Chapter 6

Small fiber neuropathy: a disabling and underrecognized syndrome

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Abstract

Purpose of review

To discuss cause, clinical manifestations, diagnostics, and treatment of small fiber neuropathy (SFN). The diagnosis is difficult and can be easily missed.

Recent findings

SFN causes high morbidity with disabling symptoms and impact on quality of life. Patients may benefit from being diagnosed with SFN, even if no underlying cause is identified and no specific treatment is yet available. Recently, genetic mutations as a possible cause of SFN were identified. Clinical diagnostic criteria have been proposed, but no gold standard exists, and each test has its limitations. The diagnosis requires a combination of typical symptoms, abnormal neurologic findings, and absence of large fiber involvement. Clinicians should be aware of overlapping symptoms of SFN and fibromyalgia. Treatment is often difficult, even when the underlying cause is identified and appropriately treated. Usually, only symptomatic relief of complaints is available.

Summary

Awareness of SFN and related symptoms is of great clinical relevance. Guidelines for appropriate diagnostic workup using a stepwise approach involving a combination of tests are warranted. Even if no treatment is available, patients may benefit from timely recognition of SFN.

Introduction

Peripheral neuropathies can be subdivided into large-fiber neuropathy and small fiber neuropathy (SFN). When large fibers or (more commonly) a combination of large and small fibers are involved, the term polyneuropathy is used, whereas isolated involvement of small fibers is generally referred to as SFN. SFN is a generalized sensory nerve disorder with structural and functional abnormalities of small fibers, characterized histopathological by degeneration of small fiber nerve endings.
Due to lack of awareness among clinical physicians, the diagnosis of SFN is probably highly underreported. In the Netherlands, a minimum estimated incidence of 12 per 100 000 population and a prevalence of 53 per 100 000 population have been reported, but even this systematic assessment underestimated the incidence and prevalence.[1]
The diagnosis of SFN may be difficult because a diagnostic gold standard is lacking. The diagnosis is mostly made on the basis of the presence of characteristic clinical features in combination with abnormalities on neurophysiological tests and/or reduced numbers of small fibers in skin biopsy. SFN is often idiopathic or it can be an epiphenomenon in many diseases, including sarcoidosis. Treatment is often difficult, even when the underlying cause is identified. Symptomatic treatment is available, but its effectiveness is limited to a subgroup of patients with SFN. Here, we discuss the cause, clinical manifestations, diagnostics, and treatment of SFN, with special emphasis on SFN in patients with sarcoidosis.

Pathophysiology

The histopathology of SFN is characterized by denervation of the thin myelinated Aδ- and unmyelinated C-fibers.[2] As these fibers perceive thermal and nociceptive (somatic) sensations and have autonomic function, denervation results in symptoms of neuropathic pain and autonomic dysfunction.[3] Morphologic changes within the axons can also be found.[4] The exact pathophysiological mechanisms are often unknown and depend on the underlying illnesses associated with SFN, such as metabolic, infectious, inflammatory, and genetic diseases (Table 6.1). More recently, hereditary SFN has been described with pathogenic mutations in sodium channels (Nav1.7 (mostly), Nav1.8 and Nav1.9) which lead to hyperexcitability of dorsal root ganglions. These gain-of-function mutations result in degeneration of small fibers.[12,13,14*]

Table 6.1 Causes of small fiber neuropathy.

