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Evidence of Abnormal Epidermal Nerve Fiber Density in Fibromyalgia

Clinical and Immunologic Implications

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Objective. **A subset of patients with fibromyalgia (FM) exhibit a large fiber demyelinating peripheral polyneuropathy akin to that seen in chronic inflammatory demyelinating polyneuropathy (CIDP). It has been suggested that this demyelinating process is likely to be immune mediated. Because it is known that similar large fiber neuropathic lesions may be associated with a cutaneous small fiber neuropathy, we sought to determine the prevalence of small fiber neuropathy, as measured by epidermal nerve fiber density (ENFD), in a series of patients with FM and clinically healthy control subjects.**

Methods. **Forty-one consecutive patients with FM and 47 control subjects underwent a 3-mm punch skin biopsy at the proximal thigh and distal leg near the ankle, for analysis of the ENFD. Patients with FM who had clinical evidence of a disorder known to be associated with small fiber neuropathy were excluded. The patients with FM also underwent pinwheel testing and vibratory testing for hypesthesia and serologic testing for a series of cytokine, circulating immune complex, and complement measurements.**

Results. **All patients with FM had evidence of stocking hypesthesia. The ENFD of patients with FM was lower than that of control subjects at both the calf (mean ± SD 5.8 ± 2.8 versus 7.4 ± 1.9; $P = 0.0002$) and thigh (9.3 ± 3.2 versus 11.3 ± 2.0; $P = 0.0007$). There was an inverse correlation between calf ENFD and age at the time of skin biopsy in patients with FM ($r = -0.29$, $P = 0.03$) but not in control subjects; however, analysis of covariance showed that this relationship could not be explained by aging alone. Serologic evaluation showed an inverse correlation between calf ENFD in patients with FM and the interleukin-2 receptor (IL-2R) level ($r = -0.28$, $P = 0.04$). However, an inverse correlation between thigh ENFD and serum IL-2R levels did not reach significance ($P = 0.08$). Analysis of thigh-to-calf ENFD ratios suggested that the ENFD decline in FM is affected by both a diffuse and a length-dependent process.**

Conclusion. **The calf and thigh ENFD in patients with FM is significantly diminished compared with that in control subjects. Advancing age alone cannot explain this finding. Calf ENFD was inversely correlated, although weakly, with serum levels of IL-2R. These findings suggest that small fiber neuropathy is likely to contribute to the pain symptoms of FM; that pain in this disorder arises, in part, from a peripheral immune-mediated process; and that measurement of ENFD may be a useful clinical tool in FM.**

The pathophysiologic basis of fibromyalgia (FM) remains a matter of debate, in part because it is commonly claimed that, despite its severity and widespread nature, FM has not been associated with an identifiable peripheral tissue lesion. As a result, the idea has developed that a central nervous system (CNS) origin for FM is the only viable explanation for its existence (1). Nevertheless, several investigators have continued to report subtle but important peripheral tissue abnormalities in FM. These findings include irregularities of muscle tissue (2), the autonomic nervous system (3), and

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the immune system (4–6). Furthermore, we (and other investigators) previously reported a significant association of FM with electrodiagnostic and clinical evidence of a demyelinating peripheral nervous system (PNS) injury, akin to that seen in chronic inflammatory demyelinating polyneuropathy (CIDP) (6).

Our interest in the PNS component of FM arose, at least in part, from the high prevalence of "neuropathic language" in this disorder. Neuropathic language is the label commonly applied to a set of verbal descriptors used by patients with peripheral neuropathic lesions. This vocabulary includes terms that may seem exaggerated or even fantastic to the uninitiated examiner (e.g., "hot," "burning," "pins and needles," "knife-like," "unbearable," and "miserable," to name a few). The interested reader is referred to previous reviews of the clinical phenomenon by Melzack and Katz (7) and Martinez-Lavin et al (8). When we examined patients with FM for such descriptors, we observed that 76% of these patients, compared with only 20% of patients with rheumatoid arthritis (RA) without FM, used such language to describe their symptoms (6). This linguistic prevalence compares well with the 84% prevalence reported by Simms and Goldenberg (9) and the 95% prevalence reported by Martinez-Lavin (8). More recently, Koroschetz et al (10) also reported that neuropathic language in FM does not differ significantly from that seen in diabetes patients with known peripheral neuropathy. All of these observations suggested the need for a better examination of the PNS in FM.

Previously, we sought tissue confirmation of these PNS findings by carrying out sural nerve biopsies on a small series of patients with FM who had a CIDP-like clinical picture (6). These biopsies were helpful in demonstrating peripheral nerve demyelination without findings of vasculitis or amyloidosis. Despite the usefulness of these biopsies in the evaluation of our patients with FM, however, obtaining sural nerve biopsy specimens, in general, continues to be problematic due to the painful, time-consuming, and costly nature of this procedure. In addition, performance of this procedure previously required the support of a university-based neuropathology service. All of these obstacles have discouraged clinicians from conducting sural nerve biopsies despite the "objective" results they may render.

