The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes

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Small fibre neuropathies are a heterogeneous group of disorders affecting thinly myelinated Aδ-fibres and unmyelinated C-fibres. Although multiple causes of small nerve fibre degeneration have been reported, including via genetic mutations, the cause of small fibre neuropathy remains unknown in up to 50% of cases. The typical clinical presentation of small fibre neuropathy is that of a symmetrical, length-dependent polyneuropathy associated with sensory or autonomic symptoms. More rarely, the clinical presentation is characterised by non-length-dependent, focal, or multifocal symptoms. The diagnostic tests to identify small fibre neuropathy include skin biopsy, quantitative sensory, and autonomic testing. Additional tests, such as those measuring small fibre-related evoked potentials and corneal confocal microscopy, might contribute to a better understanding of these neuropathies. Biochemical markers can also help in screening patients for the presence of small fibre neuropathy and to assess disease progression.

Introduction

Although many neuropathies have mixed involvement of small and large fibres,[1] the term small fibre neuropathy (SFN) refers to a group of neuropathies characterised by a selective or predominant impairment of peripheral afferent thinly myelinated Aδ-fibres and unmyelinated C-fibres.[2] SFN was thought to be rare, but an epidemiological study in the Netherlands reported an incidence of 12 cases per 100 000 inhabitants per year and a prevalence of 53 cases per 100 000.[3]

The diagnosis of SFN has evolved over the past two decades, in parallel with the availability and standardisation of skin biopsy. SFN cannot be diagnosed by nerve conduction studies—the standard diagnostic test for large fibre neuropathy—because the absence or reduced myelin of small fibres results in slow conduction velocities that are beyond the resolution of these studies.

Despite advances in our understanding of SFN, its features and natural history pose several difficulties for the development of a classification that will capture all aspects of the disorder. First, the course of neuropathy can change over time; for example, in a patient who initially presents with small fibre signs or symptoms, the disease can gradually progress and eventually present with a combination of large and small fibre dysfunction. Second, although diagnostic criteria have been established for symmetric length-dependent SFN, no criteria are available for focal or multifocal small fibre mononeuropathies, or for the ganglionic non-length-dependent presentation. Third, several of the tests used to identify SFN are time-consuming, require specific expertise, and are limited to specialist settings. Finally, loss of small fibres can also occur in conditions that are not usually considered to have the essential characteristics of peripheral neuropathy (eg, fibromyalgia,[4] motor neuron disease,[5] Ehlers-Danlos syndrome,[6] and Parkinson's disease[7]). In this Review, we describe the clinical presentations of SFN and its causes, and present a strategy for clinical examination. Autonomic features do not necessarily parallel the somatic features of the neuropathy;[8] thus, autonomic signs and symptoms and their assessment will only be mentioned if they represent an adjunct in the diagnosis of SFN. The pathophysiology and treatment of SFN are reviewed elsewhere.[9–12]

Definition of SFN and clinical presentations

Small nerve fibres are peripheral afferent unmyelinated C-fibres and thinly myelinated small Aδ-fibres. In the somatosensory nervous system, these fibres transmit information about temperature, pain, and itch, and in the autonomic nervous system, they mediate sudomotor, thermoregulatory, cardiovascular, gastrointestinal, urogenital, and other autonomic functions.[13] A disease of, or damage to, the peripheral nervous system affecting small fibres in a neuropathic distribution is termed SFN; however, there is no gold standard for the diagnosis of SFN. Pathologically, SFN is most often characterised by a degeneration of terminals of small nerve fibres, but can also occur because of excitability changes without degeneration.

The clinical presentation of SFN is characterised by the presence of negative or positive sensory phenomena, and by autonomic dysfunction (described in more detail later). SFN can present as a polyneuropathy (ie, a topographical distribution with bilateral symmetric disturbances usually in distal parts of the limbs), a focal neuropathy affecting one nerve (ie, a mononeuropathy), or a multifocal neuropathy (ie, as mononeuropathy multiplex or as ganglionopathy, with a proximal distribution).

Clinical characteristics

The clinical presentation of SFN is heterogeneous, with no single clinical pattern fitting all presentations. However, the two most common presentations are a length-dependent polyneuropathy and a non-length-dependent ganglionopathy, or monofocal or multifocal mononeuropathy.[14,15] Patients with length-dependent SFN (figure 1A) can present with neuropathic pain in the

feet—the most common of which is burning pain. However, the condition can also be pain free, with absent or reduced pain and temperature sensation.[16] Small fibre pathology can also involve the autonomic nervous system, giving rise to autonomic features, which add to the complexity and heterogeneity of the clinical picture.[8] Signs and symptoms ascend from the distal extremities (toes and feet) to the ankles and even above the knees. Once symptoms reach the knee, the upper limbs can become involved and, consistent with the length-dependent topographical pattern, the fingertips are involved first. This distal-to-proximal gradient is often seen in patients with impaired glucose intolerance or diabetes.[17] However, symptoms remain limited to the feet in most patients with pure SFN.[16] In patients with type 2 diabetes, SFN symptoms can occur early in the course of the disease and are followed by gradual large fibre involvement.[18] This raises the question whether, in diabetic neuropathy and possibly also other neuropathies, there is a continuum of features that starts as pure SFN and develops into mixed neuropathies, with the involvement of both small and large fibres. The scarcity of prospective studies precludes a conclusion at this point in time.

