Curr Pain Headache Rep (2015) 19: 55
DOI 10.1007/s11916-015-0527-7

The Role and Importance of Small Fiber Neuropathy in Fibromyalgia Pain

Xavier J. Caro[1] · **Earl F. Winter**[1]

Published online: 26 October 2015

Abstract Serious investigators of fibromyalgia (FM) realize the profound implications of finding features of small fiber neuropathy (SFN) in this disorder. For the first time, an easily reproducible and generally agreed upon, peripheral tissue lesion has been reported from multiple investigative centers. Understanding how this discovery relates to other features of FM, and how one might utilize it to better comprehend, and care for, afflicted patients' painful complaints remains a challenge, however. In this article we review how the SFN seen in FM may be placed in context, and suggest how such a tissue abnormality might be used to better understand the pathophysiology of FM, and plan for its effective treatment. We also suggest how finding SFN in FM implies the need for continued focused research within the area of neuropathic disease in FM.

Keywords Fibromyalgia · Chronic pain · Chronic widespread pain · Neuropathic pain · Small fiber neuropathy · Epidermal nerve fiber density

Introduction

Recent advances in our understanding of the fundamental mechanisms underlying fibromyalgia (FM) have shown that there is a significant peripheral neuropathic component to this disorder. This is evident by the plethora of reports, emanating from around the scientific world, showing reduced epidermal nerve fiber density (ENFD) in FM [1–3, 4•, 5, 6, 7•]. Reduced ENFD (often defined as ≤ 5th percentile of ENFD values measured in a clinically healthy, data-base group) is considered the sine qua non of "small fiber neuropathy (SFN)," a well-known and very painful neuropathic problem. It is of further interest that there are now other reports of peripheral nervous system abnormalities in FM from laboratories utilizing quantitative sensory testing [7•, 8], sudomotor axon reflex testing [9], and microneurographic recordings [10, 11•] of cutaneous nerve fibers. The common denominator amongst all of these reports is the finding of a SFN in FM. Importantly, this finding is of more than academic interest as, in our experience, addressing the SFN in FM leads to significant amelioration of the patient's painful symptoms. For example, many of the medications used to treat SFN have been shown to be efficacious in ameliorating the pain associated with FM (e.g., pregabalin, gabapentin, and the tricyclic antidepressants).

Interestingly, there has been surprisingly little comment in the medical literature regarding the etiology of this SFN in FM. Nevertheless, we have shown previously a significant inverse correlation between IL-2R, a known immune marker, and ENFD [4•]. This finding is consistent with previous laboratory investigations showing serologic and tissue evidence of immune aberration in this painful disorder [12–14, 15•, 16, 17, 18•, 19–24, 25••, 26, 27••]. As the immune system is also thought to be active in the production of "idiopathic" small fiber neuropathy [28•, 29, 30•] we conclude that it is likely that FM has a significant immune related component to its pathogenesis, and that—at least some—FM features are immune mediated.

These clinical and immunological considerations may supplement the currently predominate paradigm, which places major importance on the role of "central sensitization [31]"

This article is part of the Topical Collection on *Neuropathic Pain*

✉ Xavier J. Caro
xjcaro@earthlink.net

Earl F. Winter
earlwinter@att.net

[1] Southern California Fibromyalgia Research and Treatment Center, 18350 Roscoe Blvd. Suite 418, Northridge, CA 91325, USA

in FM. In that theoretical construct the central nervous system (CNS), at the spinal cord and brain level, becomes overly responsive to noxious peripheral input, through the phenomenon of "wind up" and "central sensitization." These phenomena are thought to perpetuate the pain seen in FM. Some thinkers advocating this mechanism of injury in FM have also postulated the presence of a significant "peripheral driver [32•]" in this disorder. All of this information, taken as a whole, suggests that SFN may be an important immune-mediated, peripheral driver in FM*.

In this paper we point out how the clinician can use all of this newer information to better understand the clinical picture seen in FM, and construct a logical approach to objectively diagnosing the neuropathic component of FM. This, in turn, should allow the treating physician to design, implement, and monitor a more effective treatment program for the patient.