Recently, skin biopsy for the determination of epidermal nerve fiber density (ENFD) has been used to investigate a variety of peripheral neuropathic lesions (11,12). Furthermore, diminished ENFD has been shown to correlate with the presence of peripheral large nerve demyelination and autonomic nerve injury (12,13). It has also been shown that ENFD measurement is more sensitive than sural nerve biopsy in demonstrating small fiber disease (14). Thus, we tested whether reduced ENFD might be observed in patients with FM, and whether reduced ENFD might serve as a marker of a significant PNS injury in this disorder; the preliminary results of this study were reported previously (15). Here, we describe our extension of that early clinical investigation and report a surprisingly high prevalence of diminished ENFD in patients with FM. We conclude that small fiber neuropathy may contribute to the symptoms of FM.

PATIENTS AND METHODS

Study population. Between January 2007 and August 2011, we studied consecutive outpatients presenting with clinical features of FM, as judged by one of the authors (XJC) who is a practicing rheumatologist with a special interest in this disorder. All patients seen by this author at his private, consultative rheumatology practice (Northridge, CA) were between the ages of 18 years and 80 years and satisfied the American College of Rheumatology 1990 criteria for the classification of FM (16). The Institutional Review Board at the Northridge Hospital Medical Center approved this study.

All patients with FM underwent bilateral lower extremity Wartenberg pinwheel and 128-Hz tuning fork sensory testing (17). Patients with FM were included in this study, irrespective of any other diagnoses, unless there was any history or laboratory evidence of one or more of the following: a family history suggestive of a hereditary sensorimotor polyneuropathy; a personal history of diabetes mellitus, systemic lupus erythematosus (SLE), sarcoidosis, Sjögren's syndrome or a diagnosis of keratoconjunctivitis sicca; a history of rheumatologic immunosuppressive therapy; active hepatitis C virus infection; any history of cancer within 5 years of the study; or vitamin D or iron deficiency that was resistant to correction using standard supplements. Clinical disorders mimicking FM, e.g., axial skeletal inflammatory disorders associated with HLA–B27, were also excluded. In addition, we studied a group of clinically healthy control subjects during the same period.

Clinical and laboratory analysis. The clinical features recorded for each patient with FM included the score for pain on a verbal analog scale (range 0–10), and the physician's global score for tenderness as assessed by one examiner (XJC) (range 0–3; 3 = maximum tenderness). We also retrospectively reviewed the clinic charts of these patients in order to determine the duration (in years) of their painful symptoms (data from 38 subjects are available).

Laboratory testing recorded for each patient with FM included measurement of the erythrocyte sedimentation rate (ESR) (using the Westergren method and an Excyte analyzer; Vital Diagnostics), C-reactive protein (CRP) (by immunoturbidmetric assay), antinuclear antibodies (ANAs) (by indirect fluorescent antibody test), IgM rheumatoid factor (RF) (by immunoturbidmetric assay), anti-Ro/La (by enzyme immunoassay/latex immunoassay), interleukin-1β (IL-1β) (by direct radioimmunoassay), IL-2 receptor (IL-2R) (by enzyme

immunoassay), IL-6 (by radioimmunoassay), tumor necrosis factor α (TNFα) (by enzyme-linked immunosorbent assay [ELISA]), circulating immune complex (CIC) and C3d (by immunoassay), C1q binding (by ELISA), Raji cells (by enzyme immunoassay), complement components C′3 and C′4 (by immunoturbidmetric assay), and C′H50 (by liposome immunoassay). Serum protein electrophoresis, spectrophotometry, capillary electrophoresis, and thyroid function testing (including measurement of thyroid-stimulating hormone [by immunoassay and immunochromatographic membrane strip assay]) were performed in all patients. Measurements of serum iron and total iron-binding capacity, rapid plasma reagin (by flocculation test), 25-hydroxyvitamin D (by liquid chromatography tandem mass spectrometry), and intact parathyroid hormone ionized calcium (by spectrophotometry, immunochromatographic membrane assay, and ion-specific electrode measurement) were also obtained.

We also retrospectively reviewed the charts of the patients for evidence of hyperlipidemia and statin treatment because of recent reports implicating a role of hyperlipidemia and (possibly) statins in some cases of peripheral neuropathy (18,19). None of the patients with FM had laboratory evidence of vitamin B_{12} deficiency, diabetes mellitus, or ongoing hepatic or renal injury (including active hepatitis C virus infection). Other than the ESR, all laboratory testing, including cytokine determinations, was performed by Quest Diagnostics Nichols Institute of Valencia. Any abnormal results of immunologic testing, including cytokine determinations, were performed in duplicate. "Abnormal" was defined as a value >2 SD or <2 SD from the mean established by the laboratory.

ENFD and routine skin biopsy analysis. A 3-mm punch biopsy of the skin was performed in an aseptic manner in both patients with FM and control subjects, as described elsewhere (20). In all subjects, the biopsy sites were the proximal anterolateral thigh, at the level of the pubis, and the distal anterolateral leg, 10 cm proximal to the lateral malleolus. The specimens were transported overnight to the testing laboratory (Therepath Neuropathology Lab, New York, NY) in 2% periodate–lysine–paraformaldehyde fixative.

