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REVIEW ARTICLE

Fibromyalgia and small fiber neuropathy: the plot thickens!

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Abstract

Several groups of investigators have described the presence of small fiber neuropathy in fibromyalgia patients. This writing discusses how this new finding could renovate fibromyalgia concept, diagnosis, and treatment. Predominant rheumatology thinking proposes fibromyalgia as a "centralized pain syndrome." An alternative hypothesis views fibromyalgia as a stress-related dysautonomia with neuropathic pain features. Dorsal root ganglia may be the key autonomic-nociceptive short-circuit sites. The recent recognition of small fiber neuropathy in a large subgroup of fibromyalgia patients reinforces the dysautonomia-neuropathic hypothesis and validates fibromyalgia pain. These new findings support fibromyalgia as a primarily neurological entity, nevertheless, rheumatologist will likely remain the best equipped specialist to diagnose fibromyalgia and differentiate it from other multi-symptomatic rheumatic syndromes. Skin biopsy and corneal confocal microscopy will probably become useful fibromyalgia diagnostic tests. Dorsal root ganglia sodium channel blockers are potential fibromyalgia analgesic medications. Subgroups of young girls with "autoimmune neuropathic fibromyalgia" may respond to immunoglobulin therapy. Multimodal intervention directed to regain autonomic nervous system resilience will likely remain the cornerstone for fibromyalgia therapy.

Keywords Dorsal root ganglia · Dysautonomia · Fibromyalgia · HPV vaccine · Postural orthostatic tachycardia syndrome · Small fiber neuropathy · Sodium channels · Sympathetic pain

Introduction

Different groups of investigators, mostly neurologists, have recently described the presence of small fiber neuropathy in a large subset of fibromyalgia patients [1–8]. This new finding brings fresh air to fibromyalgia research. The objective of this writing is to discuss how the identification of small nerve fiber pathology in the skin and eyes of fibromyalgia patients could renovate fibromyalgia concept, diagnosis, and treatment.

Methods

PubMed database was explored with the key words "fibromyalgia", "small fiber neuropathy," or the British term "small *fibre* neuropathy". Up to August 10, 2018, there were 38 PubMed publications with these key words. The data contained in the articles were reviewed. Fibromyalgia pathogenesis, diagnosis, and treatment are discussed in light of the new reports.

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Background information

Fibromyalgia: the rheumatologist unwanted child?

Since its inception as a clinical syndrome, fibromyalgia research has largely remained within rheumatology realms. Despite this fact, many rheumatologists resent seeing fibromyalgia patients. The multiplicity of symptoms these patients have, the frequently associated psychological underpinning, the lack of objective diagnostic test, and the poor response to drug therapy often leads to both patient and physician frustration [9]. Central to this patient–clinician disengagement is the lack of a coherent theoretical framework to elucidate fibromyalgia.

Current fibromyalgia pathogenic theories

Clauw et al. have championed the concept of fibromyalgia as a "centralized pain syndrome" [10]. This concept was

originally proposed by Yunus in 2007 [11]. According to this hypothesis, fibromyalgia patients have augmented pain and sensory processing in the brain, with increased functional connectivity to pro-nociceptive brain regions and decreased connectivity to anti-nociceptive areas [10].

Our group has long-proposed a different pathogenic mechanism. Fibromyalgia is clearly a stress-related disorder. Psychological and other types of stressor are often involved in the illness development and maintenance [12]. The sympathetic nervous branch is the key element of our stress response system. Diverse heart rate variability studies in fibromyalgia patients have shown changes consistent with relentless sympathetic hyperactivity associated to sympathetic *hypo-reactivity* to orthostatic stress. Such sympathetic dysfunction may explain fibromyalgia poly-symptomatic characteristic [13]. We propose fibromyalgia as a sympathetically maintained neuropathic pain syndrome. Fibromyalgia pain has clear neuropathic features. It is a stimulus-independent pain syndrome accompanied by allodynia and paresthesias. Norepinephrine reignites fibromyalgia pain [14]. Dorsal root ganglia sodium channels may play an important role in fibromyalgia neuropathic pain. Dorsal root ganglia contain small nerve fiber cell bodies. There is an association between severe fibromyalgia and a particular SCN9A gene-encoded dorsal root ganglia Nav 1–7 sodium channel genotype (rs6754031 GG) [15]. Furthermore, we propose that current linear-reductionist medical paradigm is unable to explain fibromyalgia-multifaceted clinical features. Whereas complexity theory may help to better appraise this illness and other similar maladies such as chronic fatigue syndrome/myalgic encephalomyelitis or irritable bowel syndrome [16]. Multifractal analysis reveals decreased nonlinearity and stronger anti-correlations in heart period fluctuations of fibromyalgia patients [17]. This finding exposes a degraded performance of the main complex adaptive system (the autonomic nervous system) in fibromyalgia. From a philosophical perspective, fibromyalgia can be conceptualized as a degradation of our main complex adaptive system, in a failed attempt to attune to a hostile environment. In this deranging process, nociceptive pathways are sensitized [18]. Our long-standing proposal of fibromyalgia as a dysautonomia-related neuropathic pain syndrome has been recently confirmed by the description of small fiber neuropathy in a large subgroup of fibromyalgia patients.

