Small fibre neuropathy

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Purpose of review
To provide a review on the state-of-art of clinical features, diagnostics, genetics and treatments of small fibre neuropathy (SFN).

Recent findings
The spectrum of clinical features has been widened from the classical presentation of burning feet as length-dependent SFN to that of small fibre dysfunction and/or degeneration associated with focal, diffuse and episodic neuropathic pain syndromes. The involvement of small nerve fibres in neurodegenerative diseases has been further defined, challenging the relationship between neuropathic pain symptoms and small fibre loss. The clinical reliability of skin biopsy has been strengthened by the availability of normative values for both the immunohistochemistry techniques used and their comparison, and by side and short-term follow-up analyses. Corneal confocal microscopy has implemented its diagnostic potentiality because of the availability of age-adjusted and sex-adjusted normative values. Genetic studies expanded the panel on genes involved in SFN because of the discovery of new mutations in *SCN10A* and *SCN11A*, besides the first found in *SCN9A*, and identification of mutations in COL6A5 in patients with itching.

Summary
In the last 5 years, the chapter of SFN has been widened by new clinical and genetics descriptions leading to a more comprehensive approach to patients in clinical practice and research.

Keywords
confocal corneal microscopy, intraepidermal nerve fibres, painful neuropathy, quantitative sensory testing, quantitative sudomotor axon reflex test, skin biopsy, small fibre neuropathy

INTRODUCTION

Since the introduction of skin biopsy in neurologists' diagnostic toolbox and allowing a reliable and much easier quantification of unmyelinated C and thinly myelinated Aϑ fibres loss than possible with electron microscopy, including the distinction between fibres with somatic and autonomic functions [1], small fibre neuropathy (SFN) has entered the differential diagnosis of peripheral nervous system disorders dominated by painful disturbances. The disease has been traditionally considered occurring in adulthood, but onset may be in the infancy in genetic cases [2,3] and paediatric patients have been also reported [4▪].

SFN has been traditionally considered presenting with symptoms reflecting the length-dependent impairment of unmyelinated C and thinly myelinated Aϑ fibres, most commonly reported as burning feet. Its frequency has remained uncertain for two decades because of the lack of epidemiological studies conducted with well-defined diagnostic criteria. A recent survey in The Netherland [5], showing an incidence of about 12 cases/100 000 inhabitants/year and a prevalence of about 53 cases/100 000, provided data that, while partly answering this issue, need to be confirmed in other countries. However, new epidemiological studies will be able to provide conclusive information only when shared diagnostic criteria will be convincingly adopted.

The diagnostic criteria remain a matter of debate in the scientific community, although there has been an evolution from the first structured proposal [6] to one grading SFN as possible, probable and definite [7,8]. The use of strict criteria is important to narrow the conditions neurologists have to deal with in their clinical practice. One relevant question is if the diagnosis of SFN should be considered only in patients with pure impairment of unmyelinated C and thinly myelinated Aϑ fibres or it should

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KEY POINTS

- Skin biopsy and other noninvasive methods to examine small nerve fibres have been implemented, providing more reliable diagnostic opportunities for the clinical practice.
- New phenotypes have been included among the spectrum of SFN, supporting the diagnosis of chronic neuropathic pain in some previously unrecognized clinical syndromes.
- SFN has been convincingly demonstrated to be part of some neurodegenerative diseases.
- The classification of SFN has been widened to include further systemic disorders and acquired conditions, and new genes.

include also patients with predominant symptoms and signs of small fibre dysfunction having, however, a mixed small and large fibre sensory neuropathy. Indeed, after the syndromic diagnosis of SFN is made, investigations to address cause and follow-up are planned. The nosographic classification of SFN is therefore useful in the context of a work-up that aims ruling out known associated disorders. The adoption of criteria that define SFN if only small fibres are affected rather than when their impairment is part of a mixed neuropathy has a relevant impact on this work-up and can change the prognostic appraisal in individual patients. Considering the large number of acquired and genetic disorders causing peripheral neuropathies, it is clearly important defining what type of neuropathy the patient has for starting at the best of the current knowledge of the adequate work-up.

