FIBROMYALGIA SYNDROME AND SMALL FIBER, EARLY OR MILD SENSORY POLYNEUROPATHY

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ABSTRACT: Introduction: Pain mechanisms in fibromyalgia syndrome (FMS) are not clearly understood. Growing evidence suggests a role for small fiber polyneuropathy (SFPN) in some FMS patients, as measured by epidemial nerve fiber density (ENFD). We aimed to better characterize and distinguish the subset of patients with both fibromyalgia and small fiber, early or mild sensory polyneuropathy (FM-SFSPN). Methods: 155 FMS patients with neuropathic symptoms completed a Short Form McGill Questionnaire and visual analog scale in addition to having skin biopsies, nerve conduction studies (NCS), and serologic testing. Results: Sural and medial plantar (MP) response amplitudes correlated with ENFD, with markers of metabolic syndrome being more prevalent in this subset of patients. Pain intensity and quality did not distinguish patients. Discussion: The FM-SFSPN subset of patients may be identified through sural and MP sensory NCS and/or skin biopsy but cannot be identified by pain features and intensity.

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Fibromyalgia syndrome (FMS) is a well-recognized and common disorder of chronic widespread pain characterized by specific criteria set out by the American College of Rheumatology (ACR). In 2010, these criteria were revised to remove the need for tender points on exam, leaving specific, clinical features that were deemed vital to the diagnosis: (i) widespread pain (widespread pain index of ≥7 regions); (ii) at least moderate severity (symptom severity score ≥5) of pain, fatigue, sleep disruption, and cognitive symptoms; (iii) duration of symptoms ≥3 months; and (iv) absence of a disorder that would otherwise explain the disorder. Criteria are also satisfied if only 3–6 regions are affected by pain but symptoms are more severe (severity score ≥9).2 Therefore, patient-reported metrics are central to the diagnosis. The term myalgia suggests the disorder derives at least in part from muscle. However, the co-existence of neuropathic features of pain and a burgeoning literature implicating small fiber axonal loss in the setting of fibromyalgia (FM), has raised the question of whether the pain in FMS is actually a neuropathic phenomenon.2–7

Small fiber polyneuropathy (SFPN) refers to selective loss of unmyelinated C and thinly myelinated Aδ fibers that mediate pain, heat, and cold sensation, respectively. As these fibers are not detected on nerve conduction studies (NCS) and physical exam findings may often be minimal or normal,8 the diagnosis relies heavily on the demonstration of reduced epidermal nerve fiber (ENF) density (ENFD) on skin biopsy.9–11 While reduced ENFD is not absolutely specific for SFPN, it is currently the best objective measure. SFPN is classically slowly progressive and length dependent in onset, although non-length dependent forms exist.12 Some patients present with an abrupt, generalized onset of SFPN injury, deemed small fiber ganglionopathy or non-length dependent small fiber neuropathy.12 Both of these entities of small fiber axonal loss can be associated with potentially treatable etiologies.13 Therefore, identification of a small fiber or early sensory neuropathy in the setting of widespread pain is important and carries clinical management implications.

Recent studies have demonstrated that a substantial proportion of patients who carry the diagnosis of FMS have reduced ENFD at the distal leg, as diagnosed by punch biopsy.2–6,14,15 Indeed, up to 50–61% of patients with FMS may have undiagnosed SFPN.3,15 Many studies have captured the neuropathic nature of fibromyalgia pain, using such measures as the Neuropathic Pain Symptom Inventory,
the visual analog scale (VAS), the Michigan Neuropathy Screening Instrument, the Utah Early Neuropathy, the Pain Questionnaire; electrodiagnostic study, including testing of distal (sural and plantar) nerve action potentials; quantitative sudomotor axon reflex testing (QSART); skin biopsy; and serologic studies.

Patients were included in the assessment if the diagnosis of FMS was independently confirmed using the 2010 ACR criteria. Because ACR criteria requires the absence of a disorder that would otherwise explain FMS symptoms, patients were excluded if they had exam findings suggestive of large or mixed fiber peripheral neuropathy. Therefore, in our study population, ankle jerks were preserved, strength was normal and proprioception at the toes was preserved. Similarly, patients were excluded if there was any established history of myopathy, neuropathy, polyradiculopathy, plexopathy, or other a priori neurologic diagnosis. Patients with a known co-morbid condition that would predispose to neuropathy were also excluded (e.g., diabetes mellitus, connective tissue disorder, etc).

