyroid function, folate levels, triglycerides, C-reactive protein, angiotensin converting enzyme, tests for Lyme disease, lupus, Sjögren's disease, and celiac (IgA tissue-transglutaminase autoantibodies). None of the 12 subjects tested by immunofixation had monoclonal gammopathies. All of the 11 subjects tested had vitamin B_{12} levels within the reference range.

The most common blood-test abnormalities in subjects with FMS/SFPN were serological markers of dysimmunity that have been associated with juvenile-onset SFPN [37]. Specifically, 5 of 13 subjects had elevated erythrocyte sedimentation rates ($\geqslant$25 mm/h); 4 of 13 had antinuclear antibodies at titers greater than or equal to 1:160; and 3 of 13 had low complement C4, with 2 of 3 also having low complement C3 [37]. Overall, 62% of FMS/SFPN subjects had 1 or more of the markers of dysimmune function.

3.6. Adverse events

Skin biopsy caused no adverse events, but 1 subject suffered 2 small second-degree burns during sweat testing. Detailed investigation implicated faulty grounding electrodes, and there were no further events after new ground pads were substituted.

4. Discussion

The current results demonstrate that half of a small community-based sample of patients with FMS also had symptoms, signs, and objective test results that are accepted as diagnostic for SFPN, a biologically plausible cause of their symptoms of FMS. The difference between the labels FMS and SFPN is not merely semantic; SFPN is an established disease, and considerable information has been established about pathogenesis, whereas FMS is an aggregate of symptoms without prior evidence of a biological basis. Unlike FMS, SFPN can be objectively tested for (as here), and some causes of SFPN can be definitively treated, so advancing a patient's "diagnosis" beyond FMS to SFPN suggests potential causes, some of which can be tested for and treated. Skin biopsy (Fig. 2) corroborated SFPN in 41% of FMS subjects as opposed to 3% of normal controls, whereas both groups had similar results in autonomic function testing, implicating a primarily somatic and distal small-fiber polyneuropathy affecting pain neurons. This is consistent with the centrality of CWP rather than dysautonomic symptoms as the defining feature of the FMS phenotype.

This prospective study is limited by its small size. It was designed to detect large but not small effects, so AFT should be reevaluated in a larger cohort, particularly sweat production and responses to Valsalva for which FMS patients differed from controls. The observation that FMS subjects with SFPN were more likely to be Caucasians than those without SFPN ($P = 0.003$) also needs reevaluation in a larger study. However small, our FMS group was demographically representative of larger FMS cohorts, eg, the 258 patients from whom the current ACR diagnostic criteria were derived (92% female, mean age 55 yr, 87% non-Hispanic white [51]) and a community-based cohort of 10,129 patients with FMS (63% female, mean age 46 yr, races not reported [39]). Another limitation is the uncertain sensitivity and specificity of skin biopsy and autonomic function testing. There is no absolute or gold-standard

diagnostic test for SFPN against which to measure them, so their sensitivity and specificity cannot be defined except as relative to each other. Even these best-available tests are imperfect; indeed 13% of control subjects had abnormal AFT results. Tilt-table abnormalities were most common, consistent with the prevalence of orthostatic hypotension in the general population [31]. In contrast, skin biopsy, which measures late-stage axonal degeneration, had 97% specificity among control subjects in the current study. Another limitation is that we did not test subjects for other types of neuropathy, such as demyelinating neuropathies, motor or large-fiber sensory axonopathies, focal lesions, and auditory neuropathies. There is increasing recognition that different types of neurons are affected to varying extents in most polyneuropathies, regardless of how they are classified, particularly in severe or long-standing cases, and evidence of large-fiber motor or sensory polyneuropathy does not invalidate the presence of small-fiber polyneuropathy.

Strengths of the study included recruitment from the community so as to minimize referral or investigator bias, and use of rigorous inclusion criteria for FMS. We required both a preexisting, independent FMS diagnosis plus satisfying ACR research criteria, because they can be discordant [24]. The similarly rigorous and consensus-based evaluation for SFPN was an additional strength. Of note, both physiological (AFT) and anatomical tests for small-fiber polyneuropathy were applied. We also included assessments of depression and disability, which helped to validate the representative nature of the study samples.

Another strength is that we acquired data regarding potential underlying causes of SFPN in subjects with SFPN-diagnostic skin biopsies. We did not study controls because the definition of *abnormal* in clinical blood tests is based on extensive testing in normal as well as non-normal samples. Although diabetes is the most common cause of SFPN in developed countries, we found no evidence of causal contributions from diabetes or hyperglycemia. In contrast, 2 of 11 patients tested positive for hepatitis C, including 1 previously undiagnosed patient who was referred for treatment of hepatitis C because most cases are now curable. Among our patients, several had serological markers of autoimmunity that have been associated with juvenile-onset SFPN, a newly characterized type of SFPN that is associated with organ-specific, complement-consuming, humoral dysimmunity and with some favorable responses to immunomodulatory treatments [37,38]. Although most of the FMS subjects were middle-aged at the time of study, they reported onset of their FMS in youth, meaning that some could have had long-standing cases of juvenile-onset SFPN.

It was found that 3 of the subjects with FM/SFPN were related—a mother and 2 daughters. Given these study results, other members of their family who also suffered from juvenile-onset FMS sought evaluation for SFPN, leading to revised diagnoses of objectively confirmed SFPN in at least 6 family members in 4 generations. A genetic cause was presumed, and genetic evaluation was recommended. The well-known hereditary sensory and autonomic neuropathies were considered unlikely because of the absence of trophic signs (eg, painless ulcers). SFPN has been linked more recently to gain-of-function mutations in the *SCN9A* gene encoding the Nav1.7 sodium-channel isoform that is preferentially expressed in small-fiber nociceptive neurons, but commercial tests are not yet widely available [10]. FMS has also been associated recently with a specific *SCN9A* polymorphism [46], providing potential additional evidence of the convergence between FMS and SFPN. Although there is no cure for the genetic forms of SFPN yet, a trial of L-serine is under way for hereditary sensory and autonomic neuropathy-1 [14], and identifying specific mutations can guide patients toward targeted therapies not usually considered for patients with FMS, such as sodium-channel blockers.

In conclusion, this study provides objective evidence that almost half of a small sample of patients labeled with FMS have objective evidence of a neurological cause of their CWP and other symptoms of fibromyalgia, namely SFPN, a distinct peripheral-nerve disease. Blood tests in the small group of SFPN-diagnosed patients suggested that known causes of SFPN in the young (dysimmune, genetic, and infectious) were more common than causes of SFPN in maturity (eg, diabetes, cancer, vitamin deficiencies, or toxins), and they identified some treatable or curable causes such as hepatitis C. Patients currently carrying the FMS label may wish to discuss with their physicians whether testing for SFPN and its underlying causes might help them.

Conflicts of interest statement

None of the authors have conflicts of interest with respect to this work.

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