Non-length-dependent SFN (figure 1B) is characterised by signs or symptoms caused by the functional impairment of individual or multiple nerves or nerve fibres. This pattern has been described in paraneoplastic, immune-mediated, and idiopathic cases.[14,19] Patients with mononeuropathy or ganglionopathy often present with a variable patchy sensory pattern that can affect different parts of the body, including the face, tongue, scalp, upper limb, and trunk, before the lower limbs.[20] Patients with ganglionopathy can present with a proximal pattern, involvement of upper limbs but not lower limbs, or involvement of the trunk or face.[21] Ganglionopathies have been described in small and large fibre neuronopathies, paraneoplastic conditions, and Sjögren's syndrome; however, direct pathological evidence of neuronal injury in dorsal root ganglia has only been documented in large fibre neuronopathies.[22] In focal SFN, the symptoms might be localised to the tongue and mouth in primary burning mouth syndrome,[23] or focal SFN might occur in sensory mononeuropathies such as notalgia and meralgia paraesthetica.[24] Furthermore, diffuse painless degeneration of small nerve fibres has been reported in congenital insensitivity to pain with anhidrosis.[25] Because of the unusual and variable presentations, these subtypes can be difficult to diagnose. Among conditions characterised by diffuse pain, studies have shown that at least some patients with fibromyalgia[4,26–28] or Ehler-Danlos syndrome[6] have small fibre pathology. Furthermore, small fibre pathology is also seen in conditions such as motor neuron disease[5] and Parkinson's disease,[7] but these patients do not usually present with the characteristic clinical features or characteristic neuropathic distribution required for a diagnosis of SFN.

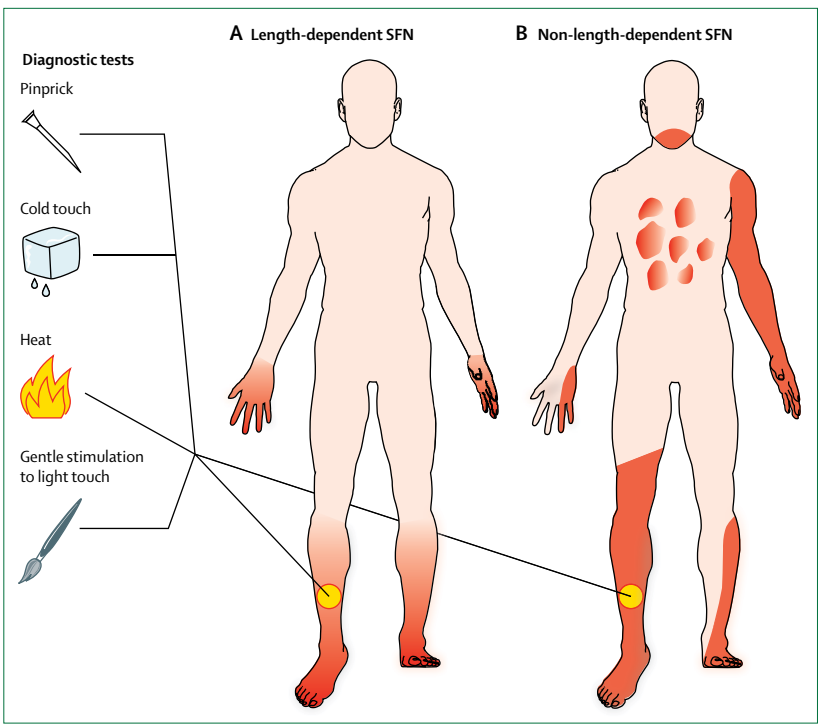

Figure 1: **Clinical presentations in small fibre neuropathy (SFN)**
A patient with typical length-dependent polyneuropathy (A) might have pain, sensory loss, or hypersensitivity to cold, warm, light touch, or pinprick in a characteristic stocking-glove distribution, with intact deep tendon reflexes and preserved proprioception and sensation to vibration. A patient with patchy non-length-dependent neuropathy (B) might have either reduced or increased small fibre function corresponding to a single or to multiple nerves.

Patients with SFN might complain of burning, prickling, aching, electric-like, or itching sensations. Some patients have nightly deep aching cramp-like pains, restless legs, or foot movements. Bed sheets might give rise to dysaesthesia or allodynia.[29] SFN might also have heterogeneous features; for example, in patients with erythromelalgia, symptoms are exacerbated when the skin is warmed and relieved when cooled.[30] In oxaliplatin-induced acute neuropathy, symptoms are exacerbated when the skin is cooled.[31] Negative symptoms reflect the degeneration of the peripheral receptors or fibres, and indicate the loss of specific sensory modalities. Patients with SFN might report reduced or absent sensitivity to cold, heat, and noxious mechanical stimuli. Sensory loss can occasionally be masked by simultaneous hyperalgesia and allodynia in the affected area.

Clinical assessment of SFN

Questionnaires

Specific questionnaires for screening SFN in clinical practice have been developed. The Small Fibre Neuropathy and Symptoms Inventory Questionnaire includes 13 items: changed sweating pattern, diarrhoea, constipation, micturition problems (eg, incontinence and hesitation), dry eyes, dry mouth, dizziness on standing from sitting or supine position, palpitations,

hot flashes, sensitive skin, burning feet, heat intolerance, and restless legs. Each item has four response options: 0=never, 1=sometimes, 2=often, and 3=always. This questionnaire has been used to screen patients with SFN associated with possible sarcoidosis or *SCN9A* mutations.[32] This ordinal scale questionnaire has also been transformed into an interval measure.[10]

