



Small fibre neuropathy

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Purpose of review

This review summarizes the most recent advances in classification, diagnostic assessment, and treatment of small fibre neuropathy (SFN).

Recent findings

Clinically based diagnostic criteria for SFN have been proposed and reliably supported by the recent availability of age-adjusted and sex-adjusted normative values for intraepidermal nerve fibre density. Apart from skin biopsy, corneal confocal microscopy and nociceptive evoked potentials have been implemented to investigate SFN of different causes, and correlated with skin biopsy findings, especially in diabetic patients. The association between SFN and several metabolic and immune-mediated systemic diseases, and drugs toxic to this subset of peripheral nerve fibres has been reported. An exciting advance has been the identification of gain-of-function mutations in the *SCN9A* gene encoding for Nav1.7 sodium channel in patients with SFN, leading to the definition of a new genetic channelopathy.

Summary

SFN represents a distinct condition encountered in patients with different acquired and genetic disorders. The recent improved definition of clinical and skin biopsy criteria allows clinicians to reliably meet the diagnosis, identify the underlying cause, and prescribe appropriate treatments. This meaningful approach permits the correct management of patients in clinical practice and the design of symptomatic and disease-modifying clinical trials.

Keywords

corneal microscopy, intraepidermal nerve fibres, painful neuropathy, skin biopsy, small fibre neuropathy

INTRODUCTION

Small nerve fibres have been traditionally considered invisible, as they could not be detected by routine nerve conduction study (NCS). This has led to the underestimation of small fibre neuropathy (SFN) as a distinct nosologic entity until this condition was fully recognized about two decades ago, after skin biopsy was introduced in clinical practice [1–3]. Indeed, the intrinsic limitations of micro-neurography, quantitative sensory testing (QST), and electron microscopy analysis of sural nerve biopsy relegated these techniques to research settings, population studies, or conditions in which more invasive examinations could be conceived.

As a matter of fact, the evolution of the concept of SFN and its introduction into the differential diagnoses of peripheral nervous system diseases have been intertwined with the development of skin biopsy. However, the dissemination and wide application of this technique led to scotomization of some of the limitations and, in particular, the need of proper normative reference values. As a consequence, the prevalence of SFN was likely overestimated in the absence of typical symptoms and signs,

and even in patients with typical risk factors such as diabetes and impaired glucose tolerance (IGT). On the other hand, in clinically well characterized patients, skin biopsy allowed confirmation of the diagnosis of SFN and identification of underlying causes, among which a genetic form has been recently recognized.

In the last few years, important advances have been achieved in the field of SFN, including diagnostic criteria, identification of conditions at risk, and development of neurophysiologic and noninvasive morphometric examinations, which provided further instruments to approach this

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KEY POINTS

- The field of SFN has been experiencing a phase of extraordinary development, particularly after the recent discovery of patients with sodium-channel mutations.
- The reappraisal of diagnostic criteria and the availability of normative reference values for skin biopsy allowed a more reliable management of patients in clinical practice.
- Noninvasive methods to examine healthy and damaged small nerve fibres, including corneal microscopy and nociceptive evoked potentials, have been implemented.
- Several acquired conditions have been recognized as potential causes of SFN, allowing disease-modifying treatments, which proved to be useful in some patients.
- Increasing knowledge about SFN has provided exciting hints on neuropathic pain, bridging functional changes in ion channel to structural axon degeneration, and the background for the development of personalized treatments.

peculiar neuropathy in clinical practice and research.

SMALL FIBRE NEUROPATHY

The approach based on the hypothesis that abnormal findings in one single test, either assessment of thermal thresholds, or analysis of polysynaptic nociceptive pathways through stimulation of skin nociceptors, or small nerve fibre morphometry in skin and cornea, could entirely support the diagnosis of SFN irrespective of the clinical status of patients did not contribute to the definition of this condition.

