British Society for Rheumatology

RHEUMATOLOGY

OXFORD

Clinical science

Foot peripheral sensory neuropathy: a frequent disabling manifestation in systemic sclerosis

Begonya Alcacer-Pitarch (ID)[1,2,*], Marco Di Battista (ID)[1,3], Anthony C. Redmond (ID)[1,2],
Anne-Maree Keenan[2,4], Stefano Di Donato[1,2], Maya H. Buch (ID)[1,2,5], Francesco Del Galdo (ID)[1,2]

[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, School of Medicine, University of Leeds, Leeds, United Kingdom
[2]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals Trust, Leeds, United Kingdom
[3]Rheumatology Unit, University of Pisa, Pisa, Italy
[4]School of Healthcare, University of Leeds, Leeds, United Kingdom
[5]Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Manchester, United Kingdom

*Correspondence to: Begonya Alcacer-Pitarch, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Leeds LS7 4SA, United Kingdom. E-mail: b.alcacer-pitarch@leeds.ac.uk

Abstract

Objectives: Peripheral sensory neuropathy (PSN) is an under-recognized feature in SSc. Moreover, SSc foot involvement is frequent but poorly investigated. We aimed to provide a detailed characterization of foot PSN in a large cohort of SSc patients, describing its associations with disease-specific features, physical disability and quality of life (QoL).

Methods: SSc patients and healthy controls (HCs) comparable by age and gender were enrolled in a cross-sectional observational case-control study. All subjects underwent a detailed quantitative sensory testing of feet evaluating touch, vibratory, thermal and pain sensitivity, ultimately investigating the presence of large and small fiber neuropathy. Patient-reported outcomes (Scleroderma Health Assessment Questionnaire, Manchester Foot Pain and Disability Index and Systemic Sclerosis Quality of Life Questionnaire) were administered to assess neuropathic symptoms, foot disability and QoL.

Results: A total of 109 SSc patients (88.1% female, median age 59.0 years) and 51 HC were enrolled. SSc patients presented with a significant impairment in each sensory parameter assessed ($P \leq 0.01$ for all). Foot PSN was present in 85.3% of the patients, with 80% having small fiber and 57% large fiber neuropathy, co-existing in 51.4% of the cases. PSN was associated with age, smoking, foot ulceration, disease duration and corticosteroids use. Precisely, 80.6% subjects with PSN reported at least one neuropathic symptom. Patients with neuropathic symptoms reported worse physical function, worse foot disability and more impaired QoL.

Conclusion: Foot PSN presents as a common and disabling manifestation in SSc patients, involving small and large fibres. Hence, foot PSN assessment should be included as a part of the SSc workup.

Keywords: systemic sclerosis, peripheral neuropathy, foot, quality of life.

Rheumatology key messages
- Foot PSN is a common and disabling SSc manifestation, involving both large and small fibers.
- Foot PSN assessment should be part of the routine SSc management.

Introduction

SSc is a chronic connective tissue disease whose pathogenesis is attributable to vasculopathy, autoimmune deregulation and tissue fibrosis. It can potentially affect any organ, thus presenting a very heterogeneous clinical expression and determining a significant burden on the patient's quality of life (QoL) [1]. Growing attention is gathering around neurological involvement in SSc, which can be expressed both as central or peripheral neuropathy as well as autonomic dysfunction including gastrointestinal involvement [2, 3]. Among those neurological manifestations, peripheral sensory neuropathy (PSN) is an under-recognized feature that has been poorly characterized; this could be attributed at least in part to the variability in definitions used for its diagnosis. Nonetheless, several studies have shown that it is by no means an uncommon problem. According to the most recent systematic reviews, the prevalence of PSN, accounting for highly variable definitions, ranges from 14.5% to 27.3% [2, 4], mostly affecting cranial, truncal and upper extremities nerves. Although PSN of the lower extremities has been reported in several studies, it has only been investigated in small cohorts [5–8]. When sensory symptoms are present,

they can vary from numbness, paraesthesia and allodynia to stabbing and burning pain; however, a subclinical presentation of foot PSN has also been reported [5–7].