Primary	Secondary
idiopathic small fiber neuropathy	*metabolic*
	diabetes mellitus[5-7,8*,9-11]
hereditary	impaired glucose tolerance[6,7,8*,9,10]
mutations in sodium channels (Nav1.7, Nav1.8, Nav1.9)[12,13,14*]	hypothyroidism[5-7,10]
	vitamin B1, B6 and B12 deficiency[6,8*,10]
hereditary sensory neuropathy[8*,15]	hyperlipidemia[18]
Fabry's disease[16,17]	*infectious*
familial amyloid polyneuropathy[19]	HIV[22-24]
Wilson's disease[20,21]	hepatitis C[7,9]
	Lyme disease[6,8*]
	toxic
	neurotoxic drugs[7,8*,9,24]
	alcohol[5,9,25]
	immune-mediated
	rheumatic diseases[6,7,9,26,27]
	Celiac disease[6,7,28]
	Crohn's disease[6,9]
	sarcoidosis[10,29,30]
	vasculitis[8*]
	fibromyalgia[31*,32]
	amyloidosis[8*,33]
	monoclonal gammopathy of unknown significance[7,8*,10]
	multiple Myeloma[33]
	acute inflammatory demyelinating polyradiculoneuropathy[7,34]
	chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)[8*,35]
	Parkinson's disease[36,37]
	amyotrophic lateral sclerosis (ALS)[38,39]
	Ehlers-Danlos[40]

The pathophysiology depends on the underlying disease. In diabetes and impaired glucose tolerance, the cause is multifactorial and includes hyperglycemia, oxidative stress, ischemia, and hypoxia.[41,42] In addition, direct neurotoxic effects (HIV, chemotherapy, retroviral drugs, and alcohol) can lead to axon loss, resulting in SFN.[22,23,42]

In other diseases (immune-mediated diseases, sarcoidosis) inflammatory mediators, such as interleukin beta (IL1-β), IL6 and IL8, and tumour necrosis factor alpha (TNF-α) concentrations were found to be elevated in SFN patients, suggesting an important role.[22,23,41,43] IL1-β and TNF-α are also known to reduce mechanical nociceptive thresholds[44,45] and have been found in higher concentrations in distal skin biopsies of patients with length-dependent SFN.[43] Moreover, TNF-α inhibition has been reported to reduce SFN symptoms in a patient with sarcoidosis.[46] TNF-α also plays a role in other immune-mediated neuropathies like acute inflammatory demyelinating polyradiculo-

neuropathy,[47] in which a positive correlation was found between serum levels of TNF-α and the severity of neuropathy.

Establishing a caused-based diagnosis is important for patients with SFN, as the underlying cause may need additional treatment and can influence prognosis. For example, patients with diabetes need to be treated with oral antidiabetics or insulin to alleviate and prevent other complications of the disease. However, despite a thorough workup, the proportion of patients with idiopathic SFN remains substantial, ranging from 23 up to 47%.[5,7]

Symptoms

Symptoms of SFN can vary widely in terms of distribution, severity, and progression. Usually, SFN is length-dependent, resulting in loss of function starting distally in the lower extremities. However, in some cases, it can be nonlength-dependent, resulting in a patchy distribution across the upper extremities, face, trunk, or other focal areas.[3] Nonlength-dependent SFN seems to be more prevalent in autoimmune and inflammatory diseases.[10] In addition, recent evidence suggests that SFN is a nonlength-dependent distal axonopathy, even in patients with a length-dependent clinical presentation.[48] When small somatic fibers are affected, patients experience neuropathic pain that can be burning, deep or electric shock-like but can also have a pruritic component.[49] Pain is usually continuous and stimulus-independent. However, some patients complain of evoked pain, such as allodynia, leading to intolerance of bedsheets and clothing or warm water.[50] Paraesthesia, hyperesthesia, numbness, and diminished discrimination of heat and cold can also occur (Table 6.2). Patients report that symptoms worsen during rest and at night, affecting sleep, and sometimes resembling symptoms of Restless Legs Syndrome.[2] The most frequent symptom of autonomic dysfunction is probably vasomotor dysregulation, presenting with fluctuating purple/blue discoloration of hands and feet.[27] Other symptoms of autonomic dysfunction are gastrointestinal and urinary complaints, abnormal sweating, sicca symptoms, sexual dysfunction, arrhythmias, and (pre)syncope (see Table 6.2). It has previously been identified as a strong predictor of morbidity and mortality.[53,54] Alternatively, symptoms, such as gait instability or weakness, suggest involvement of large fibers. SFN has substantial effects on patients' quality of life (QoL).[55]

