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REVIEW ARTICLE

Small fiber polyneuropathy as a potential therapeutic target in interstitial cystitis/bladder pain syndrome

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Abstract

Introduction and hypothesis Interstitial cystitis/bladder pain syndrome (IC/BPS) and fibromyalgia (FM) are frequently co-occurring medical diagnoses in patients referred to the urology clinic for secondary and tertiary treatment options.

Methods Abundant literature has shown that many patients with FM have small fiber polyneuropathy (SFPN) that can be confirmed via skin punch biopsy and immunological staining to measure nerve density.

Results and conclusions This finding of SFPN provides a therapeutic target for FM and in this article we hypothesize and provide rationale for the idea that this same phenomenon (SFPN) might explain, in some IC/BPS patients, the finding of widespread pain and likewise provide a therapeutic target for these patients.

Keywords Polyneuropathy · Interstitial cystitis/bladder pain syndrome · Fibromyalgia

Introduction

Polyneuropathy (peripheral neuropathy) describes a nontraumatic generalized disorder in which multiple peripheral (i.e., outside of the brain and spinal cord) nerves become damaged, resulting in dysfunction and degeneration. Motor and sensory fibers are often affected equally, but polyneuropathy can affect *either* one, solely or very disproportionately. There are multiple types of peripheral neuropathy (most are *poly*neuropathies), classified according to the type of nerve damage, the underlying cause, and the associated symptoms. Symptoms include numbness and tingling, shooting pains in the limbs, fatigue, difficulty with motor coordination, and extreme sensitivity to touch. Polyneuropathy is known to be a feature of diseases such as alcoholism, autoimmune disorders (e.g., Guillain–Barre syndrome), chronic inflammatory demyelinating polyneuropathy and necrotizing vasculitis, in addition to renal and liver diseases [1]. More recently, it has been well documented that polyneuropathy is a prominent feature of many pain-related illnesses and syndromes, including fibromyalgia (FM) [2].

Fibromyalgia, a neurological, and rheumatological disorder characterized by chronic pain throughout the body and a heightened sensitivity to pressure, has no clearly defined etiology and is often a comorbid diagnosis in women suffering from other chronic pain disorders including interstitial cystitis/bladder pain syndrome (IC/BPS) [3–5]. IC/BPS patients experience pain and tenderness in their bladder and pelvic regions, have an increase in urinary urgency and frequency, and often experience discomfort or pain while engaging in sexual activity. Patients with urological chronic pelvic pain syndrome (UCPPS), a blanket term that includes IC/BPS patients, often report pain outside the pelvic region that can be characterized as "widespread pain" [6]. Our group (and others) has reported that women with a nonbladder-centric form of IC/BPS frequently carry a multitude of comorbid pain diagnoses and experience chronic pain and discomfort throughout their bodies [5]. The etiology of this pain and hypersensitivity, particularly in BPS, could be linked to a systemic nerve disorder.

Although the relationship between IC/BPS and polyneuropathy has not been unequivocally established, there are preliminary research findings that *small fiber* polyneuropathy (SFPN), a polyneuropathy subtype, exists in approximately 50% of patients with FM [7]. The confirmation of SFPN in these patients provided the first objective evidence that they were suffering from something beyond a "functional illness". While SPFN manifests clinically in a variety of ways,

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diffuse pain is a characteristic complaint. SFPN is diagnosed by a *loss* of intra-epidermal nerve fiber density (IENF) on a skin punch biopsy [8], a finding that has been labeled as a "disruptive discovery" in FM patients given its potentially groundbreaking impact [7]. Although it may seem counterintuitive that a lower fiber density would be associated with *having* a pain syndrome, several recent studies have consistently shown a loss in IENF density in patients with neuropathic pain [9, 10]. In addition, SFPN may demonstrate structural abnormalities such as axonal swellings and sparse branching patterns [8]. Patients experiencing any sort of peripheral neuropathy experience changes and/or degeneration in the axotomy or gangliotomy. Immunohistochemistry has been consistently used to visualize this phenomenon in individuals experiencing neuropathic pain [11].

