

Small Fiber Neuropathy in Patients Meeting Diagnostic Criteria for Fibromyalgia

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Abstract

Introduction: The cause for fibromyalgia (FM) is unknown and diagnostic criteria can be nonspecific. Many patients with FM have nonspecific sensory symptoms consistent with a neuropathic process. Previous studies have shown that a significant percentage of patients diagnosed with FM have small fiber neuropathy (SFN) based on decreased intraepidermal nerve fiber density (IENFD) on according to punch skin biopsy testing. The purpose of this study was to demonstrate that punch skin biopsy testing is an effective way to identify SFN and its underlying causes in patients previously diagnosed with FM.

Methods: We studied 56 patients referred to peripheral nerve disease centers for evaluation of neuropathic pain who met the diagnostic criteria for FM. All underwent punch skin biopsy testing. If SFN was detected, patients underwent further laboratory testing to look for a potential cause for the neuropathy.

Results: Thirty-four of 56 patients (61%) had SFN, as indicated by reduced IENFD. Twenty-four of 34 patients with SFN (71%) had laboratory evidence that revealed an underlying etiology for the SFN.

Conclusions: More than half of the patients presenting with neuropathic pain and who met diagnostic criteria for FM had SFN detected by skin biopsy testing. A potential cause for neuropathy was identified in 71% of the patients with SFN. Skin biopsy testing to look for SFN is a very high-yield test in patients with FM who have neuropathic pain symptoms. Diagnosing SFN can facilitate the identification of potential causes for the neuropathy and alter their management.

Keywords: Fibromyalgia; Small fiber neuropathy; Epidermal nerve fiber density; Punch skin biopsy

Introduction

Fibromyalgia (FM) is a prevalent syndrome resulting in chronic widespread pain. The etiology of the pain is unknown; however, most models for pathogenesis involve central nervous system changes that allow for a “misinterpretation” or amplification of stimuli [1]. Many patients with FM have sensory symptoms that include dysesthesia, burning, and allodynia-symptoms that are also seen in the clinical presentation of small fiber peripheral neuropathy (SFN) [2]. Skin punch biopsy testing to assess epidermal nerve fiber density (IENFD) has emerged as the gold standard in the diagnosis of SFN [3,4]. The identification of distinctive pathology in cases of FM is helpful in recognizing specific, potentially reversible causes. These potential causes include diabetes mellitus, impaired glucose tolerance, vitamin deficiencies, Sjogren’s syndrome, and other autoimmune diseases [4-6]. Recently, several authors found a high incidence of SFN in FM patients diagnosed after testing IENFD with punch skin biopsies [7-10]. The purpose of this study was to demonstrate that punch skin biopsy testing is an effective way to identify SFN and its underlying causes in patients previously diagnosed with FM. We evaluated patients referred to 2 peripheral nerve disorder centers who met the diagnostic criteria for FM. Skin biopsy testing was performed to test for SFN. When SFN

was identified, further laboratory testing was performed to look for a potential cause of the neuropathy.

Materials and Methods

A retrospective examination was performed on 56 patients who met the diagnostic criteria for FM and were referred to 2 neurology practices for neuromuscular consultation. The patients were seen by peripheral nerve disease specialists at the Ohio State University or Phoenix Neurological Associates. Patients were given a diagnosis of FM if they met either the original [11] or revised American College of Rheumatology (ACR) criteria [12]. Skin punch biopsies were performed using a 3 mm disposable punch under sterile technique, after topical anesthesia with lidocaine. The skin biopsies were immunostained with the pan-axonal marker, protein gene product 9.5 (PGP 9.5), to permit visualization and quantification of epidermal nerve fibers using standard, recommended techniques [3]. Specimens were processed at one of two laboratories (Corinthian Reference Lab, Benbrook, TX or Therapath, New York, NY). Normal values for IENFD established by each laboratory were used to determine whether a specimen was normal or abnormal. If IENFD was abnormally decreased in at least one biopsy site, the patient was considered to have a SFN. If a SFN was diagnosed, laboratory testing was performed to look for an underlying cause of the neuropathy. This included vitamin B1, B6, and B12 levels; oral glucose tolerance testing; serum

immunofixation electrophoresis; thyroid function tests; erythrocyte sedimentation rate (ESR); antinuclear antibodies (ANA); and SSA/SSB antibodies. If indicated, testing for Fabry's disease with serum alpha-galactosidase levels was obtained.