Sarcoidosis patients with muscle and/or joint pain are often referred to a rheumatologist. If no underlying rheumatic disorder is found, the symptoms are generally associated with fibromyalgia, whereas SFN is not considered. As fibromyalgia symptoms are partially similar to those of SFN, different diagnosis (fibromyalgia or SFN)

may be established, depending on the consulting clinician (rheumatologist or neurologist). To date, functional deficits of small fibers, as commonly found in SFN, have also been detected in patients with fibromyalgia.[31*,56] Some patients with chronic pain labelled as 'fibromyalgia' may in fact have unrecognized SFN.[52]

Table 6.2 Symptoms of small fiber neuropathy, fibromyalgia, and peripheral large fiber polyneuropathy.

	SFN	Fibromyalgia	Large fiber polyneuropathy*
neuropathic pain	+	+	+
paraesthesia	+	+	+
allodynia (sheet intolerance)	+	+	+
restless legs	+	+	+
abnormal warm and cold sensation thresholds	+	-	+
weakness	-	-	+
impaired balance	-	-	+
autonomic dysfunction			
hypo- or hyperhidrosis	+	-	-
defecation disturbances: diarrhea or constipation	+	+	-
gastroparesis	+	-	-
micturition disturbances	+	+	-
sicca symptoms (dry eyes and/or dry mouth)	+	+	-
blurry vision; accommodation problems	+	-	-
hot flushes	+	-	-
orthostatic dizziness	+	+	-
sexual dysfunction	+	+	-
cardiac palpitations/(pre)syncope	+	+	-
general			
fatigue	+	+	+
waking up unrefreshed	-	+	-
cognitive disturbances	-	+	-
widespread musculoskeletal pain	-	+	-
headache	-	+	
temporomandibular disorder	-	+	-

*Polyneuropathy often involves large and small fibers leading to combination of symptoms. Adapted from.[32,50-52]

Diagnosis of small fiber neuropathy

The diagnosis of SFN is complicated by the lack of a gold standard. Various diseases that should be considered in the differential diagnosis, include polyneuropathy (large fiber neuropathy with or without SFN) and fibromyalgia (Table 6.2). Nerve conduction studies (NCS) are performed as the first diagnostic test to exclude large-fiber disorders. If NCS findings are normal, further diagnostic work-up is needed, although some argue that a typical clinical picture and a known cause of SFN might be sufficient.

Several diagnostic criteria have been proposed for diagnosing SFN,[7,57,58] combining clinical symptoms, abnormalities in neurological examinations, and abnormal neurophysiological test results (discussed below) or skin biopsy. These criteria enable possible, probable, or definite SFN to be diagnosed. Nevertheless, further studies are warranted to confirm the usefulness of these criteria. No final set of well-defined SFN criteria is as yet available. However, patients often benefit from a diagnosis of SFN, even if no underlying cause is identified and no specific treatment is available.
Various diagnostic tests are available for the assessment of SFN, which have mostly been validated in patients with diabetes and idiopathic SFN (Table 6.3).

Small fiber neuropathy screening list

An SFN screening tool has been developed for patients with sarcoidosis, called the SFN screening list (SFNSL),[85] which was intended as a first attempt to achieve early identification of patients with symptoms related to SFN. The SFNSL consists of 21 questions (total score range 0-84). A score of less than 11 is considered indicative of a normal temperature threshold testing (TTT), while a cut-off of more than 48 is considered indicative of an abnormal TTT, indicating SFN. However, a substantial proportion of patients and controls are found to be in the intermediate group (score 11-48).

Skin wrinkling test

Skin wrinkling results from vasoconstriction controlled by the sympathetic nervous system.[62,85,86*] This is a simple test using warm water, a eutectic mixture of local anaesthetics or Neuropads.[59,61]

Quantitative sensory testing

Quantitative sensory testing is a frequently used technique involving exposure to different types of mechanical and thermal stimuli. It includes TTT, which has the highest sensitivity (Table 6.3), but mechanical detection thresholds, thermal and mechanical pain thresholds can also be tested in SFN.[64,69*] It is an easy, non-invasive but time consuming method.

Table 6.3 Diagnostic tests in small fiber neuropathy.