Small fiber polyneuropathy has also been demonstrated in a small cohort of women with chronic pelvic pain. Most patients in this refractory chronic pelvic pain cohort had abnormal nerve conduction results and were diagnosed as positive for SFPN. Comorbid conditions noted in the study group included IC/BPS (18%), FM (38%), endometriosis (15%), irritable bowel syndrome (33%), lower back pain (33%), migraine (38%), and other chronic pain syndromes (36%) [9]. Because most of the chronic pelvic pain (CPP) patients in this study experienced localized polyneuropathy, which is also recognized as commonly co-occurring in FM [12], the diagnosis of FM tends to be higher (as seen in this study) in these patients compared with an IC/BPS diagnosis.

These findings, coupled with the substantial body of literature regarding SFPN and FM pain, led us to hypothesize that because IC/BPS and FM are often co-occurring conditions with substantial clinical overlap, and because FM patients are often positive for SFPN, peripheral polyneuropathy may also underlie some of the *pain syndrome* aspects of IC/BPS. It is plausible that these comorbid pain syndromes that manifest throughout the body actually derive from a common pathogenic source. Although no targeted treatments have yet been developed for SFPN, we believe that establishing SFPN as a pathogenic mechanism will be the first step toward more effective therapies. By taking a skin biopsy from our IC/BPS patients exhibiting FM and polyneuropathy-like characteristics, we may be able to determine if an abnormal IENF density is a contributory element to their disease pathogenesis.

Methods and results

Abnormalities in nerve density and function in patients with a suspected polyneuropathy can be evaluated through a relatively easy-to-procure skin punch biopsy. Using this approach, researchers were able to identify a difference in the intra-epidermal nerve fiber densities in 41 patients diagnosed with FM versus 47 healthy controls [11]. In that study, all subjects underwent a routine 3-mm punch skin biopsy procedure from the proximal thigh and distal leg and the samples were analyzed to assess epidermal nerve fiber density (ENFD). Once collected, the biopsy samples were placed in 2% periodate-lysine-paraformaldehyde fixative and frozen. Following thick-sectioning, samples were immunohistochemically stained using an immune-peroxidase method for protein gene product 9.5, a ubiquitin carboxy-terminal hydrolase. Protein gene product 9.5 (PGP 9.5) is a cytoplasmic protein present in neural and neuroendocrine tissue that has been shown to be an excellent general marker of nerve fibers [13]. Visualization of nerve fibers within the skin tissue was performed using light microscopy and epidermal and dermal nerve fibers were quantified in the study subjects versus controls via a standard counting algorithm. Overall, women with FM showed a significant decrease in ENFD from both the thigh (9.3 ± 3.2 in FM patients versus 11.3 ± 2.0 in the control subjects, $p = 0.0007$) and calf (5.8 ± 2.8 in FM patients versus 7.4 ± 1.9 in healthy controls, $p = 0.0002$). Furthermore, *age* and *calf ENFD* were inversely correlated in patients with FM [11]. Figure 1 illustrates the differences in ENFD density that are clearly visible via immunohistochemistry staining of skin biopsy tissue.

The same approach that has been used to assess nerve density and function in polyneuropathy has also been utilized for assessment of SFPN in patients who exhibit FM-like symptoms. Using an identical method of skin punch biopsy

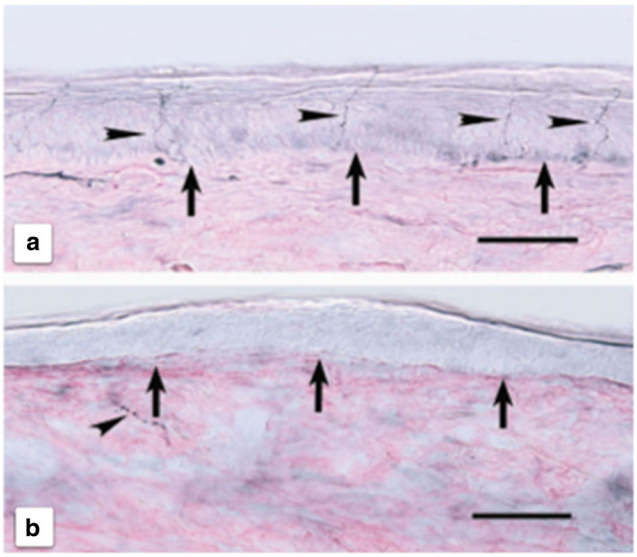

Fig. 1 **a** Skin biopsy specimen obtained from a normal subject, showing four nerve fibers (*arrowheads*) that extend from the dermis perpendicularly through the epidermis toward the upper layer of cells. **b** Skin biopsy specimen obtained from a patient with fibromyalgia and severe small fiber neuropathy, 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. (Reprinted with permission from Caro and Winter [11])

