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Expert Review of Neurotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iern20

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To cite this article: Grazia Devigili , Daniele Cazzato & Giuseppe Lauria (2020): Clinical diagnosis and management of small fiber neuropathy: an update on best practice, Expert Review of Neurotherapeutics, DOI: 10.1080/14737175.2020.1794825

To link to this article: https://doi.org/10.1080/14737175.2020.1794825

Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *Expert Review of Neurotherapeutics*

DOI: 10.1080/14737175.2020.1794825

Clinical diagnosis and management of small fiber neuropathy: an update on best practice

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Abstract

Introduction: Small fiber neuropathy (SFN) is a heterogeneous group of disorders affecting thinly myelinated Aδ and unmyelinated C-fibers. Common symptoms include neuropathic pain and autonomic disturbances, and the typical clinical presentation is that of a length-dependent polyneuropathy, although other distributions could be present.

Area covered: This review focuses on several aspects of SFN including etiology, clinical presentation, diagnostic criteria and tests, management, and future perspectives. Diagnostic challenges are discussed, encompassing the role of accurate and standardized assessment of symptoms and signs and providing clues for the clinical practice. The authors discuss the evidence in support of skin biopsy and quantitative sensory testing as diagnostic tests and present an overview of other diagnostic techniques to assess sensory and autonomic fibers dysfunction. The authors also suggest a systematic approach to the etiology including a set of laboratory tests and genetic examinations of sodium channelopathies and other rare conditions that might drive the therapeutic approach based on underlying cause or symptoms treatment.
Expert opinion: SFN provides a useful model for neuropathic pain whose known mechanisms and cause, could pave the way towards personalized treatments.

Keywords: Small Fiber Neuropathy, skin biopsy, Quantitative sensory testing, neuropathic pain, autonomic disorders, sodium channelopathy, painful evoked potentials

Article highlights

- Small fiber neuropathy is characterized by sensory and autonomic symptoms and signs associated with neural damage selectively or predominantly involving peripheral thinly myelinated Aδ fibers and unmyelinated C nerve fibers
- Skin biopsy and quantitative sensory testing are widely acknowledged as confirmatory diagnostic tests
- Diagnostic criteria are available for clinical practice and research
- Variants in genes encoding for sodium channels have been discovered as novel cause of small fiber neuropathy
- Current symptomatic treatment for neuropathic pain is based on a "trial-and-error" approach, though new studies suggested that genotype might influence the response to specific drugs
- Deep phenotyping and genotyping of patients could contribute to achieve concrete steps towards personalized management

1. Introduction

Small fiber neuropathy (SFN) defines a selective or predominant impairment of peripheral thinly myelinated Aδ fibers and unmyelinated C nerve fibers, in which neuropathic pain typically dominates the clinical picture, along with variable loss of thermal and nociceptive sensation, and dysautonomia [1]. This condition has stably entered among the differential diagnoses of painful peripheral nervous system disorders [2].

Epidemiological data on SFN have come from only one epidemiological study conducted in the Netherlands that reported an incidence of 12 cases per 100,000/year and a prevalence of 53 cases per 100,000 [3].

The adoption of widely shared diagnostic criteria is crucial for the classification of SFN and for conducting reliable epidemiological studies. One example is that of fibromyalgia which is reported to affect up to 5% of people in Europe [4] and that a recent systematic review and meta-analysis emphasized to be complicated by SFN in 49% of cases [5]. Nevertheless, the quite common lack of clinical signs of SFN and the widespread pattern on pain presentation challenge the diagnostic criteria.

The nosography of SFN suffers from some poorly defined boundaries regarding large myelinated sensory fiber involvement, the inclusion of exclusively autonomic small fiber neuropathy, the choice of the diagnostic tools and their validation against those used to define the diagnostic criteria, namely skin biopsy and quantitative sensory testing (QST) [6,7].

The introduction of skin biopsy, which allows a reliable quantification of intraepidermal nerve fiber density (IENFD), has been a milestone for the diagnosis of SFN [8,9]. In the following decades, a flourishing of studies widened the spectrum of diseases associated with small nerve fiber degeneration, from painless amyotrophic lateral sclerosis [10–13] and Parkinson's disease [14–21] to painful erythromelalgia [22]. These findings further emphasized that the diagnosis of SFN cannot disregard the clinical context and the accurate characterization of patients' phenotype.

This review aims to provide a physician-oriented approach to diagnosis and management of SFN. We describe the role of clinical evaluation and laboratory testing, the significance of available diagnostic tools and the recent advances from genetic screening as determinants for the classification of SFN in clinical practice and tailored treatment approaches.

2. Clinical presentation and phenotypes of SFN

Patients with SFN present different patterns: length-dependent polyneuropathy (i.e. first affecting the feet with later proximal involvement), non-length-dependent neuropathy (i.e. involving all limbs since the onset), and asymmetric mono/multiplex neuropathy (i.e. affecting one or more sensory peripheral nerve) (Fig 1) [23–26].