Diagnosing SFN in FM

Methods for recognizing FM itself have been the subject of numerous reviews [33], and have generated at least two sets of formal, diagnostic criteria [34, 35]. The approach to the painful SFN patient has also been the subject of several extensive reports [30•, 36•]. The clinical utility of recognizing SFN in the setting of FM has, to our knowledge, only been described once before [37•]. Herein, we will point out the important components of the FM patient encounter, and particularly the role of recognizing SFN in the care of the FM patient.

In our experience, most clinicians have little difficulty in recognizing FM, but are often limited, at that point, in further conceptualizing a pathophysiologically based approach to this complex disorder. Recognizing the neuropathic quality of the descriptors commonly used by this patient group, conducting an efficient physical examination of the neuromuscular system, and being prepared to perform and interpret the results of a skin biopsy, are important parts of this approach. Attention to these areas of the patient's evaluation will direct the examiner toward a greater appreciation of the possibility of a significant peripheral nervous system (PNS) lesion in FM.

"Neuropathic language" is a label frequently applied to a set of verbal descriptors used by the patient with a lesioned PNS. This language may seem exaggerated or even fantastic to the conventional FM examiner (e.g., terms such as "hot," "burning," "pins and needles," "knife-like," "unbearable," and "miserable," to name a few, may color the patient's pain description). Importantly, the common denominator amongst these descriptors is the frequency with which they are used by patients with peripheral neuropathic disease [38, 39]. Seventy-five percent of our FM patients, compared with only 20 % of our rheumatoid arthritis (RA) patients without FM, used such language to describe their symptoms [15•]. This prevalence of neuropathic descriptors compared well with the 84 % prevalence reported by Simms and Goldenberg [40] and the 95 % prevalence reported by Martinez-Lavin [39]. As these subjective patient complaints suggest a lesion of the PNS, the clinician is obligated to keep this possibility in mind during the FM patient's evaluation and treatment. Physical examination of the FM patient should, therefore, also include a detailed evaluation of the PNS [41].

The clinician is, then, well advised to examine the FM patient for signs of large and small nerve injury. This may include ascertaining any abnormality in the patient's ability to sense lower extremity Wartenberg pinwheel and 128-Hz tuning fork stimuli [42]. Eighty-eight percent of our FM patients demonstrated a stocking distribution hypesthesia to these modalities [15•]. Interestingly, pinwheel and thermal hypesthesia have been described as being common in isolated SFN [36•]. Devigili et al., for example, found that 52.2 % of their patients with isolated SFN had pinprick and thermal hypesthesia [43••].

The finding of abnormalities to vibratory sensation, and a commonly associated proximal muscle weakness [15•], in FM further suggests that most FM subjects have a form of "mixed fiber neuropathy" (MFN). That is, their PNS problem is composed of a disorder involving both a large fiber neuropathy (LFN) and a SFN. To our knowledge, only two previous studies have extensively described EMG or nerve conduction study (NCS) findings in FM [15•, 44]. Ersoz [44] conducted EMG and NCS in 33 FM and 17 control subjects. Originally, he believed that there was no evidence of a generalized polyneuropathy in his FM subjects, but a letter to the editor [45] prompted him to reexamine his statistical inferences. This reexamination led Ersoz to conclude that a large fiber polyneuropathy was probably present in his FM patients [46].

In a more recent study, we reported the presence of widespread demyelinating and axonopathic large nerve lesions indicative of a polyneuropathy in 90 % of 55 consecutive FM patients [47]. In contrast, large nerve abnormalities are not typically reported as being part of isolated SFN. Grant, for example, states that nerve conduction studies are, "… often completely normal in patients with [*isolated*] SFN [30•]." These findings suggest that FM patients have a more severe or more generalized painful disorder than seen with isolated SFN.

Confirmation of the SFN component of this MFN merely requires a 3-mm punch biopsy of clinically healthy skin from the proximal thigh and distal leg [48, 49]. The technique for conducting such a biopsy is well within the grasp of the practicing physician, or even their well-trained assistant. A video demonstration of punch biopsy technique is available at several sites on the World Wide Web (e.g., https://www.therapath.com/). Typically, these biopsy samples are transported overnight to the testing laboratory in 2 % periodate–lysine–paraformaldehyde fixative and stained using an immunoperoxidase method for protein gene product 9.5, a ubiquitin carboxy-terminal hydrolase that is a panaxonal marker.