Skin samples were then cryoprotected, frozen, thick-sectioned, and immunohistochemically stained using an immunoperoxidase method for protein gene product 9.5, a ubiquitin carboxy-terminal hydrolase that is a panaxonal marker. Visualization of nerve fibers within the skin tissue was performed using light microscopy, in a blinded manner, as part of the daily work routine at the laboratory. Epidermal nerve fibers crossing the basement membrane at the dermal–epidermal junction were quantitated in patients and control subjects using a standard counting algorithm. This method counts the number of fibers crossing into the epidermis in ≥5 measured sections of skin tissue. This number was then used to generate a mean "density" of such fibers per length of tissue (reported here as the number of fibers crossing per millimeter of epidermis, i.e., the ENFD) (Figure 1). Each biopsy specimen also underwent routine hematoxylin and eosin staining for microscopic evidence of vasculitis and Congo Red staining for detection of any amyloid deposition.

Statistical analysis. Because the results in patients with FM and control subjects were reasonably normally distributed, descriptive data are reported as the mean ± SD when appropriate. Group comparisons of continuous variables were performed by 1-tailed *t*-test. One-way analysis of covariance (ANCOVA) was performed using a public web-based statistical program. A measure of the degree of statistical correlation between selected clinical and 6 immunoserologic findings and ENFD values for the patients with FM was also sought. The immunoserologic variables included IL-1β, IL-2R, IL-6, and TNFα; CIC (i.e., C3d, C1q, and Raji cell assays taken as a whole); and serum complement (i.e., C′3, C′4, and C′H50 assays taken as a whole). Correlation coefficients were generated using Pearson's protocol. *P* values less than or equal to 0.05 (1-tailed) were considered significant.

Length dependency of any diminished ENFD in FM was determined by calculating a ratio of thigh ENFD to calf ENFD. This FM ratio was compared with the ratio determined in our clinically healthy control subjects. We inferred a length-dependent component if the proximal-to-distal ENFD ratio for the patients with FM was statistically significantly higher than that for the control subjects.

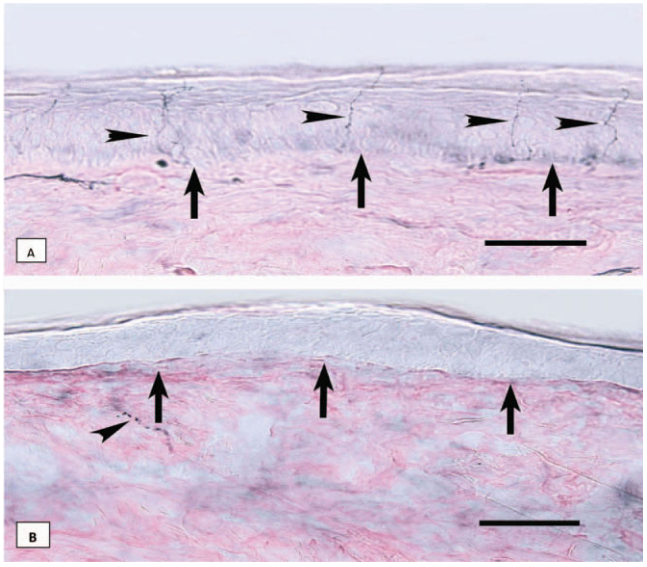

Figure 1. A, Skin biopsy specimen obtained from a normal subject, showing 4 nerve fibers (**arrowheads**) that extend from the dermis perpendicularly through the epidermis toward the upper layer of cells. **B,** Skin biopsy specimen obtained from a patient with fibromyalgia and severe small fiber neuropathy, showing the total absence of epidermal nerve fibers and the presence of 1 nerve fiber in the dermis (**arrowhead**). The **arrows** indicate the dermal–epidermal junction. Protein gene product 9.5–stained and eosin-counterstained; bars = 50 μm.

RESULTS

Demographic characteristics of the study subjects. We studied 41 patients with FM and 47 control subjects. Among the patients with FM, 34 were women, 30 were white, 9 were Hispanic, and 2 were African American. Among the control subjects, 33 were women, 24 were white, and 23 were Hispanic. Nine patients

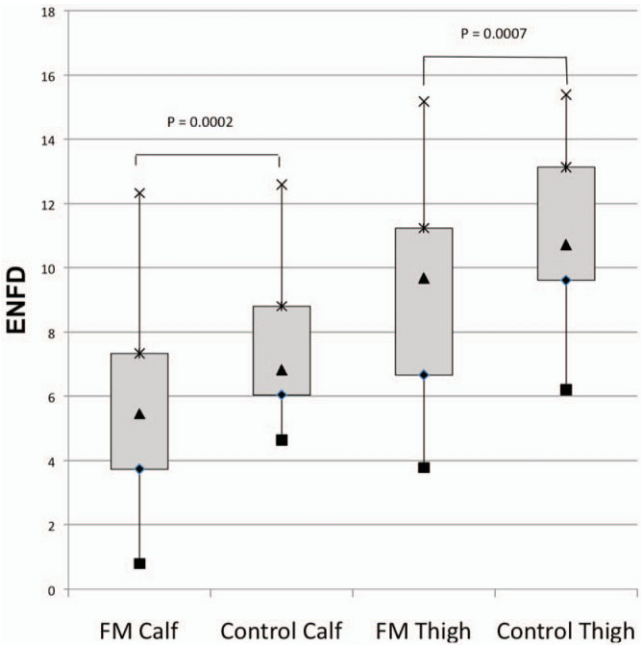

Figure 2. Calf and thigh epidermal nerve fiber density (ENFD) in patients with fibromyalgia (FM) and control subjects, demonstrating significant differences between patients and control subjects for both the calf and thigh. Data are shown as box plots. Each box represents the 25th (♦) to 75th (×) percentiles. Triangles inside the boxes represent the median. Whiskers represent the maximum (×) and minimum (■) range. *P* values were determined by *t*-test.

