Small Fiber Neuropathy: Disease Classification Beyond Pain and Burning

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ABSTRACT: Small fiber neuropathy (SFN) has a poorly understood pathology, but patients would benefit from determination of clinical phenotypes that allows for better diagnosis and treatment planning. I propose that patients should be classified dependent on whether there is sodium channel dysfunction, classic neurologic symptoms only, widespread neuropathic pain, or autonomic symptoms. Patients with SFN can then be considered in light of their clinical phenotype, allowing for focus on subsets of patients who might have diagnosable conditions or be more prone to responding to a particular type of therapy that may not be efficacious in the broader patient population with SFN. There are several therapies currently available that can address the symptoms of SFN; however, to develop novel therapeutic strategies, it will be imperative to classify patients to understand and target the underlying pathology.

KEYWORDS: neuropathy, autonomic, small fiber

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Introduction

Since the 19th century work of Ramón y Cajal and French neurologist Charcot, neurologists have focused on localization with the long-standing belief that only by understanding if a disease process affects the brain, spinal cord, nerve, and/or muscle, can the clinician begin to determine the cause of the specific pathology. In the peripheral nervous system, we now understand that some diseases can affect all types of nerves, but others can be confined to just the myelin or just the axon. Likewise, a disease can affect just large fiber neurons or small fiber neurons. Even within diseases that affect purely small fibers, we now understand that this can present as purely sensory disruption such as pain, purely autonomic dysfunction, or in some patients a combination of both sensory and autonomic. Being able to parse patients into different subsets of neuropathies allows for a better understanding of the pathophysiology and potential treatments. One disease that would benefit from a more specific determination of clinical phenotypes to allow for a more precise diagnosis and potential improvement in patient condition is small fiber neuropathy (SFN).

Small fiber neuropathy is the result of damage to peripheral nerves,[1] including those that are small and myelinated (Aδ), as well as those that are unmyelinated (unmyelinated C fibers).[2] In SFN, small somatic and autonomic fibers can be affected.[1] Normally, these fibers control thermal and pain perception and control autonomic and enteric functions. For this reason, patients with SFN can present with either autonomic or somatic symptoms, or both. Symptoms are potentially numerous and can include allodynia, burning, lower thermal sensation, hyperesthesia, paresthesia, numbness in the lower extremities with potential to affect limbs and trunk, restless leg syndrome, dry eyes and mouth, abnormal sweating, bladder control issues, gastric issues, skin discoloration, and cardiac symptoms.[3] Cardiac symptoms include syncope, palpitations, and orthostatic hypotension. Even without diffuse autonomic dysfunction, a percentage of patients with postural orthostatic tachycardia syndrome (POTS) can have SFN.

Small fiber neuropathy has a poorly understood pathology. It can be a result of a variety of diseases, including diabetes mellitus, autoimmune disorders such as Sjögren or sarcoidosis, paraproteinemia, and paraneoplastic syndrome, with diabetes mellitus being the most common cause of SFN (Table 1).[1,3] Hereditary amyloid neuropathy also results in damage to small nerve fibers.[4] Amyloid neuropathies can be multisystemic or relegated to the cardiac system or only neuropathy.[5,6] There can be some presentation of neuropathy and cardiac symptoms without being widespread. Familial amyloid neuropathies include those caused by mutations in transthyretin (TTR) amyloidosis, apoprotein A1, and gelsolin.[4]

Considerations for diagnosis and treatment of small fiber neuropathies

As shown in Figure 1, patients with SFN can present with a wide variety of symptoms, both somatic and autonomic. Although there may sometimes be significant overlap between these symptoms, patients with SFN can be thought of in terms of their clinical phenotypes as a way of focusing on smaller subsets of patients who might have diagnosable conditions or respond to specific medications that do not treat all patients with SFN. In that vein, I suggest using the term small fiber sodium channel dysfunction (SFSCD) as a way of referring to patients who have symptoms of paroxysmal neuropathic pain characteristic of mutations in sodium channel proteins such as NaV1.7, 1.8, or 1.9. These patients may previously have been labeled as having erythromelalgia or other paroxysmal pain

Table 1. Common causes of neuropathy and the corresponding confirmatory testing.