Laboratory evaluation consists of quantitating epidermal nerve fibers crossing the basement membrane at the dermal–epidermal junction using a standard counting algorithm. This methodology counts the number of fibers crossing into the epidermis from multiple sections. These numbers are then used to generate a mean "density" of such fibers per length of tissue (reported as the number of fibers crossing per millimeter of epidermis, i.e., the ENFD) (Fig. 1). Specialized laboratories usually perform these analyses.

Use of SFN Data Within the Context of FM

A continuum exists between "normal" and "abnormal" ENFD, rather than it being a simple dichotomous measure. Therefore, the clinician should, consider both "pre-test" probability and clinical context in order to interpret optimally the result of the ENFD determination. The differential diagnosis of "significantly reduced ENFD," i.e., SFN, spans a rather wide array of potential causes [30•] that may need to be kept in mind. Table 1 lists those disorders thought to be associated with SFN. In the absence of any of these specific problems one may conclude that the SFN in a given FM patient is likely to be tied closely to the patient's pain.

A review of our own experience using ENFD results in evaluating FM may be helpful to the reader. For example, in one of our recent research cohorts, consisting of 85 FM subjects, nearly all of the participants (~100 %) with an ENFD value of ≥7.00 fibers/mm had another peripheral, painful disorder significantly contributing to their symptoms. Furthermore, if the ENFD value was 6.0–6.99 fibers/mm, the chance of having another contributing disorder was 55 %. And, at an ENFD value of <6.00 fibers/mm the chance of having another contributing disorder was only about 40 %. Although the exact values for these ENFD determinations may be laboratory dependent, and require correlation within the reader's personal environment, the conceptual construct would remain. These findings show that at any ENFD value the FM patient may have another painful disorder contributing to their symptoms, but also imply that the higher the ENFD value in FM, the more likely the presence of a coincidental, pain-contributing factor (these findings are summarized in Table 2). Interestingly, the results of Devigili et al.'s study [43••] of SFN paralleled these findings. That is, in both of our experiences, ENFD was significantly lower when associated with "spontaneous" pain (i.e., stimulus-independent) than when associated with "evoked" pain (i.e., stimulus dependent).

Many of our FM patients with ENFD values of ≥7.0 fibers/mm have had a "hidden" rheumatic disease, such as rheumatoid arthritis, or another painful problem that either caused a FM-like picture (i.e., so-called, secondary FM or "pseudofibromyalgia"), or made the patient's FM pain picture much worse. Severe axial skeletal osteoarthritis, for example, in our experience, may accentuate FM pain without further reducing ENFD.

The following illustrative vignette may help point out the clinical usefulness of ENFD in the evaluation of an FM patient. AB, a 21-year-old Caucasian female college student attended our clinic with a two-year history of isolated FM, diagnosed by two prior consulting rheumatologists. They had found her painful complaints unresponsive to gabapentin or pregabalin, but her mood improved on duloxetine. At our facility a 3-mm punch skin biopsy from her calf area showed an ENFD of 15.6 nerve fibers/mm of epidermal length. As this value fell well above 7 fibers/mm, we reasoned that it was highly likely that, in addition to her FM, she had a "hidden" peripheral pain generator. Laboratory analysis showed a persistently elevated C-reactive protein determination, despite a negative or normal determination for sedimentation rate, rheumatoid factor, CCP-IgG, and antinuclear antibody. Further examination of the patient demonstrated a history of several hours of "morning stiffness," and physical findings of an associated small joint articular tenderness, without discernable

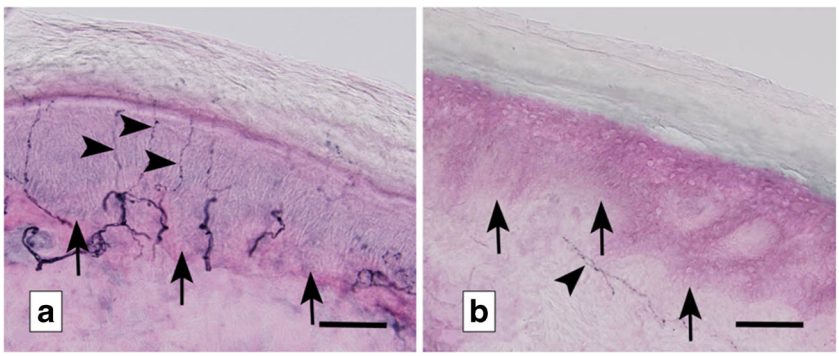

Fig. 1 **a** Skin biopsy specimen obtained from a normal subject, showing three nerve fibers (*arrowheads*) that extend from the dermis perpendicularly through the epidermis toward the upper layer of cells. **b** Skin biopsy specimen obtained from a patient with fibromyalgia and severe small fiber neuropathy, showing the total absence of epidermal nerve fibers and the presence of one 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. Photomicrograph courtesy of Therapath Laboratory (NY, NY); used with permission