with FM also had RA, but only 2 of those patients were positive for RF. Thirteen other patients with FM were initially screened for the study but were eliminated due to the presence of various exclusion criteria (diabetes mellitus [n = 6], chronic hepatitis C virus infection [n = 1], SLE [n = 2], sarcoidosis [n = 1], receiving immunotherapy [n = 1], fibromyalgia mimic [n = 2]).

The mean ± SD age of the patients with FM was 60.8 ± 12.2 years and that of the clinically healthy control subjects was 47.8 ± 10.8 years ($P < 0.0001$). To a varying degree, all patients with FM in this study had clinical evidence of a "stocking" distribution with diminished pinwheel and vibratory perception upon lower extremity sensory examination. This stocking hypesthesia paralleled that seen in our previous study, at least in a qualitative manner (6). No attempt was made to more precisely quantitate the degree of loss of either pinwheel or vibratory perception, however. Rapid plasma reagin testing was nonreactive in all subjects.

Decreased ENFD in patients with FM. The mean ± SD values for calf ENFD in patients with FM and clinically healthy control subjects were 5.8 ± 2.8 and 7.4 ± 1.9, respectively ($P = 0.0002$). The mean ± SD values for thigh ENFD in patients with FM and clinically healthy control subjects were 9.3 ± 3.2 and 11.3 ± 2.0), respectively ($P = 0.0007$) (Figure 2).

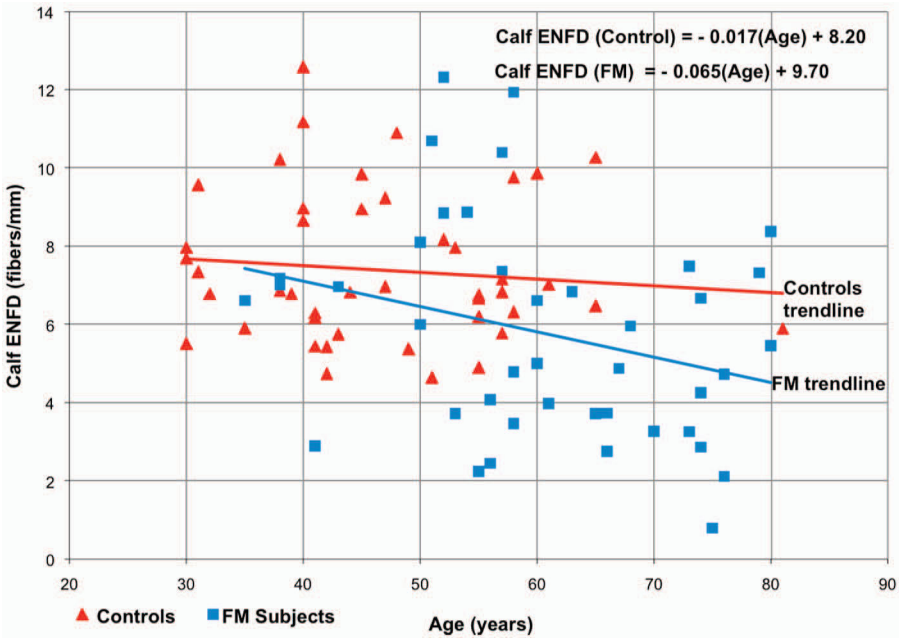

Figure 3. Relationship between age at the time of skin biopsy and calf ENFD in patients with FM and control subjects. There was a significant inverse correlation in patients with FM ($r = -0.29$, $P = 0.03$). The descending slope of the trend line in patients with FM ($y = mx + b$, where m = slope) is ~4 times as great as that in control subjects (−0.065 and −0.017, respectively). Analysis of covariance, comparing patients with FM and control subjects with adjustment for age, suggested a continued difference between group ENFD values ($P = 0.06$). See Figure 2 for definitions.

