# Small-fibre neuropathies—advances in diagnosis, pathophysiology and management

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**Abstract** | Small-fibre neuropathy (SFN), a disorder of thinly myelinated Aδ-fibres and unmyelinated C-fibres, is clinically characterized by neuropathic pain symptoms and autonomic complaints. Diagnosis of SFN is challenging as the clinical picture can be difficult to interpret and results from nerve conduction studies are often normal. In cases of suspected SFN, measurement of intraepidermal nerve fibre density and/or analysis of quantitative sensory testing can enable diagnosis. New diagnostic techniques (including measurement of nerve fibre density using corneal confocal microscopy, and nociceptive evoked potentials) may contribute to the diagnostic work-up. SFN can be associated with systemic diseases such as immune-mediated disorders, but remains idiopathic in a substantial proportion of patients. Gain-of-function variants in the $Na_v1.7$ sodium channel have recently been found in nearly 30% of patients with idiopathic SFN, but the mechanisms of axonal degeneration in the disorder remain under investigation. Identification of the systemic diseases underlying SFN will enable development of drugs that target affected pathways to improve the management of neuropathic pain and autonomic dysfunction. In this Review, we discuss recent advances in the diagnosis and pathophysiology of SFN, highlighting how improved understanding of these aspects of the disorder will contribute to better patient management.

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## Introduction

In an 1868 publication, Paul Langerhans made the first description of intraepidermal nerve fibre (IENF) endings.[1] The study included drawings depicting essentially the same architecture identified later using immunohistochemical staining of axonal cytoplasm with antibodies against protein gene product 9.5 (PGP 9.5)—a neuronal marker. Despite disagreement on Langerhans' work throughout the following decades, full recognition of his findings came in 1954 when Weddell and colleagues published a thorough review on nerve endings in mammalian skin, showing extensive epidermal innervation by fine, freely ending filament-like axons deriving from dermal stem fibres.[2,3] In the mid 20th century, the different types of peripheral nerve fibres captured the attention of researchers and physicians.[4] In 1944, Erlanger and Gasser were awarded the Nobel Prize in Physiology or Medicine for their discovery of the highly differentiated functions of single nerve fibres.[5] These investigators showed that the sense of touch is conveyed by large-diameter fibres, with temperature-encoding fibres being smaller, and fine pain-signalling fibres the finest. Subsequently, a classification of fibres into three groups (A, B and C), with subsections for the A group, was proposed. The smallest-diameter fibres were classified as Aδ-fibres and C-fibres;[5] these are the small-diameter extensions of the dorsal root ganglion (DRG) neurons. In the cutaneous layer, myelinated Aδ-fibres and unmyelinated C-fibres provide cold and warm sense, respectively, and relay the sensation of pain after their activation with noxious mechanical or thermal stimuli. Aδ-fibres have an additional role in preganglionic sympathetic and parasympathetic function, whereas C-fibres contribute to postganglionic autonomic functions. Exposure to noxious chemicals can also cause nerve activation in a subset of C-fibres.[6]

Small-fibre neuropathy (SFN) is a condition that selectively involves Aδ-fibres and C-fibres. The clinical picture of the disorder is straightforward, with 'positive' and 'negative' sensory symptoms, and autonomic complaints. Pathologically, SFN is characterized by degeneration of distal terminations of small-diameter sensory fibres, observed as low IENF density (IENFD) on histological analysis of tissue from patients with the condition (Figure 1). Sometimes, the terms 'painful neuropathy' or 'autonomic neuropathy' are used as synonyms for SFN. However, neuropathic pain can also be a symptom of large-fibre neuropathy,[7] and involvement of both small and large nerve fibres has been described in some autonomic neuropathies.[8] Recently, variants in *SCN9A*, which encodes the $Na_v1.7$ sodium channel, have been identified in patients diagnosed with idiopathic SFN.[9] These mutations lead to abnormal spontaneous firing and enhanced evoked firing of DRG neurons, and are likely to induce axon degeneration through mechanisms not yet fully understood.

**Competing interests**
The authors declare no competing interests.

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**Key points**

- Small-fibre neuropathy (SFN) is a disorder of thinly myelinated Aδ-fibres and unmyelinated C-fibres
- SFN is diagnosed on the basis of presence of typical SFN-related symptoms, normal nerve conduction studies, reduced intraepidermal nerve fibre density at the ankle, and/or abnormal quantitative sensory testing
- SFN can be associated with systemic diseases, with an immune-mediated basis proposed in some cases; however, the cause remains unclear in a substantial number of patients
- Mutations in SCN9A, which encodes the sodium channel Nav1.7, were found to underlie SFN in a subset of patients
- Therapy for SFN focuses mainly on pain relief, management of autonomic dysfunction, and disease modification where possible
- Future studies into therapies for SFN should address the efficacy of immunomodulating agents and selective sodium channel blockers