Table 1 Disorders known to cause or contribute to low ENFD

Disorder	Contributes to low ENFD
Metabolic	• Diabetes mellitus (DM)* and "glucose intolerance"
	• Metabolic syndrome (MetSyn)*
	• Rapid glycemic control in DM ("insulin neuritis")
	• Hyperlipidemia
	• Hypothyroidism
Nutritional	• Vitamin B-12 deficiency
	• Hypervitaminosis B-6
	• Celiac disease
Connective tissue diselases	• CIDP
	• Systemic lupus erythematosus
	• Sjögren's syndrome
	• Scleroderma
	• Mixed connective tissue disease
	• Sarcoidosis
	• Vasculitis
	• Inflammatory bowel disease
	• Guillain–Barre syndrome
	• Erythromelagia
	• ANS ganglionopathy
Infectious Diseases	• Lyme disease
	• HIV-1 infection
	• Hepatitis C
	• Epstein–Barr virus
Neoplastic Diseases	• Paraneoplastic syndromes
	• Multiple myeloma
	• MGUS
Medications	• Cancer chemo (e.g., Cis-platinum, Paclitaxel, etc.)
	• Isoniazad
	• Metronidazole
	• Nucleoside analogues (ddI, ddC)
	• Phenytoin
	• Thalidomide
	• Certain vaccinations
Neuropathic	• Restless leg syndrome
	• Complex regional pain syndrome, type 1
Inherited conditions	• Fabry's disease
	• Hereditary sensory and autonomic neuropathies
Toxins	• Alcohol
	• Uremia
	• Amyloidosis
	• Smoking (in combination with DM)

CIDP Chronic Inflammatory Demyelinating Polyneuropathy, *ANS* Autonomic Nervous System

*Combination of DM & MetSyn twice as likely to produce SFN

swelling. A diagnosis of early "seronegative rheumatoid arthritis" was rendered, and the patient was treated successfully with tapering corticosteroids, hydroxychloroquine, and an infusible "biologic agent," abatacept.

Table 2 Likelihood of an additional pain generator being present in an FM subject based on calf ENFD

Calf ENFD	Likelihood (Prevalence*)
≤5.99 nerve fibers/mm	Low to moderate (40 %)
6.0–6.99 nerve fibers/mm	Moderate (55 %)
≥7.00 nerve fibers/mm	High (~100 %)

ENFD Epidermal Nerve Fiber Density

*In a FM research cohort of 85 subjects

Most of our FM patients with very low ENFD values (here, arbitrarily defined as ≤3.0 fibers/mm) have another condition present at the time of skin biopsy, which is known to reduce ENFD. Concomitant disorders that might reduce ENFD values, in and of themselves, and thus produce very low ENFD readings in FM, include problems such as poorly controlled diabetes mellitus [50], untreated Vitamin B-12 deficiency [51], and many of the other conditions listed in Table 1.

We also find that supplemental electrodiagnostic (EDX) evaluation, using readily available electromyography (EMG) and nerve conduction studies, have served as useful and complimentary tools in ascertaining the nature and extent of the large fiber neuropathic lesion in FM. We expect to present a detailed description of our LFN findings in FM in the near future. In brief, however, our FM patients often have EDX findings of a polyneuropathy due to an admixture of demyelination and axonopathic injury, often accompanied by findings of muscle denervation [47]. Although LFN is generally thought of as a painless process, it may be symptomatically painful in some circumstances, particularly if large sensory nerves are involved, most often within the context of a rapidly advancing, ischemic, or inflammatory disease [52•, 53].