The Short-Form McGill Pain Questionnaire includes 15 different descriptors of pain quality.17 Pain severity was graded as mild, moderate, or severe. Of the 15 descriptors, 11 are subjective and 4 were affective. A third component of this questionnaire is a VAS pain score (maximum 10 points).

Patients underwent skin biopsy, QSART, and NCS, including bilateral sural and MP evoked responses. In the results, the average amplitude of both sides as well as the lower of the 2 values are reported. The site selected for QSART was the distal foot. Skin biopsies were analyzed by the Theraphath Neuropathology Laboratory. A biopsy was deemed positive for SFPN if the ENFD at the distal calf was reduced below the 5th percentile for age-, gender-, and body mass index-adjusted norms.

To distinguish patients with length-dependent SFPN from nonlength dependent SFPN, we designated the former group as “distal reduced” (DR; ENFD ≤ 5th percentile at the calf) and the latter group as “proximal reduced” (PR; ENFD ≤ 5th percentile at the thigh but normal at the calf). Patients with ENFD > 5th percentile at both sites were designated as biopsy negative. DR patients, but not PR patients, were included in the pain analysis in an effort to standardize the comparison group. Both DR and PR groups were included in correlative analyses. Patients were referred to as: (i) FMS before designation with skin biopsy/NCS; (ii) FM if skin biopsy and NCS were negative; and (iii) FM-SFSPN if ENFD was reduced.

Because the study was retrospective, the serologic studies that were performed were not standardized but based on the judgment of the evaluating clinician. However, there were some serologic studies that were required for inclusion: comprehensive metabolic profile, complete blood count with differential, metrics of dysglycemia (hemoglobin A1C [HgbA1C], 2-h glucose tolerance testing, fasting glucose, fasting lipid profile) and serum protein electrophoresis/immunofixation. If all patients in the analysis had other serologic testing (e.g., glutamic acid dehydrogenase antibody titers), this was also included in the analysis. Univariate statistical analysis was performed using 2-tailed Student’s ttest, with $P < 0.05$ as a threshold for statistical significance.

**RESULTS**

Demographic data for all FMS patients is detailed in Table 1. Of the 155 enrolled patients, 93 (60%) were biopsy negative, 43 (28%) DR positive, and 19 (12%) PR positive. The mean age of

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**Table 1. Demographic data for all FMS patients**

| Variable       | $n$ | Mean ± SD | Median | (min, max) |
|----------------|-----|-----------|--------|------------|
| Age (years)    | 155 | 49.4 ± 12.4 | 49     | (18, 87)   |
| MP (low, $\mu V^*$ | 155 | 8.7 ± 6.4  | 8      | (0, 48.5)  |
| MP (avg, $\mu V^*$ | 155 | 9.2 ± 6.7  | 9      | (0, 53.3)  |
| Sural (low, $\mu V^*$ | 155 | 18.0 ± 7.8 | 16     | (2.1, 43.5) |
| Sural (avg, $\mu V^*$ | 155 | 18.8 ± 7.8 | 16.8   | (2.4, 43.5) |
| ENFD (calf)     | 155 | 7.0 ± 3.2  | 6.9    | (0.27, 15.3) |
| ENFD (thigh)    | 155 | 10.1 ± 3.3 | 9.71   | (2.02, 18.7) |
| Subjective pain score | 155 | 12.2 ± 5.1 | 11     | (0.33)     |
| Affective pain score | 155 | 2.7 ± 3.0  | 2      | (0.12)     |
| VAS pain score  | 155 | 5.2 ± 3.0  | 5      | (0.10)     |
| Total pain score| 155 | 20.1 ± 12.0| 18.5   | (0.50)     |

Min, minimum; max, maximum; avg, average.
patients was 49.4 years with a range of 18–87 years. A total of 68% of participants were female, with no significant gender difference between biopsy positive and biopsy negative patients. The grouped mean MP and sural nerve action potential amplitudes were above the age-adjusted cutoffs for the lower limit of normal in our laboratory and others. ENFD at the calf and thigh demonstrated a wide range in the FMS group with the distal site reduced in relation to the proximal site.