Irrespective of the topological presentation, the clinical manifestation of SFN encompasses "negative" and "positive" symptoms and signs related to Aδ and C fiber degeneration as the result of conduction impairment and sensitization triggered by neural damage.
Patients with length-dependent SFN typically complain of spontaneous pain with burning, electric-like, pins and needles sensation starting at lower limb extremities and progressively ascending to more proximal sites, and later involving also the upper limbs in a similar distal-to-proximal fashion. The length-dependent pattern is predominantly seen in patients with metabolic causes such as diabetes and impaired glucose tolerance (IGT) or after neurotoxic exposures [24]. The clinical picture of diabetic SFN is usually dominated by "positive" sensory symptoms such as tingling and pricking sensations combined with "negative" symptoms such as numbness or decreased sensation in the extremities, with a typical "stocking-glove" distribution detectable at the clinical examination as reduced pinprick and thermal sensations. Less frequently the neurological examination can reveal positive sign such as allodynia and hyperalgesia both configuring different features of evoked pain [27].
Non-length-dependent SFN presents with proximal, diffuse or patchy distribution involving different parts of the body including face, mouth, scalp, trunk and upper limbs before or simultaneously the lower limbs. This pattern is predominantly seen in immune-mediated (e.g. Sjogren's syndrome) and paraneoplastic disorders [25,28-29]. Mono/multiplex neuropathy presentations includes burning mouth syndrome [30], notalgia and meralgia paraesthetica, vulvodynia [31–33], and Wartemberg neuropathy [34].
SFN patients can also complain of restless leg, intolerance to bed sheets, shoes and clothes causing dysesthesia or allodynia. Some symptoms seem to be much specific for some form of SFN. For example, patients with oxaliplatin-induced neuropathy are typically exacerbated by cooling [35], whereas in patients with erythromelalgia, symptoms are exacerbated by warming and relieved by cooling of the skin [36].
Autonomic nervous system disturbances add complexity and heterogeneity to SFN clinical pictures. They are due to the dysfunction of unmyelinated C-fibers and thinly myelinated Aδ-fibers innervating sweat glands (sudomotor fibers), dermal vessels (vasomotor fibers), hair follicles (pilomotor fibers), pupillary dysfunction (tonic pupil) and other exocrine glands including lachrymal and salivary glands, causing sicca syndrome (table 1). Also cardiovascular, urinary and gastroenteric systems can be involved, leading to orthostatic hypotension or intolerance, orthostatic persistent tachycardia [37] reduced heart rate

variability, palpitation, premature atrial or ventricular beats and, albeit rarely, sinus bradycardia, chronic constipation or diarrhea, and bladder dysfunction [38,39].

3. Diagnosis and management

3.1 Clinical evaluation - Practical neurological examination

Bedside examination should start with an accurate inspection to search visible signs of possible peripheral autonomic dysfunction, such as skin discoloration, dry skin and dystrophic changes. Presence and distribution of negative and positive sensory signs should be tested using a comparative assessment of affected and non-affected skin areas to differentiate the quality of the altered sensation and define the distribution (dermatomeric, mono/multineuropathic and polyneuropathic). Cutaneous sensory signs are assessed asking the patient to keep the eyes closed and to report the sensation induced by tactile stimuli (tactile hypoesthesia) and gently brushing with cotton bud and flat tip brush (dynamic allodynia) at a constant speed of 3 to 5 cm/s over the skin without changing direction, punctate skin stimulation with a stick or pin (punctate allodynia), and prickling with disposable needle (hyperalgesia). It should be considered that presence of allodynia or hyperalgesia could mask the sensory loss [40].

Thermal sensation is detect using cold/warm water tube or thermorollers kept at 40°C and 20° C. Superficial and deep mechanical sensation by finger pressure applied to skin and underlying tissue is also test to detect static allodynia and hyperalgesia [23]. Vibratory sensation should be quantified using the 128 Hz graduated tuning fork [41]. The Semmes-Weinstein 3-10 g monofilament is a simple screening method to detect mechanical hypoesthesia [42] and improve the bedside clinical evaluation. To test temporal summation, defined as an increase perception of pain after repeated stimulation, the stick or pin is applied repeatedly, at a rate of 1 to 2 Hz. The test is considered positive if painless response becomes painful or evoked pain increased in intensity. If one or more stimuli provoke pain sensation, the physician should ask the patient to rate the intensity of pain using a 0-10 Likert scale. Table 2 summarizes the bedside examination including sensory positive and negative signs and testing methods.

Signs of dysautonomia should be also evaluated, including pupil motility, skin flushing or discoloration, orthostatic hypotension, and heart frequency.

3.2 Diagnostic criteria

In the last decade, two different sets of diagnostic criteria have been proposed. The Besta criteria, published in 2008 [43] required the combination of abnormal findings in at least

two out of three assessments including: 1) clinical signs of SFN (i.e. reduced pinprick and thermal sensation, allodynia and/or hyperalgesia); 2) abnormal thermal threshold assessed at the foot by quantitative sensory testing (QST); 3) reduced IENFD at the distal leg. Clinical signs supporting large sensory fibers impairment, such as reduced vibratory sensation and deep tendon reflexes and/or electrophysiological evidence of sensory nerve involvement were considered exclusion criteria, thus delimiting the frame to pure SFN and excluding patients with mixed small and large fiber neuropathy.

The NEURODIAB criteria, published in 2010 within the update of the guideline for the diagnosis of diabetic neuropathy by the Diabetic Neuropathy Study Group of the European Association for the study of Diabetes [44], based the diagnosis on the presence of symptoms and signs of SFN, normal sural nerve conduction study (NCS) and confirmatory test including skin biopsy or QST. The diagnosis follows a three steps grading system ranging from possible to probable or definite according to abnormalities identified at different assessments (table 3). The NEURODIAB criteria require clinical signs to be present for probable and definite SFN, though their characteristics were not specified.

A recent revision of the SFN diagnostic criteria [1] compared the diagnostic power between the two sets of criteria showing a strict agreement between the two diagnostic approaches. This reappraisal and validation study investigated in a large cohort of patients the weight of clinical (symptoms and signs) psychophysical (QST) and structural (IENFD) components, confirming the significantly higher diagnostic accuracy of skin biopsy compared with QST (sensitivity 94.3%, specificity 91.9%). The presence of at least two clinical signs increased the reliability of the diagnosis of SFN, because the combination of clinical signs and abnormal QST and/or IENFD findings provided higher diagnostic power than the combination of abnormal QST and IENFD findings in the absence of clinical signs. Notably, patients with symptoms but no clinical signs reported complete recovery after a mean of 18-month follow-up and did not have abnormal skin biopsy or QST findings. Thus, symptoms alone, although suggestive, should not be considered reliable for diagnosing SFN and must be appropriately evaluated in clinical context.

