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Small fiber neuropathy: a common and important clinical disorder

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Abstract

Small fiber neuropathy (SFN) is a neuropathy selectively involving small diameter myelinated and unmyelinated nerve fibers. Interest in this disorder has considerably increased during the past few years. It is often idiopathic and typically presents with peripheral pain and/or symptoms of autonomic dysfunction. Diagnosis is made on the basis of the clinical features, normal nerve conduction studies (NCS) and abnormal specialized tests of small nerve fibers. Among others, these tests include assessment of epidermal nerve fiber density, temperature sensation tests for sensory fibers and sudomotor and cardiovagal testing (QSART) for autonomic fibers. Unless an underlying disease is identified, treatment is usually symptomatic and directed towards alleviation of neuropathic pain.

Keywords: Small fiber neuropathy; Review

1. Introduction

Peripheral neuropathy can be categorized based on the function of the involved nerve fibers or on their diameter and conduction velocity. Regarding the functions of different nerve fibers, three types of peripheral nerve fibers can be distinguished: somatic motor fibers, somatic sensory fibers and autonomic fibers. Sensory functions include sensation for touch, vibration, temperature and pain. Autonomic functions include sweating, bowel movements, lacrimation, sexual functions, blood pressure and heart rate variability. Based on size, large diameter myelinated (A-alpha and A-beta), medium size myelinated (A-gamma), small diameter myelinated (A-delta) and unmyelinated (C) nerve fibers can be distinguished. A-alpha and A-beta nerve fibers carry motor functions, vibration sense and touch. A-gamma fibers carry motor function to muscle spindles. A-delta fibers and C-fibers carry temperature and pain sensation and autonomic functions. Small fiber neuropathies (SFN) preferentially affect small-calibre myelinated and unmyelinated fibers, leaving the larger myelinated fibers relatively unaffected.

Routine electrodiagnostic studies, which primarily test large myelinated fiber function, are mostly normal in these patients [1–3]. Therefore, the syndrome of SFN has been an enigma to practitioners because of the unexplained contrast between severe pain in the extremities and a paucity of neurological and electrophysiological findings. Recent advantages in diagnostic techniques (temperature threshold testing (TTT), intra-epidermal nerve fiber density (IENFD) assessment in skin biopsy) facilitate objective confirmation of clinical diagnosis and the characterization of fiber type involvement in SFN [4,5]. This paper reviews clinical features, diagnostic tests and underlying diseases. Furthermore, opportunities for future therapeutic as well as pathogenesis studies are discussed.

2. Clinical features

Though relatively few detailed descriptions of the clinical features have been published [1–3,6,7], the clinical syndrome

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is a relatively stereotypical distinctive syndrome (Table 1). Small fiber dysfunction can be defined as a generalised peripheral neuropathy in which the small diameter myelinated and unmyelinated nerve fibers are affected, either exclusively or to a much greater degree than the large diameter myelinated fibers [8]. Although this definition is adequate for a conceptual image of SFN, it is not specific enough to apply in clinical and research settings. A good working definition was proposed by Stewart et al. [2]. Features compatible with SFN include dysesthesia, along with abnormalities on neurologic examination, limited principally to small fiber dysfunction. Exclusion criteria include proprioceptive loss in the toes, vibration loss at or above the ankles, any distal wasting or weakness, generalised areflexia or abnormal findings on electromyography (EMG) or nerve conduction studies (NCS). Although Stewart's definition is quite specific and applicable, both clinically and for research, these delineations are empirical [8].

Sensory symptoms in SFN typically consist of "positive" sensory symptoms, including pain and paraesthesias [1–9]. The pain is often of a burning, prickling or shooting character. It may be worse at night and may interfere with sleep. Allodynia and cramps may also occur. These cramps usually affect calf muscles, and may mislead clinicians to think of other diagnosis if they are not aware of this feature. Some patients present with late-onset restless legs syndrome (RLS) [10]. Especially in RLS patients without a positive family history, SFN should be evaluated. However, not all patients with SFN suffer from pain. Patients may also have "negative" sensory symptoms, including numbness, tightness and coldness. Sensory symptoms are usually distal and "length-dependent" [11], but they may sometimes be patchy or asymmetrical [7,12,13]. The latter may indicate that a pathological process takes place in the dorsal ganglion rather than a typical length-dependent neuropathy.