What is small fiber neuropathy?

Small fiber neuropathy is a disorder of the peripheral nerves that primarily affects small somatic fibers and autonomic fibers, resulting in sensory changes and autonomic dysfunction. Damage to small somatic nerve fibers induces pain, burning, tingling, or numbness that typically affects the limbs in a distal-to-proximal gradient. Autonomic symptoms include dry eyes, dry mouth, dizziness, and bladder discomfort. Physical examination reveals the presence of allodynia and hyperalgesia. Conventional electromyogram and nerve conduction studies are noncontributory. The diagnosis of small fiber neuropathy is based on the results of skin biopsy showing decreased nerve fiber density and also in the abnormal quantitative sudomotor axon reflex testing [19]. Corneal confocal microscopy is a promising noninvasive method to appraise small nerve fiber pathology [20].

Small fiber neuropathy has been associated with many medical conditions, including diabetes, autoimmune diseases, thyroid gland dysfunction, vitamin B_{12} deficiency, paraproteinemia, human immunodeficiency virus infection, hepatitis C virus infection, HPV vaccination, and celiac disease. Nevertheless, large subgroups of patients with small fiber neuropathy have no recognizable underlying illness. A gain of function mutations in SCN9A encoded sodium channel Nav1.7, which render dorsal root ganglion neurons hyperexcitable, are present in approximately a third of patients meeting strict criteria for idiopathic small fiber neuropathy [21].

Small fiber neuropathy and dorsal root ganglia sodium channels

Dorsal root ganglia are nodules that lie along the spinal column. They play a key role in pain perception. Dorsal root ganglia house the cell bodies of small sensory nerve fibers. Under normal circumstances, dorsal root ganglia have scant sympathetic innervations. Nevertheless, trauma and/or infection trigger sympathetic sprouting within dorsal root ganglia via nerve growth factor overexpression. Such aberrant neuroplasticity enables catecholamines and sympathetic traffic to induce sensory neuron firing. These mechanisms are the basis of the sympathetically maintained pain concept [22]. Sodium channels play a pivotal role in this hyperexcitability. Sodium channels located in dorsal root ganglia act as molecular gatekeepers of pain detection at peripheral nociceptors. Nine sodium channel subunits have been identified (Nav1.1–Nav1.9); each with a unique central and peripheral nervous system distribution. An isoform (Nav1.7) encoded in gene SCN9A of chromosome 2q24.3 is predominantly expressed in the dorsal root ganglia pain-sensing neurons and sympathetic ganglia neurons. Different Nav1.7 mutations induce electrical hyperactivity of sensory neurons in dorsal root ganglia and; at the same time; produce hypo-reactivity of sympathetic ganglia neurons [23].

Small fiber neuropathy in fibromyalgia: the neurologists are coming!

Three distinguished neurologist groups published evidence of small fiber neuropathy in fibromyalgia patients. The group headed by Dr. Sommer from the Wurzburg University in Germany, reported reduction in dermal unmyelinated nerve

fiber bundles in skin samples of patients with fibromyalgia syndrome compared with patients with depression and with healthy control subjects. Fibromyalgia patients also had increased cold and warm detection thresholds in quantitative sensory testing. Although Sommer et al. described small fiber pathology in fibromyalgia, they argue that the term "small fiber neuropathy" should be reserved for a distinct subgroup of sensory neuropathies that has a substantially different clinical presentation from that in fibromyalgia syndrome [1].