Another questionnaire, the Small Fibre Neuropathy Screening List, specifically developed and validated for SFN in sarcoidosis, consists of 21 questions related to neuropathic pain and autonomic dysfunction, and might be useful as an endpoint in clinical trials.[33] Further studies are needed to establish the broader usefulness of this screening questionnaire. A small-fibre symptom survey has been developed for idiopathic SFN, but has not been validated yet.[34]

The Autonomic Symptom Profile and the Composite Autonomic Symptom Score-31 (COMPASS-31) are questionnaires that have been developed specifically for autonomic dysfunctions.[35] COMPASS-31 is a validated 31-question self-assessment instrument, including six domains: orthostatic, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor functions. COMPASS-31 has very good internal validity and test–retest reliability, and the scores are significantly different between patients with and without SFN.[35]

Clinical examination tools

Inspection of the affected body parts alone (eg, discoloration, dry skin, and dystrophic changes of the feet) might suggest the presence of polyneuropathy. At the bedside examination, small fibre function is examined by testing the patient's response to heat, cold, and pain evoked by pinprick. Simple bedside testing equipment and standardised protocols are available to screen for small fibre dysfunction (panel 1).

Bedside testing of positive sensory signs includes increased pain (allodynia or hyperalgesia) in response to pressure, pinprick, heat, or cold. Patients might complain of abnormal sensations to thermal stimuli (eg, cold stimuli might be perceived as heat), and stimuli might also be accompanied by aftersensation (eg, persistent sensation of pain lasting after the stimulus). Negative sensory signs include reduced sensitivity to cold, heat, and noxious mechanical stimuli.

Standardised examination instruments are available to assist clinical bedside examination. For example, the Utah Early Neuropathy Scale (UENS) can be used to detect subtle sensory disturbances.[43] The UENS emphasises the severity and spatial distribution of pin (sharp) sensory loss in the feet and legs. UENS is a sensitive and reproducible clinical measure of sensory and small fibre nerve injury, and is a valuable outcome measure in trials of early sensory neuropathy. UENS was designed and validated to detect early SFN in patients with prediabetes or diabetes, and has been shown to have a sensitivity of 92% and an inter-rater reliability of 94%.[43] Other examination tools—primarily assessing large fibre sensory and motor function—are available, such as the Michigan Neuropathy Screening Instrument,[44] the Neuropathy Impairment Score—lower leg for distal symmetric sensorimotor polyneuropathy,[45] and the modified Toronto Clinical Neuropathy Score.[46]

The diagnostic accuracy of clinical examination in pure SFN was reported to be 54·6%, with a sensitivity of 62·6% and a negative predictive value of 53·7%.[47] One study[46] tested seven different clinical neuropathy scales and their ability to detect neuropathy in newly diagnosed patients with impaired glucose tolerance and found that all tests could distinguish patients with neuropathy from controls with a high diagnostic performance. The modified Toronto Clinical Neuropathy Score had the highest diagnostic yield, with a sensitivity of 98% and a specificity of 97%.[46] The UENS scored 85% on sensitivity and 97% on specificity.[46]

Quantitative sensory testing and other neurophysiological tests

Quantitative sensory testing (QST) can be used to assess the functional impairment of sensory nerve fibres (Aδ-fibres, Aβ-fibres, and C-fibres). QST is a non-invasive method that can evaluate both gain and loss of sensory function, and can be used to assess the features of neuropathic pain, but has some limitations: (1) QST is a psychophysical test and is thus open to bias; (2) abnormal results do not have a localising value in terms of the identification of peripheral versus central lesions; and (3) it is time-consuming and only available at specialised centres. For a detailed description of QST, see Backonja and colleagues' consensus statement.[48] The German Research Network on Neuropathic Pain[37] has developed a

Panel 1: **Bedside and neurophysiological techniques to assess sensory function in small nerve fibres**

Conventional bedside sensory tests

- Cotton
- Brush
- Monofilaments
- Needle or pinprick
- Thermorollers
- Tuning fork and reflex hammer

Neurophysiological and pathological techniques

- Nerve biopsy[36]
- Skin biopsy[24]
- Quantitative sensory testing[37]
- Quantitative sudomotor axon reflex test[38]
- Corneal confocal microscopy[39]
- Microneurography[40]
- Electrical-evoked potentials
- Laser-evoked potentials[41]
- Contact heat-evoked potentials[42]

For more on the **German Research Network on Neuropathic Pain** see http://www.neuro.med.tu-muenchen.de/dfns/e_index.html

standardised QST protocol consisting of seven different tests measuring 13 parameters. Normative reference values are available for both sexes, all age groups, and several body regions (including the face, hand, and foot). QST parameters have proven to be region specific and age dependent, and less sensitive in old patients than in young individuals.[37]

The standardisation of equipment and examination protocols and the certification of examiners should reduce variability, and thereby contribute to a more reliable classification of patients. In a study,[49] QST was suggested to be a valuable tool in the clinical delineation of SFN. A battery of bedside sensory tests exists that is suitable to use both in clinical practice and research settings.[50]

Neurophysiological techniques to assess sensory function in patients with SFN are presented in panel 1. Although nerve conduction studies cannot identify SFN, they are an essential step in the diagnostic investigation, because they can establish whether large fibres are involved or not. Furthermore, consecutive tests can show the reduction of sensory nerve action potential amplitude, reflecting progressive loss of large nerve fibres. However, the involvement of large fibres does not exclude SFN, and overlap is common.[15] Recording techniques in nerve conduction studies affect how sensory neuropathies are classified; for example, orthodromic near-nerve recording of the sural nerve[51] or of most distal nerves (eg, the medial plantar or dorsal sural nerve) can increase the sensitivity to detect subclinical large fibre involvement that would be otherwise missed by conventional surface techniques.