procurement and processing, visualization of the intra-epidermal nerve fiber density in patients with diseases linked to SFPN could also be quantified by immunohistochemistry. In one such study that evaluated SFPN in 27 patients with FM and 30 matched controls, where the visualization of sensory nerve endings in a distal-leg skin biopsy was accomplished using anti-PGP9.5 immuno-reactivity, the authors found that 41% of skin biopsies from subjects with FM, versus 3% of biopsies from control patients, were diagnostic for SFPN. In one representative finding from that study, a control subject was found to have a normal epidermal innervation density of 337 neurites/mm^2 of skin surface area (at the 76th percentile of the expected value) whereas a biopsy obtained from a FM subject showed a markedly reduced IENF innervation of 135 neurites/mm^2 of skin surface area (at the 3rd percentile of the expected value) [2]. By using this approach to assess SFPN in skin punch biopsies from individuals with complex pelvic pain versus controls, we may be able to start to better understand the polyarthralgia and chronic widespread pain (CWP) that we often witness in our nonbladder-centric IC/BPS population.

The emerging role of SFPN as a causative agent in pain syndromes has led researchers to hypothesize that a diagnostic skin biopsy might offer a better insight into the concurrent pain syndromes present in individuals with chronic pelvic pain. In 2018, Chen et al. reported the results of skin punch biopsies performed in a cohort of 39 women with refractory pelvic pain or multiple comorbid pain syndromes such as interstitial cystitis, FM, lower back pain, endometriosis, and other complex regional pain syndromes [9]. Individuals with a diagnosis of a large fiber polyneuropathy such as multiple sclerosis, spine disease, or central nervous system trauma were excluded from the study. All subjects underwent 3 × 3 mm skin punch biopsies in the right upper thigh below the ischial tuberosity, the right lower thigh above the knee, and the right distal calf approximately 10 cm above the medial malleolus. These sites were chosen because of their quality of IENF densities. Once the samples were obtained, they were stained with PGP 9.5 and CD3 neuronal and immunological markers. The diagnosis of SFPN, in 25 out of 39 patients (64%) was rendered by visually demonstrating a decrease in IENF density with immunofluorescence. This immunohistochemical staining technique simplifies the diagnosis of SFPN and permits expanded study in other pain populations.

Discussion

The results of skin punch biopsy testing and tissue processing with immunohistochemical techniques have opened a potential window of explanation into the varied and systemic pain manifestations in a subset of women previously labeled with the wastebasket terms of FM, chronic pelvic pain, and chronic bladder pain syndrome [14]. The 3-mm skin punch biopsy could be used for evidence of a reduced IENF density in women with bladder pain syndrome, a finding that provides diagnostic confirmation of SFPN.

Although approximately 50% of women with FM have proven evidence of SFPN [12, 15], this polyneuropathy has not yet been the target of more focused treatment. Current management strategies largely revolve around drugs that affect general neuropathic pain such as tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) [8, 16]. These same drugs are also commonly used as Tier 2 empiric treatment options for IC/BPS according to the American Urology Association guidelines [17]. Other treatment strategies that have been tried in SPFN patients with FM include intravenous lidocaine, IVIG, and other immunomodulatory therapies [8, 9], but none has been specifically used in IC/BPS patients. In addition to this, anti-muscarinic (medications which block the activity of the muscarinic acetylcholine receptors, inhibiting the conduction of action potentials in synapses in an effort to reduce pain) drugs, as well as psychosocial therapy and cognitive behavioral therapy have been used in patients with SFPN, BPS, and FM [16].