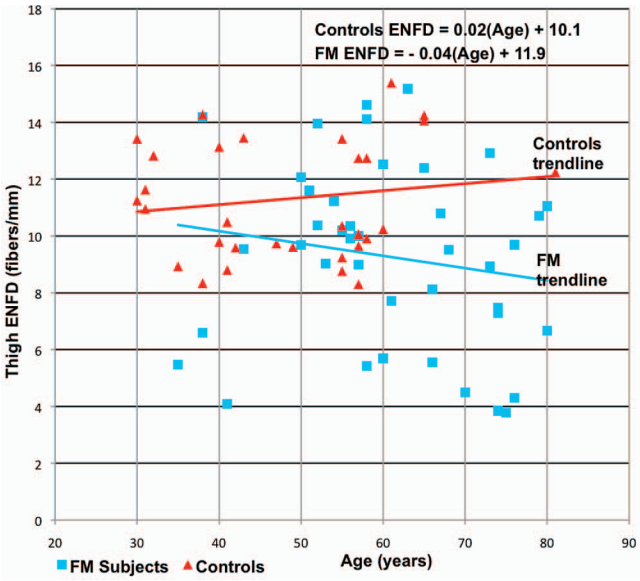

Figure 4. Relationship between age at the time of skin biopsy and thigh ENFD in patients with FM and control subjects. No significant correlation was observed in patients with FM ($r = -0.17$, $P = 0.15$) or control subjects ($r = 0.15$, $P = 0.20$). In patients with FM, the descending slope of the trend line for thigh ENFD is ~2 times as great as that for calf ENFD (see Figure 3), suggesting a minor age-related component to thigh ENFD in FM. Analysis of covariance, comparing patients with FM and control subjects with adjustment for age, suggested a continued difference between group ENFD values ($P = 0.01$). See Figure 2 for definitions.

Clinical correlations with ENFD. There was a statistically significant inverse correlation between calf ENFD and age at the time of skin biopsy in patients with FM ($r = -0.29$, $P = 0.03$) but not in clinically healthy control subjects ($r = -0.09$, $P = 0.27$) (Figure 3). Thigh ENFD did not correlate significantly with age in patients with FM ($r = -0.17$, $P = 0.15$) or in clinically healthy control subjects ($r = 0.15$, $P = 0.20$) (Figure 4). Data pertaining to hyperlipidemia were available for 40 of 41 patients with FM. Fourteen of these patients had evidence of hypercholesterolemia, and 11 had hypertriglyceridemia. During the study period, no patient with FM had a total cholesterol or triglyceride level >50 mg/dl above the laboratory normal range. Statin use at the time of the biopsy was documented in 8 of the patients with FM. No patient had a history suggestive of a temporal relationship between their hyperlipidemia or statin use and their FM symptoms.

A statistically significant inverse correlation between calf ENFD and IL-2R levels in patients with FM ($r = -0.28$, $P = 0.04$) was also observed (Figure 5). Additionally, thigh ENFD showed a trend toward a statistically significant inverse correlation with IL-2R levels in patients with FM ($r = -0.22$, $P = 0.08$). The age of our patients with FM, per se, did not correlate with IL-2R levels. There were no other significant correlations between ENFD in patients with FM and the additional immunologic markers we surveyed. ANCOVA comparing the ENFDs in patients with FM and control subjects while adjusting for age in the patients continued to render a difference in ENFD values that

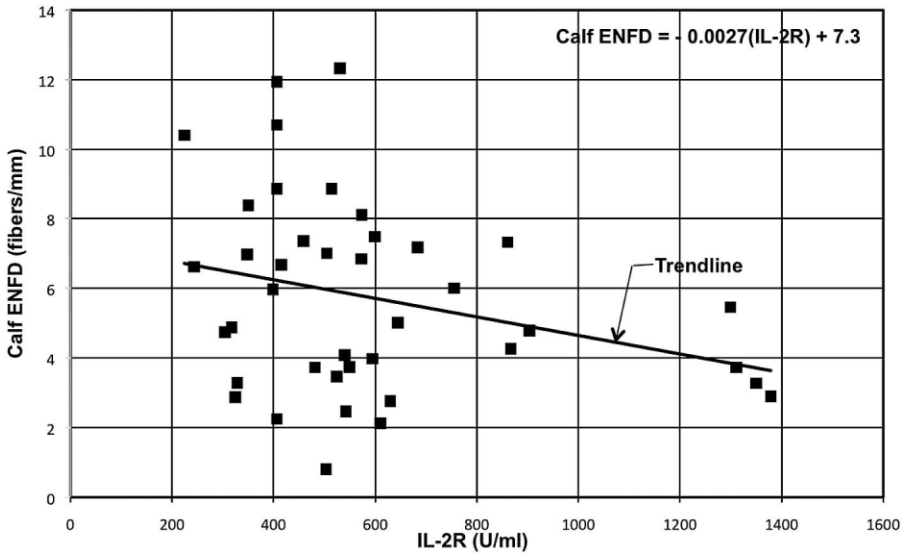

Figure 5. Relationship between calf ENFD and interleukin-2 receptor (IL-2R) levels in patients with FM (n = 40). An inverse correlation was observed ($r = -0.28$, $P = 0.04$). See Figure 2 for other definitions.

was statistically significant at the thigh ($P = 0.01$) but less so at the calf ($P = 0.06$).

FM symptom duration, in years, trended toward a statistically significant correlation with IL-2R levels ($r = -0.24$, $P = 0.07$) but not with calf or thigh ENFD. The patient's verbal analog scale score for pain and the physician's global score for tenderness were significantly correlated ($r = 0.51$, $P = 0.0005$). However, the patient's pain score did not correlate with the calf or thigh ENFD. None of the patients with FM had microscopic evidence of peripheral vasculitis or amyloidosis.

Relationship between thigh ENFD and calf ENFD. The thigh ENFD value correlated significantly with the calf ENFD value in patients with FM ($r = 0.56$, $P = 0.00008$) but not in clinically healthy control subjects ($r = 0.18$, $P = 0.16$). Nevertheless, the overall thigh-to-calf ENFD ratio in patients with FM (mean ± SD ratio 1.9 ± 1.0) was not significantly different from that in the control subjects (1.7 ± 0.4; $P = 0.07$). Interestingly, however, the slope of the trend line defining the thigh-to-calf ratios in patients with FM, when graphed against age at the time of skin biopsy, increased at a rate that was 7 times greater than the rate in control subjects (results not shown).