Table 1
Symptoms suggestive of small fiber neuropathy

Sensory symptoms
Pain[a]
Paraesthesias
Sheet intolerance
Restless legs syndrome[b]
Symptoms of autonomic dysfunction
Hypo- or hyperhidrosis
Diarrhoea or constipation
Urinary incontinence or -retention
Gastroparesis
Sicca syndrome
Blurry vision
Facial flushes
Orthostatic intolerance
Sexual dysfunction

[a] Pain in small fiber neuropathy is often burning, tingling, shooting or prickling in character.

[b] Restless legs syndrome is a disorder characterized by disagreeable leg sensations that usually occur prior to sleep onset and that cause an almost irresistible urge to move.

Because autonomic functions are also mediated by small myelinated and unmyelinated fibers, symptoms of autonomic dysfunction may also occur [9]. These may involve increased or decreased sweating, facial flushing, skin discoloration, sicca syndrome, sexual dysfunction, diarrhoea or constipation. Symptoms of orthostatic hypotension seem to be uncommon except in disorders such as amyloidosis and diabetes [7]. Occasionally, excessive localised sweating (e.g. face and chest) is associated with generalised hypohidrosis or anhidrosis, but it is only the excessive sweating that the patient is aware of. The degree and distribution of autonomic impairment in patients with painful feet have been evaluated in a prospective study by Novak et al. [14]. A preferential impairment was seen of cholinergic and skin vasomotor fibers, sparing systemic adrenergic fibers. It is important to remember that symptoms of autonomic dysfunction are not always sufficiently severe to be mentioned spontaneously by the patient. Furthermore, in clinical practice, subtle autonomic dysfunction such as acral vasomotor symptoms or mild distal extremity discoloration may not always be fully appreciated. Finally, as distal autonomic neuropathy often does not result in orthostatic hypotension, Ewing tests, which are widely used to assess autonomic function, frequently remain normal and hence autonomic dysfunction can easily be overlooked.

Some patients notice consistent worsening of symptoms with heat exposure, others with exposure to cold or with activity. Sometimes patients have increased sensitivity to pressure. Spontaneous exacerbations and remissions may also be presented. Finally, it is remarkable that many patients with SFN complain of severe and disabling fatigue.

3. Diagnostic tests

NCS and EMG, which are key in the evaluation of other (large fiber) neuropathies, are generally normal in patients with SFN [15]. However, recent advantages in diagnostic tests have facilitated confirmation of the clinical diagnosis of SFN. Nevertheless, a fundamental problem in evaluating diagnostic tests for SFN is that a gold standard for the disorder is lacking. Furthermore, in many patients, functionally different small fiber systems are affected selectively. In order to diagnose SFN and to evaluate the individual type of manifestation, complementary testing of several small somatic and autonomic fiber systems may be necessary [16]. Finally, all abnormal test results must be interpreted, taking into account the patient's history, previous treatments and other test results. Physicians, not tests, make diagnoses based on medical history, physical examination, test results and clinical judgement [17].

3.1. Quantitative sensory testing

Quantitative sensory testing (QST), which is becoming more and more available, has become an important tool in

assessing the function of small as well as large sensory nerve fibers [18,19]. Small-calibre fibers are assessed by measuring temperature thresholds and heat pain thresholds, whereas large calibre fibers are assessed by vibration thresholds.

The method of TTT has been reviewed by Yarnitsky [20]. Thermal stimuli consist of a ramp of ascending (warm) and descending (cool) thermal energy delivered through a thermode. When symptoms are regarded as the golden standard, sensitivity of TTT ranges from 60% to 85% [3,14,21–24]. Differences in sensitivity may be due to technical and patient cohort factors [7]. TTT is a psychophysical method and therefore requires the cooperation of the patient. This means that these tests are liable to loss of attention, especially in older subjects, and to malingering [18,25,26]. Furthermore, it is important to remember that it is sensation, which is assessed and not structural pathology. Finally, it must be realised that the dysfunction causing an abnormal result may in principle be located anywhere between the skin and the sensory cortex. Using two types of testing as a control, the method of levels and the method of limits, false positive results may be reduced [27,28].