PSN in SSc patients can have several different aetiologies including ischaemia, tissue fibrosis, nerve compression through calcinosis, traumatic injury, medication adverse effects and comorbid conditions such as diabetes mellitus [4, 9]. The pathophysiological mechanisms underlining PSN in SSc are not yet fully understood, but a significant reduction in the density of myelinated fibers was found in sural nerve biopsies from SSc patients with multiple mononeuropathy [10], whereas skin biopsies showed a loss of myelinated and unmyelinated sensory autonomic nerve fibres (A-delta and C-fibers) [5]. Even though classification by type of peripheral nerve fibre involved, pattern of distribution and time of onset may aid in diagnosis, such a broad array of possible causes can make peripheral neuropathy in SSc a diagnostic and management challenge for the clinician to face.

It should also be added that, unlike hand problems which are well known, foot problems in SSc have been poorly investigated. However, the few published studies on foot involvement in SSc have shown that this is a frequent and often disabling condition. In fact, the vast majority of SSc patients were found to have various degrees of morbidity and disability in all aspects of the foot, from the presence of pre-ulcerative lesions to the absence of peripheral pulses, from calcinosis to radiological abnormalities, up to biomechanical compromise. Taken all together, these factors lead to a significant burden on the patient's QoL [11–13].

The aim of this study was to provide a detailed characterization of foot peripheral neuropathy in a large cohort of patients with SSc, exploring any association with disease-specific characteristics, and assessing the impact of foot neuropathy on foot disability and QoL.

Methods

Adult consecutive patients affected by SSc according to 2013 EULAR/ACR classification criteria [14] and attending a routine visit at the Scleroderma clinic of Leeds Teaching Hospital NHS Trust were enrolled for this cross-sectional observational study along with a group of healthy controls (HCs) comparable for age and gender. HC recruitment was undertaken through SSc subjects, using a technique referred to as 'bring a friend' where patients were asked to nominate a healthy friend/relative of the same gender and age (±2 years) who was willing to participate. This recruitment strategy has been described previously in the literature as an effective method of matching for socio-economic, ethnicity and other demographic factors [15]. Ethical approval was obtained from the local ethics committee (Leeds Research Ethics Committee, ref 10/H1306/14), and all participants provided written informed consent to participate in accordance with the Declaration of Helsinki.

Demographic and SSc-specific variables and comorbidities were collected for each patient, including disease duration, lcSSc and dcSSc subset according to LeRoy [16] and modified Rodnan skin score (mRSS), autoantibody positivity distinguishing between anti-centromere and anti-topoisomerase I autoantibodies, history of ulcers specifying whether located on the foot or elsewhere in the body, current medications distinguishing between immunosuppressants, corticosteroids and vasoactive drugs. Ongoing ulcers on the feet, diabetes mellitus and the history of orthopaedic or vascular surgery of the lower extremities in the previous 12 months were considered exclusion criteria. All enrolled subjects underwent a detailed quantitative sensory testing (QST) of their feet. Patients were also questioned about the presence of neuropathic symptoms such as paraesthesia, numbness, burning or stabbing pain, according to a numerical rating scale (NRS) from 0 (no symptoms) to 10 (most severe symptoms). Finally, patient-reported outcomes (PROMs) were administered to assess physical disability and patient's QoL.

Quantitative sensory examination

The somatic sensory nerve fibres of both feet were examined for sensations of touch, vibration, temperature and pain with the different QST tools (*Somedic SenseLab, Sösdala, Sweden*). Specifically, QST investigated large-diameter myelinated fibers (A-alpha and A-beta) which carry touch and vibration sense along with motor function, as well as small diameter myelinated (A-delta) and unmyelinated (C) fibers, which carry temperature and pain sensations along with autonomic function [9, 17]. Patients were evaluated in a quiet and temperature-controlled room at $23 \pm 1.3°C$ (relative humidity $36 \pm 9\%$). During the assessments, patients were asked to close their eyes to avoid any possible visual influence.

Mechanical threshold for light touch was assessed using a calibrated nylon von Frey monofilament with a diameter of 0.26 mm, thus exerting a pressure of $7.3 \, g/mm^2$, on eight different sites for each foot (five apical fingertips, dorsal midfoot, heel and ball). The monofilament was perpendicularly applied three times for each site with a slight pressure that determines its arching so that the monofilament bends when the calibrated level is reached. Abnormal light touch testing was defined as one or more sites failing to detect two out of three applications.

Vibration threshold was assessed with a 100 Hz vibrameter using the method of limits. It was determined by the detection of onset of the vibratory stimulus on a bony prominence, the dorsal area of the first metatarsal shaft. The amplitude of the stimulus was slowly increased (1 μm/s, from 0 to 399.9 μm) until the patient reported feeling it. The vibration perception threshold was measured three times for each foot with a 10 s rest between measurements, the mean value was then calculated.