Oaklander et al. from the Neurology Department at the Massachusetts General Hospital in the USA described that 41% of skin biopsies from subjects with fibromyalgia vs 3% of biopsies from control subjects were diagnostic for small fiber neuropathy. They concluded that "some patients with chronic pain labeled as fibromyalgia have unrecognized small fiber neuropathy, a distinct disease that can be tested for objectively and sometimes treated definitively" [2].

Serra et al. from the Neurology Department MC Mutual in Barcelona Spain, reported that fibromyalgia patients have many silent nociceptors exhibiting hyperexcitability resembling small fiber neuropathy [3].

With the use of corneal confocal microscopy, our group confirmed the presence of small nerve fiber pathology in fibromyalgia [7]. Corneal confocal microscopy is a rapidly evolving technique. Age-adjusted normative values of corneal nerve fiber parameters are being developed [20]. This in vivo microscopy may become a useful and noninvasive small fiber neuropathy (and fibromyalgia) diagnostic test [7].

Other groups of investigators have confirmed the presence of small fiber neuropathy in a large percentage of fibromyalgia patients [4–6, 8].

Small fiber neuropathy, sodium channels, and the fibromyalgia concept

The proponents of fibromyalgia as a centralized pain syndrome argue that small fiber pathology is a consequence that represents a functional reorganization of the peripheral nervous system in response to central nervous system hyperactivity [24]. This appears to be an unlikely possibility. Small fiber neuropathy prototype is diabetic neuropathy. It seems difficult to frame diabetic neuropathy as a centralized pain syndrome.

As already stated, fibromyalgia is clearly a stress-related disorder. We propose that in susceptible individuals, chronic hyper-adrenergic state may lead to neuropathic pain via dorsal root ganglia hyper-excitability [23]. The recognition of small fiber neuropathy in fibromyalgia reinforces the long-held view of fibromyalgia as a dysautonomia-connected neuropathic pain syndrome.

Etymologically, "neuropathy" means "pathology of the nerves." Hence, fibromyalgia appears to be a previously unrecognized small fiber neuropathy phenotype. The identification of small fiber neuropathy in patients previously diagnosed as having fibromyalgia, in no way, rules out the fibromyalgia diagnosis. Fibromyalgia is a neuropathy! Those fibromyalgia patients not fulfilling the small fiber neuropathy criteria may have a milder neuropathic illness. As well described by Wolfe et al., fibromyalgia is not a dichotomic diagnosis but a continuous poly-symptomatic disorder [25].

Both fibromyalgia and idiopathic small fiber neuropathy are associated to SCN9A gene-encoded Nav1.7 dorsal root ganglia sodium channel variants [15, 21]. Other genetic sodium channel variants have been recently linked to widespread muscle pain syndromes [26, 27]. This evolving knowledge suggests that a subgroup of fibromyalgia patients may have a genetic sodium channelopathy.

If fibromyalgia is a neurological syndrome, should neurologist be the primary fibromyalgia physicians?

Neurologists have brought important new research to the fibromyalgia field. Clearly, fibromyalgia is a neurological disorder. Nevertheless, rheumatologist will likely remain the best equipped specialist to diagnose fibromyalgia. Differentiating fibromyalgia from Sjögren's syndrome, lupus, spondyloarthropathies, and other rheumatic entities is not always easy. Moreover, there are frequent clinical overlaps between fibromyalgia and other rheumatic illnesses. These overlaps need proper detection.

It is expected that skin biopsy, and very likely eye examination, will become useful diagnostic tools to confirm small fiber pathology in fibromyalgia. These objective tests will validate the patient symptoms and will reinforce fibromyalgia as a real clinical syndrome. The recognition of small fiber neuropathy in fibromyalgia emphasizes the need to search for genetic, metabolic, infectious, autoimmune, or vaccine-related disorders when studying fibromyalgia patients [2, 19].

Autoimmune small fiber neuropathy in fibromyalgia

Autoimmunity appears to be the underlying pathogenesis in a subgroup of young fibromyalgia patients with associated small fiber neuropathy. Oaklander et al. described a group of juvenile chronic widespread pain patients with small fiber neuropathy. Most of these patients had serologic markers of disordered immunity [28].