Results

Thirty-four of the 56 patients (61%) were found to have reduced IENFD by skin punch biopsy, which indicated SFN. Furthermore, 24 of 34 (71%) patients had laboratory evidence that revealed an underlying etiology for the SFN. These previously undiagnosed causes of SFN were glucose dysmetabolism, Sjogren's syndrome, elevated ESR and ANA, vitamin B6 or B12 deficiency, and Fabry's disease. These underlying conditions were not previously detected when FM was the only diagnosis suspected in these patients and SFN had yet to be diagnosed by punch biopsy. These results suggest that an early skin biopsy evaluation in FM patients with neuropathic pain may be valuable in the early diagnosis of SFN, leading to the treatment of a potential underlying cause which may result in the resolution of some symptoms and potentially a cure. All patients tolerated the skin biopsy procedure well, and there were no complications.

Discussion

In general, the pain associated with FM is described as a deep, muscular aching and flu-like pain. However, many patients with a diagnosis of FM report burning, numbness, tingling, or stabbing, which are symptoms often associated with neuropathy [2,6,12].

In 1990, the ACR developed diagnostic criteria for FM based on widespread pain and tender points [11]. The use of tender points in the evaluation of FM has been controversial and many clinicians have been reluctant to include this measure [13]. In 2010, the ACR proposed alternate diagnostic criteria [12]. These criteria eliminated tender points, instead focusing on widespread pain as well as the presence and severity of various somatic symptoms, to include numbness and tingling. However, these criteria are nonspecific and this is acknowledged by a core diagnostic criterion requiring that the "patient does not have a disorder that would otherwise explain the pain" [12]. Many patients with FM may have sensory symptoms such as numbness, tingling, burning, and allodynia [2]. The results presented in our study (as well as additional research to be discussed below) suggest SFN represents such a disorder that can mimic FM.

Patients with SFN typically have complaints of tingling, burning, and pain [4-6]. Usually these sensory symptoms are symmetrical, length-dependent, and persistent. However, the symptoms of SFN can be multifocal and intermittent [6]. Some patients with SFN may not have sensory symptoms but, instead, symptoms of muscle soreness, aching, or cramping [6,14]. In a recent, small study, Lopate et al. showed that 60% of patients with muscle cramps but no neuropathic symptoms met the diagnostic criteria for SFN [14].

The gold standard for the diagnosis of neuropathy has traditionally been with the use of nerve conduction studies and electromyography (NCS/EMG). However, patients with SFN have normal findings on NCS/EMG; this makes diagnosis difficult. Until recently, SFN was diagnosed by exclusion, but the ability to assess small epidermal nerve fibers by skin biopsy has revolutionized the diagnosis of SFN [3]. Detecting a decreased epidermal nerve fiber density (IENFD) in a skin punch biopsy specimen has become a standard method for diagnosing SFN [3,15].

Uceyler et al. [7] were the first to demonstrate abnormal IENFD in FM patients. In a case-control study, the researchers investigated the morphology and function of small nerve fibers in 25 patients diagnosed with FM using the 1990 ACR criteria. The results were compared to 55 healthy control subjects matched for gender and age. Two skin biopsies were collected from each participant (lower leg and thigh). The results demonstrated a statistically significant reduction in the IENFD of the FM patients compared to the control group in both the proximal and the distal biopsy sites. The authors did not provide information regarding how often IENFD were abnormal in each group. Another prospective case-control study by Oaklander et al. [8] investigated SFN-associated symptoms, pathophysiological markers, and neurological examinations in 27 FM patients and 30 age- and gender-matched controls. Diagnosis of FM was based on the 2010 ACR criteria. The authors found that 41% of the FM subjects and only 3% of the control subjects had abnormal IENFD (<5th percentile of predicted lab norms) ($p < 0.001$). A potential cause for the neuropathy was found in 11 of 13 (85%) of patients diagnosed with SFN. The investigators propose that their findings suggest that some FM patients with neuropathic pain could have undiagnosed SFN [4]. Giannoccaro et al. [9] prospectively studied 20 patients diagnosed with FM using the 1990 ACR criteria. Six of these patients (30%) were diagnosed with SFN on the basis of decreased IENFD on skin biopsy. Most recently, Caro and Winter [10] studied 41 consecutive patients diagnosed with FM using the 1990 ACR criteria. IENFD from calf and proximal thigh specimens were significantly decreased compared to those found in 47 control subjects. The percentage of patients with abnormal IENFD is not provided.