Thermal threshold and *heat-pain thresholds* were measured objectively using the Modular Sensory Analyzer Thermal Stimulator (*Somedic SenseLab, Sösdala, Sweden*). This computer-controlled device generates and documents response to highly repeatable thermal stimuli, such as warmth, cold and heat-induced pain. These stimuli are transmitted through a thermode (25×50 mm) which can be either cooled or warmed, placed dorsally over the metatarsophalangeal joints of both feet. The method of limits was again used to detect the thermal threshold and thermal-pain threshold. First, the perception threshold test (setting 'mix stimulus') was used to detect thermal sensitivity thresholds. Starting from a baseline temperature of $32°C$, five cold stimuli followed by five warm stimuli were administered at intervals of 5 s each. The stimulation rate was $1°C/s$, whereas the return to baseline rate was $3°C/s$. Patients were asked to press a switch that reversed the current at the precise moment they felt a sensation of cold or warm. The mean value of both thresholds was then calculated, and a warm–cold threshold range was finally determined. After that, for heat-pain threshold, a single heat stimulation (reaching a maximum of $50°C$) was

administered, and the patients had to press a switch to stop it at the precise moment they felt a sensation of pain.

The pathological impairment of each type of sensitivity assessed with QST was defined according to the different cut-offs reported in the literature, where there were no cut-offs from healthy subjects, those derived from diabetic neuropathy were used [18–20]. Patients were then considered as having large fiber neuropathy if at least one of the tactile and vibratory sensitivities was found pathological. Small fiber neuropathy was defined as the presence of impairment in at least one of thermal (both warm and cold) and pain sensitivities.

Patient-reported outcomes

The following PROMs were administered to assess the impact of PSN on physical disability and QoL:

- Scleroderma Health Assessment Questionnaire (SSc-HAQ): daily functional activity was assessed by 20 items grouped into 8 domains with the addition of 5 SSc-specific visual analog scales. Each item was converted in a score from 0 to 3, with higher scores corresponding to worse disability, and a final mean score was then calculated [21].
- Manchester Foot Pain and Disability Index (MFPDI): a 19-item tool developed to specifically assess foot pain and disability. Each item can score 0, 1 or 2, and the final score is their sum, with higher scores corresponding to greater foot pain and disability [22]. Disabling foot pain reflecting impaired physical function was considered when at least 1 of the 10 MFPDI function items were experienced on most/every day, i.e. with a score of 2 [23].
- SSc Quality of Life (SScQoL) questionnaire: a 29-item tool that measures the disease impact on health and well-being and that was developed using a needs-based QoL model. Each item can score 0 or 1, and the final score is their sum, with higher scores corresponding to worse health-related QoL [24].

Statistical analysis

Categorical data were described by absolute and relative frequency, continuous data were non-normally distributed and therefore summarized by median and interquartile range (IQR). To investigate the associations between QST, neuropathic symptoms and PROMs with disease characteristics, Mann–Whitney U test (two-tailed) and Fisher test were conducted to compare continuous and categorical variables among groups, respectively. False-discovery rate correction was applied for multiple comparisons. Spearman's correlation coefficient was calculated to assess the association between continuous variables. Multilinear regressions were computed to evaluate the influence of the different variables on the parameters of interest. Statistical significance was set at 0.05. All analyses were performed with R software (R Core Team 2023).

Results

Study population

One hundred and nine SSc patients (88.1% female, median age 59.0 years) were enrolled in the present study along with 51 HC comparable for median age and gender percentage.

Epidemiological and SSc-specific characteristics of the cohort are reported in Table 1. Most patients had lcSSc and more than half presented anti-centromere positivity. The median disease duration was 8.0 years and only 8 patients had a history of foot ulcers.

Neuropathic symptoms

One or more neuropathic symptoms were reported by 89 (82%) SSc patients, with a significantly higher prevalence of complaints for numbness (55%), paraesthesia (52%), stabbing pain (37%) and burning pain (35%) than HC ($P <$ 0.001 for all). Accordingly, patients had higher NRS scores in each domain (Fig. 1, $P < 0.001$ for all). Univariate analysis of each symptom against clinical features showed that burning pain was significantly associated with history of foot ulcers ($P = 0.009$), whereas stabbing pain showed a weak negative correlation with disease duration ($P = 0.001$; $\rho = -0.359$) and age ($P = 0.03$; $\rho = -0.214$). Notably, no other associations or correlations were found between neuropathic symptoms and epidemiological or SSc-specific characteristics.