In their review of QST, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology [18] concluded that QST is a potentially useful tool for measuring sensory impairment. Abnormalities, which are revealed by QST, however, must be interpreted in the context of a thorough neurological examination and other appropriate testing [18].

3.2. Current perception threshold testing

Current perception threshold testing (CPT) is a sensory quantitative test performed with a microprocessor-controlled electrical neurostimulator which delivers sinusoidal electrical stimuli via surface electrodes at three different frequencies: 5, 250 and 2000 Hz. So far, the only device to measure CPT is the Neurometer. Current intensity ranges from 0.01 to 9.99 mA [29,30]. The electrical current stimulates nerve fibers directly because the intensity is far below that required to stimulate the actual receptors in the skin. Patients are asked to identify the presence or absence of the stimulus through a “forced choice” protocol. From the fact that the perceived sensation varies with the stimulation frequency, it has been concluded that a frequency of 5 Hz activates C fibers, A-delta fibers are stimulated at 250 Hz, and large A-beta fibers are triggered with 2000 Hz. Similar to QST, CPT test requires active patient participation. It is not widely available. Furthermore, conflicting information and methodological problems exist regarding the utility of CPT [29].

3.3. Skin biopsy

Epidermal nerves are the distal terminals of small dorsal root ganglia neurons that pierce the dermal–epidermal basement membrane and penetrate the epidermis. The discovery of the antibody to the neuropeptide protein gene product (PGP) 9.5 [31] made it possible to effectively stain most nerve fibers (Fig. 1). PGP 9.5 is a ubiquitin C-terminal hydrolase and is enriched in epidermal nerve fibers [32–35]. Multiple studies have emphasized the importance of intraepidermal nerve fiber density (IENFD) assessment using PGP-9.5 immunofluorescent staining in skin biopsy in the evaluation SFN [10,21,22,36–55]. A punch biopsy is performed following established procedures [47], mostly 10 cm above the lateral malleolus after local anesthesia with 1% lidocaine. The location of the biopsy is important as IENFD show significantly higher values at proximal sites compared to distal sites consistent with the nature of length dependent neuropathy [54,56]. Therefore, a single biopsy site in the distal leg seems sufficient for the evaluation of clinically symmetric small-fiber sensory neuropathy [54].

In the main, two techniques for quantification of the number of small nerve fibers have been established. First, a technique using an image analysis system and confocal microscopy has been described [47] and validated against an unbiased stereological technique [43]. Second, Chien et al. [54] investigated the feasibility of diagnosing small fiber sensory neuropathy by using only regular light microscopy independent of image analysis systems. The nerve fiber densities of both techniques were significantly correlated (r=0.99, p<0.0001).

Normative data for IENFD have been established for both techniques [22,43,47,54–56]. In a systematic review and meta-analysis, Rosenberg et al. investigated the diagnostic value of skin biopsy in patients with small fiber neuropathy (submitted). Nine studies were included [14,21,22,39,40,47,55,57,58]. From these nine studies, sensitivity and specificity of skin biopsy appeared to be 69% and 97%, respectively, in patients with symptoms suggestive of SFN, but with normal NCS. They concluded that in this group of patients a positive skin biopsy is of important diagnostic value.

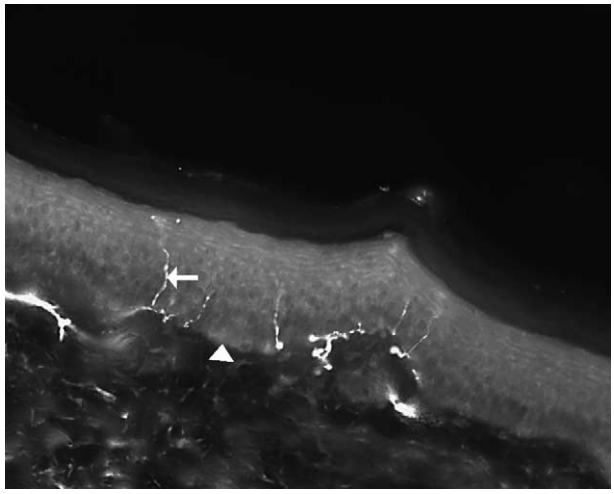

Fig. 1. Magnification 200X. Punch skin biopsy from a healthy control showing intraepidermal nerve fibers. Arrow=intraepidermal nerve fiber. Arrowhead=basal membrane (above the basal membrane the epidermis is shown, under the basal membrane the dermis is shown).