DISCUSSION

The significance of diminished ENFD has been the subject of extensive review (12,21). It is thought to be the result of one or more noxious agents contributing to the disappearance of small unmyelinated C-fibers and lightly myelinated Aδ fibers within the epidermis. The diagnostic and pathophysiologic considerations pertaining to the neuronal injury resulting in reduced ENFD are rather broad but encompass 2 main principles that are important to this discussion.

First, reduced ENFD is commonly, although not invariably, associated with significant neuropathic pain, thus the term small fiber neuropathy (22). We and other investigators have observed a high frequency of neuropathic symptoms in FM, and this observation has become one of the driving forces for our current investigation. The diminution of ENFD seen in small fiber neuropathy might, understandably, be expected to engender a clinically apparent loss of cutaneous sensation ("negative" sensory phenomena) rather than peripheral painful symptoms ("positive" sensory phenomena). Nevertheless, it is well recognized that small fiber neuropathy is associated with both (12). Therefore, the stocking hypesthesia we observed in the patients with FM in this study is not unexpected. However, the painful peripheral symptoms of small fiber neuropathy are thought to be attributable to a disproportionate hyperexcitability of the primary lesioned (but not totally defunct) small nerve fibers and a surrounding structurally normal but physiologically hyperexcitable group of secondary small nerve fibers responding collaterally (12).

Second, after allowing for certain metabolic and congenital lesions engendering diminished ENFD, what remains is a heterogeneous group of disorders with a final common pathway that is likely to be immune mediated (23,24). Thus, the demonstration of an association between FM and small fiber neuropathy might well bolster the notion of an immunopathogenic component to FM, as suggested by a number of investigators (4–6).

In this study, we excluded individuals with any history suggestive of a hereditary sensorimotor neuropathy or a metabolic/inflammatory syndrome thought to be associated with small fiber neuropathy (e.g., diabetes mellitus, uncontrolled hyperlipidemia, sarcoidosis, or SLE) (11,12). We did not, however, eliminate patients with FM who had symptoms of dry mouth or dry eye, as might be seen in patients with Sjögren's syndrome (25), even though this disorder has been associated with small fiber neuropathy (26), because these symptoms are rather common in FM (27). Nevertheless, none of our patients with FM had evidence of anti-Ro or anti-La antibodies, and none had historical evidence of keratoconjunctivitis sicca (25).

All of our current patients with FM, to a greater or lesser extent, had findings of lower extremity stocking hypesthesia upon pinwheel and vibratory examination. Because our previous study of the PNS in FM demonstrated similar clinical findings, in association with electrodiagnostic evidence of large nerve fiber involvement, we assume that most of the patients with FM in our current study also had large nerve fiber pathology (6). It is noteworthy, however, that lower extremity stocking hypesthesia is also a common clinical accompaniment to small fiber neuropathy (12,22).

We were also sensitive to the role that age might have had on ENFD, because our patients with FM were significantly older than our control subjects. There was a subtle, though measurable, decline in calf ENFD with advancing age among the control subjects and a more marked decline in calf ENFD in the patients with FM (Figure 3). The effect of aging, per se, on normal calf ENFD has been the subject of debate, with some authors contending that there is no age effect at all (28), while others contend that calf ENFD declines gradually with increasing age (29). The decline in calf ENFD values in our patients with FM compared with those in

our control subjects was certainly greater than what would be explained by age alone, however. Among the patients with FM, loss of calf ENFD occurred at a rate ~4 times faster than that among control subjects; that is, the value of the FM slope (−0.065) divided by the value of the control slope (−0.017) is ~4 (see Figure 3). The rate of decline in thigh ENFD in patients with FM was ~2 times as fast as the decline in calf ENFD in control subjects (−0.04 divided by −0.02) (Figure 4). Thus, even if we assume that the modest nerve loss in healthy subjects is age related, the accelerated nerve loss in patients with FM is likely to be the result, at least in part, of FM itself.

To further test for the effect of age on our ENFD findings, we conducted an ANCOVA comparing ENFD values between patients with FM and control subjects with adjustment for age as a covariate. This analysis showed that, irrespective of age, ENFD values at the thigh were significantly lower in patients with FM compared with control subjects ($P = 0.01$), although this difference was less significant at the calf ($P = 0.06$). There is, of course, no way to know whether any effect of aging in our study is associated with a normal neuronal, involutional phenomenon or reflects the fact that so few elderly individuals are in good health.

In this study, we also sought to determine whether the reduced ENFD observed in patients with FM might be "length dependent"; that is, whether the severity of the neuronal loss is influenced by the distance from the CNS (i.e., spinal cord). Because it is known that lower extremity ENFD decreases from proximal to distal leg sites (30), we calculated a thigh-to-calf ENFD ratio (i.e., proximal:distal) for our study participants. We reasoned that comparing this ratio between patients with FM and control subjects ought to help determine whether ENFD loss in FM is worse distally, thus suggesting length dependency. Such a length-dependent phenomenon may be seen both in cases of dying-back axonopathies and in more diffuse demyelinating nerve lesions (31).