Broader Pathophysiologic Implications of SFN/LFN in FM

In Table 3 we have summarized the clinical, laboratory, and EDX findings in the typical FM patient. Attention to these findings should allow the clinician to better comprehend the nature of FM pain and allow for the design of a more inclusive and effective treatment program for these patients than might be otherwise possible. They should also allow the clinician a better means of objectively monitoring the patient's response to therapeutic intervention. Thus, the clinician might want to supplement the routine "tender point count" [35] with a measure of change in any number of the other clinical abnormalities listed in Table 3. In our experience, for example, epidermal nerve fiber density and EDX findings vary over time according to the success or nonsuccess of clinical treatment. Other measures, such as proximal muscle strength, also typically correlate with changes in the patient's clinical state.

Table 3 FM patients' SFN and LFN mediated neuropathic pain findings

Clinical and laboratory findings	EMG and NCS findings
FM Tender points present≥11/18	EMG/NCS evidence of UE & LE Polyneuropathy=90 %[c]
Subjective parasthesias=76 %[a]	Polyneuropathy features[c]: • Demyelinating • Motor axonopathy • Nondermatonal denervation by EMG • Meets CIDP criteria in 40 % of FM patients
Stocking Hypesthesia=88 %[a]	Carpal tunnel syndrome=24 %[c]
Significant UE & LE proximal muscle weakness compared to non-FM rheumatic disease patients[a]	
Increased serum IL-2R levels[b]	
Small fiber neuropathy: thigh and/or calf (reduced ENFD) [b]	

SFN small fiber neuropathy, *LFN* large fiber neuropathy, *EMG/NCS* electromyography/nerve conduction studies, *UE & LE* upper extremity and lower extremity, *CIDP* chronic inflammatory demyelinating polyneuropathy

[a] Reference 15

[b] Reference 4

[c] Reference 47

In the absence of another identifiable cause, the presence of significant SFN, and also of LFN, in FM implies a significant role for the immune system in this disorder. We believe this to be likely, based on the plethora of data in the medical literature suggesting an immunologic connection to FM [12–14, 15•, 16, 17, 18•, 19–24, 25••, 26, 27••], our own finding that IL-2R levels demonstrate a significant inverse correlation with ENFD [4•], and the suggestion that idiopathic SFN is probably an immune-mediated disorder [28•, 29, 30•].

Therapeutic Implications of SFN in FM

One might expect that successful treatment of neuropathic pain in FM would require separate treatment of the large and small nerve components of this disorder. Fortunately, however, many of the currently available treatment modalities for PNS lesions overlap in their effect on large and small fiber pathology [54]. Furthermore, our previous data and everyday experience shows that a substantial subset of FM subjects respond to immunotherapeutic modalities, such as IVIg [15•].

Future Directions for SFN Research in FM

The common denominator amongst those conditions known to be immunologically mediated, and ending in a SFN, then may be envisioned as "a disturbance or malfunction" of the immune system. This type of immune disturbance is typically seen in the presence of excessive tissue injury or in the presence of a persistent offending agent; we see no reason for FM to violate these common axioms. Therefore, one must ask, "What is the inciting and/or persistent agent in FM?" And, what is the nature, and location, of the suspected agent and any bodily inflammatory response to it? Finally, within what context does such a disordered bodily reactivity occur?

For example, how are FM patients biologically different from normal individuals, and how does their immune reactivity differ from "normals?" Could FM actually presage other inflammatory disorders, such as seronegative rheumatoid arthritis? Might there be a "continuum" between the FM lesion and other, better defined disorders? Might there be a "common" underlying genetic and/or situational predisposition to both FM and these better understood inflammatory problems? Finally, could an immune system hyperreactivity in these conditions be arising from a common source of perturbation? To us, the gastrointestinal microbiome, particularly as seen in dysbiosis, seems a leading candidate for this kind of stimulus, as has been suggested in a number of other autoimmune and inflammatory disorders [55–59].