One of the most explicative examples is that of familial amyloid polyneuropathy (FAP) [9]. Amyloidosis is typically taken as a possible cause of SFN, but no study has convincingly demonstrated that pure SFN, namely in the absence of any other finding of large fibre sensory neuropathy, can be the feature of overt FAP. A recent study demonstrated that asymptomatic carriers of transthyretin (*TTR)* mutations could have a loss of small nerve fibres [10▪▪]. However, this finding, while suggesting that painless SFN may predict FAP in carriers of *TTR* mutations, does not answer the key question whether *TTR* gene sequencing should be required or not in all pure SFN patients. On the contrary, mutations in genes encoding for sodium channels, first identified in pure SFN patients [11], have been also found in patients with painful diabetic mixed neuropathy [12]. Therefore, the conceptual approach to the classification of SFN should take into account the different clinical background.

One further challenging issue is the definition of patients with nonlength-dependent distribution of symptoms and signs, such as those complaining of focal or diffuse pain. In these contexts, conclusive criteria could overcome the diagnostic difficulties of conditions like, for example, burning mouth syndrome, notalgia paraesthetica and fibromyalgia. Specular to this is the condition of patients with neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) [13▪], Parkinson's disease [14] and Pompe disease [15] a large percentage of whom show a painless loss of small nerve fibres, thus questioning the relationship between their degeneration and pain, and more widely the concept behind the diagnosis of SFN.

This article aims providing an updated review on the diagnostic challenges, criteria and clinical approach to patients with possible SFN, underlying causes and pathogenesis, and the state-of-art on usefulness and limitations of the currently available screening techniques. It is focused on the classical predominantly somatic form of SFN dominated by neuropathic pain, to which various degree of autonomic dysfunction can be associated. Therefore, it does treat in detail primary autonomic neuropathies and strictly related clinical features and examinations.

DIAGNOSTIC CRITERIA FOR THE CLINICAL PRACTICE

Patients with SFN are expected to have severe pain symptoms with little evidence of neuropathy at clinical examination and nerve conduction study (NCS). For this reason, the diagnosis may result difficult and, mainly in patients not afferent to referral centres, occur long time after the onset. Opinion of the authors is that the criteria developed by the NeuroDiab expert panel [7] for diabetic SFN can be extended in clinical practice to any patient. Indeed, these criteria are intended to grade the probability that a patient has SFN and, like for NCS, there is no reason why a specific cause can affect the diagnostic judgement.

The diagnosis of SFN is considered possible in patients complaining of length-dependent sensory symptoms and/or signs presenting as spontaneous (e.g. burning, deep, itching and paroxysmal) and/or evoked (e.g. thermal allodynia, light tough allodynia and hyperalgesia) pain. NCS is the first step of the diagnostic work-up and normal sural nerve action potential (SNAP) amplitude and conduction velocity findings, in the presence of the above clinical picture, are in support of a probable pure SFN. The diagnosis is definite when confirmatory tests such as skin biopsy at the ankle with intraepidermal

nerve fibre (IENF) quantification and/or quantitative sensory testing of thermal and nociceptive threshold are abnormal. The quantitative sudomotor axon reflex test (QSART) showed to increase the diagnostic yield of these criteria and should be included among the confirmatory examinations [16].