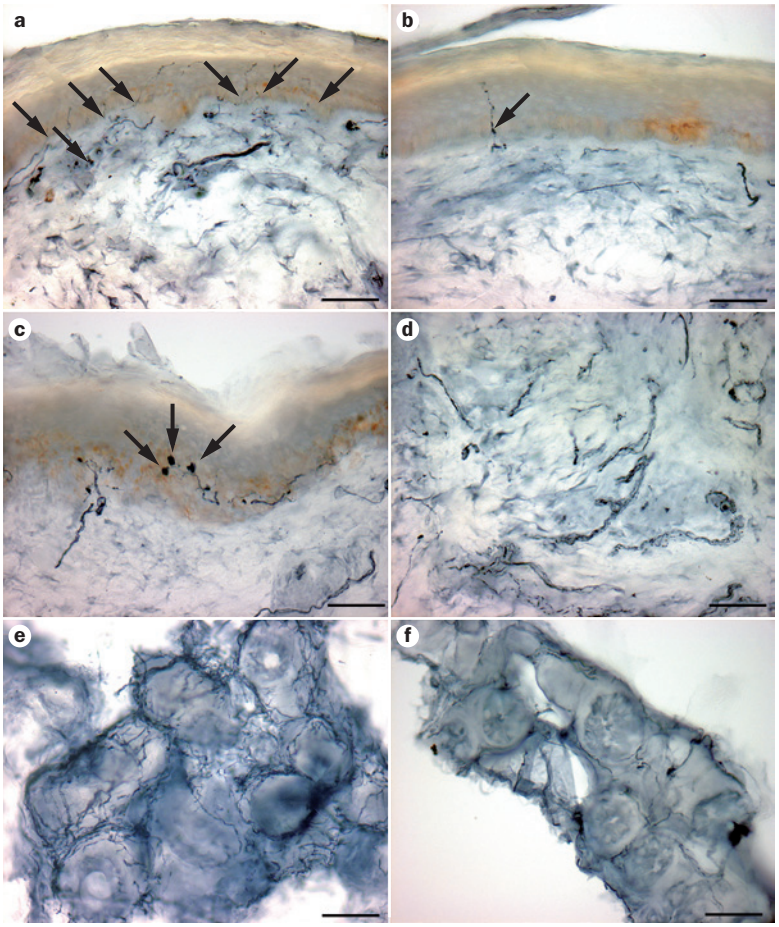


**Figure 1** | Evidence of denervation in the skin of patients with SFN. Images show bright-field magnification of sections of skin biopsies from the distal part of the leg. Nerve fibres are stained with anti-PGP 9.5. **a** | Skin biopsy from a healthy individual, showing extensive intraepidermal nerve fibres (arrows). **b** | Staining of skin biopsy from a patient with SFN reveals severe depletion of intraepidermal nerve fibres (arrow) and dermal nerve bundles. **c** | Large swellings of intraepidermal nerve fibres (arrows) in a patient with SFN are considered to be pre-degenerative axonal changes. **d** | Fragmented dermal nerve fibres in a patient with SFN, which are weakly stained. **e**,**f** | Staining of sweat gland tissue shows extensive innervation in a healthy individual (e) and denervation in a patient with SFN (f). Bar is 50 μm in all images. Abbreviation: SFN, small-fibre neuropathy.

Accurate diagnosis of SFN is important as it provides a basis for aetiological work-up and treatment decisions. In this Review, we focus on advances in diagnosis, pathophysiology and management in SFN. Improvements in both the methods for diagnosis and understanding of the underlying mechanisms of disease will be essential to provide better patient care.

## Epidemiology

The prevalence of SFN, either idiopathic or associated with systemic diseases, is unknown. Epidemiological information obtained from studies that focused on the diagnosis of SFN in selected subgroups of patients may have been biased owing to the selection criteria used.[10,11] Furthermore, before the availability of diagnostic tools for SFN, diagnostic criteria for the disorder were not uniform. Consequently, patients with SFN were either undetected or misdiagnosed, thus limiting epidemiological analysis.

## Symptoms and clinical features

Patients diagnosed with SFN experience multiple types of pain, described mainly as a burning sensation, shooting pains, prickling or itching.[12,13] Sheet or sock intolerance and restless legs syndrome may be present, often aggravating the foot pain sensation. Cramps and tingling may occur, mainly in the lower legs and feet, and are possibly induced following dysfunction of muscle nociceptors.[12,14,15] Negative symptoms can include thermal sensory loss, loss of pinprick sensation, and numbness or tight feeling.[12] Autonomic dysfunction may lead patients to complain of dry eyes or mouth, orthostatic dizziness, bowel disturbances (constipation, diarrhoea, irritability, gastroparesis, cramps), micturation disturbances, changes in sweating (hyperhydrosis or hypohydrosis), accommodation problems, impotence, diminished ejaculation or lubrication, hot flushes, or cardiac palpitations (Box 1).[14,16–18]

Sensory symptoms in SFN usually occur in a symmetrical length-dependent pattern; that is, starting in the feet and expanding proximally.[19] However, a non-length-dependent pattern of symptoms has been reported, showing a patchy distribution of neuropathy in the face, scalp, tongue or trunk.[9,13,20–22] A syringomyelia-like syndrome has been described in Tangier disease,[23] which, similar to Fabry disease and familial amyloid polyneuropathy (FAP), is a multiorgan disease that can include SFN.[24–26] FAP generally presents with SFN symptoms and signs, but rapidly evolves to a full mixed polyneuropathy.[27]

## Diagnosis

### Definition of SFN

Many diagnostic definitions have been proposed for pure SFN.[12,14,16,17,28] In general, the diagnosis should be considered in the presence of symptoms and/or clinical signs of small-fibre damage (such as neuropathic pain, autonomic dysfunction, loss of pinprick sensation, thermal sensory loss, allodynia, or hyperalgesia) and in the absence of large-fibre involvement (such as muscle weakness, loss of light touch and/or proprioceptive or vibratory sensation, hypoflexia, or areflexia).[10,11,14] In addition, nerve conduction studies, which are used to assess conduction in large-diameter fibres, should be normal.[10–12,29] Skin biopsy with quantification of IENFD and quantitative sensory testing (QST) are considered the

cardinal additional tests that can be used to confirm the diagnosis of SFN.[11,14]