POTENTIAL CAUSE	TESTS TO ORDER
Diabetes mellitus	Fasting glucose, HbA_{1c}
Impaired glucose tolerance	2-h oral glucose tolerance test
Sjögren syndrome	SS-A and SS-B
Primary systemic amyloidosis	Serum immunofixation
	Quantitative immunoglobulins
	Serum-free light chains
	Tissue biopsy
	Skin
	Fat pad
	Rectal
Sarcoidosis	Serum angiotensin-converting enzyme
Familial amyloidosis	Transthyretin gene sequencing
Fabry disease	α-galactosidase
Lupus, connective tissue disease	ANA
Immune mediated	Anti-potassium channel antibody
	Anti-nicotinic-ganglionic receptor antibody
Vitamin B_{12} deficiency	B_{12}, methylmalonic acid
Inherited	SCN9A (mutation in Nav1.7 ion channel)
	SCN10A (mutation in Nav1.8 ion channel)
Celiac	Gliadin antibody
	Transglutaminase antibody
Alcohol, chemotherapy, drug, trauma exposure	History
HIV	HIV testing

Abbreviation: HbA_{1c}, hemoglobin A_{1c}; ANA, anti-nuclear antibody.

disorders. These patients may differ from other patients with SFN as they may have genetically proven mutations in their sodium channels and physiologically proven nerve hyperexcitability without having a reduced intraepidermal nerve fiber density. While current sodium channel–blocking agents are not always effective, novel sodium channel blocking drugs could be revolutionary for this subset of patients, although not helpful to patients with other causes of painful SFN.[7,8]

In addition to patients with sodium channel–mediated SFN are patients with SFN who have classic neuropathic symptoms such as burning, tingling, stabbing, and numbness. These patients can be classified into the group small fiber–mediated painful neuropathy (SFMPN). These patients will have reduced intraepidermal nerve fiber density on skin biopsy in addition to the classic neuropathic symptoms. Another group of patients who have recently been shown to have objective evidence for damage to their small fibers are patients who have more widespread pain, experiencing muscle cramps and muscle pain, and in many cases, these patients have been confused as having fibromyalgia. I propose labeling the group of these patients who have evidence for objective loss of small nerve fibers as having small fiber–mediated widespread pain (SFMWP). These patients often have symptoms such as headache, fatigue, irritable bowel syndrome, cognitive dysfunction, and sleep disturbances. In an extreme form of these disorders, patients have objective evidence for autonomic dysfunction: abnormal gastric emptying studies with nausea and vomiting, abnormal tilt table tests, and abnormal quantitative sudomotor autonomic reflex testing. These patients should be labeled as having small fiber–mediated autonomic dysfunction (SFMAD), as their clinical phenotype is often overshadowed by gastrointestinal symptoms, heart rate dysregulation, temperature sensitivities, fatigue, and irritable bowel syndrome.