Finally, focal epidermal nerve fiber swellings have been observed at a time when IENFD remain in the normal range and may be pre-degenerative [40,42,59]. However, its significance has not been well established. A limitation of skin biopsies is that they are available in only a few academic centers. The histological technique is moderately complicated and, before implementing it, a relatively large subset of healthy controls should be studied as the normative range is wide.

3.4. Sural nerve biopsy

Pathological diagnosis of neuropathy has traditionally depended on ultrastructural examination of nerve biopsy specimens, particularly for sensory neuropathies affecting unmyelinated and small myelinated nociceptive nerves. However, abnormalities may be subtle and difficult to recognize, and require electron microscopy with technically demanding, precise morphometric studies. Moreover, nerve biopsy may eventually cause hypoesthesia, deafferentiating pain and neurinoma. Therefore, sensory nerve biopsies are not routinely indicated in evaluating patients with small fiber neuropathy, unless amyloidosis, vasculitis or another inflammatory process is suspected.

3.5. Laser-evoked potentials

Evoked potentials to sensory and noxious stimulation of skin may provide objective information about the integrity of the nociceptive afferents as part of the peripheral nervous system as well as brain response to selective stimulation of certain types of sensory fibers. Thermal stimulation with an infrared CO_2 laser results in a radiant heat pulse, which is absorbed by superficial layers of the skin. It produces a rapid rise in skin temperature and generates a pure pain sensation, which is conveyed through both small myelinated A-delta and unmyelinated C fibers to the cerebral cortex. Recordings with scalp electrodes reveal the occurrence of evoked potentials with long and ultralong latencies (200–500 and 750–1200 ms for A-delta and C fibers, respectively) [60,61]. A cerebral potential at the vertex is generated and its amplitude correlates with the stimulus intensity and the reported intensity of the perceived pain [62]. Repeated stimuli induce minimal habituation and there is no evidence of tissue damage [30]. The evoked cortical response has greater amplitude than early somatosensory-evoked potentials and requires the averaging of 25–40 responses [62]. Although this test seems to have important merits, its availability is currently limited [63].

3.6. Contact heat-evoked potential stimulators

Contact heat-evoked potential stimulators (CHEPs) have been difficult to elicit due to slow temperature rise times. A recently developed heat-foil with an extremely rapid heat rising time (70 °C/s) can elicit pain and CHEPs [64–67]. Recordings are made from the scalp area overlying the sensory-motor cortex, using scalp electrodes. At low stimulus intensity, only a shallow, very late positive wave is observed at the vertex Cz site. In contrast, three clear peaks (Cz/N550, Cz/P750 and Pz/P1000) can be identified and isolated at painful levels. The late Cz/N550 component may be in association with A-delta fiber activation since its conduction velocity has been estimated at 10 m/s. The very late Pz/N1000 component at 800–1000 ms may be in association with C-fiber activation, with the conduction velocity estimated at 2–3 m/s. Thus, the isolation of late Cz/N550 and very late Pz/P1000 components may allow the inference of the integrity of A-delta and C-fiber peripheral afferent. However, the potential value and application of this technique requires further exploration.

3.7. Microneurographic C-fiber recordings

Microneurographic C-fiber recording is primarily a research tool, is time consuming and requires that both observer and patient be highly motivated for the successful acquisition of useful data [62,68]. The examiner percutaneously inserts a special needle electrode (diameter 200 μm, uninsulated tip of 1–15 μm) into a nerve that innervates an area of the involved skin. The electrode is connected to an amplifier with attached audiomonitors and an oscilloscope to permit the examiner to monitor neural activity. The recording of skin and muscle sympathetic activity, A-beta low-threshold mechanoreceptors, A-delta nociceptor and C nociceptor afferent activity can provide pathophysiological information regarding the mechanisms of the different kinds of neuropathic pain.