Diagnostic criteria

The recent reappraisal of the diagnostic criteria by the NeuroDiab expert panel [4] provided a clinically based definition that emphasized the need of symptoms and signs suggestive of SFN and the plausibility of their distribution. Accordingly, the diagnosis should be graded as follows: possible – presence of length-dependent symptoms and/or clinical signs of small fibre damage; probable – presence of length-dependent symptoms, clinical signs of small fibre damage, and normal sural NCS; and definite – presence of length-dependent symptoms, clinical signs of small fibre damage, normal sural NCS, and altered intraepidermal nerve fibre (IENF) density at the ankle and/or abnormal QST thermal thresholds at the foot.

These criteria were proposed for diabetic SFN, in which a length-dependent presentation of symptoms is expected. However, they should be applied in each patient with suspected SFN, independent of the underlying cause and including patients with non-length-dependent and focal symptoms.

Epidemiology

There are no studies providing conclusive data on the prevalence and incidence of SFN, and the diagnostic criteria used in the past were not narrow enough to permit retrospective analyses. Moreover, the frequency of SFN in case series was likely biased by selection criteria.

SFN has been considered to be particularly frequent among patients with diabetes, IGT, and connective tissue disease, although no epidemiological studies are available. In one study [5], the cause of SFN was attributed to diabetes and IGT in 6 and 42% of the patients formerly diagnosed with idiopathic SFN, respectively. In a larger case series [6], SFN was found in 25% of diabetic and 11% of IGT patients. One further study [7] reported that 50% of patients (three out of six) with IGT and 37.5% of patients with diabetes (nine out of 24) had definite SFN. These studies were performed using different diagnostic criteria and skin biopsy techniques and before the availability of age-adjusted and sex-adjusted normative reference values for IENF density. Therefore, they need to be confirmed. Indeed, the only prospective and controlled study in patients with idiopathic neuropathy [8], though not restricted to SFN, and another on patients with suspected sensory neuropathy [9] did not find any difference in the prevalence of IGT between patients and controls.

Presentation and clinical examination

SFN has been considered prototypical of painful neuropathy, and burning feet is the most common complaint reported. The quality of neuropathic pain may differ, though about 60% of patients described it as spontaneous (e.g., burning, sunburn-like, paroxysmal, pruritic, deep), with worsening at rest and during the night, sometimes associated with thermal evoked pain (cold or warm) and/or allodynia. Sensation of cold feet, although warm at touch, or legs constricted in thigh boots can be reported. Symptoms of restless legs syndrome can coexist. When neurological examination was focused to feet and soles, thermal and/or pinprick hypoesthesia was detected in 40% and hyperalgesia or after sensation in 10–20% of the patients [6]. Autonomic dysfunction mediated by skin cholinergic and vasomotor

fibres was reported to be more severe than that mediated by systemic adrenergic fibres, leading to more frequent vascular deregulation in lower limbs than cardiovascular autonomic impairment [6].

In most patients, SFN starts distally and shows a length-dependent course with later involvement of legs and hands. However, patients with diffuse and asymmetric symptoms suggesting sensory neuronopathy were described [10,11]. SFN has been suggested in patients with focal burning pain, such as notalgia [12] and burning mouth syndrome [13,14].

Questionnaires and scales

SFN Symptom Inventory Questionnaire (SFN-SIQ) is the only validated tool. This questionnaire includes 13 items, each having four response options: 0, never; 1, sometimes; 2, often; 3, always (Table 1). It allowed demonstration of a correlation between the number of symptoms and the loss of IENF in patients with sarcoidosis [15] and was used to identify SFN associated with *SCN9A* mutations [16].

As SFN is dominated by neuropathic pain, both spontaneous and evoked (allodynia and hyperalgesia) symptoms should be graded using the 11-point Likert pain scale or the visual analogue pain scale to verify the efficacy of analgesic treatments.

Aetiology

Pure SFN was described in association with several systemic diseases (Table 2) [17–45,46,47–52, 53,54–56,57]. However, many were anecdotal

reports, making a causal correlation rather doubtful. Diabetes and IGT are the most common conditions. In 20–40% of the patients, the metabolic dysfunction was identified after the diagnosis of SFN [6]. In diabetic patients, a rapid decrease in hyperglycaemia can cause a transient somatic and autonomic SFN [20]. SFN was advocated as a potential cause of microvascular dysregulation and neurogenic inflammation in the complex regional pain syndrome (CPRS) type 1 [50].