In 2010, a practical diagnostic grading definition was proposed for diabetic SFN: possible SFN is defined as the presence of length-dependent symptoms and/or clinical signs of small-fibre damage; probable SFN as the presence of length-dependent symptoms, clinical signs of small-fibre damage, and normal sural nerve conduction studies; and a diagnosis of definite SFN is given if there are length-dependent symptoms, clinical signs of small-fibre damage, normal sural nerve conduction studies, altered IENFD at the ankle, and/or abnormal QST thermal thresholds at the foot.[10] As damage of small nerve fibres is not disease-specific, these diagnostic criteria can be applied to any patient with suspected SFN—including the idiopathic form—independently of the aetiology. Although most cases of SFN present with length-dependent distribution of symptoms and signs, non-length-dependent types have been reported.[13,20]

We have recently developed and validated the SFN Symptom Inventory Questionnaire (SFN-SIQ).[28] This specific screening tool involves questioning the individual about 13 symptoms (Box 1) to which they can rate their experiences using a score of 0–3: never, 0; sometimes, 1; often, 2; or always, 3. A diagnosis of SFN is made in patients with at least two answers of score 1 or above, with evidence of IENFD and/or thermal threshold QST abnormalities, and after large-fibre impairment is ruled out. This tool has been used to screen patients with possible sarcoidosis-associated SFN or *SCN9A* mutations.[9,28]

No formal criteria for grading the severity of SFN exist, but simple, clinically orientated questionnaires, such as the SFN-SIQ, may be useful tools to determine the span and severity of SFN-related sensory and autonomic symptoms.[9,28]

**Box 1** | Symptoms of small-fibre neuropathy

For the diagnosis of small-fibre neuropathy, at least two of the following symptoms, not otherwise explained, are required.

**Sensory**
- Pain (burning, shooting, prickling or itching)
- Paraesthesias
- Allodynia
- Thermal sensory loss
- Pinprick loss
- Sheet or sock intolerance
- Restless legs syndrome

**Autonomic**
- Sicca syndrome
- Accommodation problems
- Hyperhydrosis or hypohydrosis
- Micturation disturbances
- Impotence and/or diminished ejaculation or lubrication
- Bowel disturbances (constipation, diarrhoea, irritability, gastroparesis, cramps)
- Hot flushes
- Orthostatic dizziness
- Cardiac palpitations

## Skin biopsy

Skin biopsy is a minimally invasive, safe, largely painless and inexpensive investigative tool. Assessment of the biopsied tissue enables quantification of epidermal nerve endings—the distal ends of axons originating from DRG and trigeminal ganglia that cross the dermo-epidermal junction and terminate within the epidermis.[30] In 1983, an antibody against cytoplasmic PGP 9.5 was developed, and was shown to stain neurons better than did previously used antibodies, including those against neuropeptides, owing to the fact that anti-PGP 9.5 stains not only epidermal but also dermal nerve fibres.[31,32]

### *Punch biopsy*

For diagnostic purposes in cases of suspected SFN presenting with length-dependent symptoms and signs, a skin biopsy can be taken from the distal part of the leg, within a region 10 cm above the lateral malleolus.[33] A more proximal biopsy (for example, from the thigh) may be considered in patients with non-length-dependent presentations, such as in suspected ganglionopathy. Notably, no normative values for PGP 9.5 staining are available for locations other than the distal leg. Bright-field immunohistochemistry or immunofluorescence, either with or without confocal microscopy, are used to assess IENF loss,[32,34] but normative reference values adjusted for decade of life and sex are available only for immunohistochemical analysis.[35]

IENFs are counted under the optical microscope and the number is divided by the length of the epidermal surface to obtain a linear density per millimetre; the density reported is the mean of the values calculated from at least three sections from the same biopsy. The diagnostic value of skin biopsy in patients with SFN has been established.[33] In healthy individuals, IENFD in the distal leg is lower in males than in females, and the values decline with age.[28,35–37] An IENFD below the fifth percentile is usually considered confirmatory for a diagnosis of SFN.

In addition to IENF analysis, investigation of skin biopsies can reveal degenerative changes both in IENFs, such as progression to large axonal swellings (Figure 1c), and in dermal nerves, observed as fragmented and weak PGP 9.5 staining (Figure 1d). Moreover, skin biopsy can be used to investigate autonomic structures and innervation, such as in sweat glands (Figure 1d,e) and arrector pili muscles. Skin biopsy also provides the opportunity to quantify the innervation of dermal nerve fibres.[38–40] IENFD is normal in about 12% of patients with symptoms of SFN,[11] possibly representing pre-degenerative functional impairment of the nerve fibres. The combined assessment of IENFD and dermal nerve fibres can increase the sensitivity and specificity of skin biopsy for establishing a diagnosis of SFN.[39] In one study published in 2011, a reliable method for quantifying the innervation density of dermal nerves was presented; using this technique, the researchers found a correlation between dermal nerve morphometry and IENFD, and good interobserver agreement was demonstrated.[38]

Skin biopsy has also been used in prospective studies to evaluate the course of SFN. For example, in toxic and hypothyroid neuropathies, skin biopsy analysis enabled

researchers to conclude that reinnervation of the skin occurred after discontinuation of the toxic agent.[41–43] In patients with Guillain–Barré syndrome, skin biopsy assessment was used to demonstrate that loss of IENFs began in the early phase of disease, and to reveal a correlation between nerve fibre loss and severity of neuropathic pain.[44]