3.8. Sympathetic skin response

The sympathetic skin response (SSR) is an old, simple, widely available and inexpensive method for assessing small fiber sudomotor function. It is a reflex change in the sweat-related electrical potential of an area of skin, as elicited by various unexpected “adrenergic” stimuli, such as an electric shock to a somatic nerve. The recording electrodes are commonly applied to the dorsal and ventral surfaces of the foot or hand. There is general agreement that a loss of SSR is abnormal [69]. There is some controversy as to whether a reduction in electrical potential and a change in latency are reliable abnormalities [70]. A major advantage is that it can be measured on routine electromyographic (EMG) equipment and that it can be performed in any EMG lab [71]. However, sensitivity as well as specificity of the SSR are considered to be low [7,24,69,72].

3.9. Quantitative sudomotor axon reflex test (QSART)

In QSART, axons in the skin are activated locally through acetylcholine iontophoresis. Its exact mechanism

is not fully understood. Antidromic transmission to an axon branching point may elicit action potentials that travel orthodromically to release acetylcholine from nerve terminals producing sweat. The sweat response is measured at the skin surface using a sudorometer to determine the sweat volume [7,73,74]. In controls and diabetics, QSART appears to be sensitive, reproducible and only modestly time consuming. Sensitivity in SFN ranges from 59% to 80% [2,14,22,23,74]. A previous study has shown that patients with SFN may have abnormalities in both skin biopsy and QSART [22]. However, abnormalities in these two tests do not always overlap. There are several abnormal QSART patterns. The response may be (1) normal, (2) reduced, (3) absent, (4) excessive or (5) persistent. Pattern 5, consisting of persistent sweat response when the stimulus ceases, is often seen in patients with hyperalgesia such as SFN [8]. However, special equipment is necessary and therefore this test is not widely available.

3.10. Other tests of sudomotor function

Other tests to assess sudomotor function include the thermoregulatory sweat test (TST) and the silastic skin imprint method [8]. TST involves dusting a patient with an indicating powder (alizarin red, sodium carbonate and cornstarch) that turns purple when moist. The patient is placed in a hot enclosure and the pattern of the body surface covered by sweat is assessed semiquantitatively. Normal results show relatively uniform sweating over the entire body with characteristic areas of heavier or lighter sweating [69]. Sensitivity of the thermoregulatory sweat test appears to be high. It may be one of the most sensitive tests for SFN, showing sweat loss in the feet [69]. Disadvantages of the test are that it is messy, semiquantitative, time consuming and requires a sweat cabinet (air temperature 44–50 °C, relative humidity 35–45%).

The silastic skin imprint method was described by Kennedy as a quantitative study of sweat droplet morphometry [75]. Silastic material that hardens in 1 or 2 min is applied to the skin. Iontophoresis of pilocarpine or acetylcholine are used to stimulate sweat. Sweat drops imprint in the silastic material and quantification is determined by measuring the number of activated sweat glands per square centimetre. Sensitivity of the silastic method has not been evaluated [75,76].

3.11. Skin vasomotor temperature testing

In skin vasomotor testing, surface skin temperature is measured using a non-contact, infrared thermometer on multiple sites bilaterally, including the lateral and medial thighs, legs and feet. The distribution of skin temperature on the lower limbs is considered abnormal when site-to-site differences are >1 °C on at least three sites [14,77]. The advantage of this method is that it is easily evaluated and may therefore be widely applied.

3.12. Laser Doppler flowmetry

Laser Doppler flowmetry (LDF) is a technology that makes use of the fact that red blood cells move through the capillaries of the skin. It is based on the Doppler effect, which occurs when laser light is directed into the skin and reflected back from moving red cells. A detailed description of the method and its applications is given by Shepherd and Oberg [78]. Spatial differences in skin blood flow may markedly influence the values obtained. As laser Doppler imaging (LDI) evaluates larger skin areas in comparison with LDF, LDI may be more representative for the tissue evaluated than that measured by LDF [79].