Measures that are useful for research purposes, but are rarely necessary or applicable in most clinical settings, include laser-evoked potentials,[41] contact heat-evoked potentials,[42] microneurography,[40] and non-sudomotor C-fibre axon reflex measures, such as the axon flare response and pilomotor axon reflex tests.[52,53]

Pathological examination: nerve and skin biopsy

Peripheral nerve biopsy was a key diagnostic and research tool in the 20th century, and is still used for the assessment of some neuropathies of uncertain diagnosis. Nowadays, sensory nerve biopsy (sural or peroneal) is considered only when other diagnostic tests have been insufficient, or if the biopsy can add information that other tests cannot (eg, in patients with vasculitis, atypical chronic inflammatory neuropathies, amyloidosis, or some inherited neuropathies).[54] The diagnostic accuracy of nerve biopsy for neuropathies can range from 24% to 94%.[36]

The pathological hallmark of SFN is decreased density of intraepidermal nerve fibres, which occurs in approximately 85% of cases.[47] Patients with erythromelalgia or oxaliplatin-induced acute neuropathy can have altered small fibre function without loss of intraepidermal nerve fibres.[55]

Normative reference values for intraepidermal nerve fibre density at the distal leg adjusted for sex and age are available for both bright-field microscopy and immunofluorescence techniques,[56,57] and are used to diagnose individual patients on the basis of defined cutoffs. A study[58] that compared the agreement between the two methods found consensus on SFN diagnosis in about 93% (59 of 63) of cases and a similar diagnostic accuracy. In two studies, little or no side and time variability of intradermal nerve fibre density occurred as the density was roughly the same between the right and left leg, as well as between biopsies taken 20 days apart, which is the average time of epidermal renewal.[58,59]

Skin biopsy is a key method to diagnose SFN (figure 2), with a high diagnostic accuracy. The procedure is fast and simple, and the resultant wound heals within a few days. Disease progression can therefore be followed up over time by repeated skin biopsies.[59] Skin biopsy can also distinguish between somatosensory and autonomic nerve fibres.[60]

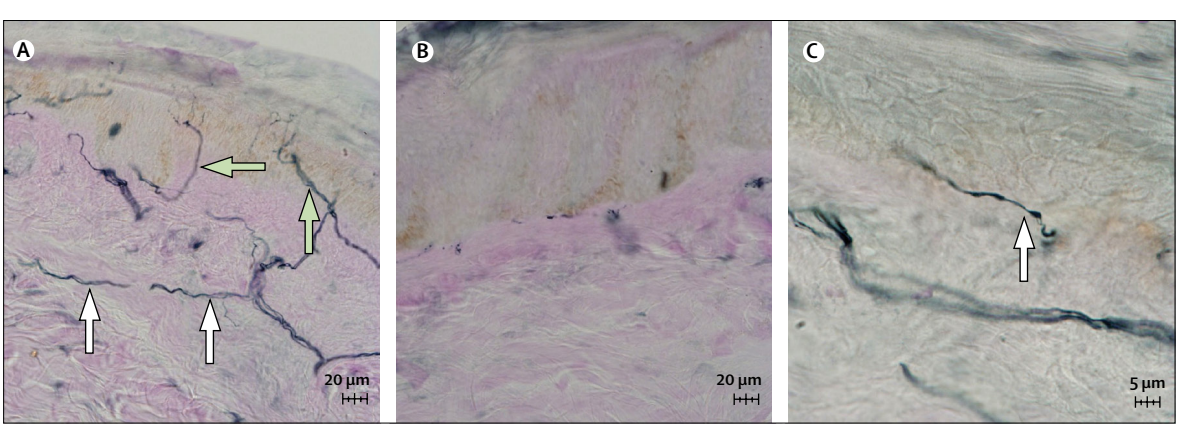

Figure 2: **Skin nerve fibres**
In a punch skin biopsy, a sample that is usually 3 mm in diameter is removed. After overnight fixation, the sample is frozen and cut into 50-µm thick cryosections (vertically to the direction of the epidermis) and then immunostained with PGP9.5 antibody, to visualise the fibres and estimate their density. (A) Intraepidermal nerve fibres (green arrows) and dermal nerve fibres (white arrows) in a healthy individual. (B) Loss of skin nerve fibres in a patient with painful diabetic neuropathy. (C) Axonal swelling of intraepidermal nerve fibres (white arrow) in a patient with painful diabetic neuropathy.

Other measures include estimation of the length density of the remaining nerve fibres in the epidermis and dermis,[61,62] sweat gland innervation,[63] and quantification of axonal swellings.[61,62] Patients with painful diabetic neuropathy or other types of painful neuropathies have significantly higher swelling ratios (swellings per intraepidermal nerve fibre or per nerve fibre length density) than controls. Even patients with diabetes but without signs of neuropathy have significantly higher swelling ratios than controls.[64] Axonal swellings might represent pre-degenerative changes of intraepidermal nerve fibres and predict their loss, but their clinical significance and role in the pathogenesis of pain and sensory deficits unclear, and further studies are warranted.[61]

The relationship between structure and function of small nerve fibres is of key concern. The correlation between intraepidermal nerve fibre density and functional test measures, such as QST, is still unclear, because the quantification of intraepidermal nerve fibre density reveals structural changes, but does not predict the degree of functional changes. The remaining fibres can thus be sensitised, hypofunctional, or normal. The diagnostic accuracy of intraepidermal nerve fibre quantification in SFN is high, with sensitivity and specificity rates of around 90%—considerably higher than QST, which showed a diagnostic accuracy of 46·9% in patients with pure painful SFN and normal nerve conduction studies.[47]