3.3 Causes of SFN

The growing number of associations between SFN and systemic diseases, some supported by strong evidence others reported in small case series or as anecdotal cases, makes the definition of the etiology often challenging. Moreover, up to 50% of cases remain idiopathic [45]. Laboratory screening is crucial to unravel the most common causes among metabolic, infectious, immune-mediated, toxic and genetic diseases (table 4).

Diabetes accounts for about 20% of cases, but the prevalence increases if impaired fasting glucose (IFG) and oral glucose tolerance test (OGTT) are included [46,47]. Glycated hemoglobin (HbA1c) is considered a predictors of diabetic neuropathy[48] and should be tested routinely. The high prevalence of neuropathy in patients with prediabetes and the poor preventing effect of glycemic control in type 2 diabetes (T2DM) compared to type 1 diabetes (T1DM) [49] suggest a role for other causes including hyperlipidemia and metabolic syndrome [50–53].

SFN has been reported in patients with HIV infection [54], immune-mediated disorders such as Sjogren's syndrome, celiac disease and sarcoidosis, and after exposure to neurotoxic drugs.

One major advance has been the identification of gain-of-function sodium channel mutations which now include *SCN9A*, *SCN10A and SCN11A* genes encoding Nav1.7, Nav1.8 and Nav 1.9 α-subunits [55–57] and β-subunits [58].Most variants in VGSCs genes have been associated with distal pain in SFN patients, but single mutations can cause different phenotypes and electrophysiological changes [59], though some variants have been associated to specific phenotype such as the G856D variant in *SCN9A* gene identified in a complex phenotype including severe pain, dysautonomia and acromesomeli [6, 60]. Besides sodium channels, mutation in *COL6A5* gene coding for a collagen protein have been described in a peculiar phenotype of familial and sporadic SFN characterized by neuropathic itch [61].

Other genetic conditions associated with SFN include presymptomatic stage of familial amyloidosis due to *TTR* gene mutations, whereas a mixed neuropathy more often characterizes the symptomatic stages. SFN could rarely complicate Fabry disease [62] [63] (small nerve fibers are predominantly affected in Fabry neuropathy [62,64], however it represents a rare condition, therefore genetic analysis is not recommended in isolated SFN and should be performed only in presence of other clinical features of the disease [63]). SFN has been reported in patients with Gaucher disease as possible explanation for neuropathic origin of chronic pain [65]. Finally, SFN has been also described in association with disorders characterized by widespread pain such as fibromyalgia [5] and Ehlers-Danlos syndrome [66], and in neurodegenerative diseases like Parkinson's disease [14–21] and ALS [10–13].

4 Diagnostic tools

4.1 Skin biopsy

The quantification of IENFD can be considered the “gold standard” for the diagnosis of SFN when associated with clinical signs [1]. Nerve fibers crossing the dermal-epidermal junction is quantified in three non-consecutive 50 μm thick slices, then divided by the length of epidermis, resulting in a linear epidermal innervation density value expressed in number of fibers per millimeter (IENF/mm) [67] (figure 2). Normative reference value for IENFD at distal leg, adjusted for sex and age, are available both for bright field [68] and immunofluorescence[69] microscopy techniques, with a study reporting similar diagnostic accuracy [70]. The reliability of IENFD parameter has been further strengthened by the demonstration of its stability in healthy subject and patients with length-dependent SFN regardless the side and within the time of keratinocytes turnover [71].

In patients with normal IENFD, the presence of axonal swellings suggest pre-degenerative changes predicting the loss of fibers [72]. This has been confirmed by further studies [73–75], although it seems not a discriminating feature between painful and painless diabetic neuropathy [76].

Also the assessment of dermal has been shown to reliably discriminate healthy individuals from SFN patients [77]. Moreover, the innervation of sweat glands, pilomotor muscles and vessels can be also quantified [78,79].

Skin biopsy is a minimally invasive procedure that can be safely repeated for longitudinal disease monitoring in clinical practice and trials. However, it should be considered a surgical procedure with rare and mild complications such as bleeding, infection and keloid scar formation.

4.2 Quantitative sensory testing

QST is based on measurements of responses to graded sensory stimuli (e.g. mechanical, thermal) and it could be considered as an extension of the routine bedside clinical examination of the somatosensory system [80]. It is a non-invasive psychophysical examination based of two main detection methods: the method of limits where the stimulus starts on a neutral level and increases until it is stopped, and the method of levels that include a force choice algorithm after a pre-defined stimulus (i.e. thermal, mechanical stimuli). This latter, being not a time-dependent reaction has the advantage to reduce the bias related to cognitive and behavioral variables. Indeed, it is method of choice to test children, resulting more reliable than the method of limits that, on the contrary, requires the patient to push a button as soon as a change in temperature is perceived. The method of levels showed better diagnostic efficacy than that of limits for diagnosing SFN [81], especially if performed bilaterally [1].

QST has some limitations: it is a psychophysical method and in relation to the complexity of the protocol used it is time-consuming and requires training and active collaboration of the patient. However, if applied through standardized algorithms during which also subjects' responses are predefined according to standardized instructions, the reliability improve significantly as well as the diagnostic sensitivity [80]. QST allows assessing warming, cooling, and heat-pain sensation detection thresholds, as well as hypersensitivity and thermal allodynia [82]. Thus, in standardized conditions it can help in characterizing both single sensory modality threshold and peculiar pattern of sensory abnormality related to neuropathic painful as well as signs of central sensitization [84,85]. However, it is not able to discriminate between central and peripheral impairment of the somatosensory system [83].