Diagnostic test	Sensitivity	Specificity	Limitation	Sarcoidosis
SFNSL score <11	100%	31%	only validated in sarcoidosis	+
SFNSL score >48	19%	100%		
Skin wrinkling[59-62]	66-82%	67-75%	training of staff necessary, no correlation with IENFD, poor NPV	no research available
QST (mainly TTT)[7,63-67]	57-93% TTT: 84%[63]	37-94% TTT:94%[63]	requires conscious integration of patients, difficult to distinguish between faked and true loss of sensation, central and peripheral nervous system abnormalities can lead to same deficit	sensitivity TTT 69%; abnormalities feet vs. hands (54% vs. 38%), 15% both[64]
LEP/CHEP/PREP[68-72,73**]	64-94%	69-87%	abnormal test not only small fibers (entire nociceptive pathway), seasonal differences in heat conductivity in CHEP (less reliable outcome), limited availability and needs well-trained staff	no research available
Skin biopsy/IENFD[7,29,74,75]	33-90% Pure SFN: >90%[2,74]	58-95% Pure SFN: >90%[2,74]	requires training, limited availability/not generally distributed (only a few centers), unclear in case of patchy disease, time consuming	sensitivity of 32.8% with age-dependent decrease (men <women)[29]
CCM/CNFD[76*,77*,78,79]	50-86%	52-84%	not widely available, high acquisition costs, uncertainties about age-related decline and racial differences in corneal nerve measurements	50% reduction in corneal nerve fibers in painful SFN compared to healthy controls[77*]
Autonomic function				
CAFT	low			abnormal in only 12.5% of SSFN patients[80]
QSART[66,81,82]	59-80%	-		no research available on QSART or sudoscan. SSR abnormal in <10% of SSFN[64]
Sudoscan[83,84]	65-78%	80-92%		
MIBG-scan			no standardized methodology or normative values, discontinuation of some drugs is needed	>50% involvement cardiac autonomic dysfunction[80]

CAFT=cardiovascular autonomic testing; CCM=corneal confocal microscopy; CHEP=contact heat-evoked potential; CNFD=corneal nerve-fiber density; IENFD=intraepidermal nerve fiber density; LEP=laser-evoked potential; MIBG-scan=metaiodobenzylguanidine-scan; NPV=negative predictive value; PREP=pain-related evoked potential; QSART=quantitative sudomotor axon reflex test; QST=quantitative sensory testing; SFNSL=small fiber neuropathy screening list; SSFN=sarcoidosis small fiber neuropathy; TTT=temperature threshold test.

Nociceptive-evoked potentials

Nociceptive-evoked potentials include laser-evoked potential (LEP), contact heat-evoked potential (CHEP), and pain-related evoked potential (PREP). Both LEP and CHEP result from selective activation of Aδ-fibers and C-fibers, whereas PREP results from activation of only Aδ-fibers.[87] The amplitude potential correlates inversely with the reported pain intensity.[68,70]

Skin biopsy

A 3-mm punch biopsy is obtained from the distal part of the leg (10 cm above the malleolus). This is a minimally invasive technique. Decreased intraepidermal nerve-fiber density (IENFD) does not correlate with neuropathic pain.[88] In addition to decreased IENFD, axonal swelling - an early marker of SFN - or decreased sweat gland innervation can be found in SFN.[4,75,89]

Corneal confocal microscopy

The cornea is innervated by Aδ-fibers and C-fibers, originating from the ophthalmic branch of the trigeminal nerve. Corneal confocal microscopy is a reproducible, noninvasive clinical technique detecting early nerve damage.[79,90*,91] Correlation has been established between severity of neuropathy and progressive corneal nerve degeneration.[79,92]

Autonomic function tests

Autonomic dysregulation can contribute to fatal arrhythmias and unexplained sudden death and involvement of small autonomic fibers predicts cardiovascular mortality.[53,93] Different diagnostic modalities can be used, mainly to establish the severity of the complaints. SFN involvement may be unrecognized in sarcoidosis patients with cardiac symptoms.