In amyloid-associated neuropathy, symptoms of SFN may dominate the clinical picture [53], although damage of large nerve fibres is most frequently identified [58,59]. In a series of 65 patients, only three were diagnosed with SFN based on normal NCS [60]. Similarly, chemotherapy-associated neuropathy can present with early symptoms reflecting SFN, but NCS almost invariably shows, with the exception of bortezomib in a small percentage of patients [29,30], the involvement of large sensory fibres. Also, paraneoplastic neuronopathies can be dominated by painful symptoms, but pure SFN has never been documented [46]. Early degeneration of small nerve fibres and correlation with neuropathic pain was described in Guillain-Barré syndrome [61], confirming previous observations in demyelinating neuropathies [62–64].

Among genetic diseases, somatic and autonomic SFNs characterize hereditary sensory neuropathy (HSAN) type IV, also known as congenital insensitivity to pain with anhidrosis [51]. About one decade after the first description of familial SFN cases [55,56], mutational analysis of the *SCN9A* gene encoding for the Nav1.7 subunit of sodium channel demonstrated single amino acid substitutions in about 30% of patients formerly diagnosed with idiopathic SFN [16]. All these variants produced distinct patterns of dorsal root ganglion (DRG) neuron hyperexcitability [65] compared with those typical of inherited erythromelalgia (IEM) and paroxysmal extreme pain disorder (PEPD) [66]. Phenotypic variability has been described, including acromesomelia (small hands and small feet) [35], features of IEM, PEDP, dysautonomia, and typical SFN [67,68] in patients harbouring same mutations. In a substantial proportion of patients, ranging from 25 to 90%, the cause of pure SFN remained unknown [6,69].

Pathogenesis

Despite the association of SFN with multiple acquired and genetic conditions, the pathogenesis underlying the degeneration of small fibres remains unknown. For example, diabetes and HIV reduce the ability of IENF to regenerate [70,71], suggesting an

Table 1. Small nerve fibre symptom inventory questionnaire (at least two are required) used for the screening of patients with suspected sarcoidosis and genetic sodium-channel associated small fibre neuropathy

Sensory	Autonomic
Peripheral pain (burning)	Sicca syndrome (dry mouth/eyes)
Paraesthesia	Accommodation disturbances
Allodynia	Hyperhydrosis/hypohydrosis
Diminished temperature sensation	Micturation disturbances
Diminished pain sensation	Impotence/diminished lubrication
	Gastroparesis
	Diarrhoea/constipation
	Facial flushing
	Orthostatic complaints
	Palpitations

Table 2. Acquired and genetic diseases associated with pure and predominantly somatic small fibre neuropathy, and most common distribution of symptoms and signs (length and non-length-dependent)

	Cause	Length-dependent	Non-length-dependent	References
Metabolic	Diabetes	+		[5,6,9,17–19]
	Impaired glucose tolerance	+		[5,6,9,17–19]
	Rapid glycaemia control in diabetes	+		[20]
	Hypothyroidism	+	+	[6,21–23]
	Vitamin B ₁₂ deficiency		+	[22]
Infectious disease	HIV	+		[24,25]
	Influenza		+	[26]
	Hepatitis C	+	+	[27]
Drugs and toxics	Antiretroviral drugs	+		[25]
	Metronidazole	+		[28]
	Bortezomib	+		[29,30]
	Statin	+		[31]
	Nitrofurantoin		+	[32]
	Flecainide	+		[33]
	Linezolid	+		[34,35]
	Chronic alcohol abuse	+		[36,37]
Immune-mediated	Celiac disease		+	[38]
	Sarcoidosis	+		[15,39]
	Sjögren's syndrome	+	+	[6,11,40–42]
	Systemic lupus erythematosus	+		[43,44]
	Rheumatoid arthritis		+	[10,42]
	Inflammatory bowel diseases	+	+	[10,45]
	Paraneoplastic syndrome	+	+	[46 [■]]
	Monoclonal gammopathy	+	+	[6,11,47–49]
	Complex regional pain syndrome type 1		+	[50]
Genetic	HSAN type IV		+	[51]
	Fabry's disease	+	+	[52]
	Familial amyloidosis	+		[53 [■]]
	Hemochromatosis	+		[54]
	Familial burning feet syndrome	+		[55,56]
	Sodium channel mutations (<i>SCN9A</i>)	+		[16 [■] ,57 [■]]
Idiopathic	Unknown	+	+	[6,10]

HSAN, hereditary sensory neuropathy.

impairment of axonal transport of which, however, there is no clue. Intriguingly, a rapid decrease in hyperglycaemia in diabetic patients can also induce the degeneration of somatic and autonomic skin fibres, followed by their recovery after metabolic stabilization [20].

