SMALL NERVE FIBER INVOLVEMENT IN PATIENTS REFERRED FOR FIBROMYALGIA

MARIA PIA GIANNOCCARO, MD,[1] VINCENZO DONADIO, PhD,[2] ALEX INCENSI, BSc,[2]
PATRIZIA AVONI, PhD,[1,2] and ROCCO LIGUORI, MD[1,2]

[1] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[2] IRCCS Istituto delle Scienze Neurologiche di Bologna, Ospedale Bellaria, Via Altura 3, 40139 Bologna, Italy

Accepted 23 December 2013

ABSTRACT: *Introduction:* Fibromyalgia (FM) is a chronic syndrome characterized by widespread pain often accompanied by other symptoms suggestive of neuropathic pain. We evaluated patients for small fiber neuropathy (SFN) who were referred for fibromyalgia (FM). *Methods:* We studied 20 consecutive subjects with primary FM. Patients 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. *Conclusions:* A subset of FM subjects have SFN, which may contribute to their sensory and autonomic symptoms. Skin biopsy should be considered in the diagnostic work-up of FM.

Muscle Nerve **49**:757–759, 2014

Fibromyalgia (FM) is a chronic syndrome characterized by widespread pain accompanied by muscle stiffness, fatigue, sleep disturbances, and cognitive and mood disorders.[1] In FM patients, sensory symptoms and signs are common,[2] including numbness, prickling and burning, allodynia, and hypersensitivity to thermal and mechanical stimuli.[3,4] These features suggest a neuropathic etiology. Because many studies have failed to demonstrate large fiber neuropathy,[2,5] involvement of small nerve fibers was suggested and has been supported by histopathological findings[6] and quantitative sensory tests.[7,8] We investigated for small fiber neuropathy (SFN) in patients referred for FM.

METHODS

We studied 20 consecutive subjects (19 women, mean age 40.1 ± 6.4 years) with primary FM using the criteria of the American College of Rheumatology.[9] Patients were recruited prospectively by rheumatologists and referred only if they met none of the exclusion criteria, specifically secondary FM syndrome, presence of major medical comorbidities, or family history of neuropathy.

Patients underwent neurological examination; laboratory screening for autoimmune, inflammatory, metabolic, oncologic, and infectious diseases; and nerve conduction studies (NCS). Tibial nerve somatosensory evoked potentials (SEPs) were obtained from 5 subjects. Skin biopsies from distal leg (10 cm above the lateral malleolus) and thigh (15 cm above the patella) were obtained using a 3-mm punch. Specimens were fixed, sectioned, and incubated with primary antibodies,[10] including the pan-neuronal marker protein gene product 9.5 (PGP 9.5), collagen IV, and specific autonomic antibodies to mark cholinergic fibers innervating sweat glands (SG) and dopamine beta-hydroxylase (DβH)[11] to visualize adrenergic fibers innervating arrector pili muscles (APM).[10] The epidermal nerve fiber (ENF) density identified by PGP 9.5 was calculated per linear millimeter of epidermis.[12,13] Quantification of autoimmune innervation was performed as described previously[14] by using PGP.

Thirty-two age-matched healthy subjects without neurological dysfunction or history of chronic pain served as controls.[14] Procedures were approved by the local ethics committee. All participants provided written consent.

RESULTS

All patients noted diffuse pain, muscle tension, and fatigue. In some patients, symptoms were associated with insomnia, anxiety, and/or depression. Clinical and demographic data are shown in Supplementary Table 1. Paresthesia and spontaneous burning pain were present in 15 subjects (75%). Six subjects (30%) reported worse symptoms at night, and 1 noted worsening with cold exposure. Sensory disturbances had a stocking or stocking–glove distribution, but 1 patient also complained of stabbing, migrating pain. Autonomic symptoms included vasomotor dysfunction in the hands (2 patients), urinary incontinence in (1 patient), and gastrointestinal disturbances (1 patient).

Neurological examination disclosed mild decreased vibratory perception in 4 patients.

Additional Supporting Information may be found in the online version of this article.