In young women, there is an overlap between fibromyalgia and postural orthostatic tachycardia syndrome (POTS). POTS patients frequently have profound fatigue, sleep disturbances, and chronic pain [29]. Patients with POTS have exaggerated orthostatic tachycardia often following a viral illness or vaccination, suggesting autoimmunity may play a pathophysiological role in POTS [30]. A subset of POTS patients harbor mild small fiber neuropathy [31]. There is a clear link between adrenergic autoantibodies and POTS [32].

Independent clinicians have reported young girls developing severe fibromyalgia-like illness soon after HPV vaccination [33]. Small fiber neuropathy [34, 35] and antibodies against adrenergic or muscarinic receptors have been found in some of these patients [36, 37]. HPV vaccination syndrome may become a new tragic fibromyalgia model [38].

Adult individuals with Sjögren's syndrome or systemic lupus erythematosus may also harbor fibromyalgia [39] and small fiber neuropathy [40, 41]. This "autoimmune neuropathic fibromyalgia" subgroup needs proper detection and may respond to different type of therapy.

New therapeutic drugs for "neuropathic" fibromyalgia

Current fibromyalgia analgesic-anti-neuropathic drugs are primitive and largely ineffective. Clearly, novel analgesics are needed. Dorsal root ganglia sodium channels are attractive fibromyalgia therapeutic targets. Nav1.7 and Nav1.8 sodium channel structure is well defined. Different types of sodium channel blockers are being developed [42, 43]. It is expected these new compounds will have more specific analgesic properties for fibromyalgia with less adverse effects. Additionally, Nav1.7 genomically guided, precision pharmacotherapy is in the horizon [44].

The "autoimmune" fibromyalgia subgroup may respond to different type A therapy. Oaklander et al. described good response to corticosteroids and immunoglobulin therapy in young individuals with widespread pain and underlying dysimmunity [28, 45]. "Autoimmune" POTS may also respond to intravenous immunoglobulin therapy [46]. There is little information on the use of immunoglobulin therapy in adult individuals with Sjögren's syndrome or systemic lupus harboring small fiber neuropathy.

Even if the new more focused neuropathic pain medications prove its efficacy, multimodal therapy directed to regain autonomic nervous system resilience will probably remain the most effective fibromyalgia therapy.

Conclusion

Recent research has demonstrated the presence of small fiber neuropathy in a large percentage of fibromyalgia patients. This new information reinforces fibromyalgia pain authenticity. Skin biopsy and corneal confocal microscopy will likely become objective procedures to confirm the presence of small fiber neuropathy in fibromyalgia. The recognition of small fiber neuropathy in fibromyalgia supports fibromyalgia dysautonomia nature. Dorsal root ganglia sodium channel blockers are potential therapeutic targets. A subgroup of young individuals with autoimmune neuropathic fibromyalgia may respond to corticosteroids and immunoglobulin therapy.

Compliance with ethical standards

Disclosures None.

References

1. Uceyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Schmid A et al (2013) Small fibre pathology in patients with fibromyalgia syndrome. Brain 136(Pt 6):1857–1867
2. 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
3. Serra J, Collado A, Sola R, Antonelli F, Torres X, Salgueiro M et al (2014) Hyperexcitable C nociceptors in fibromyalgia. Ann Neurol 75:196–208
4. 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
5. Caro XJ, Winter EF (2014) Evidence of abnormal epidermal nerve fiber density in fibromyalgia: clinical and immunologic implications. Arthritis Rheum 66:1945–1954
6. Kosmidis ML, Koutsogeorgopoulou L, Alexopoulos H, Mamali I, Vlachoyiannopoulos PG, Voulgarelis M, Moutsopoulos HM, Tzioufas AG, Dalakas MC (2014) Reduction of Intraepidermal Nerve Fiber Density (IENFD) in the skin biopsies of patients with fibromyalgia: a controlled study. J Neurol Sci 347:143–147
7. Ramírez M, Martínez-Martínez LA, Hernández-Quintela E, Velazco-Casapía J, Vargas A, Martínez-Lavín M (2015) Small fiber neuropathy in women with fibromyalgia. An in vivo assessment using corneal confocal bio-microscopy. Semin Arthritis Rheum 45: 214–219
8. Erkan Turan K, Kocabeyoglu S, Unal-Cevik I, Bezci F, Akinci A, Irkec M (2018) Ocular surface alterations in the context of corneal in vivo confocal microscopic characteristics in patients with fibromyalgia. Cornea 37:205–210
9. Martínez-Lavín M (2013) Fibromyalgia. How stress becomes real pain and what to do about it. E-book Amazon Kindle Edition. USA
10. Clauw DJ (2015) Fibromyalgia and related conditions. Mayo Clin Proc 90:680–692
11. Yunus MB (2007) Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum 36:339–356
12. Martinez-Lavin M (2007) Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. Arthritis Res Ther 9:216–219
13. Martínez-Lavín M, Hermosillo AG (2000) Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. Semin Arthritis Rheum 29:197–199
14. Martínez-Lavín M, Vidal M, Barbosa RE, Pineda C, Casanova JM, Nava A (2002) Norepinephrine-evoked pain in fibromyalgia. A randomized pilot study ISCRTN 70707830. BMC Musculoskelet Disord 2:3 (16 Jan 2002)
15. Vargas-Alarcon G, Alvarez-Leon E, Fragoso JM, Vargas A, Martinez A, Vallejo M, Martinez-Lavin M (2012) A SCN9A gene-encoded dorsal root ganglia sodium channel polymorphism associated with severe fibromyalgia. BMC Musculoskeletal Dis. https://doi.org/10.1186/1471-2474-13-23
16. Martinez-Lavin M, Infante O, Lerma C (2008) Hypothesis: the chaos and complexity theory may help our understanding of fibromyalgia and similar maladies. Semin Arthritis Rheum 37:260–264
17. Reyes-Manzano CF, Lerma C, Echeverría JC, Martínez-Lavín M, Martinez-Martínez LA, Infante O, Guzmán-Vargas L (2018) Multifractal analysis reveals decreased nonlinearity and stronger