1. *Cardiovascular autonomic function test (CAFT):* cardiovascular autonomic function can be assessed using five tests (Ewing tests), establishing heart rate variability and blood pressure in supine position, in upright position, during deep respiration, during Valsalva maneuver, and while rapidly changing position from supine to upright. CAFT is considered abnormal when at least two of these five tests are abnormal.[64] It is easy to perform but has low sensitivity in SFN.[64,82]
2. *Sudomotor and vasodilator function tests:* the most commonly used sudomotor function test is quantitative sudomotor axon reflex test (QSART). QSART evaluates the volume and rate of sweat production (reflecting small C-fiber function). As it is

a time-consuming technique, a new device called sudoscan was developed, which is easy to perform and rapid. This technique has been used in various studies to detect SFN in patients with diabetes and Fabry disease.[69*,84,94*,95]

3. *Sympathetic skin response (SSR), thermoregulatory sweat test (TST), skin vasomotor reflex (SVR):* these tests are not frequently used, due to difficulties of assessment (TST), poor reproducibility (SSR), and low sensitivity and specificity (SSR and SVR).[64,69*,96,97]
4. *Metaiodobenzylguanidine (MIBG)-scintigraphy:* this imaging technique may be a promising new tool to study the heart's innervation, currently mainly used in clinical studies. Cardiac sympathetic dysfunction and related symptoms have been reported in patients with SFN. When cardiac symptoms are present in SFN patients, the myocardial sympathetic nervous system, and thus autonomic function[80] can be assessed by iodine-123 MIBG (I-123 MIBG) scintigraphy (Figure 6.1). I-123 MIBG is a norepinephrine analog which has identical mechanisms of storage, uptake, and release in neurons. MIBG scintigraphy can show reduced I-123 MIBG uptake in the myocardium, regional defects, or a higher washout of I-123 MIBG.[80,98,99*,100-102] Cardiac sympathetic dysfunction seems to be heterogeneous and dependent on the presence or absence of SFN.[80] I-123 MIBG can unravel, so far unknown, relationships between innervation, vascularization, and endothelial integrity. Other diagnostic tools, such as MRI and CT, do not have this capacity. In some symptomatic cases, both FDG PET and MRI can be normal, whereas I-123 MIBG scintigraphy is abnormal.[103]

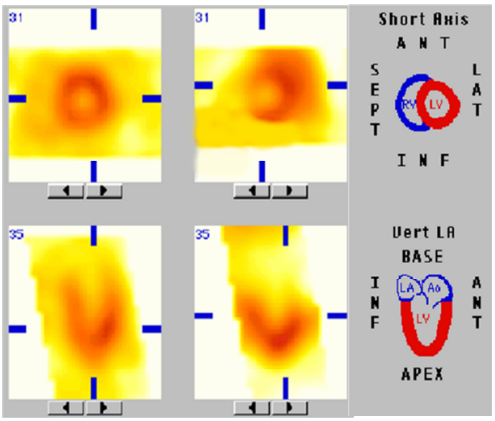

Figure 6.1 Thallium versus MIBG scintigraphy of a sarcoidosis patient with collapses and palpitations demonstrating impaired I-123 metaiodobenzylguanidine uptake without myocardial perfusion disturbances found by thallium scintigraphy. Part of this figure was previously published in ref[80].

Treatment

Treatment of SFN depends on the underlying disease, if identified. Symptoms are often disabling and difficult to treat, even when the cause is identified and adequately treated, leading to high morbidity and decreased QoL.[55] Usually, only symptomatic relief of complaints is achieved. Consensus guidelines for neuropathic pain have been adapted for the treatment of pain in SFN.

Neuropathic pain

Symptomatic treatment prescribed for neuropathic pain includes antidepressants (TCAs and selective serotonin norepinephrine reuptake inhibitors [SSNRIs]), anticonvulsants, opioids, and topical drugs (Table 6.4). Unfortunately, these drugs often provide only partial relief from pain, have no effect on autonomic dysfunction and are associated with (sometimes severe) side effects in a high proportion of patients. Treatment of neuropathic pain is mainly based on studies of large-fiber neuropathies, only one study having examined SFN.[105] This randomized controlled study with crossover design involving 18 patients showed that gabapentin and tramadol significantly reduced pain scores (p=0.001 and 0.018, respectively).