Abbreviations: APM, arrector pili muscles; DβH, dopamine beta-hydroxylase; ENF, epidermal nerve fiber density; FM, fibromyalgia; NCS, nerve conduction studies; NLS, neuropathic-like symptoms; PGP 9.5, pan-neuronal marker protein gene product 9.5; SFN, small fiber neuropathy; SG, sweat gland; SEP, somatosensory evoked potential; VIP, vasoactive intestinal peptide

Key words: autonomic dysfunction; fibromyalgia; neuropathic pain; small fiber neuropathy; skin biopsy

Correspondence to: M.P. Giannoccaro; e-mail mpgiannoccaro@gmail.com

Published online 28 December 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.24156

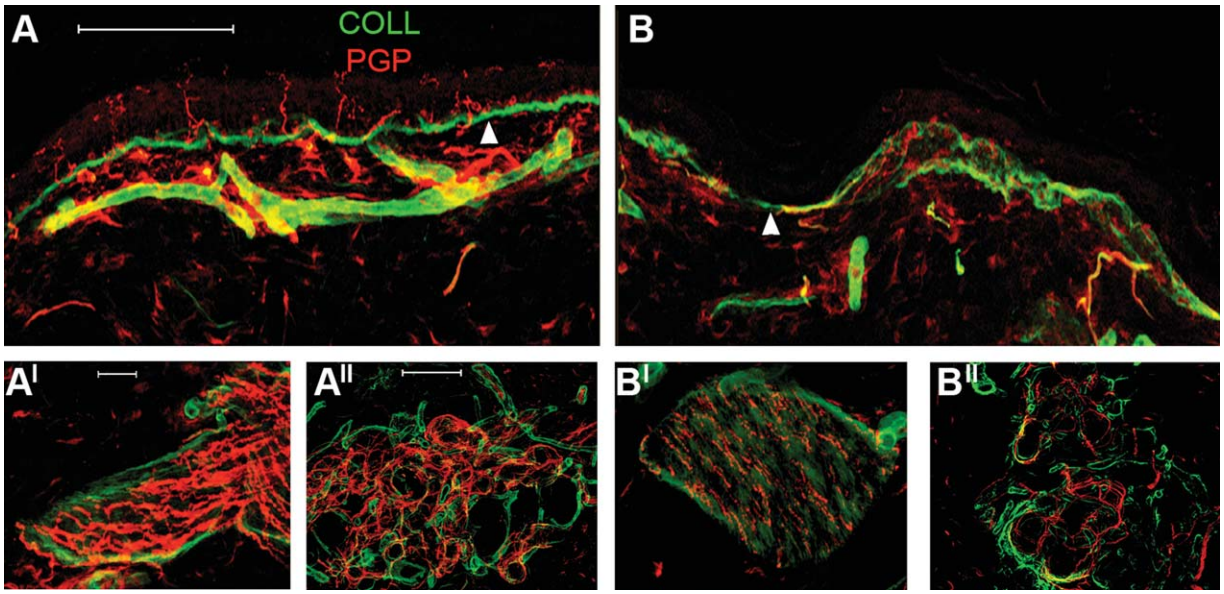

FIGURE 1. PGP 9.5 immunoreactive nerve fibers (red) in the epidermal layer **(A, B)**, APM **(AI, BI)**, and around a sweat gland **(AII, BII)** in a control subject **(A, AI, AII)** and in a fibromyalgia patient **(B, BI, BII)**. The control subject had several fibers in the epidermal layer **(A)** that crossed the basal membrane (arrow head) and a large amount of fibers in the arrector pili muscles **(AI)** and sweat glands **(AII)**. The patient had decreased innervation in the epidermal layer **(B)**, arrector pili muscles **(BI)**, and sweat glands **(BII)**. In addition, skin nerve fibers often displayed morphological abnormalities, including swelling and fragmentation.

Fasting blood glucose and hemoglobin A1c were normal in all patients. NCS and SEPs were normal.

Skin biopsy findings are detailed in Supplementary Table 1. In normal controls, ENF density was 15 ± 3 ENFs/mm in the leg (lower limit of normal 9.5 ENFs/mm) and 21 ± 4 ENFs/mm in the thigh (lower limit of normal 13.5).[14] ENF values below normal were found in 6 patients in the leg and in 5 at the thigh. The mean ENF values in these patients were 8 ± 0.89 ENFs/mm for leg and 12 ± 1.2 ENFs/mm for thigh. No clear denervation pattern was found except for length-dependent denervation in 1 patient.