Other cellular structures can be identified and quantified from skin biopsies. For example, Langerhans cells are thought to play a role in the generation or maintenance of neuropathic pain because patients with painful diabetic neuropathy or painful SFN have an increased number of these cells, compared with patients with non-painful neuropathy or healthy controls.[65] However, these cells are not commonly included in the skin biopsy protocol for the diagnosis of painful neuropathy, and their role is yet to be determined. Inflammatory cells such as macrophages (identified with anti-IbA1 antibody) might also be relevant, because they might be increased in the epidermis and dermis in painful SFNs, such as painful diabetic neuropathy and chemotherapy-induced painful neuropathy (Shepherd and colleagues, Washington University School of Medicine, unpublished observations). Other proteins have been investigated and, although still at an early stage, CD68 receptors, which are expressed on macrophages, calcitonin gene-related peptide (CGRP), the tyrosine kinase Ret (the receptor for GDNF in non-peptidergic nerve fibres) and Trk A (the receptor for NGF in peptidergic fibres) might be of interest.[12] A study showed that CGRP-positive fibres in the dermis correlated with electrical stimuli and heat pain thresholds, indicating that these fibres might be important in peripheral sensitisation and pain perception.[66] Trk A-positive axonal swellings were reported to be increased in patients with painful diabetic neuropathy, compared with those who were pain free, indicating a potential role of this receptor tyrosine kinase in axonal sensitivity, allodynia, and hyperalgesia.[64]

Test of sudomotor function

Unmyelinated or thinly myelinated sympathetic nerve fibres with primarily cholinergic neurotransmission innervate sweat glands. Sweat testing methods can provide an early diagnosis of sudomotor dysfunction and can be used to monitor disease progression or recovery. Sudomotor function can be measured by several non-invasive methods. The quantitative sudomotor axon reflex test (QSART) assesses the postganglionic sympathetic cholinergic sudomotor function in the extremities. Acetylcholine 10% is iontophoresed into the skin to stimulate unmyelinated C-fibres. A standardised collection from the forearm, proximal leg, distal leg, and foot is used, and sweating is measured and quantified by a sudorometer.[38] The QSART requires special equipment, can be technically challenging, is moderately time-consuming, and demands careful control of the test conditions and patient preparation to obtain adequate reliability. A normal response indicates intact function of postganglionic sudomotor axons. QSART detects length-dependent or generalised changes, can be used to follow up autonomic dysfunction, and was shown to have a sensitivity of around 50% in the diagnosis of SFN.[67]

The postganglionic sympathetic cholinergic sudomotor function can be measured dynamically by quantitative direct and indirect axon reflex testing (QDIRT). The sweat glands are stimulated directly by acetylcholine iontophoresis. Sweat is then displayed over time via an activator dye and consecutive digital photographs. QDIRT is simple and inexpensive, but this new technique has only been used in selected patients with SFN and requires further study in disorders of the autonomic nervous system. Other autonomic-testing methods are the sympathetic skin response test, silastic imprint method, and electrochemical sweat conductance methods.[68,69]

Corneal confocal microscopy

This novel technique allows for the quantification of small fibres located near the centre of the cornea. Corneal confocal microscopy is non-invasive and fast, and thus might be a useful method to confirm small nerve fibre pathology. Different reproducible parameters can be obtained from these confocal microscopy images (nerve fibre density, nerve fibre length density, nerve fibre branch density, and nerve fibre tortuosity);[39] however, the way in which laboratories capture, sample, and analyse the images can differ. Nonetheless, several studies have used the same standardised protocol and normative reference values have been reported.[70,71]

The diagnostic sensitivity and specificity of this technique in diabetic polyneuropathy are 91% and 93%, respectively,[72] and the quantification of small fibres in the cornea by use of corneal confocal microscopy has been

shown to be associated with the severity of diabetic polyneuropathy.[73] Similarly, corneal confocal microscopy parameters improve following better diabetes control. Patients with diabetes who substituted multiple insulin injections by an insulin infusion pump not only had more stable glycaemic control but also improved corneal confocal microscopy parameters.[74] Furthermore, a decline in corneal confocal microscopy parameters has been reported in patients with SFN.[75] Despite the promising findings of corneal confocal microscopy to date, additional studies are needed to determine its specificity and sensitivity for different neuropathic conditions with suspected small fibre involvement before this method can be used as a tool to diagnose SFN in clinical practice and research settings.

The causes of SFN

Although several causes of SFN have been identified (panel 2),[76] in 30–50% of cases the underlying cause is unknown.[77] Metabolic causes are important: diabetes is most common, causing approximately a third of cases.[39] SFN might develop insidiously in patients with diabetes and be present before the metabolic syndrome is diagnosed,[17] or it might occur acutely, as is the case in treatment-induced neuropathy[78] caused by fast glycaemic diabetic regulation. Hypothyroidism and uraemia are other common metabolic conditions that can present with SFN.[20]

Although HIV and antiretroviral therapy are known causes of SFN,[79] anecdotal association with other infections and vaccinations have been reported.[80–82] Among neurotoxic agents, alcohol[83] and chemotherapeutic agents[84] might induce SFN. SFN might also occur in systemic autoimmune and inflammatory disorders (panel 2), or in rare genetic disorders, such as transthyretin amyloidosis[85] and Fabry disease.[86]