Our data show that both proximal (i.e., thigh) and distal (i.e., calf) ENFD in FM fall away sharply from control values with advancing age (Figures 3 and 4). In addition, the slope of the trend line for the thigh-to-calf ENFD ratio in patients with FM compared with the slope of the trend line in control subjects suggests that nerve loss is greater distally than proximally with advancing age in patients with FM (with the slope of trend line in FM being ~7 times steeper than that in controls; data not shown). Thus, our clinical findings show that ENFD loss in FM is a diffuse process affecting both proximal and distal sites. Our statistical analysis, however, implies that length dependency may remain an important factor in FM, with distal sites at greater risk than proximal sites. Clearly, further investigation of length-dependent phenomena in FM-related ENFD loss is warranted.

The precise cause of ENFD loss in FM is not entirely self-evident. Nevertheless, in the absence of data implicating any other known neuropathic disorder in the genesis of this lesion, we consider it likely that an immunopathogenic mechanism is at work in this patient population, at least insofar as their skin and PNS function is concerned. More specifically, patients with FM have shown evidence of increased cutaneous neurogenic inflammation and flare response (a process that is thought to involve Aδ fibers and C-fibers) (32), altered vasoconstrictory responsiveness (33), and the physical findings of livedo reticulares (34) and Raynaud's phenomenon (35).

Other subtle, potentially inflammatory phenomena involving the skin of patients with FM include findings of enhanced vascular permeability (34), dermal–epidermal junction (34,35) and dermal matrix IgG deposition (36), increased skin mast cell populations (36,37), and local activation of the proinflammatory "contact system" (38). Other studies have shown findings suggestive of an ultrastructural, cutaneous injury pattern in FM, as measured, in part, by electron microscopy, including abnormalities of unmyelinated nerve fibers and Schwann cell populations (39) and collagen structure (40). Furthermore, Pay et al (41) described elevated serum levels of fibronectin, suggestive of vascular injury and endothelial dysfunction in FM. Salemi et al (42) described elevated levels of the inflammatory cytokines IL-1β, IL-6, and TNFα in the skin of patients with FM, and Burda et al (43) reported a significant correlation between HLA–DR4, a known autoimmunity-associated HLA type, and FM. Last, intravenous immunoglobulin, a known immune-modulating agent, has been shown to ameliorate painful symptoms in some patients with FM (6).

In this study, we observed that serum levels of IL-2R, a known T cell and monocyte/macrophage activation and proliferation marker (44), correlated inversely with calf ENFD in our patients with FM. As a signal, IL-2R has been thought to be reliable enough to be used to monitor the course of some autoimmune diseases (45). These T cell and monocyte/macrophage components of the immune system, in turn, are thought to participate in the production of certain human neuroimmune disorders such as CIDP and multiple sclerosis (46).

A cytokine-related lesion in FM, as marked by the inverse correlation between serum IL-2R levels and calf ENFD in our study subjects, is, at least in theory, not unexpected. The participation of cytokines in rheumatic disease is well known and is frequently posited as a mediator of injury in FM. Bazzichi et al (47), for example, described elevated levels of IL-10, IL-8, and TNFα in FM, and an intravenous infusion of IL-2 may produce an FM-like clinical picture in some cancer patients (48). Furthermore, our finding of an IL-2R abnormality in relation to calf ENFD in patients with FM remained constant throughout our early (15) and late study findings. Interestingly, proinflammatory cytokines, in general, have also been implicated as one of the more likely noxious agents in the production of small fiber neuropathy, particularly "idiopathic" small fiber neuropathy (12,49). Despite all of these considerations, however, further research will be necessary to verify meaningful associations between IL-2R (or any other cytokine marker) and ENFD in FM.

Currently, the chronically painful symptoms of FM are thought, by most investigators, to be attributable to abnormal pain modulation within the CNS, ostensibly due to "wind-up" and "central sensitization" (1). Nevertheless, wind-up and central sensitization are likely to be secondary rather than primary in FM. For example, there is no credible scientific or clinical evidence that reducing or even eliminating central sensitization downregulates pathologic peripheral pain input at all. However, according to our own experience, extinguishing the peripheral, painful components of FM eliminates the dysfunctional nature of body pain in this disorder, suggesting the elimination of central sensitization. It is also noteworthy that although central sensitization is an important conceptual construct within the FM superstructure, it remains difficult to utilize the idea of central sensitization as a viable clinical tool except in the research laboratory. Nonetheless, attention to the PNS lesion in FM, regardless of neuroimmunity, lends itself well to everyday clinical management of FM (50).