Conclusion

FM is a rather common disorder characterized by widespread pain, and accompanied by a number of constitutional symptoms. Until recently, there has been little in the way of agreement as to the nature and cause for the constellation of peripheral findings seen in this disorder. The robustness of the reports of SFN in FM suggests that SFN is likely to be a fundamental component of this malady. Further, once the SFN is placed in context, there arises the inevitable conclusion that many of the symptoms seen in FM are likely to be immune mediated. Additionally, ongoing work suggests that another important lesion, a large fiber neuropathy, exists in FM. In combination, all of these considerations provide a reasonable schematic for planning the treatment and monitoring of the painful complaints in this disorder. They also imply the potential for continued, fruitful, and focused research in FM. No other avenue of study offers such attraction for the FM researcher. Finally, many of the considerations put forth within this article imply that we are entering an exciting era of shifting paradigms in this enigmatic disorder.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Doppler K, Rittner HL, Deckart M, Sommer C. Reduced dermal nerve fiber diameter in skin biopsies of patients with fibromyalgia. Pain. 2015.
2. Levine TD, Saperstein DS. Routine use of punch biopsy to diagnose small fiber neuropathy in fibromyalgia patients. Clin Rheumatol. 2015;34:413–7.
3. Kosmidis ML, Koutsogeorgopoulou L, Alexopoulos H, Mamali I, Vlachoyiannopoulos PG, Voulgarelis M, et al. Reduction of intraepidermal nerve fiber density (IENFD) in the skin biopsies of patients with fibromyalgia: a controlled study. J Neurol Sci. 2014;347(1–2):143–7.
4. • Caro XJ, Winter EF. Evidence of abnormal epidermal nerve fiber density in fibromyalgia: clinical and immunologic implications. Arthritis Rheumatol. 2014;66:1945–54. **This study demonstrates a measureable immune component to the SFN seen in fibromyalgia**.
5. Giannoccaro MP, Donadio V, Incensi A, Avoni P, Liguori R. Small nerve fiber involvement in patients referred for fibromyalgia. Muscle Nerve. 2014;49:757–9.
6. Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. Pain. 2013;154:2310–6.
7. • Üçeyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Schmid A, et al. Small fibre pathology in patients with fibromyalgia syndrome. Brain. 2013;136:1857–67. **This ambitious study surveys SFN and function using a variety of approaches**.
8. Blumenstiel K, Gerhardt A, Rolke R, Bieber C, Tesarz J, Friederich HC, et al. Quantitative sensory testing profiles in chronic back pain are distinct from those in fibromyalgia. Clin J Pain. 2011;27(8):682–90.
9. Thieme K, Turk DC. Heterogeneity of psychophysiological stress responses in fibromyalgia syndrome patients. Arthritis Res Ther. 2006;8:R9.
10. Donadio V, Liguori R. Microneurographic recording from unmyelinated nerve fibers in neurological disorders: an update. Clin Neurophysiol. 2015;126(3):437–45.
11. • Serra J, Collado A, Solà R, Antonelli F, Torres X, Salgueiro M, et al. Hyperexcitable C nociceptors in fibromyalgia. Ann Neurol. 2014;75(2):196–208. **This study demonstrates that the SFN lesion in FM is not merely anatomical, but functional as well**.
12. Caro XJ. Immunofluorescent detection of IgG at the dermal-epidermal junction in patients with apparent primary fibrositis syndrome. Arthritis Rheum. 1984;27:1174–9.
13. Caro XJ, Wolfe F, Johnston WH, Smith AL. A controlled and blinded study of immunoreactant deposition at the dermal-epidermal junction of patients with primary fibrositis syndrome. J Rheumatol. 1986;13:1086–92.
14. Caro XJ. Is there an immunologic component to the fibrositis syndrome? Rheum Dis Clin N Am. 1989;15:169–86.