Hereditary sensory and autonomic neuropathies are inherited disorders of the peripheral sensory and autonomic neurons, with loss of pain and thermal sensation being prominent features.[87] These painless conditions can be associated with ulceration, mutilation, or amputations of the feet and hands, along with other symptoms. Some patients complain of pain without marked sensory loss. Hereditary sensory and autonomic neuropathy type I occurs in the second or later decades in adulthood, whereas the onset of the other types of hereditary neuropathies is in infancy and childhood. The type II primarily affects the sensory neurons and might cause mild abnormalities of the autonomic nervous system. Hereditary sensory and autonomic neuropathy type III (familial dysautonomia) is predominantly seen in Jewish infants and children. In type IV disease, insensitivity to pain and thermal sensation with anhidrosis dominates the clinical presentation. Hereditary sensory and autonomic neuropathy type V is characterised by affected deep pain perception, and thus, severe injuries such as bone fractures and joint injuries.

The discovery of mutations in genes encoding voltage-gated sodium channels has allowed the spectrum of genetic SFN to be widened. After the first identification of gain-of-function mutations in *SCN9A*, the gene that encodes the Nav1.7α subunit,[32] patients harbouring gain-of-function mutations in *SCN10A* and *SCN11A*, encoding the Nav1.8α[88] and Nav1.9α[89,90] subunits, have been reported. These mutations have been found to produce

***Panel 2:* Causes of small fibre neuropathy**

Metabolic causes
- Diabetes, impaired glucose tolerance, and rapid glycaemic control in the setting of chronic hyperglycaemia (treatment-induced neuropathy of diabetes)
- Hypothyroidism
- Hypertriglyceridaemia
- Uraemia

Vitamin deficiency
- Vitamin B12

Neurotoxic exposure or vitamin intoxication
- Alcohol
- Antiretroviral agents
- Chemotherapeutic agents
- Organic solvents
- Pyridoxine B6 intoxication
- Statins
- Anecdotal cases: antiarrhythmic drugs (flecainide), antibiotics (metronidazole, nitrofurantoin, linezolid, ciprofloxacin), ingestion of *Clostridium botulinum* toxin, heavy metals (thallium, lead), and tumour necrosis factor α inhibitors

Infections
- Hepatitis C virus
- HIV
- Influenza
- Leprosy
- Severe sepsis, septic shock, and critical illness
- Anecdotal cases: Epstein-Barr virus, herpes simplex infection, mycoplasma pneumonia, rubella, syphilis, vaccination for rabies, varicella or Lyme disease, and hepatitis B virus

Immunological causes
- Autoimmune autonomic ganglionopathy
- Coeliac disease
- Guillain-Barré syndrome, monoclonal gammopathies, and primary amyloidosis (immunoglobulin light chain associated)
- Paraneoplastic syndrome
- Sarcoidosis
- Scleroderma
- Sjögren's syndrome
- Systemic lupus erythematosus
- Vasculitis

Hereditary causes
- Familial amyloid polyneuropathy (transthyretin amyloidosis)
- Hereditary sensory and autonomic neuropathies
- Fabry disease
- Mutations in COL6A5 and genes encoding voltage-gated sodium channels
- Pompe's disease

Idiopathic small fibre neuropathy

Panel 3: Biochemical markers of small fibre neuropathy

Initial screening in polyneuropathy

Glucose dysmetabolism
- Fasting plasma glucose
- Glycosylated haemoglobin (HbA_{1c})
- Oral glucose tolerance test in selected cases with normal HbA_{1c}

Renal, thyroid, and liver function

Vitamin deficiency
- Cobalamin
- Homocysteine
- Folate
- Methylmalonic acid

Haematological disease
- Serum protein electrophoresis with immunofixation electrophoresis

Other causes
- Erythrocyte sedimentation rate
- Complete blood count
- IgM, IgA, IgG

Biochemical screening in definite small fibre neuropathy

Acute or subacute development of autonomic dysfunction
- Ganglionic acetylcholine receptor antibodies
- Onconeuronal antibodies (anti-Hu antibodies, anti-CV2 antibody, voltage-gated calcium channel antibody, voltage-gated potassium channel antibody, Purkinje cell cytoplasmic antibody type 2)

Autoimmune or connective tissue disorder
- Rheumatoid factor
- Antinuclear antibody
- Antineutrophil cytoplasmic antibody screening
- Cryoglobulin
- Interleukin-2 receptor antibody
- Total and free calcium ion
- Serum and urine protein immunofixation electrophoresis
- CSF analysis

Sjögren's syndrome
- Anti-RO (SSA), anti-La (SSB)

Infection
- HIV tests
- Fluorescent treponemal antibody absorption test
- Hepatitis B and C
- CSF analysis

Diseases of the gut
- Antibodies for coeliac disease (gliadin, transglutaminase, and endomysial)
- Vitamin B and E concentrations

Porphyria
- Blood, urine, and stools for porphyrins

Neurotoxins
- Urine and blood toxicology

Hereditary causes
- Leucocyte α-galactosidase A enzyme activity in men and genetic tests in women for suspected Fabry disease when systemic features of the disease are present
- Genetic testing for *SCN9A* and *SCN10A* in patients with suspected Nav1.7α, 1.8α, or 1.9α sodium channelopathies
- Genetic testing for familial transthyretin amyloidosis

profound changes of the excitability and voltage-gate properties of the channels in primary nociceptors of dorsal root ganglia. Some mutations have been found to impair the function of sodium channels in sympathetic autonomic neurons, explaining the dysautonomia associated with neuropathic pain in patients with SFN.[91] Altered functioning of the sodium–calcium exchanger, leading to increased intracellular calcium concentrations, is thought to be one mechanism underlying sodium channel-related degeneration of small nerve fibres.[92] Pathogenicity of sodium channel mutations found in patients with SFN can be assessed by electrophysiological assays.[93,94] These assays allow for the identification of changes in the biophysical properties of nociceptors and autonomic neurons.[95,96]