4.3 Corneal confocal microscopy

Corneal confocal microscopy (CCM) is a non-invasive method able to examine the microstructures of the cornea. By means of a light beam focusing on the corneal layer, CCM allows at in vivo visualizing unmyelinated C fibers originating from the ophthalmic division of the trigeminal nerve [85]. Most of the studies have been performed in diabetic polyneuropathy and reported sensitivity of 91% and specificity of 93% [6]. Corneal fiber degeneration has been associated with the severity of diabetic polyneuropathy [86] and improvement of CCM parameters following better diabetes control has been reported in type 1 diabetes patients [87].

Studies conducted on small cohorts of patients with length-dependent [88,89] (25 and 14 patients) and non-length-dependent SFN [90] (6 patients) reported a reduction of corneal nerve fiber density suggesting a diagnostic utility of this tool. CCM is currently available in few centers and its diagnostic use in clinical practice remains limited.

4.4 Conventional neurophysiological tests

In pure small fiber neuropathy, conventional nerve conduction study (NCS) is expected to show no abnormality and it should be performed as part of the first-line diagnostic work-up to explore the involvement of large sensory and motor nerve fibers. Sensory nerve action potential amplitude and conduction velocity of sural nerve should be examined [91]. The evaluation of terminal distal branches such as dorsal the medial dorsal cutaneous and dorsal sural nerves, exploring more distal sites, may enhance diagnostic sensitivity of NCS [93,94].

4.5 Microneurography

Microneurography is a valuable neurophysiological technique developed to record the activity of single C-nociceptors, thermoceptors, mechanoreceptors and sympathetic fibers from peripheral nerves in awake subjects. This technique provided data regarding the physiological activity of C-fiber and elucidated the pathophysiological correlates of clinical phenomena in painful syndromes such as spontaneous activity, sensitization and hyperexcitability [94]. In SFN and other conditions characterized by peripheral neuropathic pain, microneurography could detect abnormal C-nociceptor activity [20]. Furthermore, it allowed investigating the effect of drugs on blocking the abnormal on-going activity of C-nociceptors [95]. Its application in clinical practice, however, remains partly limited by complex technical requirements, time to perform the exam, and collaboration of the patient.

4.6 Nociceptive evoked potentials

Nociceptive-evoked potentials are recorded from scalp by painful stimuli applied to the skin obtained through fast heating generated either with laser stimulator (laser evoked potentials, LEPs) or plate having extremely rapid heating rate up to 70°C/sec (contact heat-evoked potentials, CHEPs). Electrical stimulation delivered using customized electrodes has also been used to obtain selective Aδ and C fiber activation (pain-related-evoked potentials, PREPs), even though there are concerns about the nociceptive specificity [96].

Skin denervation induced by topical capsaicin causes a decrease of LEP vertex potential amplitude, indicating a correlation with the innervation density [97].In diabetic neuropathy LEP diagnostic accuracy showed sensitivity of 78% and specificity of 81% using skin biopsy as reference [7]. However, LEP vertex potential does not reflect a nociceptive-specific neural activity because it can be elicited also by non-nociceptive somatosensory stimuli[98] and its amplitude is mainly due to the stimulus saliency rather than its intensity[99]. Furthermore, LEP amplitude shows a wide inter-individual variability [100].

CHEPs based on age- and gender-adjusted normative values have been used to investigate SFN [101] showing a good correlation with the degree of skin innervation [102]. However, CHEPs can be absent also in healthy individuals [101].

Recently also cool-evoked potentials have been introduced as a valuable method to study the Aδ- fiber free nerve endings and spinothalamic pathway [103], however the diagnostic value in SFN has not been investigated.

Finally, like QST, nociceptive-evoked potentials are not able to discriminate between a central and peripheral involvement of the somatosensory system. Therefore, nociceptive-evoked potential findings should be interpreted with caution and within the clinical context.

4.7 Autonomic testing

Autonomic changes can be an early manifestation of SFN and several diagnostic techniques have been introduced to investigate sudomotor, vasomotor and cardiovascular functions [39].

Cutaneous autonomic small fibers constitute the most peripheral segments of the sympathetic and parasympathetic nervous system and a valuable window on its functioning. Sudomotor nerves are unmyelinated or thin myelinated fibers, with primarily cholinergic neurotransmission. The principal neurotransmitter is acetylcholine, even though several other neurotransmitters are involved, including vasoactive intestinal peptide (VIP), calcitonin gene related polypeptide (CGRP), ATP and substance P. Adrenergic transmission mediated by epinephrine and norepinephrine is also present, as immunohistochemical studies established [104,105].

Several techniques have been standardized to quantify sweating and the innervation of sweat glands. They allow the identification of postganglionic lesions, providing quantitative measures of disease progression and recovery [106]. Among those more useful in clinical practice and based on iodine and starch skin application, there are the thermoregulatory sweat test (TST), the iontophoretic stimulation with acetylcholine or pilocarpine, the dynamic sweat test (DST) [107] and the quantitative sudomotor axon reflex testing (QSART) [108] (Fig 3). QSART is a sensitive and reproducible techniques[109] that can assess sudomotor nerve fiber damage also in SFN [109,110], showing a sensitivity of about 50% [111] and increase of the diagnostic efficacy [110]. Postganglionic sympathetic cholinergic sudomotor function can also be investigated by the quantitative direct and indirect axon reflex testing (QDIRT), which uses a humidity-activated dye to display sweating over time. The process is dynamically observed and acquired through consecutive digital photographs[108]. This tool requires further studies to address its diagnostic value in the disorders of the autonomic nervous system.

Another well-established method to detect sudomotor nerves dysfunction is the sympathetic skin responses (SSRs). It is a multi-synaptic reflex that depends on the integrity of both central and peripheral nervous system. Thus, it has limited sensitivity and cannot localize the site of lesion. On the other hand, it is easy to record.