The technique is often used to measure vasoconstrictor responses to stimuli such as cooling [80], arousal stimuli [81] and deep inspiration [16] and vasodilator responses to heating [80], and acetylcholine introduced electrophoresis [82]. Heating, for example, causes a release of sympathetic vasoconstrictor tone. Accordingly, a lack of rise in blood flow during heating strongly argues for a defect in sympathetic nerve function. However, it is also important to remember that responses seem to decrease with age [80].

3.13. Cardiovascular reflex testing

The sympathetic and parasympathetic nervous system are assessed by the Valsalva maneuver, by blood pressure response to standing or tilt and by measuring the heart rate variation during deep breathing and during the Valsalva maneuver (Ewing tests) [83]. Cardiovascular reflex testing is widely available. However, sensitivity appears to be relatively low in SFN [2,14,24].

3.14. Metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy

Iodine-123 meta-iodobenzylguanidine (^{123}I-MIBG), an analogue of norepinephrine, is a tracer for the functioning of sympathetic neurons. ^{123}I-MIBG is administered intravenously and cardiac sympathetic nerves take up ^{123}I-MIBG, which radiolabel the vesicles in the terminals. This allows visualisation of the sympathetic innervation of the heart by scintigraphy, after the injection of ^{123}I-MIBG [84]. An imbalance of the cardiac autonomic tone is considered to increase the propensity to develop fatal arrhythmias and ^{123}I-MIBG appears to have prognostic value [85]. Cardiovascular reflex testing (Ewing tests) provides indirect measures of sympathetic nervous system effects on the heart and seems inherently less precise and sensitive than MIBG [86]. However, as there is no golden standard for cardiac denervation, sensitivity and specificity are unknown. MIBG myocardial scintigraphy can be performed safely and does not require special equipment. Therefore, MIBG myocardial scintigraphy may become widely available and utilized.

4. Pathogenesis and etiology

In some cases SFN is part of an underlying disease (Table 2). However, no specific etiology is identified for the majority of SFN patients encountered in neurology practice, especially in the elderly (in up to 93%) [22]. Only case reports are published of most causes; therefore, the frequencies of the different causes are not known. The neuropathology has remained largely unexplored. However, there is some support for a role of ischaemia, cytokines and oxidative stress:

4.1. Ischaemia

From an animal model using arterial infarction, there is some support that small nerve fibers are more vulnerable to ischaemia than are large diameter nerve fibers [87]. Ischaemia may be due to vasculitis [88].

4.2. Cytokines

Suarez et al. [89] postulated an immune mediated mechanism as the cause of idiopathic autonomic neuropathy. Moreover, it is remarkable that SFN seems to be frequent in immune mediated diseases such as sarcoidosis [24,90], Sjögren's disease [91] and SLE [92], leading to the hypothesis that there might be a common pathway in immune mediated diseases resulting in SFN. Gorson and Ropper [1] suggested that an auto-immune mechanism causes idiopathic SFN, as three out of four of their patients improved on intravenous gamma globulin treatment. Further support for an immune mediated role is found in pharmacological and physiological studies suggesting that pro-inflammatory cytokines such as tumor necrosis factor alpha (TNFα) are strongly involved in the generation and maintenance of neuropathic pain [93–95].

Table 2
Causes of small fiber neuropathy

Idiopathic [1]	
Inherited	Familial amyloidosis [107]
	Autosomal recessive hereditary neuropathy [51,142,143]
	Hereditary sensory and autonomic neuropathy [144]
	Fabry's disease [49,145,146]
	Ross syndrome [37]
	Friedreich's ataxia [22,147]
	Tangier disease [7]
Acquired	Diabetes mellitus [148,149]
	Impaired glucose tolerance [57]
	Alcoholism [150–152]
	Systemic amyloidosis [153–155]
	Vasculitis [88,156]
	Sarcoidosis [24,90]
	Sjögren's disease [91]
	Systemic lupus erythematosus [92,157]
	Guillain-Barre syndrome [158]
	Antecedent viral infection [89,159]
	HIV [48,160,161]
	Antisulfatide antibodies [22,162]
	Hyperlipidemia [163]
	Complex regional pain syndrome [164–166]
	Paraneoplastic syndrome [167,168]
	Neurotoxic medication [169–171]

4.3. Oxidative stress

The role of oxidative stress also needs further exploration. A growing body of evidence suggests that oxidative stress is implicated in the pathogenesis of diabetic neuropathy [96–102]. Furthermore, a decreased level of nicotinamide adenine dinucleotide phosphatase (NADPH) was found in the erythrocytes of sarcoidosis patients [103]. As NADPH is a necessary factor in the defence against oxidative stress, this suggests a decreased anti-oxidant defence capacity in sarcoidosis. It is tempting to speculate that oxidative stress might be the common pathway in different diseases causing SFN.