Biochemical markers

In panel 3, we present biochemical tests that can be used to screen for SFN, including conditions ranging from pure SFN to neuropathies with combined small and large fibre involvement. Screening laboratory tests are those recommended for distal symmetric polyneuropathy;[97] other tests have also been suggested.[98] The first step at the initial visit at the neurological clinic should include sampling of fasting blood glucose and serum vitamin B12 with metabolites (methylmalonic acid with or without homocysteine) and serum protein immunofixation electrophoresis, because these tests have the highest yield of abnormality. However, other widely used screening tests include a complete blood count, erythrocyte sedimentation rate, renal, liver, and thyroid function tests, and an impaired glucose tolerance test, particularly in patients with a high body-mass index and a family history of SFN.[97] Further biochemical investigations will depend on the clinical features, for which no general recommendations exist; thus, the proposed recommendations are based on our opinion and clinical experience. Testing for autoimmune conditions and infection might also be of relevance. Lumbar puncture is of low diagnostic yield when done routinely,[97] so should primarily be done in cases of suspicious inflammatory, immune-mediated, or paraneoplastic causes of SFN. When patients present with symptoms characteristic of a specific disorder, such as amyloidosis, sarcoidosis, a genetic or paraneoplastic condition, or autoimmune autonomic ganglionopathy, the laboratory screening should be expanded to include these disorders. Furthermore, patients with monoclonal gammopathies should be referred to the department of haematology for additional investigations, including examination for cryoglobulinaemia, macroglobulinaemia, chronic lymphocytic leukaemia, myeloma, and primary amyloidosis.[97] Targeted genetic analysis of sodium channel genes should be considered in cases of SFN with unknown cause, mainly in young onset and familial cases. Clarification of the aetiology can reveal potentially treatable causes and allow patient recovery, as has been

shown in impaired glucose tolerance, hypothyroidism, and inflammatory-related SFN.[17,20,76]

Diagnostic criteria for SFN

In a study published in 2008,[40] patients were considered to have SFN when at least two of the following examinations were abnormal: (1) clinical signs of small fibre impairment (pinprick and thermal sensory loss or allodynia or hyperalgesia, or any combination of the three), whichever distribution was consistent with peripheral neuropathy (length-dependent or non-length-dependent neuropathy); (2) abnormal warm or cold threshold, or both, at the foot assessed by QST; or (3) reduced intraepidermal nerve fibre density at the distal leg. The presence of the clinical features of large fibre impairment or abnormalities in nerve conduction studies excluded a diagnosis of SFN. A subsequent guideline,[99] from the Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes (NEURODIAB), adopted a probabilistic approach to length-dependent SFN, grading it as: (1) possible (ie, presence of length-dependent symptoms or clinical signs of small fibre damage, or both); (2) probable (ie, presence of length-dependent symptoms, clinical signs of small fibre damage, and a normal sural nerve conduction study); and (3) definite (ie, presence of length-dependent symptoms, clinical signs of small fibre damage, normal sural nerve conduction study, and abnormal QST thresholds at the foot or reduced intraepidermal nerve fibre density at the ankle, or both). In a position paper from the same group,[100] the presence of abnormalities in nerve conduction studies was not incompatible with the probable and definite grades.

To enhance the diagnostic criteria for SFN, the incorporation of a quantitative measure of autonomic function, like sweat (eg, QSART), has been suggested.[38] Thus, a diagnosis of SFN would require abnormalities of at least two measures among QSART, QST, and skin biopsy.[38]

At this time, the adoption of a flexible approach to the diagnostic criteria on the basis of the setting in which they are used seems reasonable. For example, in genetic studies[101] the use of rigorous diagnostic criteria, such as those recently proposed,[47] seems appropriate. Diagnostic criteria for clinical trials are not yet established. In figure 3, we propose a diagnostic approach to the identification of SFN.

The order of diagnostic testing for SFN

The diagnostic approach to SFN should be systematic; thus, clinical history and examination are the essential first steps in the process. In patients with diabetes, tests for HIV and other known causes of SFN might not be needed. If clinical examination points to a length-dependent or non-length-dependent neuropathy, nerve conduction studies can be done to establish large fibre involvement. As recommended by the American Academy of Neurology,[98] at the same time as nerve conduction studies are undertaken, blood tests can be helpful; for example, full blood count, vitamin B12 and methylmalonic acid concentrations, serum protein immunofixation electrophoresis, fasting blood glucose, HbA_{1c}, thyroid function tests, serum electrolytes, and creatinine. If nerve conduction studies are normal, a skin biopsy, QST, or sweat test can be done to establish small fibre involvement. The choice between the skin biopsy, QST, or sweat test will depend on the availability of expertise at clinical centres. In patients with documented SFN, but unknown underlying cause, additional blood tests and genetic analysis can be done, as detailed in panel 3. Questionnaires specific to SFN can also be done to further characterise the disorder.