Recently, skin electrochemical conductance (ESC) has been introduced as another quantitative tool that based on reverse iontophoresis can capture chloride ions produced by sweat glands. Since the stimulus is electrical, it is possible to modulate the intensity of the stimulation and improve the reliability of the method [112]. ESC has been used in several types of sensory neuropathies and showed good sensitivity (65-78%) and specificity (80-92%)[107,108].

Different techniques have been applied to detect the neural control of microvascular reactivity mediated by vasomotor autonomic small nerve fibers. These tests are all based on axon-reflex detection that can be evoked directly by thermal, pharmacological, electrical, or mechanical stimuli, and recorded by laser Doppler flowmetry or laser speckle contrast imaging. The axon-reflex generated in cutaneous nerve fibers induces the release of vasoactive substances mediating a vasodilatory response into a skin area adjacent to the area of stimulation [114]. Vasogenic and neurogenic responses can be differentiated temporally and topographically [115]. Patients with SFN showed reduced or absence of skin flare areas [38,111].

Cardiovascular autonomic tests (CATs) encompass a standardized battery of provoked tests able to investigate both parasympathetic and sympathetic autonomic system. CATs are a well-established method to identify presence of cardiovascular autonomic neuropathy (CAN) in diabetes [117] a traditional risk factor for cardiovascular events and sudden death. However, in the context of SFN, the cardiovascular autonomic dysfunction seems an independent measures of SFN and no association has been found between autonomic reflexes and sensory clinical signs, IENF density or QST [38].

Overall autonomic functional tests can improve the diagnosis of SFN exploring the dysfunction of autonomic nerve fibers in addition to those focused on somatic nerve functioning. They should be considered complementary to the achievement of the diagnosis of dysautonomia in patients with SFN and supportive to follow-up evaluations.

5. Treatment: a practical approach

In SFN, neuropathic pain is supposed to arise from different mechanisms, which can be summarized in increase peripheral excitability and central sensitization phenomena. The damage of terminal nerves and presence of local inflammation, pro-inflammatory cytokines and peptides, increase the neuronal excitability at the DRG and dorsal horn. However, these likely account only for a limited part of the mechanisms underlying the generation and maintenance of neuropathic pain. Others could be related to the so-called *maladaptive*

brain responses after nociceptors terminals degeneration and consequent central sensitization [118]. Additionally, chronic pain may lead to structural changes in the brain. A study with resting-state functional MRI showed increase brain activation of limbic and striatal in diabetic painful neuropathy and SFN, providing presence of pathological brain plasticity and suggesting the central nervous system involvement also in primary peripheral nervous system [115,116].

5.1 Treatment of underlying conditions and disease modifying treatment

Current pharmacological and non-pharmacological treatment of neuropathic pain is still unsatisfactory [121]. In SFN related to a known etiology, therapeutic strategy should be focalized to the management of the underlying condition. This means the correction of vitamin deficiency if present, or correction of metabolic or hormonal unbalance. In diabetic SFN, lifestyle interventions and better glycemic control resulted in neuropathic pain relief, however the glycemic control should be achieved gradually in order to avoid the risk of acute worsening of painful neuropathy [122].

In case of immune-related SFN, the use of immunomodulatory drugs as corticosteroids should be considered. Conversely, it is still controversial the use of intravenous immunoglobulin (IVIG), actually reported in few studies in Sjogren syndrome, systemic lupus erythematosus and sarcoidosis [123,124]. A significative improvement of pain sarcoidosis has been achieved by anti-TNF treatment [124].

In SFN associated to sodium channel disorders, a selective block of peripheral sodium channel is supposed to improve sensory symptoms. Erythromelalgia has been successfully treated with mexiletine [125]. Most recently lacosamide, an anticonvulsant that acts on Nav1.3, Nav1.7, and Nav1.8, showed significant effect on pain, wellbeing and sleep quality in SFN patients harboring Nav1.7 mutations [126]. One further study demonstrated that lacosamide can selectively enhance fast inactivation of the channel only in responders, unraveling the biophysical variability underpinnings the responsiveness [127].

5.2 Symptomatic treatments of neuropathic pain

The presence of pain is usually the most invalidating symptom in SFN patients and the management a challenging task. The most effective and recommended drug classes are represented by antidepressants, anticonvulsants, opioids and localized therapies. The choice of the medication is usually empirical following a “trial and error” process, but guided by safety profile, comorbidities and concomitant medication [128] (table 5). There

are also several guidelines and recommendations that reported similar indications for painful peripheral neuropathy [129].

Tricyclic antidepressants (amytriptiline, nortriptyline) have been proven effective in pain improvement with relatively high sides effects. The serotonin-norepinephrine reuptake inhibitors duloxetine and venlafaxine has been the most useful antidepressant characterized by better safety profile and suggested as the first line drug in neuropathic pain [130]. The efficacy of gabapentin and pregabalin is established in particular for peripheral neuropathic pain. Among other antiepileptic drugs, carbamazepine and oxcarbazepine have a well-established use in trigeminal neuralgia. A phenotype-stratified study in peripheral neuropathy patients reported the effectiveness of oxcarbazepine in neuropathic pain due to “irritable nociceptor” phenotype [131].

Clonazepam is empirically largely used at low dosage even if without supporting evidences in the literature. Also combination therapy has been poorly investigated in rigorous scientific setting, despite a quite diffuse use in clinical practice. Pregabalin and gabapentin were suggested to an additional effect if combined with TCAs [128,129]. Conversely, a large multicentric study [134] on combination therapy with pregabalin and duloxetine at moderate dosages did not show improvement of pain severity compared with single drugs in monotherapy at high dosages.

In severe painful syndromes, a combined treatment that includes opioids as add-on treatment is appropriate for a short period limited to the first line drugs tapering [135].