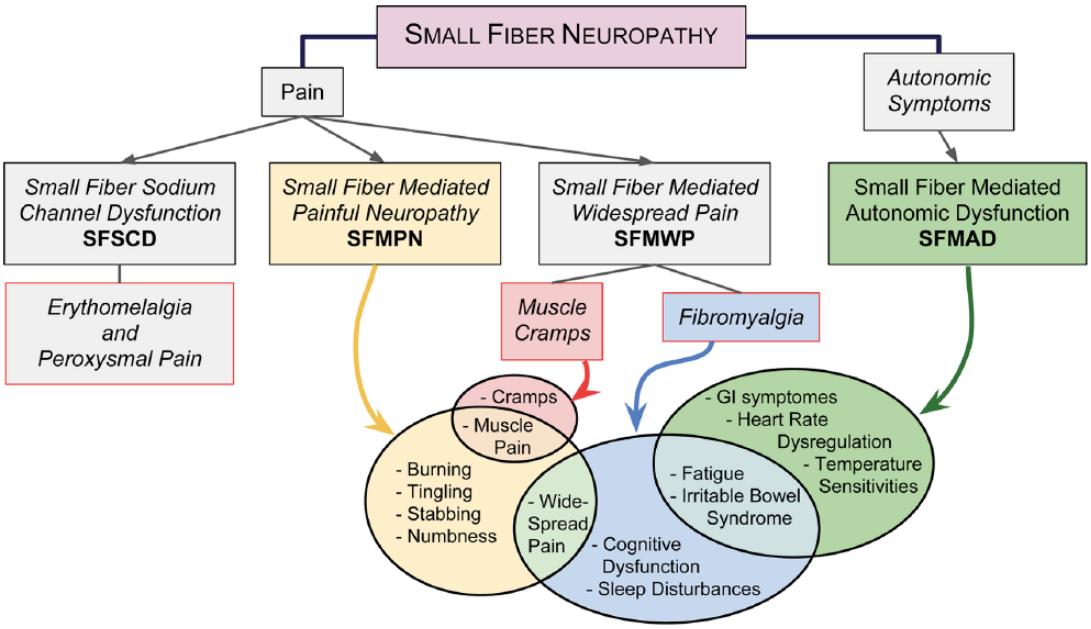

Figure 1. Small fiber neuropathy symptom clusters and neuropathy classifications.

It is clear to see in Figure 1 that there are a variety of symptoms that overlap between these different categories of SFNs. This would be expected as in these cases, the localization of the pathophysiology is the small nerve fibers. Patients who experience small fiber hyperexcitability in SFSCD may not be the same type of patients who experience small fiber medaited autonomic dysfunction (SFMAD) and thus it may be inappropriate to approach their diagnostic algorithm and treatment in the same way.

Diagnosis

To properly place a patient into the subcategories of SFN, ie, SFSCD, SFMPN, SFMWP, SFMAD, it is essential to take a comprehensive history of all the patient's symptoms. Patients may need skin biopsies, autonomic reflex screens, gastric emptying studies, etc, to know how many of their symptoms can be objectively defined. Once a patient is diagnosed as having a small fiber–mediated disorder, a thorough investigation to look for potential causes of the neuropathy is required. It is important to note that this article examines only those patients with pure SFN, defined as normal neurologic examinations and normal nerve conduction studies. Table 1 lists common causes of neuropathy and the corresponding tests to rule those causes out. A detailed patient history should be taken to determine whether there is family history of neuropathies, human immunodeficiency virus risk factors, hepatitis C infection, history of exposure to neurotoxins, and chemotherapeutics. Furthermore, laboratory testing including blood counts, metabolic enzymes, lipids, erythrocyte sedimentation rate, thyroid hormones, antinuclear antibodies, angiotensin-converting enzyme level, immunofixation testing, vitamin B_{12}, and a glucose tolerance test should be administered. In some cases, special laboratory testing may be necessary depending on the specific medical history of the patient. In severe cases, more aggressive evaluation can include lumbar puncture, fat pad, and rectal biopsies, as well as sural nerve biopsies.

Treatments

In the case of SFN that can be attributed to a particular underlying cause, the underlying cause should be addressed to modify the SFN (ie, glucose control, exercise for dysglycemia-associated SFN).[3] Pain management and other symptomatic therapies are crucial components of the treatment regimen for patients with neuropathy, as pain may be ameliorated by up to 50%, although elimination of pain is not usually achieved.[9,10] Limited evidence for specific therapies in the treatment of neuropathic pain syndromes exist; however, there are some treatment options that can be effective in treating a variety of types of SFN.

Two therapies recommended for neuropathic pain include tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Tricyclic antidepressants have a high level of evidence that support their use in treating neuropathy. They have been suggested to be a first-line therapeutic for the treatment of chronic neuropathic pain.[10] Use of these drugs potentially requires a process of dose escalation and proper timing of the dose to mitigate sedating or stimulating side effects.[10] Typically, the doses used for patients with chronic neuropathic pain are less than those used to exert antidepressant effects. Serotonin-norepinephrine reuptake inhibitors are also used to reduce pain associated with neuropathy; their efficacy derives from their ability to potentiate nociceptive inhibitory pathways. The dosing for SNRIs to be effective at reducing pain is typically higher than the doses used for antidepressant purposes.[10] Although this class of drug may be effective for pain reduction, the side effect profile associated with antidepressants

may limit their usefulness in certain patients and/or prevent proper dose escalation.[11]