Besides a role in establishing the diagnosis of SFN, skin biopsy can be used to aid in the identification of the underlying cause of the disorder. In some studies, attempts to define the diagnosis in patients with suspected SFN prompted an aetiological work-up that revealed impaired glucose tolerance (as observed in 20–40% of patients) or other underlying systemic diseases.[11,45,46] Skin biopsy assessment can reveal perivascular inflammation and vascular injury in cutaneous vasculitis resulting from systemic lupus erythematosus or eosinophilia.[47,48] IgM deposits on skin nerves were observed in patients with anti-myelin-associated glycoprotein neuropathy.[49] Moreover, skin biopsy has been used to study the rate of degeneration and regeneration of IENFs after chemical-induced denervation with topical capsaicin or axotomy with punch biopsy, thus providing a method to investigate the potential therapeutic effects of neuroprotective drugs.[50–55]

#### *Skin blister technique*

An alternative method to obtain a skin biopsy is the skin blister technique.[56] Exertion of negative pressure on the skin leads to blistering, causing the epidermis to separate from the underlying dermis and enabling excision of the blister roof. IENFs in the tissue can be counted following immunostaining for neuronal markers. Skin blistering has benefits over skin punch biopsy: topical anaesthesia is not needed and bleeding is reduced. IENFD determined from immunostained tissue obtained via the skin blister technique was found to correlate with values obtained using tissues from punch biopsy.[57] Additional studies are required, however, to establish normative age-related and sex-related values and the reliability of this technique for use in the diagnosis of SFN.

### Quantitative sensory testing

In the 1970s, the first automated systems to investigate different sensory modalities were developed.[58,59] Since this time, routine assessment of thermal and vibration sensation in a quantitative manner has become possible. For the evaluation of small nerve fibre dysfunction, only temperature thresholds are measured. Usually, two types of testing—the method of levels and the method of limits—are used.[60,61] Several studies have shown that QST may be useful in efforts to establish a diagnosis of SFN.[11,62] However, this technique has some limitations. For reliable results, QST requires the patient to be alert and cooperative. Furthermore, a number of different QST instruments with different testing protocols, algorithms and normative values are available,[63] and no consensus has been reached as to which method should be used as the standard approach.[64,65] IENFD seems to be inversely correlated with both cold and warm thresholds on QST, but the correlation between nerve fibre density and specific sensory modalities is unclear.[11,33] QST is not a specific test of peripheral nerve function; as such, CNS dysfunction owing to disorders such as stroke or multiple sclerosis may also produce QST abnormalities. For some organizations, QST has been considered more useful in population studies than as an aid for diagnosis in individual patients.[64]

### Corneal confocal microscopy

Over the past decade, the noninvasive technique of *in vivo* confocal microscopy of the cornea has been developed, mainly for use in patients with diabetic neuropathy. Confocal microscopy in healthy individuals has confirmed that the cornea is innervated by both Aδ-fibres and C-fibres of trigeminal origin.[66] The technique allows observation of the living eye *in situ*, at the cellular level.[67] A correlation between low corneal nerve fibre density and severity of the somatic neuropathy and IENF loss in the distal leg has been described.[68–71] Studies in the past few years have suggested that confocal microscopy might be useful in the diagnosis of idiopathic SFN, Fabry disease and immune-mediated SFN.[71–74]

### Nociceptive evoked potentials

Selective activation of both Aδ-fibres and C-fibres is used in two types of nociceptive evoked potentials: laser-evoked potentials (LEPs) and contact heat-evoked potentials (CHEPs). Induction of pain-related evoked potentials (PREPs) involves the preferential stimulation of Aδ-fibres.[75] A relationship between poor nociceptive evoked potential response and severity of IENFD loss has been described.[76–78] Intraepidermal electrical stimulation (IES) may also contribute to the detection of functional changes in peripheral fibres in SFN.[79]

#### *Laser-evoked potentials*

To obtain LEPs, the skin is stimulated with short radiant heat pulses that are emitted by a $CO_2$ laser. Brain potential at the vertex can be subsequently recorded. Late LEPs reflect Aδ-fibre activation (200–400-ms latency range), and ultra-late LEPs reflect C-fibre activation (1000-ms latency range),[80,81] with the amplitude of cerebral response correlating with the reported intensity of the perceived pain.[82] An abnormal LEP can represent a disorder of the peripheral nerve, nerve plexus, nerve root, or spinal or brainstem nerves, and the technique seems to be diagnostically useful in SFN.[83–85] However, laser stimulators are not widely available and the ultra-late LEPs are technically difficult to obtain.[84]

#### *Contact heat-evoked potentials*

Following the development of a heat-foil CHEP stimulator with extremely rapid heat rising time (70 °C/s), elicitation of pain and CHEPs can be achieved.[86] Compared with LEPs, contact heat stimulators cause mechanical activation of the skin and stimulate a larger surface area, which makes missed stimulation of fibres less likely, even when only a few intact fibres remain.[76] The stimulus of contact heat stimulators is natural and can be controlled very precisely.[86,87] Furthermore, the technology is easy to use in the clinic, does not require eye protection, and has a low risk of causing skin irritation.[77] Similar to LEPs, late CHEPs are

associated with Aδ-fibre activation, and ultra late CHEPs with C-fibre activation.[86,88] However, the diagnostic value of this method in SFN has not yet been systematically investigated, and normative values are lacking.