There are few RCT studies with topic analgesics in painful neuropathies. Significant improvement has been reported in diabetic neuropathy with application of lidocaine 5% patch, high-concentration capsaicin patches and topical use of clonidine[129]. Botulinum toxin is a promising treatment that needs confirmatory data [136].

Finally, the use of cognitive–behavioral techniques able to develop of coping strategies should also be considered in the context of pain treatment [137].

5.3 Pharmacological treatment of autonomic symptoms

Autonomic dysfunctions require specific management, in particular in presence of orthostatic hypotension, constipation, secretomotor dysfunctions of sweating, salivation, and impaired pupillomotor accommodation.

Orthostatic hypotension can be a disabling symptom that more frequently occur, in diabetic and amyloid neuropathy [138]. Non-pharmacological interventions have poor effect, and patients require pharmacological treatment as midodrine, an alpha-1 sympathomimetic agent, mineral corticoids as fludrocortisone, or droxidopa, a precursor of norepinephrine

able to cross the blood-brain barrier. However, clinically meaningful improvements are often difficult to achieve in severe orthostatic hypotension. Genito-urinary and gastroenteric dysfunction require a multidisciplinary approach and specific treatment are beyond the purposes of the review.

6. Expert opinion

SFN is a distinct nosologic entity, clinically relevant for the impact on patients' quality of life and important as for the research in the field of neuropathic pain [139].

In the last decade, the diffuse use of skin biopsy for the investigation of epidermal and dermal innervation in a variety of clinical conditions, either painful or painless, leaded to the widening of the spectrum of clinical conditions associated, leading to the new definition of small fiber pathology in some of them.

SFN should be considered when plausible symptoms and signs of small nerve fiber damage are present. Skin biopsy should be performed as a confirmatory diagnostic test within a defined clinical context. Therefore, we suggest an accurate clinical evaluation as crucial starting of the diagnostic workup. The standardization of the clinical evaluation has important implications also in clinical research for the definition of inclusion and exclusion criteria in trials [140]. The important role of the clinical signs has been recently confirmed by a validation study that confirmed their reliability and strengthened the relevance to address the diagnosis with the major contribution of skin biopsy findings [1]. Conversely, the presence of symptoms alone, without clinical sign, should not drive to diagnostic conclusion [1].

Although the degeneration of nerve fibers is the hallmark of SFN, studies have not demonstrated any strong correlation between neuropathic pain symptoms and the extent of epidermal denervation [42]. Furthermore, is still poorly known if the degenerative processes, and the regeneration attempts, influence the peripheral pain generator and the central mechanisms of sensitization. The discovery of gain-of-function pathogenic mutations in genes encoding for sodium channel subunits involved in the generation and propagation of the action potential in nociceptors contributed to shed light on molecular mechanisms underlying neuropathic pain and confirmed that small nerve fibers can be either degenerated, like in SFN-associated sodium channelopathy, or normal like in inherited erythromelalgia. The genetic characterization has become important for a comprehensive evaluation of SFN patients. However, the transition from a Mendelian familial pain disorders like inherited erythromelalgia to a much more common condition like

SFN showed the complexity to unravel the genetic substrate of this painful disorder in which many more genes might contribute together with environmental factors to compose the variability of the clinical picture, the intensity of pain and the response to drugs. Another issue, relevant for pathophysiological and clinical purposes, regards the presence and entity of autonomic abnormalities, which have been investigated only in few systematic studies [38,110]. Some patients can have subclinical autonomic impairment [38], whereas others show a severe invalidating involvement of gastrointestinal, genitourinary and cardiovascular systems. Mutation in some genes could explain this variability [141,142]. Several tests have been proposed to improve the characterization of the autonomic involvement and increase the diagnostic efficacy.
Pharmacological treatment remains disappointing due to the limited efficacy of available analgesics and the impossibility to predict response to drugs. As a matter of fact, no phenotype-driven approach can be reliably used in clinical practice and the "trial-and-error" approach is that used to manage individual patients. Recent studies provided promising results, suggesting that SFN patients harboring specific sodium channels variant could achieve satisfactory pain relief with selective sodium channel blockers [126] based on peculiar biophysical features [127]. These findings, along with deep phenotyping and genotyping of patients, have been paving the way to personalized pain medicine, which remains neurologists' secret wish.

Funding
This paper was not funded.

Declaration of interests
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Figure 1. Clinical phenotypes of small fiber neuropathy

Small fiber neuropathy can have different clinical presentations. The typical pattern of a length-dependent polyneuropathy (A) includes pinprick and thermal sensory loss as well as evoked or spontaneous pain having a stocking-glove distribution. Some patients could complain of patchy or diffuse distribution of symptoms in a non-length-dependent manner (B). In particular cases such as burning mouth syndrome or vulvodynia, a focal involvement is observed (C).

Figure 2. Skin biopsy

Pattern of cutaneous innervation at the distal leg in a healthy subject (left) and a patient with small fiber neuropathy (right). Arrows indicate intraepidermal nerve fibers that are counted throughout the section.

Figure 3. Analysis of sweating

Dynamic sweat test patterns at the distal leg in a healthy subject (A) and a patient with small fiber neuropathy (B, C). In A, the normal pattern of sweat imprint. In B and C a marked reduction of active sweat gland density and anhidrotic areas patients with idiopathic (B) and diabetic small fiber neuropathy (C).

Table 1. Symptoms of small fiber neuropathy

Table 2. Bedside assessment. Practical approach to clinical evaluation

Table 3. Diagnostic criteria for small fiber neuropathy

Table 4. Laboratory screening. Suggested laboratory tests for first-line screening of small fiber neuropathy and special tests for rare conditions

Table 5. Pharmacological treatment for neuropathic pain

Table 1.