MP nerve action potential amplitude was reduced below threshold values in 31.6% of patients (43/155). Both the MP and sural nerve action potential amplitudes correlated with distal ENFD at a statistically significant level. The correlation was stronger for the MP response amplitude than for the sural response amplitude (Table 2). A receiver operating characteristic (ROC) curve of MP and sural amplitudes as a function of

| Biopsy | DR |
|--------|----|
| negative (n = 93) | (n = 43) | P-Value |
| BUN     | 12.13 | 14.5 | 0.023 |
| GTT 1h  | 130.5 | 176.7 | 0.011 |
| GTT 2h  | 102.97 | 131.7 | 0.031 |
| HDL     | 50.74 | 45.13 | 0.07 |
| HgbA1C  | 5.4 | 6.07 | 0.034 |
| GAD65 AB | 0.2825 | 0 | 0.05 |
| Serum IFE IgM | 132.97 | 101.44 | 0.03 |

Average pain has shifted over the past decade from one of pain descriptors. A significantly greater number of FM-SFSPN patients had indices of glucose intolerance (abnormal 2-h glucose tolerance testing, HgbA1C) (Table 3). Low high density lipoproteins (HDLs), another index of metabolic syndrome, did not attain statistical significance (P > 0.05). No significant differences were found in other serum indices, namely complete blood count, renal function, or hepatic function.

**DISCUSSION**

The paradigm in our understanding of FMS pain has shifted over the past decade from one of

![FIGURE 1. Sensitivity, specificity, positive predictive value, and negative predictive value of MP nerve action potential amplitude as predictor for reduced ENFD in FMS patients. An ROC curve is demonstrated for both MP and sural nerve action potential amplitudes, indicating better performance of MP amplitudes. [Color figure can be viewed at wileyonlinelibrary.com]](image-url)
only central sensitization to one of peripheral nervous system injury. Recent evidence points to somatic small fiber dysfunction. Spontaneous activity and peripheral sensitization of silent (type 1B) C fiber nociceptors was found in a substantial proportion of patients with FMS. Phenotypically, the problem is compounded by the notable overlap in clinical complaints between patients with such varying diagnostic labels as FM, SFPN, postural tachycardia syndrome (PoTS), and systemic exercise intolerance disorder, formerly referred to as chronic fatigue syndrome. Further adding to this diagnostic uncertainty is the lack of a typical “stocking-glove” phenotype in nonlength dependent or focal (burning mouth syndrome, complex regional pain syndrome, etc.) SFPN. Whether SFPN is an initiating event leading to FMS, a finding in a subset of FMS patients, or a coincident but separate disorder remains unclear.

Our study provided several key insights: (i) lower extremity sensory nerve action potential amplitudes correlated well with ENFD; (ii) pain intensity did not correlate well with ENFD; (iii) the quality and quantity of pain did not distinguish FM-SFSPN from FM; (iv) patients with FM-SFSPN are more likely to have abnormal glucose metabolism and possibly metabolic syndrome than those with FM; (v) differences in QSART at the distal foot were not identified between groups.

**Lower Extremity Sensory Nerve Action Potential Amplitudes Correlated Well with ENFD.** Significant correlations were seen for sural and MP response amplitudes with ENFD at the calf, but not the thigh. This is consistent with previous reports in which MP amplitudes correlated with skin biopsy findings. Unlike previous studies, we specifically did not stratify for neuropathy because patients did not have exam evidence for distal large fiber dysfunction (although they all fulfilled 2010 ACR criteria for FMS). The implication of this correlation in FM-SFSPN is that early or mild subclinical loss of distal sensory axons occurs in a subset of patients with FMS. Even in the absence of objective examination evidence of distal large sensory fiber loss, skin biopsy and MP studies can improve diagnostic yield for distal sensory neuropathy in FMS patients.

**Pain Intensity Did Not Correlate Well with Reduced ENFD.** In our cohort, pain scores correlated with neither ENFD nor MP amplitudes. This is consistent with other reports. In their cohort of 30 FMS patients who underwent skin biopsy, Kosimidis and colleagues found no correlation between scores on the Neuropathic Pain Symptom Inventory and ENFD. This does not suggest that SFSPN is not painful, but rather that the experience of pain does not correlate well with axon loss. Axon injury to small nerve fibers may incite a cascade of pain-generating events such as neurogenic inflammation, changes in ion flow in sensory neurons or up-regulation of pain generating receptors or voltage gated channels that are independent of the amount of axon loss that has occurred. The lack of correlation of axon loss with pain may also relate to the complexities of the pain pathway or subjective experience of pain.