Immune-mediated mechanisms were advocated for SFN associated with connective tissues disorders (e.g., sarcoidosis and Sjögren's syndrome) based on the response to immunoglobulin or immune-suppressant treatments in single patients or small case series [72–74]. However, this hypothesis has

neither been proven yet nor been replicated by serum transfection experiments in animal models.

Even the evidence that mutations in Nav1.7 cause DRG small neuron hyperexcitability cannot explain the degeneration of small nerve fibres. Sodium overload in neurons and axons might increase intracellular calcium, as sodium–calcium exchanger is co-localized with Nav1.7 [75], but this has not been proven yet. Moreover, it has not been possible thus far to define a correlation between phenotype, genotype, and cell electrophysiological changes.

Natural course

In a cohort of pure SFN [6], the cause was determined in 60% of patients. In particular, diabetes or IGT accounted for about 35% of cases, Sjögren's syndrome for 7%, and hypothyroidism for 5%, whereas SFN remained idiopathic in about 40%. At 2-year follow-up, diabetes or IGT was found in 20% of the patients formerly diagnosed with idiopathic SFN. About 10% of patients with first diagnosis of SFN showed a progression to a mixed (large and small fibre) neuropathy. In most patients with SFN, the clinical picture did not change over time, although about 30% of them experienced a worsening of neuropathic pain intensity.

INVESTIGATIONS IN SMALL FIBRE NEUROPATHY

SFN should be first considered as the complication of an underlying systemic disease and the diagnostic work-up should be directed at discovering it.

Laboratory tests

As diabetes is one of the most common causes of SFN, fasting glucose, glycosylated haemoglobin, and oral glucose tolerance test should be performed. Among immune-mediated disorders, Sjögren's syndrome, sarcoidosis, and celiac disease should be considered. Amyloidosis should be also suspected, mainly in patients with dysautonomia and cardiac and/or liver involvement. Fabry's disease is a rare condition including SFN; when suspected, protein assay and mutations in alpha-galactosidase gene should be searched for, also in female carriers who can develop an overt clinical picture. Screening of the *SCN9A* gene should be considered in patients with idiopathic SFN, especially if they have positive familial history.

Neurophysiologic studies

NCS should be normal in pure SFN. Abnormal findings in plantar sensory nerve recordings were reported in some patients [76], demonstrating the involvement of the most distal large myelinated fibres in some patients. Among nonconventional techniques, cutaneous silent period [77], laser-evoked potentials [78–80], contact heat-evoked potentials [34,81,82,83], pain-related evoked potentials [24,84], and intraepidermal electrical stimulation [85,86] have been used to investigate SFN patients. Different issues, including the lack of controlled studies, make these techniques nonspecific for diagnosing SFN in individual patients.

Microneurography allows single A δ and C fibre activity recording and significantly contributes to the knowledge on the physiology of nociceptors and the mechanisms underlying their sensitization [87,88], showing specific dysfunction in SFN [78–80].

Quantitative sensory testing

The assessment of the perception thresholds to warm, cold, and pain has been the most popular technique to investigate SFN. However, the expected correlation between cold and/or warm threshold and IENF density was found in some [89–93] but not all the studies [47,94,95]. Despite its widespread use, QST has some drawbacks that limit the reliability of results in individual patients, making it more useful in population studies [96,97].

QST has been used to investigate whether the individual pattern of signs and symptoms could provide a mechanism-based classification of neuropathic pain. The analysis of 13 QST parameters including measurements of negative (e.g., hypoesthesia) and positive (e.g., hyperesthesia) sensory thresholds performed in a cohort of 1236 neuropathic pain patients did not confirm this hypothesis [98]. Indeed, there was a remarkable phenotypic heterogeneity across the major neuropathic pain syndromes, which included an overlap between central and peripheral nervous system diseases. A further study [99] in two groups of patients with nerve injury with and without neuropathic pain did not find any difference except for a higher frequency of allodynia in the pain group.