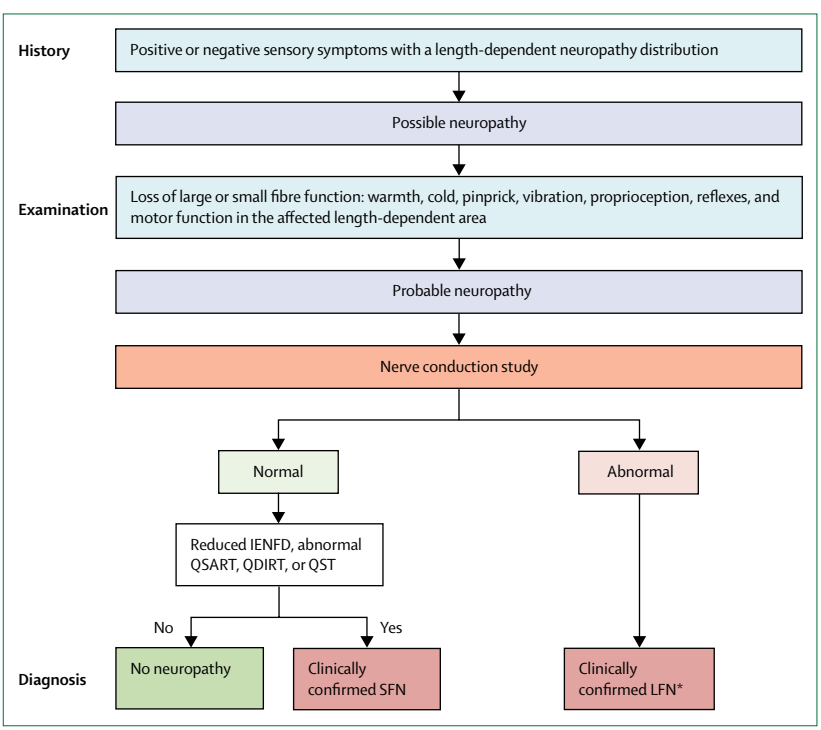

Figure 3: **Proposed diagnostic approach to the investigation of distal polyneuropathy**
The clinical history to support a diagnosis of possible distal neuropathy must include positive or negative sensory symptoms with a length-dependent polyneuropathy distribution. The bedside examination should reveal the presence of sensory dysfunction in the affected area by conventional bedside sensory tests for thermal and pain perception (panel 1). If nerve conduction studies are normal, a diagnosis of small fibre neuropathy (SFN) is confirmed by quantitative sensory testing (QST), skin biopsy, or quantitative sudomotor axon reflex test. If these test results are also normal, the patient does not meet the clinically confirmed criteria for an SFN (although this result does not exclude the possibility of a mild or early SFN, and such patients should still undergo investigation for SFN and are candidates for treatment with medications for neuropathic pain).[11] We propose that one abnormal neurophysiological or structural measure (ie, abnormal intraepidermal nerve fibre density) is required for a clinically confirmed diagnosis of SFN. More rigorous diagnostic criteria might include two or more abnormal measures, or an abnormal intraepidermal nerve fibre density (IENFD). If nerve conduction studies are abnormal and the patient has a history and bedside examination consistent with SFN, the diagnosis will be of large fibre neuropathy (LFN) with probable SFN. This flowchart is only intended for generalised (ie, distal) polyneuropathy. Although this figure portrays a model for a complete approach to the evaluation of the patient with peripheral neuropathy, these investigations need not necessarily be done on all patients with a peripheral neuropathy. The clinical judgment of the treating physician is required for test selection and the order in which tests are done. QSART=quantitative sudomotor axon reflex testing. QDIRT=quantitative direct and indirect testing of sudomotor function. *If structural and functional tests for an SFN are abnormal, the diagnosis is a clinically confirmed mixed large and small fibre neuropathy.

Microneurography, corneal confocal microscopy, and other measures are either for research purposes or still under development.

Conclusions and future directions

The SFNs are a group of neuropathies that affect small fibre function, such as pain, temperature sensation, and autonomic responses. Negative symptoms include numbness and sensory loss, and positive symptoms include pain, allodynia, and hyperalgesia. The onset can be in childhood or adulthood, and the presentation can be sporadic or familial. Metabolic, inflammatory, and neurotoxic conditions are common causes of SFN. Other causes include mutations in genes encoding ion channels and other inherited diseases. In clinical practice, diagnosis is based on clinical history, focused clinical examination, nerve conduction studies, skin biopsy, and functional assessment of small fibres with psychophysical and autonomic tests. Other tests, including corneal confocal microscopy and microneurography, might enter the SFN diagnostic toolbox in the future. Before a patient is started on disease-modifying therapies or symptomatic treatment for pain, a correct diagnosis is needed.

The research priorities for SFN are many. A gold standard for the diagnosis of the disorder is desperately needed, as are diagnostic biomarkers. Degeneration and regeneration are key elements in SFN pathology; however, it is unknown if peripheral pain generators can be identified in degenerating or regenerating axons and, if so, how this input will influence central processing mechanisms. Systematic studies of autonomic abnormalities in different patient populations of SFN are scarce. The detailed analysis of the molecular changes in ion channels and receptors in skin cells and nerve fibres, and their relationship with functional clinical findings are promising areas of research.

Contributors

TSJ coordinated the writing of the Review. AJT and PK did the literature research, wrote the first draft, prepared panels and figures, and finalised the manuscript. All authors contributed to the writing and revisions of the manuscript.

Declaration of interests

RF and TSJ have received personal fees from Pfizer outside the submitted work. All other authors declare no competing interests.

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