Anticonvulsant medications are also frequently used in patients with neuropathic pain. Gabapentin blocks the flux of calcium through calcium channels in the central nervous system, whereas pregabalin reduces the calcium influx in both peripheral and central neurons.[10] Both γ-aminobutyric acid analogues are considered first-line therapeutics.[10]

Recently, the use of opioids has become controversial. The Centers for Disease Control and Prevention, as well as the Food and Drug Administration, has issued guidelines regarding the use of opioids in an effort to combat the growing public health problem that is opioid abuse and misuse.[12,13] However, it is possible to use opioids, which typically target the μ-opioid receptor, to ameliorate pain associated with neuropathy, although use of opioids in those with SFMAD may be problematic, as exogenous opioids target the enteric nervous system and worsen gastrointestinal function.[14] Because opioids can be abused and misused and may not be efficacious in patients with SFNs, it is imperative that novel therapeutics are developed that more specifically target the pathophysiology of SFNs. Currently, opioids should be considered as a treatment option only in patients who have resistance to other nonopioid mechanisms of treatment and there are very specific guidelines regarding how to use these drugs.[10,12,13] In addition, related drugs such as μ-opioid receptor agonist norepinephrine reuptake inhibitors not only act at the μ-opioid receptor but also act to prevent norepinephrine reuptake.

Topical treatments may also be used to alleviate pain. Patches that contain drugs such as lidocaine can act locally to inhibit sodium channels and therefore nerve conduction. Capsaicin patches can also be used; however, capsaicin targets the vanilloid TRPV1 receptor; it leads to deterioration of nerve fibers in the skin which can regenerate within 3 months, therefore providing temporary relief. Both pain patches can be used alone or in combination with other therapeutics.[10] Novel treatments under study include targeting transient receptor potential channels, angiotensin II type 2 receptor (ATR2) antagonism, intrathecal delivery of medications to reduce systemic exposure, and use of erythropoietin (EPO).

In the case of immune-mediated SFNs, there are different approaches to treatment that have shown preliminary efficacy in addressing SFN. One retrospective study of patients with sarcoidosis-associated SFN demonstrated that use of intravenous immunoglobulin G, anti-tumor necrosis factor, or a combination thereof resulted in improvement of symptoms.[15] There is currently one clinical trial exploring the utility of IVIg in patients with idiopathic SFN (clinicaltrials.gov: NCT02637700). ARA 290 is a small molecule that is in development to address sarcoidosis-related SFN and it has had early positive results. It is a small peptide derived from EPO that targets the innate repair receptor complex.[16,17] Preclinical data indicate that ARA 290 is capable of supporting the growth of intraepidermal nerve fibers, and preliminary clinical reports indicate that ARA 290 can induce small nerve fiber growth and provide relief from neuropathy symptoms.[18,19]

Inherited amyloid polyneuropathies can be treated; however, the treatments can range from conventional neuropathy drugs to surgical intervention. For example, a first-line treatment for individuals with familial amyloid polyneuropathy (FAP) due to the Val30Met mutation is liver transplantation. Removal of the source of the mutant protein and replacement with a liver donation effectively allow for a 95% reduction in variant protein from the blood and ultimately has an impact on disease progression.[4,20] In severe cases, liver transplant may be accompanied by a heart transplant due to cardiomyopathy.[20] Neither of these approaches, however, address the production of amyloid proteins in other tissues such as the eyes or central nervous system.[20] Although transplantation is an accepted treatment for FAP, the outcomes for patients have been poor.

Novel approaches to addressing the mutated protein have been explored. One such tactic is the use of tafamidis.[21] It is capable of selectively binding to TTR to stabilize and prevent dissociation and aggregation to amyloid deposits.[22] Tafamidis is typically indicated for use in symptomatic TTR-FAP with proven amyloid deposits.[22] In clinical trials, it has been shown to reduce worsening of nerve function.[23] Diflunisal is a nonsteroidal anti-inflammatory drug (NSAID) that can also bind to TTR and stabilize the tetramer.[24,25] A phase 1 study initially indicated that the generic NSAID was able to stabilize circulating TTR, reducing available substrate for amyloid formation.[25] A 2-year study of the use of diflunisal in patients with this disease has shown that it can inhibit disease progression.[26] A regimen of doxycycline and tauroursodeoxycholic acid has been explored in a phase 2 study that indicated that the combination can stabilize disease.[27]