**Quality and Quantity of Pain Did Not Distinguish FM-SFSPN from FM.** Qualitative ‘neuropathic’ pain descriptors such as ‘sharp’ and ‘splitting’ did not have predictive value in distinguishing FM-SFSPN from FM. Giannoccaro and colleagues evaluated 20 consecutive patients with FMS and divided them into 2 categories, those with neuropathic like symptoms (paresthesias, burning, tingling, and prickling) and those without. Interestingly, only 40% of those in the neuropathic group had decreased ENFD. Some authors have clustered pain phenotypes, reporting more pressure pain, pain attacks and thermal sensitivity in patients with FMS than those with diabetic neuropathy. Despite this tendency, the authors also pointed out considerable overlap in phenotype. The “neuropathic nature” of FMS pain is supported by a report in which patients with FMS were found to have pain of dysesthetic, evoked, paroxysmal, and thermal quality, in comparison to patients with rheumatoid arthritis. These results support that, although FMS pain goes along with specific neuropathic descriptors, it is not specific enough to distinguish FM from FM-SFSPN.

**Patients with FM-SFSPN Are More Likely to Have Abnormal Glucose Metabolism and Possibly Metabolic Syndrome.** Glucose tolerance testing and HgbA1c, but not low HDL, were significantly more common in the FM-SFSPN than the FM groups. This is in contrast to a previous study in which 13 FM-SFPN patients had normal HgbA1c values and most (8 of 11) had normal 2-h glucose tolerance test results. Two larger studies found different results. Loevinger and colleagues found a nearly sixfold increase in incidence of metabolic syndrome among 109 women with FMS compared with 46 healthy control women. Higher triglyceride and hemoglobin A1c levels as well as increased waist circumference were also noted in the FMS group. Another study of 33 FMS women reported elevated levels of biochemical markers of metabolic syndrome, leptin, in FMS patients independent of adipose status.
Differences in QSART at the Distal Foot Were Not Identified between Groups. Our study found no significant differences on QSART testing between FM-SFSPN and FM patients. In the Oaklander series, autonomic function testing results were comparable between both FM and control subjects. In a smaller cohort from Italy, 5/6 patients with FM demonstrated reduced innervation to sweat glands and erector pili muscles at the distal leg and thigh in patients, all of whom showed morphologic changes in autonomic nerve fibers. Four of the 6 patients had autonomic symptoms. Myofascial pain similar in character to FMS is described in patients with PoTS, a disorder defined by its autonomic manifestations. Whether an overlap of FM, FM-SFSPN, and PoTS exists requires further clarification.

Our study faced certain limitations. The retrospective design precluded a control arm without FMS. This makes it difficult to establish SFSPN as an independent factor in the generation of pain. It also makes it more difficult to seriously consider muscle pain within the spectrum of neuropathic pain descriptors especially in the absence of clear exam findings or correlation with ENFD. Indeed, an interpretation of this data is that the pain is indistinguishable because it derives from the same source in both FM and FM-SFSPN, and this source is unrelated to the SFSPN. This is compounded by the fact that FMS remains a clinical diagnosis based on subjective features. Although we cannot rule out this interpretation, the high incidence of DR positive patients and reduced MP amplitude (32%) makes this interpretation less tenable in our view. We would be reluctant to dismiss the interpretation that: (i) SFSPN may account for a proportion of individuals labeled as FM; or that (ii) myalgia is neuropathic given the neurologic exam is insensitive for mild sensory and small fiber axonal loss and pain has not been shown to correlate with axon loss. Rather than invoking SFSPN as causation for the larger defined group of FMS, we would propose that the clinical distinction between these entities is nonspecific and, therefore, less reliable than ancillary testing.

In conclusion, we have recapitulated the findings of others in identifying a subset of patients with FMS who have concomitant SFSPN. In addition, we identified MP amplitude as a useful electrophysiologic correlate to ENFD, and thus, a potential means to separate FM-SFSPN from FM patients. The data in this report suggest that a syndrome of widespread pain indistinguishable from FM-SFSPN. Pain characteristics may not be helpful in distinguishing the 2 entities but skin biopsy, evaluating for ENFD, and conduction studies of distal sensory nerves may help the clinician to distinguish FMS from neuropathy. The other consideration that is raised, but not addressed, by this study is whether SFSPN in the FMS population is intrinsically different from SFSPN in non-FMS populations. Future studies including skin biopsy and NCS data on individuals without pain will help to clarify this question. The detection of SFSPN may have management implications if a reversible etiology such as glucose intolerance is detected.

Ethical Publication Statement: The authors confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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