Herein, we have described an important relationship between diminished ENFD, as measured by skin biopsy, and the diagnosis of FM. Other investigators have also recently reported this relationship (51,52). This abnormality appears to affect both proximal and distal lower extremity biopsy sites but is also associated with a significant length-dependent quality (that is, the loss of nerve tissue is greater at more distant sites). The cause of this lesion is not readily apparent but appears to be part of a more generalized cutaneous proinflammatory diathesis in FM. Our study demonstrates the important contribution of the PNS to the symptoms and chronicity of FM. The results of our study also imply a significant role of small fiber neuropathy in these patients. Because this cutaneous neuropathic lesion cannot be explained by any known biochemical or hereditary disorder in our patients with FM, we suggest that this loss of ENFD in FM is likely to have an immune-mediated origin. According to our data, this nexus between the immune system and FM is likely to be influenced by a T cell–mediated arm (53). It may also involve factors within a system commonly referred to as "neurogenic inflammation" (32). Taken as a whole, these observations indicate that the current operative paradigm in FM, in which central sensitization is viewed as the prime mover in this disorder, requires modification.

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AUTHOR CONTRIBUTIONS

Both authors were involved in drafting the article or revising it critically for important intellectual content, and both authors approved the final version to be published. Dr. Caro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Caro.
Acquisition of data. Caro.
Analysis and interpretation of data. Caro, Winter.

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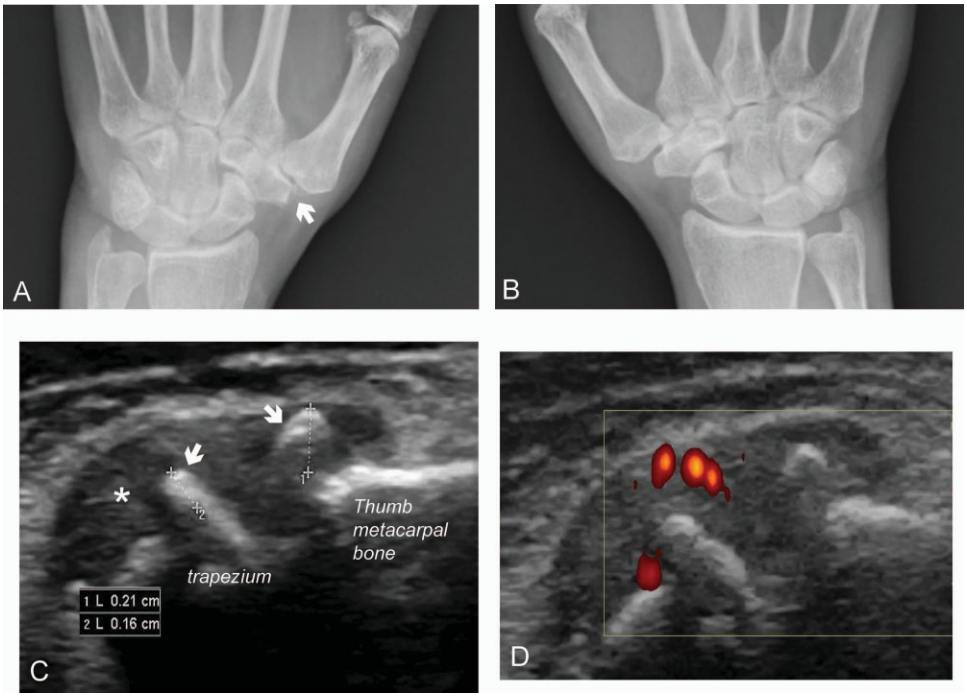
Clinical Images: Is ultrasonography better than radiography for determining the need for surgical treatment in patients with carpometacarpal osteoarthritis?



The patient, a 67-year-old woman, presented with moderate pain at the base of the right thumb and tingling in the index and middle fingers. On physical examination, she exhibited moderate pain and crepitus of the right carpometacarpal (CMC) joint as well as prominent atrophy of the thenar eminence. Test results for both Tinel's sign and Phalen's maneuver were positive. Radiography of the right hand showed joint space narrowing (**A**) (**arrow**) and mild sclerosis of the CMC joint. No osteophytes or cystic changes were observed. Radiography of the left CMC joint was unremarkable (**B**). A transverse ultrasound image of the volar aspect of the right wrist disclosed an enlarged bifid median nerve (cross-sectional area 0.13 cm^2). Osteophytes of a moderate size (**C**) (**arrows**), moderate effusion (**C**) (**asterisk**), and a mild Doppler signal (**D**) were observed in a longitudinal ultrasound image of the volar aspect of the CMC joint. Radiographs failed to reveal any osteophytes, cystic bone formation, or bone attrition in the CMC joint, thus making the patient a less likely candidate for surgery. However, ultrasonography revealed osteophytes (1.6 mm and 2.1 mm) at the trapezium and first metacarpal bone, respectively. Based on the ultrasound findings, the patient was referred for evaluation by a hand surgeon. A recent systematic review demonstrated that radiographs are not a reliable system for classification of disease severity (Berger AJ, Momeni A, Ladd AL. Intra- and interobserver reliability of the Eaton classification for trapeziometacarpal arthritis: a systematic review. Clin Orthop Relat Res 2014;472:1155−91). Because ultrasonography is very sensitive for the detection of synovitis and osteophytes (Kloppenburg M, Boyesen P, Smeets W, Haugen I, Liu R, Visser W, et al. Report from the OMERACT Hand Osteoarthritis Special Interest Group: advances and future research priorities. J Rheumatol 2014. E-pub ahead of print), further investigations should address whether the presence of effusion, synovial hypertrophy, osteophytes, and Doppler signal as visualized by ultrasonography might be more helpful than radiographs in making decisions regarding therapy.

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