5. Natural course and prognosis

Longitudinal natural history studies are not available to date. From follow-up, it is known that at least some patients evolve from a strict SFN to large fiber sensory neuropathy [22,104]. In our experience, the progression of SFN seems to be slow, and although pain and autonomic dysfunction are troublesome symptoms, patients seem not to become physically disabled. Spontaneous remission sometimes occurs [1]. Tobin et al. [23] found that about one-third of their patients with idiopathic SFN experienced continuous symptoms, another third intermittent symptoms and that one-third had a monophasic course with resolution of symptoms after months to years.

Involvement of cardiac sympathetic nerves might play a role in prognosis, as indices of autonomic cardiac dysfunction have been identified as strong predictors of cardiovascular morbidity and mortality [105–113]. However, this aspect needs further study.

6. Therapy

Unless an identifiable treatable cause (see Table 2) is found, the management of SFN usually centers upon the treatment of neuropathic pain [7,114]. Literature regarding painful neuropathies can be divided into three groups: diabetic neuropathies (the most extensively studied pathological condition), HIV-related neuropathies and remaining neuropathies. There appears to be an important difference in HIV-related neuropathy on one hand and diabetic and remaining neuropathies on the other hand; drugs that are efficacious in diabetic and other neuropathies have been proved in-efficacious in HIV-related neuropathy. As there appears to be no difference in treatment effect between diabetic and other neuropathy,

one can most probably extrapolate the different diabetic studies to all painful neuropathies, excluding HIV-related neuropathy.

Useful and frequently prescribed drug classes in painful neuropathy, with the exclusion of HIV-related neuropathy, include anticonvulsants [115–117], tricyclic antidepressants [114,117,118], opiates [116,119] and topical capsaicine cream [120–122] (Table 3). Treatment should be titrated until benefit is achieved to the maximum tolerable dose. Most of the drugs that are efficacious reduce pain intensity only 30–50% and such a reduction rarely meets patients' expectations [114]. In diabetics, the number needed to treat (NNT) values for most drugs is around 3 (Table 3). This means that in neuropathic pain, three patients have to be treated in order to obtain one patient with more than 50% pain relief. Tricyclic antidepressants have been studied most extensively and may at the moment be the drugs of first choice; drugs such as gabapentin, carbamazepin and tramadol may be tried if contraindications or tolerability problems are encountered with the tricyclics [123]. It remains uncertain whether adequate pain relief can be achieved with a multi-drug strategy, particularly with the use of pharmacological agents targeted at more than one site in the pain pathway [114].

Table 3
Commonly used treatment of painful sensory neuropathy

Drug	Starting dose and increase[a]	Usual range of doses	NNT
Tricyclic antidepressants[b]			
Amitriptyline	10 mg/day, increase by 10 mg/week	75–100 mg/day	2.6 (2.2–3.3)
Nortriptyline	10 mg/day, increase by 10 mg/week	75–100 mg/day	
SSRI			
Citalopram	10 mg/week, increase by 10 mg/week	20–60 mg/day	6.7 (3.4–435)
Paroxetin	10 mg/week, increase by 10 mg/week	20–60 mg/day	
Anticonvulsants[b]			
Gabapentine	300 mg/day, increase by 300 mg/week	1800–3600 mg/day	3.7 (2.4–8.3)[c]
Carbamazepin	200 mg/day, increase by 200 mg/week	800–1600 mg/day	3.3 (2.0–9.4)
Oxcarbazepin	300 mg/day, increase by 300 mg/week	1200–2400 mg/day	ND
Lamotrigin	50 mg/day, increase by 100 mg biweekly	200–600 mg/day	ND
Phenytoin	100 mg/day, increase by 100 mg/week	300–500 mg/day	2.1 (1.5–3.6)[d]
Opioids[b]			
Tramadol	150 mg/day, increase by 50 mg/week	200–400 mg/day	3.4 (2.3–6.4)
Morphine	15–30 mg every 8 h	90–360 mg/day	ND
Topical therapy			
Capsaicin cream	0.075%	apply to painful area 4 times/day	5.9 (3.8–13)