The first challenging issue is whether sensory NCS has to be normal or may be abnormal. The implication is not simply related to the academic distinction between pure and mixed SFN, but mainly to the consequent work-up approach to discover the underlying cause. Being it related to the clinical picture, the definition of the neuropathy is of extreme importance to narrow the examinations. For example, there is no evidence that pure SFN is part of the spectrum of paraneoplastic neurological disorders [17,18]. Although the diagnosis of pure SFN cannot exclude a malignancy [19▪], the probability that a patient has an occult neoplasm is lower than in a patient with painful mixed sensory neuronopathy. Therefore, diagnostic work-up and prognostic appraisal should be measured on this current knowledge. Moreover, NCS findings can be influenced by several variables, thus differently addressing the diagnosis. For example, oedema of the leg may result in low or not-recordable sural SNAP amplitude, temperature can inversely affect SNAP amplitude and conduction velocity and the technical approach may increase the probability to detect large sensory nerve fibre impairment. Indeed, some studies demonstrated the higher sensibility of orthodromic near-nerve recording of sural or more distal medial plantar or dorsal sural nerves rather than routine antidromic surface-recording in otherwise considered pure SFN patients [20▪,21]. Although distal sensory nerves might be not recordable in some patients due to causes other than neuropathy (e.g. chronic traumatisms of the feet), these electrophysiological findings suggest that a perspective assessment of SFN patients may be useful in classically pure SFN. Indeed, about 10% of pure idiopathic SFN progressed to mixed neuropathy at 2-year follow-up [6], a finding recently confirmed in a subgroup of five of 48 patients longitudinally assessed [22▪▪]. However, further studies are needed to figure out whether the impairment of distal sensory nerves in patients with normal sural NCS can predict the evolution of pure SFN to overt mixed sensory neuropathies and increase the probability to identify specific causes. Opinion of the authors is that pure SFN should be classified as a separate entity and that antidromic surface-recording of sural nerve should be considered the gold standard to rule out large sensory fibre impairment and define in clinical practice the diagnosis. However, an international consensus on sural SNAP amplitude normal lower cut-off values in the different age decades should be achieved besides the normative reference that each laboratory has to develop, in order to move towards a homogenous definition of pure SFN.

The second challenging issue regards the distribution of symptoms that, based on the above criteria, would make SFN possible. Traditionally, SFN has been considered when patients complained of length-dependent symptoms, most typically burning feet [23]. In the last few years, evidence in favour of SFN in patients with diffuse, nonlength-dependent symptoms and signs of neuropathic pain and diagnosed with ganglionopathy [24▪], fibromyalgia [25–27] or Ehlers–Danlos syndrome [28▪▪] have been provided. Moreover, small fibre degeneration has been confirmed [29▪,30▪] in patients with burning mouth syndrome [31], a condition in which the clinical assessment of the distribution of pain can help addressing the diagnostic suspicion [32]. Similarly, focal degeneration of small nerve fibres has been found in notalgia paraesthetica [33], a condition of unknown pathogenesis causing intense pain and itching in a small area of the back [34▪]. On the basis of these data, opinion of the authors is that the same diagnostic approach and criteria used for possible length-dependent SFN should be applied in patients with diffuse or focal symptoms of possible SFN, which should be considered different presentations of the disorder.

The third challenging issue is the nosographic classification of asymptomatic SFN associated with neurodegenerative disorders. On the basis of skin biopsy results, up to 75% of patients with ALS or Parkinson's disease [13▪,14] could be diagnosed with SFN. However, the assessments have been primarily performed to address research hypotheses rather than clinical questions. Indeed, most of these patients did not complain of symptoms clearly suggesting neuropathic pain as defined by consensus criteria [35,36▪]. Opinion of the authors, based on available data, is that painless patients with neurodegenerative disease should not be candidate to SFN-specific diagnostic work-up, and skin biopsy should be considered in clinical practice when further studies will demonstrate the relevance of small nerve fibre loss in these disorders, for example as proxy of presymptomatic stage or phenotypic subgroups.