Amitriptyline is a TCA and is the first-line treatment for neuropathic pain, mainly based on years of experience. However, unbiased supportive studies evaluating the effect of amitriptyline are lacking, and the effect might be overestimated.[106] Gabapentin and pregabalin have been shown to be effective in painful neuropathies in randomized controlled studies.[50,107-109] Overall, these drugs are well tolerated. Other anticonvulsant drugs have been found to have little to no effect, apart from certain indications (topiramate and lamotrigine)[110,111] or have low-quality evidence with high risk of bias (carbamazepine).[112] Of the SSNRIs, duloxetine has been found to be a more potent inhibitor than venlafaxine, and is therefore preferred.[42] Selective serotonin reuptake inhibitors are not recommended, due to limited data on their efficacy. Tramadol and oxycodone can reduce pain in diabetic painful neuropathies and can be used for breakthrough pain.[107] However, they should be avoided due to risk of addiction and tolerance to their analgesic effect.

Topical treatment can be an option in localized neuropathic pain. Two drugs have been registered for this indication, namely lidocaine 5% patches[113*] and capsaicin 8% patches. Capsaicin has proven to be effective in diabetic and HIV neuropathy, reducing pain by 22.8-40%.[113*] A retrospective study also found 75% reduction of pain intensity.[114] It can be a good alternative to oral drugs, with lesser side effects.

Table 6.4 Medical treatment for small fiber neuropathy.

Drug	Dosage recommendations	Common side effect
antidepressants		
amitriptyline (TCA, first line)	20-150 mg	anticholinergic effects, sedation, nausea, weight gain, palpitations
nortriptyline (TCA, first line)	20-150 mg	anticholinergic effects, sedation, nausea, weight gain
desipramine (TCA, first line)	20-200 mg	anticholinergic effects, sedation, nausea, weight gain
duloxetine (SSNRI, first line)	30-120 mg	nausea, sedation, dizziness, headache, weight loss
venlafaxine (SSNRI, first line)	150-225 mg	dizziness, headache, nausea, perspiration
anticonvulsants		
gabapentin (first line)	300-3600 mg	somnolence, dizziness, ataxia, edema, tremor
pregabalin (first line)	150-600 mg	somnolence (less), dizziness, ataxia, edema, tremor
topiramate (third line)	25-400 mg	weight loss, sedation, diarrhea, nausea, dizziness, paraesthesia
lamotrigine (third line)	25-400 mg	headache, rash, dizziness, nausea, sedation, tremor
carbamazepine (third line)	200-1200 mg	dizziness, ataxia, nausea, vomiting, sedation, rash, liver-enzymes elevation
opioids		
tramadol (second line)	50-400 mg	constipation, pruritus, dizziness, nausea, vomiting, sedation, impaired concentration, ataxia
oxycodon (third line)	10-100 mg	constipation, pruritus, dizziness, nausea, vomiting, sedation, impaired concentration, ataxia, potential addiction abuse
topical		
capsaicin 8% patch (second line)	3-4 times daily	burning sensation, erythema, local edema
lidocaine 5% plaster (second line)	2 times daily	burning sensation, erythema, local edema, rash
other		
immunoglobulins (clinical trial stage)	Loading dose 2g/kg, maintenance 0.75-1 g/kg every 3 weeks	hypertension, headache, nausea, vomiting, diarrhea, rash, flu-like disease
infliximab (TNF-α inhibition)	3 mg/kg every 4-6 weeks	infections, fever, headache, dizziness, paraesthesias, tachycardia, bone marrow depression, liver-enzymes elevation
cibinetide (ARA290, preclinical stage)	2 mg 3 times/week 4 mg daily	diarrhea

TCA=tricyclic antidepressant; SSNRI=serotonin norepinephrine reuptake inhibitor; TNF-α=tumour necrosis factor alpha. Adapted from[104**]