Quantitative sensory examination

Consistent with patient-reported PSN symptoms, sensory testing showed statistically significant differences between SSc and HC in all domains (Table 2). SSc cases presented with a significant median reduction of areas with preserved tactile sensitivity (14 IQR 4 vs 16 IQR 2; $P < 0.001$) and a delayed vibration perception threshold (1.7 μm IQR 3.0 vs 1.1 μm IQR 1.3; $P = 0.01$). There was a greater number of SSc patients with impaired tactile sensitivity (54% [$n = 59$] vs 31% [$n = 16$]; $P = 0.007$), and a similar trend was observed for pathological vibratory sensitivity with no statistical significance (12% [$n = 13$] vs 6% [$n = 3$]; $P = 0.2$). When assessing thermal sensitivity, SSc patients showed a median cold threshold of 27.0°C (IQR 3.0) which was significantly lower compared with 28.2°C (IQR 2.9) from HC ($P < 0.001$). Similarly, SSc cohort revealed a higher median warm

Table 1. Epidemiological and disease-specific characteristics of the cohort

	SSc ($n = 109$)	HC ($n = 51$)	P-value
Age, years[a]	59.0 (51–66)	52.0 (43–63.5)	0.07
Female	96 (88.1%)	43 (84.3%)	0.7
BMI, kg/m^2[a]	25.9 (21.8–30.3)	24.9 (22.1–28.7)	0.6
Smoking habit	55 (50.5%)	21 (41.2%)	0.3
Current smoker	14 (12.8%)	5 (9.8%)	0.6
Disease duration, years[a]	8.0 (4.0–14.0)		
Skin subset			
dcSSc	24 (22%)		
lcSSc	85 (78%)		
mRSS[a]	2.0 (0.0–6.0)		
Autoantibody			
Anti-centromere	61 (56%)		
Anti-topoisomerase I	14 (12.8%)		
Other	34 (31.2%)		
History of foot ulcers	8 (7.3%)		
History of ulcers elsewhere	34 (31.2%)		
Immunosuppressants	24 (22%)		
Corticosteroids	23 (21.1%)		
Vasoactive drugs	98 (89.9%)		

No statistically significant differences between SSc and HC for every item reported.
[a] Data are reported in median (IQR) and n (%).
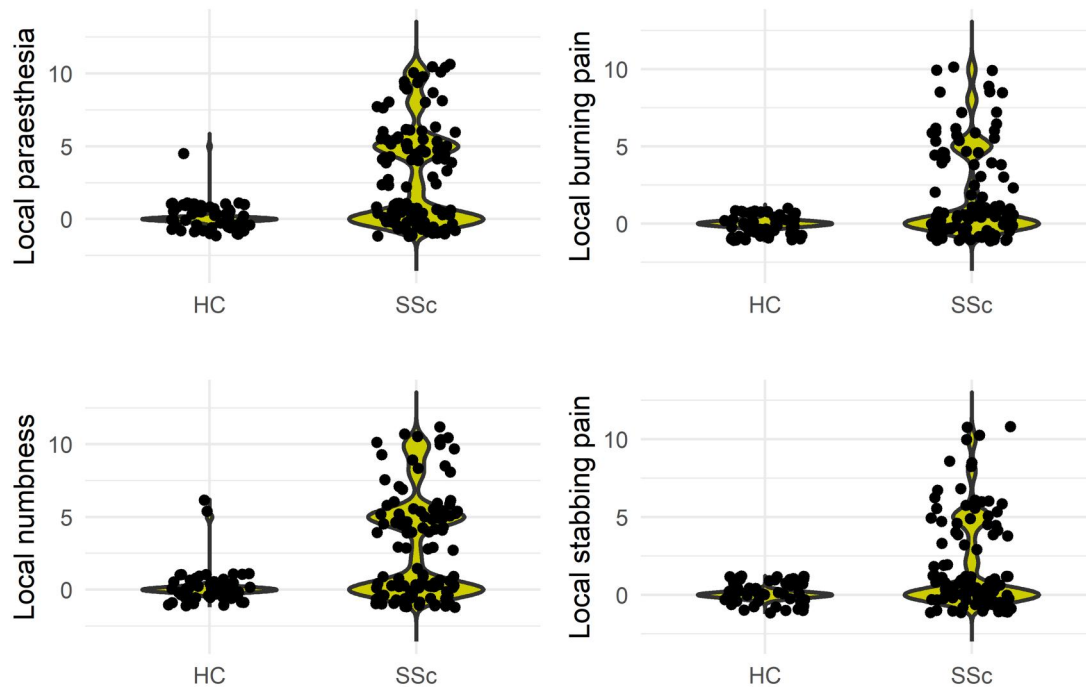mRSS: modified Rodnan skin score.