*Pain-related evoked potentials*

Compared with LEPs and CHEPS, the technique to assess PREPs is less time-consuming and easier to perform.[75] PREPs are obtained through the use of a concentric planar electrode that delivers electrical stimuli solely to the superficial layer of the dermis. The stimulus primarily depolarizes superficial nociceptive Aδ-fibres, thereby excluding the possibility of activation of deeper non-nociceptive fibres.[75] In patients with HIV-related SFN, a correlation between reduced IENFD and abnormal PREPs was found.[78] Results from one study in patients with diabetes suggest that measurement of PREPs may contribute to early detection of SFN, although this study did not include assessment of IENFD by skin biopsy.[89]

*Intraepidermal electrical stimulation*

For IES, a pushpin-like electrode of 0.2 mm in length is gently pressed against the skin, inserting the needle tip adjacent to the thin nerve endings in the skin. After delivery of an electrical stimulus, the evoked potential is measured in the same way as in the other nociceptive evoked potentials, and leads to preferential activation of Aδ-fibres.[79] The utility of IES for the detection of SFN remains to be validated.

## Microneurography

Microneurography has made recording of single Aδ-fibre and C-fibre activity possible, and provides a direct method for measuring sympathetic activity. This technique has contributed substantially to improving our knowledge of the physiology of nociceptors and the mechanisms underlying their sensitization.[90–93] However, the application of microneurography requires both an expert investigator and a collaborative patient, and is invasive and time-consuming, thus limiting the routine use of this technique in the clinical setting.[82,94]

## Autonomic testing

Autonomic involvement in SFN can be difficult to demonstrate. Cutaneous innervation of the dermal autonomic adnexa (such as sweat glands, hair follicles, blood vessels and pilomotor muscles) has been studied by staining biopsies from these tissues with antibodies against PGP 9.5 or vasoactive intestinal peptide and dopamine β-hydroxylase.[95–97] Several tests to assess autonomic dysfunction also exist.

The Ewing battery for cardiovascular autonomic reflex testing is easy to perform, but has low sensitivity for the detection of autonomic dysfunction in patients with SFN.[16,62,98] Sudomotor and vasodilator function tests include the Quantitative Sudomotor Axon Reflex Test (QSART), Thermoregulatory Sweat Test, Sympathetic Skin Response (SSR), Skin Vasomotor Reflex (SVR), and Axon Reflex Flare Size (ARFS).[82,94,99] QSART seems to be sensitive in SFN, but as the application of this test requires specific skills and instrumentation, it is only available in specialized centres worldwide.[16,98–100] By contrast, SSR and SVR are simple methods and can be used in any clinical neurophysiology laboratory, although their diagnostic value in SFN is reported to be poor.[62,82,99] In one study, use of both SSR and SVR in combination with microneurography enabled differentiation between patients with autonomic SFN, those without autonomic complaints, and controls.[101]

The ARFS is a noninvasive method, the results of which seem to correlate with IENFD.[102] This technique is used to measure the size of axon-reflex flare following electrical stimulation that simultaneously activates axon reflexes of sudomotor fibres and nociceptors. This mode of stimulation causes the release of vasodilating calcitonin gene-related peptide from C-fibre endings and acetylcholine from sympathetic nerve endings. Scanning laser Doppler flowmetry enables the measurement of skin blood flow in perfusion units, which represent the product of velocity and concentration of the blood cells moving within the volume measured. Using thermostatic laser Doppler probes that include both recording and heating elements, the underlying skin area is heated while blood perfusion is recorded. This examination can be performed in the area from where a skin biopsy is obtained, thus allowing direct correlation with findings from histological analysis. The parameters analysed using scanning laser Doppler flowmetry are basal cutaneous blood flow, vasoconstriction reflexes induced by deep breathing and postural variation (venoarteriolar reflex), and vasodilatation induced by local heating (from 32 °C to 44 °C for 6 min). Vasoconstriction reflexes induced by deep breathing can be used to examine sympathetic adrenergic function, whereas venoarteriolar reflex (caused by postural variation) and vasodilatation induced by local heating are used to investigate skin axonal reflexes carried by somatic C-fibres. By using scanning laser Doppler flowmetry, researchers measured the size of the flare caused by the vasodilation and showed that ARFS is reduced in patients with SFN.[102,103]

Two new techniques have been recently introduced to quantify the innervation density of sweat glands[96] and arrector pili muscles,[97] and these tools could widen the diagnostic yield of skin biopsy in diabetic SFN. Sweat gland nerve fibre density was initially quantified by manual morphometry after staining biopsied tissue with anti-PGP 9.5 antibodies.[96] In the past few years, a new computerized area-based morphometric technique has been developed that involves counterstaining of the nerve fibres with Congo red. This technique has reduced variation in sweat gland area measurement compared with the manual method.[104] In diabetic neuropathy, the sweat gland innervation index obtained using this new technique was found to correlate with glycaemic control and autonomic symptoms.[105] A novel technique to quantify pilomotor nerves also showed good discriminative and reliability values in patients with diabetic neuropathy.[97] Although both techniques seem very promising and may complement the investigation of IENFD for diagnosis of SFN, normative age-matched and sex-matched values are needed for both tools before they can be implemented for general clinical use.