Different diseases causing SFN may respond differently to these drugs. In HIV neuropathy, amitriptyline, topical lidocaine, and pregabalin failed to relieve pain.[115-118]

Only lamotrigine and capsaicin were found to be moderately effective.[107] In chemotherapy-induced neuropathy, no evidence was found for the efficacy of amitriptyline, nortriptyline, or gabapentin.[119-121]
Immunoglobulins and TNF-α inhibition have been reported to be effective in patients with SFN with various causes.[46,122-128] Recently, a large retrospective cohort study of sarcoidosis associated SFN found that immunoglobulins and TNF-α inhibition caused improvement in 75 and 67% of cases, respectively.[129*] Whether these very expensive treatments should be initiated as causative treatment for SFN is unclear and currently being investigated. Cibinetide (ARA290) seems a promising new drug to relieve pain and increase corneal and skin-nerve-fiber density[77*,130,131] in sarcoid and diabetic neuropathy. Further clinical trials are needed before this drug can be registered.

Autonomic dysfunction

Treatment of autonomic neuropathy depends on the type of symptoms patients report. In patients with cardiac autonomic neuropathy (arrhythmias), improvement can be obtained with carvedilol.[132,133] Treatment of postural orthostatic hypotension should involve stopping or modifying medication that can cause or worsen orthostatic hypotension and start nonpharmacological measures (increased salt intake, stockings, etc.). Pharmacologic treatment can consist of midodrine[134,135] or droxidopa.[136,137] Hyperhidrosis may respond to clonidine, amitriptyline, or botulin toxin.[138]

Discussion

SFN is an underrecognized clinical condition that has been associated with substantial burden on individuals' QoL. Patients often feel misunderstood and are limited in daily activities by their complaints. SFN can be caused by multiple underlying diseases, of which diabetes mellitus is the most frequent (Table 6.1). Studies of the true incidence and systematic reports on underlying causes of SFN have been scarce.[5-7] Extensive screening for underlying disease and the detection of heritability as a possible cause of SFN has reduced the proportion of patients with idiopathic SFN to approximately half of diagnosed patients.
A protocolled approach to diagnosing SFN is of great importance to rule out treatable causes of SFN and differentiate it from large-fiber neuropathy and fibromyalgia (Table 6.2). The diagnosis of SFN can be difficult and no gold standard is available. Unlike in large-fiber neuropathy, NCS are generally normal in SFN.

All diagnostic modalities summarized in this review have their limitations, although skin biopsy is considered by some to be the 'silver standard'. What is important, however, is that a normal skin biopsy does not completely exclude SFN, possibly due to its sometimes patchy distribution. Moreover, skin biopsy does not always correlated with complaints.[75,88] Just as in diagnosing idiopathic pulmonary fibrosis, we consider combining multiple diagnostic tests in a consecutive order to be the best option, although the best combination and sequence of tests remain to be determined. Diagnostic criteria have been suggested, and skin biopsy will not always be necessary.[57,58,64,72,76*,139]

Treatment of SFN depends on the underlying illness, and is generally difficult. Responses to treatment are poor-to-moderate, and many patients experience side effects. The question remains for which patient treatment should be initiated, and at what stage. Most importantly, a multidisciplinary approach is recommended and more collaboration between centers of excellence is necessary.

Conclusion

SFN is a disabling generalized sensory nerve disorder with a widespread spectrum of symptoms, affecting QoL. The disorder can accompany many different diseases. SFN is difficult to diagnose, as a gold standard is still lacking. There is a need for additional reliable, valid, and responsive tests to diagnose SFN, as well as a clinical diagnostic guideline using a stepwise approach and a combination of tests. Treating the underlying disease is only effective in some cases. In the majority of cases, the only option is symptomatic treatment, which usually produces only partial pain relief. Identifying and understanding the pathological basis of SFN will facilitate further studies on diagnostic methods and novel treatment approaches. Prospective research is warranted to improve the diagnostic process, treatment, and outcome.

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