15. • Caro XJ, Winter EF, Dumas A. A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy (CIDP) and appear to respond to IVIg. Rheumatology (Oxford). 2008;47:208–11. **This study is the first to show large nerve involvement in FM and potential responsiveness to IVIg treatment**.
16. Dinerman H, Goldenberg DL, Felson DT. A prospective evaluation of 118 patients with fibromyalgia syndrome: prevalence of Raynaud's phenomenon, sicca symptoms, ANA, low complement, and Ig deposition at the dermal-epidermal junction. J Rheumatol. 1986;13:368–73.
17. Smart PA, Waylonis GW, Hackshaw KV. Immunologic profile of patients with fibromyalgia. Am J Phys Med Rehabil. 1997;76:231–4.
18. • Salemi S, Rethage J, Wollina U, et al. Detection of interleukin 1 beta (IL-1beta), IL-6, and tumor necrosis factor-alpha in skin of patients with fibromyalgia. J Rheumatol. 2003;30:146–50. **This study demonstrates abundant, local inflammatory markers in FM skin samples suggesting immune participation in FM skin pathology**.
19. Hernanz W, Valenzuela A, Quijada J, et al. Lymphocyte subpopulations in patients with primary fibromyalgia. J Rheumatol. 1994;21:2122–4.
20. Wallace DJ, Bowman RL, Wormsley SB, Peter JB. Cytokines and immune regulation in patients with fibrositis. Arthritis Rheum. 1989;32:1334–5.
21. Wilson RB, Gluck OS, Tesser JR, Rice JC, Meyer A, Bridges AJ. Antipolymer antibody reactivity in a subset of patients with fibromyalgia correlates with severity. J Rheumatol. 1999;26:402–7.
22. Shanklin DR, Stevens MV, Hall MF, Smalley DL. Environmental immunogens and T-cell-mediated responses in fibromyalgia: evidence for immune dysregulation and determinants of granuloma formation. Exp Mol Pathol. 2000;69:102–18.
23. Macedo JA, Hesse J, Turner JD, Ammerlaan W, Giesens A, Hellhamer DH, et al. Adhesion molecules and cytokine expression in fibromyalgia patients: increased L-selectin on monocytes and neutrophils. J Neuroimmunol. 2007;188:159–66.
24. Burda CD, Cox FR, Osborne P. Histocompatibility antigens in the fibrositis (fibromyalgia) syndrome. Clin Exp Rheumatol. 1986;4:355–8.
25. •• Bazzichi L, Rossi A, Massimetti G, Giannaccini G, Guiliano T, De Feo F, et al. Cytokine patterns in fibromyalgia and their correlations with clinical manifestations. Clin Exp Rheumatol. 2007;25:225–30. **This comprehensive study surveys multiple inflammatory markers in FM and suggests their elevation is more than coincidental**.
26. Wallace DJ, Margolin K, Waller P. Fibromyalgia and interleukin-2 therapy for malignancy. Ann Intern Med. 1988;108:909.
27. •• Uceyler N, Kafke W, Riediger N, He L, Necula G, Toyka KV, et al. Elevated proinflammatory cytokine expression in affected skin in small fiber neuropathy. Neurology. 2010;74:1806–13. **Subjects with length dependent SFN had significantly higher cytokine gene expression in affected skin, suggesting a role in pain production**.
28. • Parambil JG, Tavee JO, Zhou L, Pearson KS, Culver DA. Efficacy of intravenous immunoglobulin for small fiber neuropathy associated with sarcoidosis. Respir Med. 2011;105(1):101–5. **This paper suggests that SFN may be successfully treated with IVIg**.
29. Sheikh KA, Zhang G, Gong Y, Schnaar RL, Griffin JW. An antiganglioside antibody-secreting hybridoma induces neuropathy in mice. Ann Neurol. 2004;56(2):228–39.
30. • Grant IA. Cryptogenic sensory polyneuropathy. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. Philadelphia: Elsevier; 2005. p. 2321–33. **Excellent general review of SFN**.
31. Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states: maybe it is all in their head. Best Pract Res Clin Rheumatol. 2011;25:141–54.
32. • Staud R, Smitherman ML. Peripheral and central sensitization in fibromyalgia: pathogenetic role. Curr Pain Headache Rep.