Symptoms suggesting small fiber neuropathy (SFN)
Sensory symptoms • Pain (burning sensations, tingling, painful cold sensation, shooting pain, pins and needles) • Dysesthesia (e.g. sensation of feet constriction) • Allodynia in response to rubbing • Hypoesthesia to heat, cold, and pinprick
Dysautonomic symptoms • Hypo/anhydrosis • Hyperhydrosis • Sicca syndrome • Erythromeralgia • Cutaneous vasoparalysis • Gastrointestinal symptoms (early gastric empty, constipation, diarrhea, intestinal pseudo-obstruction) • Urinary incontinence or retention • Erectile dysfunction • Disorders of accommodation with blurred vision, photophobia, tonic pupil • Orthostatic hypotension, orthostatic intolerance

Table 2. Bedside assessment. Practical approach for clinical evaluation.

Negative signs	Bedside assessment
Tactile hypoesthesia	cotton bud
Pinprick hypoesthesia	disposable needle; monofilament stimulus
Thermal hypoesthesia	cold/warm water tube; 40°C-20°C termoroller
Allodynia	
Mechanical – punctate (static)	stick or pin
Mechanical (dynamic)	flat tip painter's brush
Thermal	cold/warm water tube
Pressure	gentle finger pressure
Hyperalgesia	
pinprick hyperalgesia	disposable needle
pressure-evoked hyperalgesia	deeper finger pressure
Temporal summation	stick or pin applied 10 times to a single site 1 Hz

Table 3 – Diagnostic criteria

SFN CRITERIA 2008[42]	
Presence of at least two of the following:	**Absence of the following:**
Clinical signs of small fiber neuropathy, including pinprick and thermal sensory loss or reduction and/or the presence of positive signs (allodynia and hyperalgesia)	Reduced vibratory sensation Loss of deep tendon reflexes Altered sensory nerve conduction
Abnormal thermal threshold assessed at the foot by QST	
Reduced IENFD at the distal leg	

NEUROPATHY CRITERIA[43]	
Possible	length-dependent symptoms and/or clinical signs of small-fiber damage
Probable	length-dependent symptoms, clinical signs of small-fiber damage, and normal sural NCS
Definite	length-dependent symptoms, clinical signs of small-fiber damage, normal sural NCS, and reduced IENFD at the ankle and/or abnormal QST thermal thresholds at the foot

Table 4 – Laboratory screening

Suggested laboratory tests for initial screening of SFN
Diabetes or pre-diabetes ▪ Fasting plasma glucose ▪ Oral glucose tolerance test ▪ glycated haemoglobin HbA1c **Other metabolic causes** ▪ Thyroid function ▪ Renal function ▪ Vitamins B12 (cobalamin) ▪ Folate **Infectious disease** ▪ HIV test ▪ Hepatitis B and C serology ▪ Hematological disease: ▪ Serum electrophoresis and immunofixation ▪ Complete blood count **Immune-mediated** ▪ Antinuclear antibody (ANA) ▪ Extractable nuclear antigen (ENA) ▪ Antineutrophil cytoplasmic antibody screening (ANCA) ▪ Cryoglobulin ▪ Rheumatoid factor ▪ Erytrocyte sedimentation rate (ESR) ▪ Anti-RO (SSA), anti-La (SSB) – (Sjogren's syndrome) ▪ Antibodies for gliadin, transglutaminase and endomysial – (Celiac disease) **Paraneoplastic syndromes** ▪ Onconeuronal antibodies (anti-Hu, anti-CV2)
Special tests for rare conditions
Genetic disease ▪ Sodium channelopathy - **SCN9A, SCN10A, SCN11A genes** ▪ Familial amyloidosis - **Transthyretin** gene ▪ Fabry disease* - **Enzymatic assay for alpha-Gal A activity / Genetic test of alpha-Gal A (GLA)** ***to test if clinical suspicion is supported by systemic features**

Table 5. Pharmacological treatment for neuropathic pain.

Recommendation in peripheral neuropathy	Drugs	Mechanism of action	Adverse effects	Precautions, contraindications
First-line therapy	**TCAs (Amitriptyline, Nortriptyline)**	- Monoamine reuptake inhibition; - sodium channel blockade; - anticholinergic effects	- anticholinergic effects - weight gain, - somnolence, - xerostomia - orthostatic hypotension	Cardiac disease, glaucoma, prostatic adenoma, seizure; cautions with adults > 65 years
	Duloxetine Venlafaxine	- Serotonin and norepinephrine reuptake inhibition	- Nausea, - abdominal pain, - hyperhidrosis - hypertension (venlafaxine)	Hepatic disorder (duloxetine) Hypertension Cardiac disease Use of MAO inhibitors Use of tramadol
	Gabapentin Pregabalin Enacarbil	- decreases central sensitization ($\alpha 2$-δ subunit of voltage-gated calcium channels)	- Sedation, - dizziness, - peripheral edema - weight gain	Reduce dose in renal insufficiency
Second-line Third-line therapy	**Tramadol Tapentadol**	- Mu receptor agonist; - Monoamine reuptake inhibition	- Nausea, - vomiting, - constipation, - dizziness - somnolence	History of substance abuse, suicide risk, use of antidepressant in elderly patients
Third-line therapy	**Strong opioids (e.g. morphine, oxycodone)**	- Mu receptor agonist; - kappa receptor antagonism (oxycodone)	- Nausea, - vomiting, - constipation, - itch, - dizziness - somnolence	History of substance abuse, suicide risk, Psychotropic effects risk of misuse on long-term use
Topical/localized agents				
Second-line therapy	**Lidocaine 5% plasters**	Sodium channel blockade	- Local erythema, - Itching	-
First-line therapy Second-line therapy	**Capsaicin cream / high concentration patches (8%)**	Transient receptor potential vanilloid type 1 agonist (TRPV1)	- Pain, - erythema, skin - lesions,	Skin lesion, caution in progressive neuropathy
Third-line	**Botulinum toxin type A**	Acetylcholine release inhibitor; axonal reflex block possible central effects	- Pain at injection site	hypersensitivity