Another approach to reduce the amyloid-forming ability of mutated TTR is to prevent its production in the first place. Short synthetic oligonucleotides (ASOs) directed against TTR messenger RNA have been explored as a method of protein reduction. Current clinical data regarding the use of ASOs are primarily from healthy volunteers, but there are ongoing trials to assess the ability of ASOs to control disease progression.[20] Small-interfering RNAs (RNAi) have been brought to phase 2 trials, designed as a lipid nanoparticle delivering RNAi directed against a 3′ untranslated region of both mutant and wild-type TTR. A single dose of ALN-TTR02 reduced TTR production[28]; phase 2 data indicate that ALN-TTR02 dose dependently reduces circulating TTR protein.[29] Monoclonal antibodies have been produced that are designed to target serum amyloid P component, although this is a common component of amyloid deposits, not unique to TTR. There are currently ongoing clinical trials with amyloid depleting antibodies; a phase 1 study has been initiated in patients with systemic amyloidosis to determine the efficacy in clearing serum amyloid. It is currently unclear whether this will affect disease

progression in patients with TTR amyloidosis or lead to improved nerve function.[20]

Conclusions

To improve patient outcomes for those who have dysfunction of small nerve fibers and autonomic nerve fibers, it is imperative to be able to parse them into different subgroups. We have proposed and made an argument that patients should be classified as follows:

- SFSCD, those with sodium channel dysfunction
  - Patients with normal nerve density but known abnormalities of their voltage gated sodium channels causing nociceptive dysfunction without loss of intraepidermal nerve fiber density.

- SFMPN, those with classic neurologic symptoms
  - Patients with normal electromyography (EMG)/nerve conduction velocity (NCV) and neurologic examinations who have reduced intraepidermal nerve fiber density and neuropathic pain as their predominant complaint.

- SFMWP, those with widespread neuropathic pain
  - Patients with normal EMG/NCV and neurologic examinations who have reduced intraepidermal nerve fiber density who have muscle pain, achy pain as opposed to neuropathic pain as their predominant complaint.

- SFMAD, those with autonomic symptoms
  - Patients who have autonomic dysfunction as their predominant complaint, such as POTS, autonomic instability, and gastroparesis.

Patients should be classified by the type of SFN they experience to improve management of disease and patient outcomes. Distinction between patients who have autonomic dysfunction in addition to the painful neuropathy induced by small fiber dysfunction is critical to proper treatment and disease management. For example, individuals diagnosed with SFMPN may be likely to respond to anticonvulsants and channel blocking drugs, whereas those with SFMWP may be more likely to respond to TCAs and SNRIs. Until patients are classified into the appropriate groups and treatment algorithms adjusted to accommodate the various characteristics of the pathology, will it be possible to address issues related to the lack of efficacy of some therapeutics in individuals having SFN.

Not only is patient management affected by the appropriate classification of a patient's disease but also future work to develop novel therapeutics and approaches may be hindered if the root causes of each disease are not uncovered. Pursuit of novel therapeutic strategies and agents may stem from grouping patients together more appropriately and studying the similarities and differences and systemic effects experienced.[30] Ultimately, classifying patients more specifically by the symptomology with which they present may lead to understanding the underlying mechanism of the development of neuropathy, particularly in determining what causes widespread neuropathy as compared with amyloid neuropathy that primarily affects particular systems.