2002;6(4):259–66. **A comprehensive discussion of the potential role of undiagnosed peripheral pain generators, feeding central sensitization, in FM**.

33. Katz RS, Wolfe F, Michaud K. Fibromyalgia diagnosis: a comparison of clinical, survey, and American College of Rheumatology criteria. Arthritis Rheum. 2006;54(1):169–76.
34. 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;33:160–72.
35. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res. 2010;62(5):600–10.
36.• Tavee J, Zhou L. Small fiber neuropathy: a burning problem. Cleve Clin J Med. 2009;76(5):297–305. **A very readable review of SFN; excellent for the clinician**.
37.• Caro XJ. Fibromyalgia: evaluation and therapy of a neuroimmune disorder. In: Mahmoudi M, editor. Challenging cases in rheumatology and diseases of the immune system. New York: Springer; 2013. p. 257–84. **The author shows how to use ENFD (skin biopsy) in the evaluation of FM. Case examples are presented**.
38. Melzack R, Katz J. Pain assessment in adult patients. In: McMahon SB, Koltzenburg M, editors. Wall and Melzack's textbook of pain. 5th ed. Philadelphia: Elsevier; 2005. p. 291–304.
39. Martinez-Lavin M, Lopez S, Medina M, Nava A. Use of the Leeds assessment of neuropathic symptoms and signs questionnaire in patients with fibromyalgia. Semin Arthritis Rheum. 2003;32:407–11.
40. Simms RW, Goldenberg DL. Symptoms mimicking neurologic disorders in fibromyalgia syndrome. J Rheumatol. 1988;15:1271–3.
41. Katirji B. Clinical assessment in neuromuscular disorders. In: Katirji B, Kaminski HJ, Preston DC, Ruff RL, Shapiro BE, editors. Neuromuscular disorders. Boston: Butterworth Heinemann; 2002. p. 3–19.
42. DeJong RN. The neurologic examination: incorporating the fundamentals of neuroanatomy and neurophysiology. 4th ed. Cambridge: Harper & Row; 1979. p. 44–9. **67–8**.
43.•• Devigili G, Tugnoli V, Penza P, Camozzi F, Lombardi R, Melli G, et al. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. Brain. 2008;131:1912–25. **Excellent study of the pathophysiology of SFN and how its neuropathology translates into clinical findings**.
44. Ersoz M. Nerve conduction tests in patients with fibromyalgia: comparison with normal controls. Rheumatol Int. 2003;23:166–70.
45. Caro XJ, Winter E. Nerve conduction tests in patients with fibromyalgia syndrome. Rheumatol Int. 2005;25(1):77–8.
46. Ersoz M. Nerve conduction tests in patients with fibromyalgia: comparison with normal controls. Rheumatol Int. 2005;25(1):79–80.
47. Caro XJ, Galbraith RG, Winter EF. Is there peripheral large nerve involvement in fibromyalgia? A systematic EMG / nerve conduction study evaluation of 55 consecutive FM patients [abstract]. Arthritis Rheumatol. 2015; 67 (suppl 10). http://acrabstracts.org/abstract/is-there-peripheral-large-nerve-involvement-in-fibromyalgia-a-systematic-emg-nerve-conduction-study-evaluation-of-55-consecutive-fm-patients/.
48. Hays AP. Utility of skin biopsy to evaluate peripheral neuropathy. Curr Neurol Neurosci Rep. 2010;10:101–7.
49. Kennedy WR, Wendelschafer-Crabb G, Polydefkis M, McArthur JC. Chapter 34: pathology and quantitation of cutaneous innervation. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 869–95.
50. Polydefkis M, Griffin JW, McArthur J. New insights into diabetic polyneuropathy. JAMA. 2003;290(10):1371–6.
51. Rehman HU. Re: vitamin B12 deficiency. BMJ. 2014;349:g5226.
52.• Scadding JW, Koltzenburg M. Painful peripheral neuropathies. In: McMahon SB, Koltzenburg M, editors. Wall and Melzack's textbook of pain. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2013. p. 926–51. **A comprehensive review of peripheral neuropathic pain mechanisms**.
53. Dyck PJ, Lambert EH, O'Brien PC. Pain in peripheral neuropathy related to rate and kind of fiber degeneration. Neurology. 1976;26:466–71.
54. Gilron I, Baron R, Jensen T. Neuropathic pain: principles of diagnosis and treatment. Mayo Clin Proc. 2015;90(4):532–45.
55. Davis-Richardson AG, Triplett EW. A model for the role of gut bacteria in the development of autoimmunity for type 1 diabetes. Diabetologia. 2015;58(7):1386–93.
56. Gomez A, Luckey D, Taneja V. The gut microbiome in autoimmunity: sex matters. Clin Immunol. 2015;6:S1521–6616.
57. Rogier R, Koenders MI, Abdollahi-Roodsaz S. Toll-like receptor mediated modulation of T cell response by commensal intestinal microbiota as a trigger for autoimmune arthritis. J Immunol Res. 2015;2015:527696.
58. Van Praet JT, Donovan E, Vanassche I, Drennan MB, Windels F, Dendooven A, et al. Commensal microbiota influence systemic autoimmune responses. EMBO J. 2015;34(4):466–74.
59. Geuking MB, Köller Y, Rupp S, McCoy KD. The interplay between the gut microbiota and the immune system. Gut Microbes. 2014;5(3):411–8.