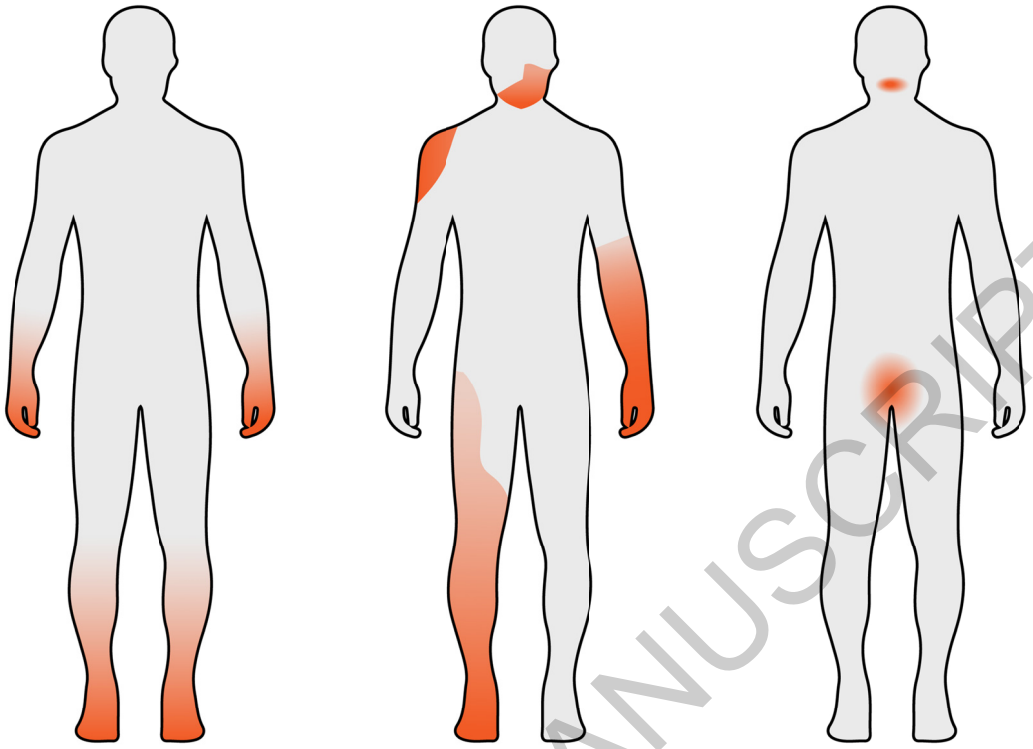


Fig 1

Fig 2

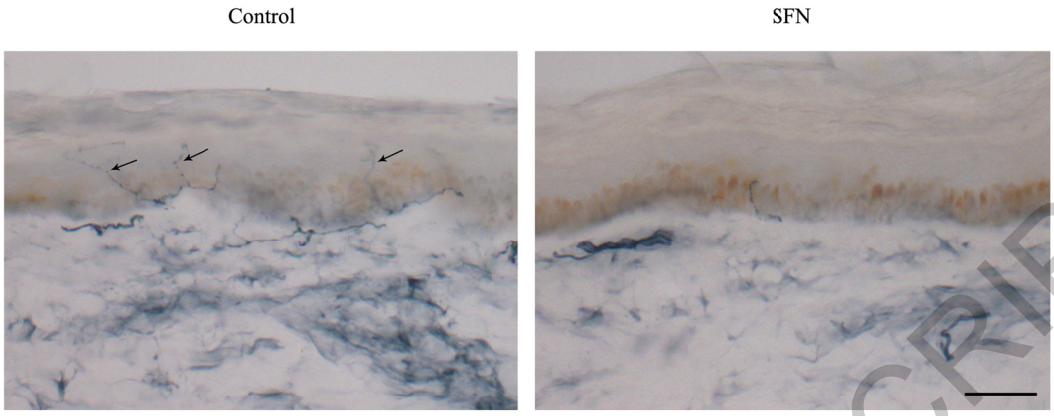
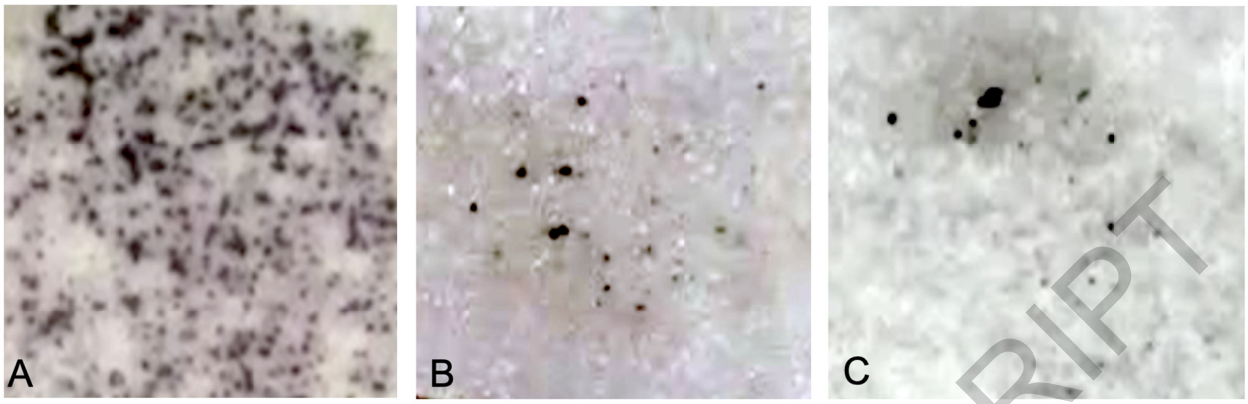


Fig 3



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