**Box 2** | Conditions associated small fibre neuropathies

**Pure and predominantly somatic small-fibre neuropathy**

Metabolic
- Impaired glucose tolerance,[45,46] hyperlipidaemia[110] hypothyroidism[147]

Immune-mediated
- Sarcoidosis,[111] Sjögren syndrome,[148] coeliac disease,[21] inflammatory bowel diseases,[112] paraneoplastic neuropathy[149]

Infectious
- Leprosy,[150] Epstein–Barr virus[151]

Toxic and drugs
- Antiretroviral drugs, bortezomib, metronidazole,[152,153] flecainide,[154] nitrofurantoin,[155] alcohol abuse[109,136]

Hereditary
- $Na_v1.7$-mutations,[9] Fabry disease,[108] erythromelalgia,[141] Ross syndrome,[156] haemochromatosis[157]

Idiopathic
- Idiopathic small-fibre neuropathy,[19] burning mouth syndrome[120]

**Small-fibre neuropathy progressing to mixed-fibre neuropathy**

Metabolic
- Diabetes,[10] chronic kidney disease[158]

Immune-mediated
- Amyloidosis,[133] vasculitis,[106] systemic lupus erythematodes,[47] Guillain–Barré syndrome[159]

Infectious
- HIV,[107] hepatitis C,[160] Lyme neuroborreliosis[161]

Toxic and drugs
- Hypervitaminosis $B_6$[162]

Hereditary
- Familial amyloidosis,[27] Fabry disease,[108] Tangier disease,[23] Friedreich ataxia,[163] cerebrotendinous xanthomatosis,[164] hereditary sensory autonomic neuropathies[113]

**Disorders with reduced intraepidermal nerve fibre density (no clear small-fibre neuropathy)**

Neurodegenerative
- Spinobulbar muscular atrophy (Kennedy disease),[118] amyotrophic lateral sclerosis,[116] Parkinson disease[117]

Idiopathic
- Complex regional pain syndrome type I[119]

## Causes

After an SFN diagnosis is made, the aetiology must be investigated to detect underlying causes, as some are potentially treatable (Box 2).[14,17,18] Diabetes mellitus, HIV, hyperlipidaemia, amyloidosis, Fabry disease, coeliac disease, sarcoidosis and other systemic illnesses can all cause SFN.[10,21,27,28,45,46,106–112] Among the hereditary sensory and autonomic neuropathies, types I, IV and V are characterized by predominant small nerve fibre involvement.[24,113] Despite a comprehensive work-up of patients with SFN, the proportion of individuals diagnosed with idiopathic or cryptogenic forms remains substantial, ranging from 24% to 93% in different series depending on the definition of SFN used.[11,17,114] In our cohort, no underlying cause was found in approximately one-third of patients.[9] Some disorders cause pure SFN, whereas others cause SFN that may evolve to a mixed (small-fibre and large-fibre) neuropathy (Box 2).

Diabetes mellitus is the disease most frequently associated with SFN. About 50% of all patients with diabetes will develop neuropathy that generally involves both large and small nerve fibres.[7,10] Nerve dysfunction may also be seen in patients with impaired glucose tolerance,[45,115] a condition that predisposes individuals to diabetes. A glucose tolerance test should, therefore, be part of the routine work up in patients with suspected SFN.

Reduced IENFD has been described in patients with neurodegenerative disorders such as amyotrophic lateral sclerosis and Parkinson disease, and could contribute to the autonomic complaints in individuals with these conditions.[116,117] A reduced IENFD has also been described in individuals with Kennedy disease; however, this finding is not surprising as the disorder typically causes sural nerve conduction abnormalities, a change that indicates large sensory fibre damage.[118]

The symptoms of some unexplained pain syndromes might also be the result of small nerve fibre dysfunction; for example, complex regional pain syndrome type I was linked to focal SFN in one study.[119] Burning mouth syndrome has been described as a trigeminal SFN, a contention supported by evidence of low nerve fibre density in tongue biopsies from subgroups of patients.[120,121]

## Pathophysiology

Several pathophysiological mechanisms have been proposed to cause peripheral neuropathy. However, details of the pathogenesis in these disorders are incompletely understood, and much remains to be learned about the pathophysiology of isolated SFN. Some pathophysiological mechanisms have been identified in mixed polyneuropathies, and these mechanisms may also have a role in SFN.

### Diabetes and other metabolic disorders

Several hypotheses for neuropathic dysfunction in diabetic neuropathy have been suggested, with most evidence obtained from studies in rat models of the disease. One suggestion is that hyperglycaemia might disturb the polyol pathway, which would result in an increased level of sorbitol. This and other changes in the pathway may lead to production of reactive oxygen species that can cause nerve damage.[122]

Evidence suggests that vascular disease in patients with diabetes can lead to ischaemia, creating oxidative stress and resulting in the production of noxious reactive oxygen species. In a rat model of induced nerve infarction (which leads to ischaemia), neuropathy preferentially affected smaller myelinated and unmyelinated fibres.[123] Furthermore, hypoxia without ischaemia has been suggested as the underlying cause of degeneration in unmyelinated axons in patients with chronic obstructive airways disease.[124]

Impaired neurotrophic transport has been suggested as a pathophysiological mechanism that contributes to the development of SFN in diabetes.[125] Decreased proliferation of keratinocytes in the skin of individuals with

diabetes may lead to low levels of nerve growth factor (NGF)—a cytokine that is necessary for the survival of sympathetic fibres and for maintenance of phenotypic properties of small-diameter sensory fibres. In addition, NGF is reported to increase the resistance of the nerve cell to injury from oxidative stress.[125] As such, lack of NGF could lead to nerve dysfunction.