In controls, autonomic innervation of SG and APM was abundant (Fig. 1). Autonomic innervation data in controls are shown in Supplementary Table 1. Cut-off values of 10% and 12% were assumed for leg and thigh, respectively.[14]

Autonomic innervation in FM patients was similar to controls except in SFN patients who displayed autonomic nerve fiber swelling and fragmentation (Fig. 1). Autonomic quantitative analysis showed values below the established cut-off for SG and APM innervation in 5 of 6 affected patients in both the lower leg and thigh.

Patients were divided into 2 categories: those with neuropathic-like symptoms (NLS), including paresthesias, burning, tingling, and prickling (75% of all patients); and all others, who lacked such symptoms. All patients with NLS symptoms were considered to possibly have SFN based on history, but only 40% demonstrated decreased ENFs. The comparison of sensory symptoms between patients with and without SFN showed no significant differences in pain distribution or neurological examination findings. Specifically the quality of sensory disturbances in patients with NLS and SFN did not differ significantly from those without SFN. Burning pain was present in 66% of patients in both groups, and paresthesias were present in 50% of those with SFN and in 55% of those without SFN. Tingling, shooting pain, stabbing pain, or prickling occurred with similar frequencies. All SFN patients noted worsening of NLS symptoms at night, and 3 had autonomic symptoms. Autonomic neuropathy was confirmed by skin biopsy in all patients with autonomic symptoms and in 2 patients without such symptoms.

DISCUSSION

The high prevalence of sensory symptoms suggestive of neuropathic pain in patients with FM is not surprising, as a previous study reported dysesthesic sensory disturbances in up to 84% of FM patients,[2] sometimes in a stocking–glove distribution typical of peripheral neuropathy.[15] By contrast, the worsening of paresthesias and/or burning pain during the night, a symptom frequently associated with neuropathy, could be valuable when assessing for possible underlying SFN.

Autonomic involvement has been reported in FM,[16] and, albeit infrequently, signs of autonomic dysfunction were observed in a subset of subjects diagnosed with SFN who in almost all instances

displayed autonomic denervation on skin biopsy. Somatic and autonomic involvement occurred concurrently in all patients except for 1, who had only somatic involvement. Therefore, SFN in FM patients appears generally mixed, with both somatic and autonomic involvement. However, due to the small number of SFN patients in this study, a larger cohort of patients is needed to better clarify the characteristics of SFN underlying FM.

Although central sensitization is an accepted mechanism for widespread hyperalgesia in FM,[1] it is not clear what input is necessary to initiate and maintain abnormal pain processing. As tonic impulses from C-nociceptive fibers can induce short- and long-term plastic changes in dorsal horn neurons,[17] the peripheral nociceptors could be implicated in persisting FM pain in a subset of patients. Koroschetz *et al.* used questionnaires to compare the sensory symptoms of patients with FM to those with neuropathic disorders. They observed an overlap of sensory symptoms in 20–35% of patients in each group, suggesting a common pathophysiological mechanism.[4] We found peripheral C-fiber damage in a subgroup of these patients, usually with mixed somatic and autonomic involvement. Based on results of this pilot study, it is not possible to determine whether FM itself is often accompanied by SFN or whether some SFN patients may be misdiagnosed as having fibromyalgia due to the unusual presentation of their symptoms as non–length-dependent SFN.[18] However, although we failed to identify a clear length-dependent pattern of denervation, many patients reported neuropathic symptoms in a length-dependent distribution. Our findings seem to be supported by those of Üçeyler *et al.*,[19] who reported small nerve fiber involvement in 25 of 25 FM patients, although not all patients showed reduced ENFs. The high rate of small nerve fiber involvement in that study compared with our findings could be explained by the different methodological approach involving neurophysiological tests associated with skin biopsy. Oaklander *et al.*[20] recently reported diagnoses of SFN in 11 of 27 (41%) patients with FM. In contrast to Üçeyler *et al.*[19] and to our study, they found an underlying, mainly dysimmune etiology in most patients.

A limitation of our study is the lack of glucose tolerance testing, particularly because diabetes is one of the most common causes of SFN in Western countries.[21] The normal serum glucose and hemoglobin A1c levels make diabetes less likely, but does not exclude this possibility. Future studies in a larger cohort of patients are needed to confirm our data and to shed light on the relationship between SFN and FM so we may better understand the etiology of SFN in these patients.