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REFERENCES

1. Hovaguimian A, Gibbons CH. Diagnosis and treatment of pain in small-fiber neuropathy. *Curr Pain Headache Rep*. 2011;15:193–200.
2. Brouwer BA, de Greef BT, Hoeijmakers JG, et al. Neuropathic pain due to small fiber neuropathy in aging: current management and future prospects. *Drugs Aging*. 2015;32:611–621.
3. Tavee J, Zhou L. Small fiber neuropathy: a burning problem. *Cleve Clin J Med*. 2009;76:297–305.
4. Shin SC, Robinson-Papp J. Amyloid neuropathies. *Mt Sinai J Med*. 2012;79:733–748.
5. Conceicao I, Gonzalez-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. 2016;21:5–9.
6. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8:31.
7. Tang Z, Chen Z, Tang B, Jiang H. Primary erythromelalgia: a review. *Orphanet J Rare Dis*. 2015;10:127.
8. Fertleman CR, Baker MD, Parker KA, et al. SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. *Neuron*. 2006;52:767–774.
9. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14:162–173.
10. Binder A, Baron R. The pharmacological therapy of chronic neuropathic pain. *Dtsch Arztebl Int*. 2016;113:616–625.
11. Atreya S. Pregabalin in chemotherapy induced neuropathic pain. *Indian J Palliat Care*. 2016;22:101–103.
12. Services USDoHaH. *Abuse-Deterrent Opioids: Evaluation and Labeling* (ed. Administration Fad). Silver Spring, MD: US Food and Drug Administration; 2015:29.
13. Dowell DHT, Chou R. *CDC Guideline for Prescribing Opiods for Chronic Pain: United States, 2016* (ed. Control Cfd, Vol. 65). Atlanta, GA: Center for Surveillance, Epidemiology, and Laboratory Services, Centers for Disease Control and Prevention, US Department of Health and Human Services; 2016:52.
14. Poulsen JL, Brock C, Olesen AE, Nilsson M, Drewes AM. Evolving paradigms in the treatment of opioid-induced bowel dysfunction. *Therap Adv Gastroenterol*. 2015;8:360–372.
15. Tavee JO, Karwa K, Ahmed Z, Thompson N, Parambil J, Culver DA. Sarcoidosis-associated small fiber neuropathy in a large cohort: clinical aspects and response to IVIG and anti-TNF alpha treatment. *Respir Med*. 2017;126:135–138.
16. Brines M, Patel NS, Villa P, et al. Nonerythropoietic, tissue-protective peptides derived from the tertiary structure of erythropoietin. *Proc Natl Acad Sci U S A*. 2008;105:10925–10930.
17. Brines M, Cerami A. The receptor that tames the innate immune response. *Mol Med*. 2012;18:486–496.
18. Dahan A, Dunne A, Swartjes M, et al. ARA 290 improves symptoms in patients with sarcoidosis-associated small nerve fiber loss and increases corneal nerve fiber density. *Mol Med*. 2013;19:334–345.
19. Brines M, Dunne AN, van Velzen M, et al. ARA 290, a nonerythropoietic peptide engineered from erythropoietin, improves metabolic control and neuropathic symptoms in patients with type 2 diabetes. *Mol Med*. 2015;20:658–666.
20. Hawkins PN, Ando Y, Dispenzeri A, Gonzalez-Duarte A, Adams D, Suhr OB. Evolving landscape in the management of transthyretin amyloidosis. *Ann Med*. 2015;47:625–638.

21. Adams D, Suhr OB, Hund E, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol*. 2016;29:S14–S26.
22. Waddington CM, Benson MD. A review of tafamidis for the treatment of transthyretin-related amyloidosis. *Neurol Ther*. 2015;4:61–79.
23. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology*. 2012;79:785–792.
24. Miller SR, Sekijima Y, Kelly JW. Native state stabilization by NSAIDs inhibits transthyretin amyloidogenesis from the most common familial disease variants. *Lab Invest*. 2004;84:545–552.
25. Sekijima Y, Dendle MA, Kelly JW. Orally administered diflunisal stabilizes transthyretin against dissociation required for amyloidogenesis. *Amyloid*. 2006;13:236–249.
26. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA*. 2013;310:2658–2667.
27. Obici L, Cortese A, Lozza A, et al. Doxycycline plus tauroursodeoxycholic acid for transthyretin amyloidosis: a phase II study. *Amyloid*. 2012;19:34–36.
28. Coelho T, Adams D, Silva A, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. *N Engl J Med*. 2013;369:819–829.
29. Suhr OB, Coelho T, Buades J, et al. Efficacy and safety of patisiran for familial amyloidotic polyneuropathy: a phase II multi-dose study. *Orphanet J Rare Dis*. 2015;10:109.
30. Levine TD, Saperstein DS. Routine use of punch biopsy to diagnose small fiber neuropathy in fibromyalgia patients. *Clin Rheumatol*. 2015;34:413–417.