Results from studies of induced denervation following topical capsaicin application have suggested an impairment of axon trafficking in diabetes, with reduced nerve fibre regeneration demonstrated in individuals with diabetes compared with healthy controls.[51] Other findings suggest that impaired vascular regeneration may have a role in diabetic neuropathy.[53] In light of the observation that nerve cells in patients with end-stage kidney disease were in a chronically depolarized state, one study suggested that hyperkalaemia may be a major contributor to nerve damage in this condition.[126]

### Immune-mediated SFN

Several immune-mediated diseases may cause SFN (Box 2); in these instances, contribution of the immune system to small nerve fibre degeneration seems likely. Activation of the immune system stimulates mast cells and macrophages, which can lead to recruitment of neutrophils and monocytes that release chemokines and other mediators such as tumour necrosis factor-α (TNF-α), IL-1β, IL-6 and/or nitric oxide—cytokines involved in microglial cell activation. Evidence suggests that both the activation of the immune system at a peripheral level and the change in processing of sensory information in the CNS have a role in pain associated with peripheral neuropathy.[127,128] In patients with length-dependent SFN, higher levels of the cytokines TNF-α, IL-1β and IL-8 were found in the affected distal skin than in the non-affected skin. Moreover, IL-6 and IL-8 expression was increased in patients with SFN compared with healthy individuals. Collectively, this evidence supports the idea that elevated local proinflammatory cytokines may be involved in the pathophysiology of pain in SFN.[129]

Another indication of immunological involvement in SFN is the presence of serum autoantibodies, such as peripherin-IgG, anti-myelin-associated glycoprotein and antisulphatide antibodies, which have all been reported in patients with SFN.[130,131]

Although large-diameter nerve fibres are considered to be the main target of immunological attacks in chronic inflammatory demyelinating polyneuropathy, small nerve fibre reduction has also been demonstrated.[132] Amyloid neuropathy predominantly involves small nerve fibres, although large-fibre dysfunction is often found. In amyloidosis, nerve fibre degeneration may be a result of mechanical compression by amyloid deposits.[133] Compression of DRG, plexus and distal trunks could explain distal axonal degeneration of nerve fibres, with longer fibres more likely to be damaged on a probabilistic basis.[134] However, toxic or metabolic factors might also have a role in amyloidosis-associated neuropathy.[133] Cutaneous vasculitis, as observed in systemic lupus erythematosus and eosinophilia-associated neuropathy, can also be associated with SFN; in this context, the pathogenesis includes vasculitic injury and eosinophilic neurotoxicity.[47,48]

### Alcohol abuse

Axonal degeneration in SFN related to alcohol abuse has been attributed to the direct toxic effect of ethanol on nerve fibres, contrary to the previously suggested hypothesis that nutritional deficiency might be the main cause.[109,135,136] Ethanol can cause metabolic disturbances with inhibition of axonal transport;[135] however, alcohol abuse usually causes a mixed axonal neuropathy.

### Ion channel dysfunction

Channelopathies have recently been linked to multiple pain syndromes.[137] Different members of the transient receptor potential (TRP) family of cation channels have been studied in animal models. Studies in a rat model of paclitaxel-induced painful peripheral neuropathy have demonstrated a role for the cation channel subfamily member Trpv4.[138] Blockade of the ion channel Trpa1 in diabetic rats was reported to reduce loss of cutaneous nerve fibre function.[139]

A recent study has demonstrated the presence of single amino acid substitutions of the voltage-gated sodium channel $Na_v1.7$—which is preferentially expressed within DRG and sympathetic ganglion neurons—in a substantial fraction of patients with idiopathic SFN.[9] A total of 28.6% of patients with idiopathic SFN were found to carry a gain-of-function variant in $Na_v1.7$. The variants, each affecting a single amino acid residue along the $Na_v1.7$ channel protein backbone (Figure 2), produced a variety of pro-excitatory changes in channel function, impairing various forms of channel inactivation and enhancing resurgent current production by the channels. When introduced into cultured DRG neurons, the mutations caused inappropriate spontaneous firing and enhanced responsiveness to depolarizing stimuli; this effect is proposed to cause small nerve fibres to degenerate.

$Na_v1.7$ mutations have also been linked to inherited erythromelalgia (IEM) and paroxysmal extreme pain disorder—two diseases that show some clinical similarities with SFN.[9,140] Both IEM and SFN can present with distal burning pain. IEM is defined by the presence of a red discolouration of the extremities that tends to be triggered by warmth and exercise.[140] Skin discolouration is seen in one-third to two-thirds of patients with SFN. Moreover, most patients with IEM describe relief with cooling, a feature that is seen in some but not all patients with SFN. Importantly, the autonomic complaints that are characteristic of SFN (Box 1) and the myalgias seen in some patients with SFN are not—or are only rarely—observed in IEM. Interestingly, SFN has been reported in some patients with erythromelalgia,[141] and the relationship between IEM and SFN is under investigation.