anticorrelations in heart period fluctuations of fibromyalgia patients. Front Physiol. https://doi.org/10.3389/fphys.2018.01118
18. Martinez-Lavin M (2012) Fibromyalgia when distress becomes (un)sympathetic pain. Pain Res Treat 2012:1–6. https://doi.org/10.1155/2012/981565
19. Tavee J, Zhou L (2009) Small fiber neuropathy: a burning problem. Cleve Clin J Med 76:297–305
20. Tavakoli M, Ferdousi M, Petropoulos IN, Morris J, Pritchard N, Zhivov A, Ziegler D, Pacaud D, Romanchuk K, Perkins BA, Lovblom LE, Bril V, Singleton JR, Smith G, Boulton AJ, Efron N, Malik RA (2015) Normative values for corneal nerve morphology assessed using corneal confocal microscopy: a multinational normative data set. Diabetes Care 38:838–843
21. Faber CG, Hoeijmakers JG, Ahn HS, Cheng X, Han C, Choi JS et al (2012) Gain of function Nav1.7 mutations in idiopathic small fiber neuropathy. Ann Neurol 71:26–39
22. Chen SS, Zhang JM (2015) Progress in sympathetically mediated pathological pain. J Anesth Perioper Med 2:216–225
23. Martinez-Lavin M, Solano C (2009) Dorsal root ganglia sodium channels and fibromyalgia sympathetic pain. Med Hypotheses 72:64–66
24. Clauw DJ (2015) What is the meaning of "small fiber neuropathy" in fibromyalgia? Pain 156:2115–2116
25. Wolfe F, Walitt B, Rasker JJ, Häuser W (2018) Primary and secondary fibromyalgia are the same: the Universality of Polysymptomatic Distress. J Rheumatol. https://doi.org/10.3899/jrheum.180083
26. Suokas K, Palmio J, Sandell S, Udd B, Hietaharju A (2018) Pain in SCN4A mutated P.A1156T muscle sodium channelopathy-a postal survey. Muscle Nerve 57:1014–1017. https://doi.org/10.1002/mus.26050
27. Castoro R, Simmons M, Ravi V, Huang D, Lee C, Sergent J, Zhou L, Li J (2018) SCN11A Arg225Cys mutation causes nociceptive pain without detectable peripheral nerve pathology. Neurol Genet 4:e255. https://doi.org/10.1212/NXG.0000000000000255. eCollection
28. Oaklander AL, Klein MM (2013) Evidence of small-fiber polyneuropathy in unexplained, juvenile-onset, widespread pain syndromes. Pediatrics 131:e1091–e1100. https://doi.org/10.1542/peds.2012-2597
29. Benarroch EE (2012) Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. Mayo Clin Proc 87:1214–1225
30. Blitshteyn S, Brook J (2017) Postural tachycardia syndrome (POTS) with anti-NMDA receptor antibodies after human papillomavirus vaccination. Immunol Res 65:282–284
31. Haensch CA, Tosch M, Katona I, Weis J, Isenmann S (2014) Small-fiber neuropathy with cardiac denervation in postural tachycardia syndrome. Muscle Nerve 50:956–961
32. Fedorowski A, Li H, Yu X, Koelsch KA, Harris VM, Liles C, Murphy TA, Quadri SMS, Scofield RH, Sutton R, Melander O, Kem DC (2017) Antiadrenergic autoimmunity in postural tachycardia syndrome. Europace 19(7):1211–1219
33. Martínez-Lavín M, Amezcua-Guerra L (2017) Serious adverse events after HPV vaccination: a critical review of randomized trials and post-marketing case series. Clin Rheumatol 36:2169–2217