ACCEPTED CONFIRMATORY DIAGNOSTIC EXAMINATIONS

Skin biopsy

This technique, available for about 20 years, can provide a reliable quantification of somatic and

autonomic small nerve fibres using both bright-field immunohistochemistry (BFI) and indirect immunofluorescence approaches. For both, age-adjusted and sex-adjusted normative reference values of IENF density are available, allowing the diagnosis of SFN in individual patients [37,38▪▪]. Normative values are now available for children also [39]. BFI and immunofluorescence have high agreement and comparable diagnostic validity [40]. An innovative semiautomated method showed high reproducibility in IENF counting [41▪]. Furthermore, one study demonstrated that the direct observation with epifluorescence microscopy is reliable as the more time-consuming analysis of IENF density by three-dimensional digital images acquired with confocal immunofluorescence microscope, thus increasing the feasibility of this approach [42].

The reliability of skin biopsy has been strengthened by the evidence that the value of IENF density is consistent comparing biopsies taken from right and left ankle both in healthy individuals and SFN patients, and that it is stable at 3-week follow-up, which is the mean time of epidermal renewal [43]. These information further emphasize that skin biopsy can be considered a reliable tool if IENF density is chosen as outcome measure in a clinical trial testing neuroregenerative drugs. Normative values are provided as 5th centile, but the diagnostic judgement should be cautious when values very close to the cut-off (e.g. ± 1 IENF) are found and a follow-up biopsy, in agreement with the clinical course, should be considered. In these cases, the quantification of IENF swellings, which have been suggested to represent predegenerative changes predicting the loss of fibres [44], might be of help. Indeed, more recent studies have confirmed these early observations, showing an increasing ratio of IENF swellings from healthy individuals to diabetic patients without neuropathy and diabetic patients with overt neuropathy [45].

The quantification of dermal nerve fibres can differentiate healthy individuals from SFN patients [46] and a stereological reappraisal of the manual assessment has confirmed its reliability [47]. However, the analysis of dermal nerves has not entered yet the routine assessment of skin biopsies and further studies should be designed to define the relationship between dermal nerve density, diagnosis of SFN and prognosis.

Finally, small nerve fibres with autonomic functions innervating skin structures, such as sweat glands, arrector pilomotor muscles and vessels, can be measured by morphometric approaches [48▪]. While widening the spectrum of applications of skin biopsy in the field of autonomic neuropathies, further studies are warranted to investigate whether the denervation of autonomic organs in the skin may predict major outcomes such as symptomatic orthostatic hypotension, neurogenic arrhythmias and sudden cardiac death.

Quantitative sensory testing

It is used to determine the functional impairment of small nerve fibres by measuring warmth, cooling and pain thresholds through noninvasive psychophysical tests. Quantitative sensory testing (QST) can assess both gain and loss of function phenomena related to the clinical features of neuropathic pain. However, this technique suffers from the variability of instruments and methodological approaches for location, stimulus application and sensation qualities examined, challenging its reliability in diagnosing individual patients [49].

Applications, interpretation of results and limitations have been summarized by a consensus paper [50]. While confirming its utility for the diagnosis of sensory neuropathies, particularly diabetic and SFN, the consensus emphasized that QST is not recommended as a stand-alone examination for diagnosing neuropathic pain, that predefined methodology, validated algorithms and reference values adjusted for anatomical site, age and sex should be used, that patients' mood and cognitive settings could make the results not reliable and that the results should be interpreted considering the clinical context. A study demonstrated that temperature threshold assessment could be optimized using the method of levels achieving a good discriminatory ability for diagnosing SFN [51]. Most recently, QST performed by the cluster analysis of 13 quantitative sensory profiles has been used to stratify a test cohort of 902 and a validation cohort of 233 neuropathic pain patients into three subgroups defined as sensory loss (42%) showing small and large fibre function impairment and paradoxical heat sensations, thermal hyperalgesia (33%) showing normal sensory functions with heat and/or cold hyperalgesia and/or mild dynamic mechanical allodynia and mechanical hyperalgesia (24%) showing small fibre impairment with pinprick hyperalgesia and dynamic mechanical allodynia [52▪▪].