SSRI=selective serotonin reuptake inhibitor; NNT=numbers needed to treat (95% CI) to obtain one patient with more than 50% pain relief, data according to Sindrup and Jensen [116,123]; ND=not done.

[a] Data according to Mendell and Sahenk [114].

[b] Oral.

[c] At a dose of 3600 mg/day. In a study with a much lower dose (900 mg/day), no effect was found [173].

[d] It is important to note that a second placebo-controlled study with phenytoin failed to demonstrate a significant effect [172].

The efficacy of intravenous gammaglobulin in idiopathic SFN deserves further study [1]. The older aldose reductase inhibitors do not reduce pain in diabetic neuropathy [124–126]. A newer aldose reductase inhibitor, fidarestat, may be beneficial but further study needs to be done before this treatment can be recommended [127]. Intensive diabetes therapy can also reduce painful diabetic neuropathy [128]. One needs to aim at a stable metabolic situation and avoid hypoglycaemias as patients with autonomic neuropathy may not be aware of their hypoglycaemias. Finally, there has been therapeutic interest in nerve growth factor (NGF) [129] and lipoic acid [99,100]. In several, although not all studies, intravenous administration of the antioxidant lipoic acid has been shown to ameliorate major neuropathic symptoms and also to improve heart rate variability in diabetics [99–102,130]. However, oral administration of lipoic acid appears to be in-efficacious [102].

As pro-inflammatory cytokines such as TNFα contribute to the development of neuropathic pain [93–95], one may hypothesize that anti-TNFα therapy such as infliximab could be beneficial in SFN.

NGF is trophic for small sensory neurons and stimulates the regeneration of damaged nerve fibers [131]. NGF levels have been found to be reduced in sympathetic target tissue shortly after inducing diabetes in rats [132]. On the other hand, recombinant human NGF improved diabetic, chemotherapy-induced and HIV-related sensory neuropathies [133–135]. It is not clear whether the benefits from NGF treatment is from its trophic effect or others like analgesic effect. NGF, anti-TNFα and antioxidants all deserve further study.

Amitryptylin and capcaicin cream are not effective in treating HIV-related neuropathy [136–138]. Data on the effect of lamotrigin in HIV-related painful neuropathy are contradictory [139,140]. Possibly, there is some effect of lamotrigin in HIV patients who use neurotoxic antiretroviral therapy (ART) [140].

Nonpharmacological methods for pain management may also be helpful. Some patients find relief with cool soaks, heat, massage, elevation or lowering of the limbs. Shoes must not be tight and exercise may be beneficial as well [7]. In the only controlled study of acupuncture for peripheral nerve pain related to HIV, there was no difference in effect when needles were placed in traditional sites rather than in sham sites [137]. Transcutaneous electrotherapy (TENS) ameliorates pain and discomfort associated with diabetic neuropathy [141]. Spinal cord stimulators and intrathecal

morphine may be helpful in a select group of patients, but the long-term benefit is unknown [7].

7. Conclusions

SFN is a relatively common disorder resulting in severe and troublesome symptoms, which may be difficult to control. Standard electrophysiological tests such as nerve conduction studies and EMG remain normal in SFN. Therefore, the syndrome may easily be overlooked. Whether patients with SFN are at risk for sudden life threatening arrhythmias when they develop cardiac denervation is unknown and needs further study. Future studies regarding pathophysiology and treatment are warranted as well. As SFN seems to be frequent in several immune mediated diseases such as sarcoidosis, SLE, Sjögren's syndrome and vasculitis, there might be a common pathway in immune mediated diseases resulting in SFN. In this regard oxidative stress and pro-inflammatory cytokines such as TNFα may be candidate and deserve further analysis.

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