34. Blitshteyn S (2014) Postural tachycardia syndrome following human papillomavirus vaccination. Eur J Neurol 21:135–139
35. Kinoshita T, Abe RT, Hineno A, Tsunekawa K, Nakane S, Ikeda S (2014) Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine. Intern Med 53:2185–2200
36. Hendrickson JE, Tormey CA (2016) Human papilloma virus vaccination and dysautonomia: considerations for autoantibody evaluation and HLA typing. Vaccine 34:4468. https://doi.org/10.1016/j.vaccine.2016.05.029
37. Schofield JR, Hendrickson JE (2017) Autoimmunity, autonomic neuropathy, and the HPV vaccination: a vulnerable subpopulation. Clin Pediatr (Phila) 57:603–606. https://doi.org/10.1177/0009922817728701
38. Martínez-Lavin M (2018) HPV vaccination syndrome: a clinical mirage, or a new tragic fibromyalgia model. Reumatol Clin (English Edition) 14:211–214. https://doi.org/10.1016/j.reumae.2018.01.001
39. Choi BY, Oh HJ, Lee YJ, Song YW (2016) Prevalence and clinical impact of fibromyalgia in patients with primary Sjögren's syndrome. Clin Exp Rheumatol 34(Suppl 96):S9–S13
40. Pavlakis PP, Alexopoulos H, Kosmidis ML, Mamali I, Moutsopoulos HM, Tzioufas AG, Dalakas MC (2012) Peripheral neuropathies in Sjögren's syndrome: a critical update on clinical features and pathogenetic mechanisms. J Autoimmun 39:27–33. https://doi.org/10.1016/j.jaut.2012.01.003
41. Oomatia A, Fang H, Petri M, Birnbaum J (2014) Peripheral neuropathies in systemic lupus erythematosus: clinical features, disease associations, and immunologic characteristics evaluated over a twenty-five-year study period. Arthritis Rheum 66:1000–1009
42. Zakrzewska JM, Palmer J, Morisset V, Giblin GM, Obermann M, Ettlin DA, Cruccu G, Bendtsen L, Estacion M, Derjean D, Waxman SG, Layton G, Gunn K, Tate S (2017) Safety and efficacy of a Nav1.7 selective sodium channel blocker in patients with trigeminal neuralgia: a double-blind, placebo-controlled, randomised withdrawal phase 2a trial. Lancet Neurol 16:291–300. https://doi.org/10.1016/S1474-4422(17)30005-4
43. Li M, Wu Y, Zou B, Wang X, M L, Yu H (2018) Identification of WB4101, an α1-adrenoceptor antagonist, as a sodium channel blocker. Mol Pharm 94:896–906. https://doi.org/10.1124/mol.117.111252
44. Yang Y, Mis MA, Estacion M, Dib-Hajj SD, Waxman SG (2018) NaV1.7 as a pharmacogenomic target for pain: moving toward precision medicine. Trends Pharmacol Sci 39:258–275. https://doi.org/10.1016/j.tips.2017.11.010
45. Oaklander AL (2016) Immunotherapy prospects for painful small-fiber sensory neuropathies and Ganglionopathies. Neurotherapeutics 13:108–117. https://doi.org/10.1007/s13311-015-0395-1
46. Schofield JR, Blitshteyn S, Shoenfeld Y, Hughes GR (2014) Postural tachycardia syndrome (POTS) and other autonomic disorders in antiphospholipid (Hughes) syndrome (APS). Lupus 23:697–702