Thus, using appropriate standards, QST can provide reliable data regarding small and large nerve fibre functioning as a complementary assessment to other diagnostic tests, and also identify the somatosensory profile of patients. New studies are needed to define whether clustering patients into distinct subgroups potentially reflecting different underlying pathophysiological backgrounds can concretely help in personalizing symptomatic treatments.

OTHER USEFUL DIAGNOSTIC EXAMINATIONS

Quantitative sudomotor axon reflex test

This technique assesses the integrity of postganglionic sympathetic cholinergic sudomotor nerves through the iontophoresis of acetylcholine that stimulates cutaneous unmyelinated C-fibres, and sweating quantified by a sudorometer. When abnormal QSART findings were associated with local autonomic symptoms, the technique allowed increasing the diagnostic yield for SFN based on skin biopsy and QST [16]. Normative data should be developed to allow the use of QSART in clinical practice.

Corneal confocal microscopy

Recent studies have strengthened the use of this noninvasive and repeatable technique that rapidly evolved from a predominantly research application to a clinical tool [53] that has been already applied to neuropathies of several causes [54–63]. Automated analysis of corneal nerve images [64–67] and the development of normative values [68] have made corneal confocal microscopy (CCM) more reliable for diagnosing SFN. Moreover, CCM showed a good agreement with skin biopsy in SFN [69] and was successfully used to investigate nerve fibre regeneration in diabetic patients [70] and after pancreas transplantation [71,72], suggesting a potential use as outcome measure in clinical trials. However, a recent study [73▪▪] comparing randomized and manual sampling method of corneal nerve fibre length density and branch density suggested that values should be adjusted to cornea area and emphasized the importance of improving and better standardizing the analysis of the CCM images to obtain more objective corneal nerve fibre measurements.

CAUSE AND LABORATORY SCREENING

Several causes can underlie SFN, some of which potentially treatable [74]. Potential causes should be ruled out before SFN is defined as idiopathic. However, the clinical context should be always taken into account in order to appropriately address the laboratory screening. We propose a nosographic classification of SFN based on four main categories: acquired, hereditary, syndromic and idiopathic (Table 1) [2,3,6–9,10▪▪,11,12,13▪,14,15,24▪,25,27,28▪▪,54,57,60,75,76▪▪,77–81,82▪,83–102,103,104▪▪,105▪▪,106–108,109▪–111▪,112].

Acquired small fibre neuropathy

Diabetes and impaired glucose tolerance (IGT) are the leading causes among acquired conditions. Diabetes is responsible for about 20% of cases of SFN [6] and the frequency rises to 56% if prediabetes conditions with impaired oral glucose tolerance test (OGTT) are included [75]. Neuropathy is milder in patients with IGT than in patients with diabetes [75,113], suggesting that OGTT can enhance the diagnostic sensitivity in otherwise considered idiopathic SFN [76▪▪]. In diabetic patients, a rapid glycaemic control may be responsible of an acute somatic and autonomic treatment-induced neuropathy, formerly known as 'insulinic neuropathy', whose severity correlates with the magnitude and rate of HbA1c reduction [77].

There is a raising interest in metabolic syndrome as a possible cause of SFN, based on studies suggesting a high incidence [78]. More recently, a direct correlation between triglycerides levels and impairment of SFN function was demonstrated in normoglycaemic individuals [114]. This evidence, in addition to the little effect that glucose-lowering therapies have on the prevention of polyneuropathy in patients with type 2 diabetes [115], suggests a possible additional role of hyperlipidaemia or other metabolic syndrome components in the pathogenesis of SFN.

Among infectious disease, the only strong association is with HIV [79], whereas that with hepatitis C is weak and based on anecdotal reports [80,81]. The lack of brain–blood barrier at level of dorsal root ganglia and the selective vulnerability of small nerve size in some patients might explain the occurrence of SFN after the exposure to neurotoxic drugs. Nevertheless, in most of the cases, the association was based on small case series or anecdotal reports, thus making the causal correlation between SFN and antibiotics (e.g. metronidazole, nitrofurantoin and linezolid) [83–88], statin [89,90], heavy metals (e.g. thallium), chemotherapics and immunemediate drugs (e.g. bortezomib and tumour necrosis factor inhibitors) [91,92] and alcohol [93–95] quite weak.