Based on the available data, it is plausible that a subset of IC/PBS patients is affected by SFPN and could benefit from a targeted therapeutic approach, similar to what is anticipated for CPP and FM patients with confirmed SFPN. This new avenue of research into an alternative explanation for women with non-bladder centric IC/BPS is rational and easily tested by a well-designed prospective trial. By following a protocol similar to what has been used in the studies cited here (i.e. taking a 3-mm skin punch biopsy from the distal leg to assess nerve density), it may be possible to facilitate a more complete understanding of the etiology behind the chronic widespread pain seen in our IC/BPS patient population. A decrease in IENF density would indicate that these individuals have SFPN, which could serve as an explanation and therapeutic target for their systemic disease manifestation.

In conclusion, although we are not aware of published evidence that confirms the role of SFPN in IC/BPS, the rationale for the hypothesis that SFPN *might* play an etiological role in *some* IC/BPS patients comes primarily from the following observations: first, a large percentage of patients with FM, a common comorbid condition in IC/BPS, are also known to have confirmed SFPN, and second, many IC/BPS patients appear to have a systemic pain disorder of uncertain etiology for which SFPN may present a logical explanation. We plan to apply the established skin biopsy techniques and immunohistochemical testing protocols for IENF density to a well-characterized cohort of women with nonbladder-centric IC to test this hypothesis.

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Compliance with ethical standards

Conflicts of interest None.

References

1. 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.
2. 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.
3. Clauw DJ, Schmidt M, Radulovic D, Singer A, Katz P, Bresette J. The relationship between fibromyalgia and interstitial cystitis. J Psychiatr Res. 1997;31:125–31.
4. Chelimsky G, Heller E, Buffington CA, Rackley R, Zhang D, Chelimsky T. Co-morbidities of interstitial cystitis. Front Neurosci. 2012;6:1–6.
5. Walker SJ, Zambon J, Andersson KE, Langefeld CD, Matthews CA, Badlani G, et al. Bladder capacity is a biomarker for a bladder centric versus systemic manifestation in interstitial cystitis/bladder pain syndrome. J Urol. 2017;198:369–75.
6. Lai HH, Jemielita T, Sutcliffe S, Bradley CS, Naliboff B, Williams DA, et al. Characterization of whole body pain in urologic chronic pelvic pain syndrome at baseline—a MAPP research network study. J Urol. 2017;198:622–31.
7. Oaklander AL. What is the meaning of "small-fiber polyneuropathy" in fibromyalgia? An alternate answer. Pain. 2016;157:1366–7.
8. Levine TD. Small fiber neuropathy: disease classification beyond pain and burning. J Cent Nerv Syst Dis. 2018;10:11795735518771703.
9. Chen A, De E, Agroff C. Small fiber polyneuropathy is prevalent in patients experiencing complex chronic pelvic pain. Pain Med. 2018;20:521–7.
10. Levine TD, Saperstein DS. Routine use of punch biopsy to diagnose small fiber neuropathy in fibromyalgia patients. Clin Rheumatol. 2015;34:413–7.
11. Caro XJ, Winter EF. Evidence of abnormal epidermal nerve fiber density in fibromyalgia: clinical and immunologic implications. Arthritis Rheumatol. 2014;66:1945–54.
12. Grayston R, Czanner G, Elhadd K, Goebel A, Frank B, Uceyler N, et al. A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: implications for a new paradigm in fibromyalgia etiopathogenesis. Semin Arthritis Rheum. 2019;48:933–40.
13. Christmas TJ, Rode J, Chapple CR, Milroy EJG, Turner-Warwick RT. Nerve fibre proliferation in interstitial cystitis. Virchows Arch A Pathol Anat Histopathol. 1990;416:447–51.
14. Oaklander AL. Immunotherapy prospects for painful small-fiber sensory neuropathies and ganglionopathies. Neurotherapeutics. 2016;13:108–17.
15. Caro XJ, Winter EF. The role and importance of small fiber neuropathy in fibromyalgia pain. Curr Pain Headache Rep. 2015;19:55.
16. Mullins C, Bavendam T, Kirkali Z, Kusek JW. Novel research approaches for interstitial cystitis/bladder pain syndrome: thinking beyond the bladder. Transl Androl Urol. 2015;4(5):524–33.
17. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP, et al. Interstitial cystitis guidelines panel of the American urological association education and research, Inc. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol. 2011;185:2162–70.