## Management

When an underlying condition has been demonstrated, causative treatment should be instituted if possible. For idiopathic SFN, treatments can be administered to control the symptoms of pain. However, the effects of treatment

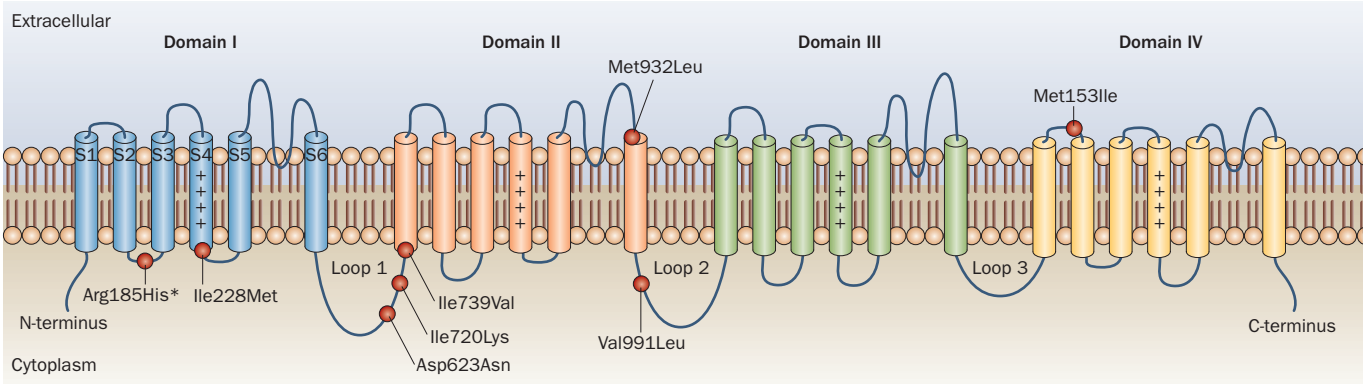


**Figure 2** | SFN-associated variants in the $Na_v1.7$ sodium channel. Schematic representation of the $Na_v1.7$ sodium channel showing the locations of the variants found in patients with idiopathic SFN. *Two patients had an Arg185His substitution. Abbreviation: SFN, small-fibre neuropathy. Modified from Faber, C. G. *et al.* Gain of function $Na_v1.7$ mutations in idiopathic small fiber neuropathy. *Ann. Neurol.* **71**, 26–39 (2004) © John Wiley and Sons.

on the course of SFN have thus far not been studied for most conditions involving SFN.

### Diabetic neuropathy

In diabetic neuropathy, tight glycaemic control seems to contribute to prevention of neuropathy and even to amelioration of symptoms.[10] As evidence has linked diabetic neuropathy to hypertension, smoking, obesity, elevated triglyceride levels, and the presence of cardiovascular disease, treatment of these potentially modifiable cardiovascular risk factors might influence the course of the neuropathy.[15]

### Fabry disease

Replacement of α-galactosidase A—the enzyme that is lacking in patients with Fabry disease—has been shown to reduce neuropathic pain, restore the sweating reflex, and reduce the detection threshold for cold and warm temperatures in the hands and feet in patients with the disorder.[142] However, no epidermal nerve fibre regeneration has been demonstrated.[143]

### Immune-mediated neuropathy

In immune-mediated conditions, some case studies of immunomodulatory therapy seem to show efficacy of this approach in relieving SFN symptoms.[144,145] However, large, prospective, controlled studies are needed to confirm these results.

### Idiopathic SFN

For patients with idiopathic SFN, treatments can generally target only symptomatic outcomes with the aim of ameliorating neuropathic pain. Tricyclic antidepressants and serotonin–norepinephrine reuptake inhibitors are recommended as first-line treatment for neuropathic pain.[146] Opioids can be used to treat exacerbations of pain, and efficacy of lamotrigine has been demonstrated in HIV-associated polyneuropathy.[146] Unfortunately, the available drugs for SFN often provide only partial relief from pain. More insight into the pathophysiology of neuropathic pain could contribute to better management of pain and, perhaps, to the development of more-effective pharmacotherapies. Selective $Na_v1.7$ blockers are currently under development, and might prove effective, especially in patients with *SCN9A* mutations.[9]

## Conclusions

As diagnostic methods have improved and awareness of SFN within the clinical community has increased, SFN has become more widely recognized in clinical practice. Understanding of the pathophysiology of this disorder has also improved. In the absence of a gold-standard diagnostic test, the SFN diagnosis is established by the presence of typical SFN-related symptoms, normal nerve conduction studies, reduced IENFD at the ankle, and/or abnormal QST. New techniques, such as determination of dermal nerve fibre density in skin biopsy, nociceptive evoked potentials, and corneal confocal microscopy, are emerging. The capacity of these techniques to aid in the diagnosis of SFN will, hopefully, soon be determined.

Several potentially treatable conditions have been linked to SFN and should be the focus of an aetiological work-up in patients with this condition. The pathophysiology of SFN, although still incompletely understood, is the focus of current studies. Prospective controlled studies are needed to investigate the effects of immunomodulatory therapy and other approaches, including subtype-selective sodium channel blockade in SFN associated with $Na_v1.7$ mutations. Results of these studies will almost certainly enhance our understanding of SFN, and may reveal new avenues for therapy.

**Review criteria**

A literature search was performed to find studies and reviews published on small-fibre neuropathy (SFN). If appropriate, historical papers were also included. A PubMed search was performed using the keywords "small fiber (fibre) neuropathy", in combination with any of the following keywords: "etiology", "pathogenesis", "diagnosis", "prognosis", "treatment", "skin biopsy", "quantitative sensory testing", "nerve conduction study (studies)". Furthermore, the bibliographies of all articles published between 1997 and 2012 regarding SFN were checked.

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**Author contributions**

All authors contributed equally to researching data for the article, discussion of content, writing the article, and to the editing and review of the manuscript before submission.