Hereditary small fibre neuropathy

This subgroup of SFN has emerged after the discovery of gain-of-function mutations in *SCN9A* encoding for the Nav1.7 α-subunit [11]. In the following few years, gain-of-function mutations in *SCN10A* and *SCN11A* encoding for the Nav1.8 [12] and Nav1.9 [103,116] α-subunit have been described in SFN patients. The pathogenicity of these mutations has been assessed by current and voltage-clamp electrophysiological studies that can demonstrate the changes in nociceptor and autonomic neuron membrane excitability and biophysical properties of the sodium channels [117] and correlate with the clinical picture [118]. A recent work

Table 1. Causes of small fibre neuropathy

Causes of pure SFN		References
ACQUIRED		
Metabolic	**Diabetes and IGT**	[7,8,54,57,75,76▪▪]
	Hypothyroidism	[76▪▪,112]
	Folate deficiency	[76▪▪]
	Vitamin B_{12} deficiency	[76▪▪]
	Treatment-induced in diabetes	[77]
	Metabolic syndrome	[78]
Infectious	**HIV**	[79]
	Hepatitis C	[80,81]
	Chagas disease	[82▪]
Drugs and toxins	**Metronidazole**	[83–85]
	Nitrofurantoin	[86]
	Linezolid	[87,88]
	Statins	[89,90]
	Bortezomib	[91]
	TNF inibitor	[92]
	Alcohol	[93–95]
	Thallium	[96,97]
Immune-mediated	**Sjogren's syndrome**	[24▪]
	Celiac disease	[76▪▪,82▪]
	Sarcoidosis	[98]
	Systemic lupus erythematosus	[99,100]
	Inflammatory bowel diseases	[101]
	Monoclonal gammopathy	[102]
HEREDITARY	**Sodium channelopathies (SCN9A; SCN10A; SCN11A)**	[2,3,11,12,103,104▪▪]
	Familial amyloidosis	[9,10▪▪]
	Fabry disease	[60]
	COL6A5 mutations	[105▪▪]
SYNDROMIC	**Fibromyalgia**	[25,27,106–108]
	Elhers–Danlos syndrome	[28▪▪]
	Parkinson's disease	[14,109▪,110▪]
	Amyotrophic lateral sclerosis	[13▪,111▪]
	Pompe disease	[15]
IDIOPATHIC	**Unknown**	[6]

In bold, well-established causes of SFN by studies with exhaustive number of patients and pathological evidence. The remaining causes refer to anecdotal reports, small case series or patients with SFN as part of a mixed sensory neuropathy.
IGT, impaired glucose tolerance; SFN, small fibre neuropathy; TNF, tumor necrosis factor.

examining how pathogenic *SCN9A* mutations altered the interatomic bonds and caused rearrangement of the molecular connectivity identified an in-silico marker able to differentiate pathogenic Nav1.7 variants from benign variants and polymorphisms with 76% sensitivity and 83% specificity [104▪▪]. This finding might implement the pipeline for the choice of candidate variants to undergo cell electrophysiology assays, which are costly and time-consuming. Phenotype–genotype associations and recommendation for the diagnostic approach to sodium channel-related SFN have been published to better address the clinical practice [2].

Sodium channel-related SFN can onset in the childhood, adolescence or adulthood and either sporadic or familial cases have been identified. The clinical picture is most commonly characterized by burning feet, but single mutations can cause different phenotypes and cell electrophysiological changes [119]. The phenotypic variability has been further widened by the description of painful and autonomic SFN in a family with acromesomelia

[120]. The mechanism leading to the preferential degeneration of small nerve fibres in sodium channel gene mutations is thought to involve the altered functioning of the sodium-calcium exchanger causing increased intracellular calcium levels [121,122▪]. Although other genes encoding for ion channels are expected to be identified in SFN patients, mutations in *COL6A5* have been first described in familial and sporadic patients with neurogenic itch and SFN [105▪▪].