These studies, in addition to the current work, suggest that about half of patients diagnosed with FM may have SFN. The yield of IENFD testing may be highest in patients presenting with prominent symptoms, such as paresthesias and dysethesias; however, this is yet to be established as muscle pain may be the only symptom reported. The cause for the pain of FM is commonly considered to result from abnormal central pain processes [16]. It is uncertain whether FM patients with abnormal IENFD have FM as well as SFN or simply have SFN causing pain symptoms mimicking FM. The answer to this question cannot be determined from existing studies. However, we suspect that patients with neuropathic symptoms have SFN as the cause of their symptoms and simply happen to meet criteria for FM that are lacking in specificity. Patients with SFN who meet the revised 2010 FM criteria may be more likely to be misdiagnosed.

In a study that evaluated the utility of punch biopsy in the diagnosis of SFN, Burchow et al. [16] demonstrated that in 52% of patients being evaluated for possible SFN, the diagnosis and treatment was changed as a result of punch biopsy. Furthermore, identifying a SFN on the basis of a skin punch biopsy can predict a patient's likelihood of responding to medications used to treat neuropathic pain [6]. Identifying SFN in a patient previously suspected of having FM allows for further diagnostic testing that may reveal a potentially treatable cause for the patient's symptoms [8].

Conclusion

About half of patients diagnosed with FM, patients have been found to have objective diagnostic evidence of SFN as evidenced by reduced IENFD on skin biopsy. Given that there are specific secondary conditions associated with small fiber axonal loss, this suggests that many FM patients may be inaccurately diagnosed and might not receive the most appropriate treatment. Objective diagnostic testing

with a skin punch biopsy in all FM patients can identify patients with reduced ENFD, leading to a definitive diagnosis of SFN. This diagnosis can then direct further testing to identify the underlying etiology of SFN, leading to appropriate treatment and resolution or stabilizations of symptoms. In addition to potentially altering treatment, a diagnosis of SFN can provide patients with an objective diagnosis as opposed to an often less satisfying diagnosis of FM.

Conflict of Interest and Source of Funding

Dr. David Saperstein and Dr. Todd Levine have a financial interest in Corinthian Reference Laboratory, a facility that performs IENFD testing for SFN. The authors of this article have full control of all primary data and agree to allow the journal to review their data if requested.

References

1. Clauw DJ (2014) Fibromyalgia. *JAMA* 311: 1547.
2. Simms RW, Goldenberg DL (1988) Symptoms mimicking neurologic disorders in fibromyalgia syndrome. *J Rheumatol.* 15: 1271-1273.
3. Lauria G, Hsieh ST, Johansson O, Kennedy WR, Leger JM, et al. (2010) European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol* 17: e903-e949.
4. Hovaguimian A, Gibbons CH (2011) Diagnosis and treatment of pain in small-fiber neuropathy. *Curr Pain Headache Rep* 15: 193-200.
5. Devigili G, Tugnoli V, Penza P, Camozzi F, Lombardi R, et al. (2008) The diagnostic criteria for small fiber neuropathy: From symptoms to neuropathology. *Brain* 131: 1912-1925.
6. Saperstein DS, Levine TD, Levine M (2013) Usefulness of skin biopsies in the evaluation and management of patients with suspected small fiber neuropathy. *Int J Neurosci* 123: 38-41.
7. Uceyler N, Zeller D, Kahn AK, Kewenig S, Schneider SK, et al. (2013) Small fiber pathology in patients with fibromyalgia syndrome. *Brain* 136: 1857-1867.
8. Oaklander AL, Herzog ZD, Downs HM, Klein MM (2013) Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain* 154: 2310-2316.
9. Giannoccaro MP, Donadio V, Incensi A, Avoni P, Liguori R (2014) Small nerve fiber involvement in patients referred for fibromyalgia. *Muscle Nerve* 49: 757-759.
10. Caro XJ, Winter EF (2014) Evidence of abnormal epidermal nerve fiber density in fibromyalgia: Clinical and immunologic implications. *Arthritis Rheumatol* 66: 1945-1954.
11. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, et al. (1990) The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. *Arthritis Rheum* 33: 160-172.
12. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, et al. (2010) The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)* 62: 600-610.
13. Wolfe F (2010) New American College of Rheumatology criteria for fibromyalgia: A twenty-year journey. *Arthritis Care Res (Hoboken)* 62: 583-584.
14. Lopate G, Streif E, Harms M, Wehl C, Pestronk A (2013) Cramps and small-fiber neuropathy. *Muscle Nerve* 48: 252-255.
15. England JD, Gronseth GS, Franklin G, Carter GT, Kinsella LJ, et al. (2009) Evaluation of distal symmetric polyneuropathy: the role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). *Muscle Nerve* 39: 106-115.
16. Boruchow SA, Gibbons CH (2013) Utility of skin biopsy in management of small fiber neuropathy. *Muscle Nerve*. 48: 877-882.