In conclusion, our findings suggest that skin biopsy should be considered in the diagnostic work-up of FM to search for SFN, mainly in patients who complain of nocturnal exacerbation of burning pain. In these patients, appropriate screening, including dysimmune markers and glucose tolerance tests, should be performed to exclude acquired neuropathy.

The authors thank A. Collins and A. Laffi for English revision of the manuscript.

REFERENCES

1. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum 2007;36:339–356.
2. Simms RW, Goldenberg DL. Symptoms mimicking neurologic disorders in fibromyalgia syndrome. J Rheumatol 1988;15:1271–1273.
3. Geisser ME, Casey KL, Brucksch CB, Ribbens CM, Appleton BB, Crofford LJ. Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia: association with mood, somatic focus, and catastrophizing. Pain 2003;102:243–250.
4. Koroschetz J, Rehm SE, Gockel U, Brosz M, Freynhagen R, Tölle TR, et al. Fibromyalgia and neuropathic pain—differences and similarities. A comparison of 3057 patients with diabetic painful neuropathy and fibromyalgia. BMC Neurol 2011;11:55.
5. Ersoz M. Nerve conduction tests in patients with fibromyalgia: comparison with normal controls. Rheumatol Int 2003;23:166–170.
6. Kim SH, Kim DH, Oh DH, Clauw DJ. Characteristic electron microscopic findings in the skin of patients with fibromyalgia—preliminary study. Clin Rheumatol 2008;27:407–411.
7. Kosek E, Ekholm J, Hansson P. Sensory dysfunction in fibromyalgia patients with implications for pathogenic mechanisms. Pain 1996;68:375–383.
8. Hurtig IM, Raak RI, Kendall SA, Gerdle B, Wahren LK. Quantitative sensory testing in fibromyalgia patients and in healthy subjects: identification of subgroups. Clin J Pain 2001;17:316–22.
9. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160–172.
10. Donadio V, Cortelli P, Elam M, Di Stasi V, Montagna P, Holmberg B, et al. Autonomic innervation in multiple system atrophy and pure autonomic failure. J Neurol Neurosurg Psychiatry 2010;81:1327–1335.
11. Donadio V, Nolano M, Provitera V, Stancanelli A, Lullo F, Liguori R, et al. Skin sympathetic adrenergic innervation: an immunofluorescence confocal study. Ann Neurol 2006;59:376–381.
12. Liguori R, Di Stasi V, Bugiardini E, Mignani R, Burlina A, Borsini W, et al. Small fiber neuropathy in female patients with fabry disease. Muscle Nerve 2010;41:409–412.
13. Giannoccaro MP, Donadio V, Gomis Pèrez C, Borsini W, Di Stasi V, Liguori R. Somatic and autonomic small fiber neuropathy induced by bortezomib therapy: an immunofluorescence study. Neurol Sci 2011;32:361–363.
14. Donadio V, Incensi A, Giannoccaro MP, Cortelli P, Di Stasi V, Pizza F, et al. Peripheral autonomic neuropathy: diagnostic contribution of skin biopsy. J Neuropathol Exp Neurol 2012;71:1000–1008.
15. Caro XJ, Winter EF, Dumas AJ. A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy and appear to respond to IVIg. Rheumatology (Oxford) 2008;47:208–211.
16. Furlan R, Colombo S, Perego F, Atzeni F, Diana A, Barbic F, et al. Abnormalities of cardiovascular neural control and reduced orthostatic tolerance in patients with primary fibromyalgia. J Rheumatol 2005;32:1787–1793.
17. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009;10:895–926.
18. Gemignani F, Giovanelli M, Vitetta F, Santilli D, Bellanova MF, Brindani F, et al. Non-length dependent small fiber neuropathy. a prospective case series. J Peripher Nerv Syst 2010;15:57–62.
19. Uçeyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Schmid A, et al. Small fibre pathology in patients with fibromyalgia syndrome. Brain 2013;136:1857–1867.
20. Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. Pain 2013.
21. Devigili G, Tugnoli V, Penza P, Camozzi F, Lombardi R, Melli G, Broglio L, et al. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. Brain 2008;131:1912–1925.