Early degeneration of small nerve fibres has been documented in the presymptomatic stage of patients carrying *TTR* mutations [10▪▪], whereas in the symptomatic stage of familial amyloid neuropathy patients more likely present a mixed neuropathy [123▪▪].

Fabry disease is a prototypical example in which SFN is a common adjunctive feature of a genetic disorder, and it has been typically included among the conditions to rule out in idiopathic cases. Recent study on adult patients demonstrated that the association is extremely low and therefore genetic sequencing and protein-level assay should be considered only if other clinical features of the disease are present [124▪,125▪].

Syndromic small fibre neuropathy

Loss or dysfunction of small nerve fibres has been assessed in patients with clinical picture or diagnosis different from classical SFN as defined by the above-described criteria. Among them, patients with diffuse pain like fibromyalgia have been investigated and small fibre impairment has been detected by skin biopsy [25,106], microneurography [26], laser evoked potentials [27] and CCM [107] studies in about 40% of fibromyalgia patients [108]. In fibromyalgia patients, an RNA signature correlating with small nerve fibre loss has also been identified [126].

Ehlers–Danlos syndrome is a further condition characterized by recurrent and migratory arthralgias in childhood with a slow progression towards widespread chronic pain symptoms in adulthood [127]. A clinical and skin biopsy study has described the loss of small nerve fibres in a cohort of 25 patients irrespective of the phenotype and genotype, suggesting that SFN is part of the clinical picture and might be responsible for chronic pain [28▪▪]. However, the pathophysiological correlation between small nerve fibre loss and diffuse pain remains unanswered, although mechanisms of abnormally enhanced nociceptive response in the central nervous system, known as central sensitization [128], might be involved.

SFN was also described in patients with neurodegenerative diseases not primarily characterized by neuropathic pain, such as Parkinson's disease [14,109▪,125▪,129], ALS [13▪,111▪,130] and Pompe disease [15]. In Parkinson's disease, a possible toxic effect of levodopa on small nerve fibres has been hypothesized [110▪], whereas the accumulation of a splicing variant of peripherin has been demonstrated to cause the selective degeneration of small size dorsal root ganglion neuron in ALS mouse models, thus providing a biological explanation for SFN in patients [131▪▪].

Idiopathic small fibre neuropathy

This diagnosis is made when, after the diagnostic work-up, no evident cause has emerged. An early study reported a prevalence of about 31% of idiopathic cases among pure SFN patients at 2-year follow-up [6]. No further studies have been designed to address this issue and the only recent prospective work provided the same prevalence including all neuropathy cases and not SFN alone [82▪]. A recent retrospective study [76▪▪] reported the probability of about 45% to have at least one abnormal result among erythrocyte sedimentation rate, antinuclear antibodies, low C3, thyroid-stimulating hormone and autoantibodies for Sjögren's and celiac syndromes, or elevated angiotensin-converting enzyme had a probability of about 45% to be abnormal. It did not find a different percentage of individuals with low vitamin B_{12} comparing SFN patients and the general population, whereas folate deficiency was reported to have a stronger association. However, the study did not use standardized diagnostic criteria and results provided were not stratified by pure SFN and mixed neuropathy.

CONCLUSION

In the last 5 years, advances in the methodological and technical approaches to the assessment of small nerve fibre damage and dysfunction have contributed in making more reliable the diagnosis of SFN in clinical practice and clinical research. Advances in the conceptual approach to SFN widened the spectrum of clinical presentation, leading to the inclusion of new phenotypes, the association with further systemic disorders and the discovery of new causes. Among them, mutations in new genes have been recognized, expanding the diagnostic work-up mainly in idiopathic SFN and prompting new targeted clinical trials for neuropathic pain.

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Conflicts of interest

The authors have no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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