These findings emphasized that QST can provide information on the nociceptive pathway functions in different painful conditions, including pure SFN, but needs to be used in a clinical context and along with other diagnostic tests.

Skin biopsy

In suspected SFN, biopsy should be taken 10 cm above the lateral malleolus within the territory of the sural nerve. IENF density proved to be the most reliable technique to diagnose SFN [6]. It correlated with the loss of pinprick sensation in idiopathic SFN [100] and both symptoms and quality of life in patients with sarcoidosis [15]. In HIV neuropathy, a baseline reduction in IENF density predicted the risk of developing neuropathy symptoms over a 2.9-year period, which was 14-fold higher in patients with a density lower than 10 IENF/mm [101].

Recent guidelines detailed the entire procedure [102]. The frequency of side effects was 1.9 : 1000 in

about 35 000 biopsies from 10 centres. The most common side effects were mild infection that recovered with topical antibiotic therapy, or excessive bleeding that did not require suturing. Normative reference values for IENF density at the distal leg based on the 5th percentile cut-off adjusted per age decade and sex are available for bright-field immunohistochemistry [103]. A novel method to measure dermal nerve length correlated with IENF density and demonstrated high performance in distinguishing SFN from healthy individuals [104[¶]]. New morphometric techniques for the quantification of sweat gland and pilomotor muscle innervation proved to correlate with autonomic dysfunction and validated scales in diabetic neuropathy [105,106].

Blister biopsy

Blister biopsy is based on the suction of the epidermis alone [107]. It does not cause bleeding, and there is no need of local anaesthesia. A comparative analysis of IENF density in healthy patients showed a good concordance with punch biopsy [108]. This technique allowed investigation of the clustering of IENF, which was suggested to be altered in diabetic neuropathy [109]. Normative reference values are needed before its use in clinical practice.

Corneal confocal microscopy

Corneal confocal microscopy has demonstrated *in vivo* the loss of trigeminal A δ and C fibres in diabetic, idiopathic, immune-mediated, chemotherapy, and Fabry's disease-associated neuropathy [110–114]. Patients with decreased corneal innervation also showed low IENF density. Patients with diabetic SFN demonstrated significant correlation between skin biopsy and neuropathy disability score [91]. However, this noninvasive technique has been used so far in relatively small groups of SFN patients and has not been compared yet with adjusted normative values, limiting its use for diagnosing individual patients in clinical practice.

TREATMENTS FOR SMALL FIBRE NEUROPATHY

Causative therapies, based on the treatment of the underlying disease (e.g., hypothyroidism), should be given whenever possible. In diabetes, the occurrence of transient somatic and autonomic SFN should be taken into account when a rapid correction of hyperglycaemia is achieved [20]. Steroids, immunosuppressants, or intravenous immunoglobulin may be considered in patients with evidence

of systemic immune-mediated diseases. Indeed, response has been reported in single patients or small case series of sarcoidosis and Sjögren's syndrome-associated SFN [72–74]. Conversely, there is no evidence of efficacy for these treatments in idiopathic SFN. In Fabry's disease, enzyme replacement therapy failed to induce the regeneration of IENF [115].

Most patients with SFN need treatments for neuropathic pain for which updated guidelines are available [116]. Evidence is based on studies in painful neuropathies of different cause, whereas no clinical trial was focused on SFN.

CONCLUSION

Important advances on SFN have been achieved in recent years. New diagnostic criteria and normative values for skin biopsy made the diagnostic approach more reliable in clinical practice and clearer for future trials. Other techniques, from corneal microscopy to nociceptive evoked potentials, have been developed and will contribute to the characterization of SFN. Several acquired and genetic diseases have been recognized among causes. In particular, mutations in *SCN9A* encoding for Nav1.7 sodium channel explained otherwise idiopathic SFN and will hopefully prompt studies with selective channel blockers for the therapy of neuropathic pain.

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None.

Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 643).

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