Figure 1. NRS scores for neuropathic symptoms between SSc and HC, showing data distribution by violin plots (*P* < 0.001 for all comparisons)

Table 2. Quantitative sensory testing results for SSc patients and healthy controls

	SSc (*n* = 109)	HC (*n* = 51)	*P*-value
Light touch mechanical threshold, n. areas with preserved sensitivity[a]	14.0 (12.0–16.0)	16.0 (14.0–16.0)	**<0.001**
Tactile sensitivity impaired, *n* (%)	59 (54)	16 (31)	**0.007**
Vibratory threshold, μm[a]	1.7 (1.0–4.0)	1.1 (0.6–1.9)	**0.01**
Vibratory sensitivity impaired, *n* (%)	13 (12)	3 (5.9)	0.2
Large fiber neuropathy, *n* (%)	62 (57)	17 (33)	**0.006**
Warm thermal threshold, °C[a]	38.4 (36.7–41.3)	37.2 (35.5–39.5)	**0.003**
Warm sensitivity impaired, *n* (%)	89 (82)	31 (61)	**0.005**
Cold thermal threshold, °C[a]	27.0 (25.3–28.3)	28.2 (26.5–29.4)	**<0.001**
Cold sensitivity impaired, *n* (%)	95 (87)	41 (80)	0.3
Warm–cold threshold range, °C[a]	11.2 (9.0–15.9)	8.9 (6.7–12.6)	**<0.001**
Thermal sensitivity impaired, *n* (%)	81 (74)	24 (47)	**<0.001**
Heat pain threshold, °C[a]	44.8 (43.1–46.6)	43.1 (41.0–44.6)	**<0.001**
Pain sensitivity impaired, *n* (%)	52 (48)	14 (27)	**0.015**
Small fiber neuropathy, *n* (%)	87 (80)	28 (55)	**0.001**

[a] Data are reported in median (IQR). Bold text indicates significant *P*-values.

threshold (38.4°C IQR 4.6 *vs* 37.2°C IQR 4; *P* = 0.003). As a result, SSc patients presented a median warm–cold threshold range of 11.2°C (IQR 6.9) which was significantly greater compared with 8.9°C (IQR 5.9) from HC (*P* < 0.001). The percentage of SSc patients with an impaired thermal sensitivity was meaningfully greater than HC (74% *vs* 47%; *P* < 0.001). Lastly, patients with SSc had a statistically significant reduction in pain perception when compared with HC (48% *vs* 27%; *P* = 0.015). They presented with a median heat pain threshold of 44.8°C (IQR 3.5), significantly higher compared with 43.1°C (IQR 3.6) from HC (*P* < 0.001), thus accounting for a greater reduction in pain perception in patients with SSc.

On the basis of these results, the presence of PSN was found in 93 (85.3%) SSc patients (Fig. 2A). In detail, 62 (57%) of them were classified as having large fiber neuropathy and 87 (80%) as having small fiber neuropathy (Fig. 2B), in both cases with significantly higher percentages than HC (*P* = 0.006 and *P* = 0.001, respectively). More than

half of SSc subjects had the co-presence of both large and small fiber neuropathy (Fig. 2C).

Out of 93 patients with PSN, 75 (80.6%) reported at least one neuropathic symptom. Interestingly, a subgroup of 18 (19.3%) SSc subjects who had PSN according to sensory testing did not report any neuropathic symptom. Ten (55.5%) of these patients had large fiber neuropathy, 16 (88.8%) had small fiber neuropathy, and 8 (44.4%) subjects presenting with both (Fig. 2D).

Association with disease characteristics

The relationship between sensory neuronal parameters and SSc disease characteristics was evaluated. We observed a weak negative correlation between age and the number of areas with preserved tactile sensitivity (*P* = 0.003, ρ = −0.287). Vibration threshold was found significantly higher in patients with smoking habit (*P* = 0.007) and history of foot ulcers (*P* = 0.03), showing a moderate direct correlation
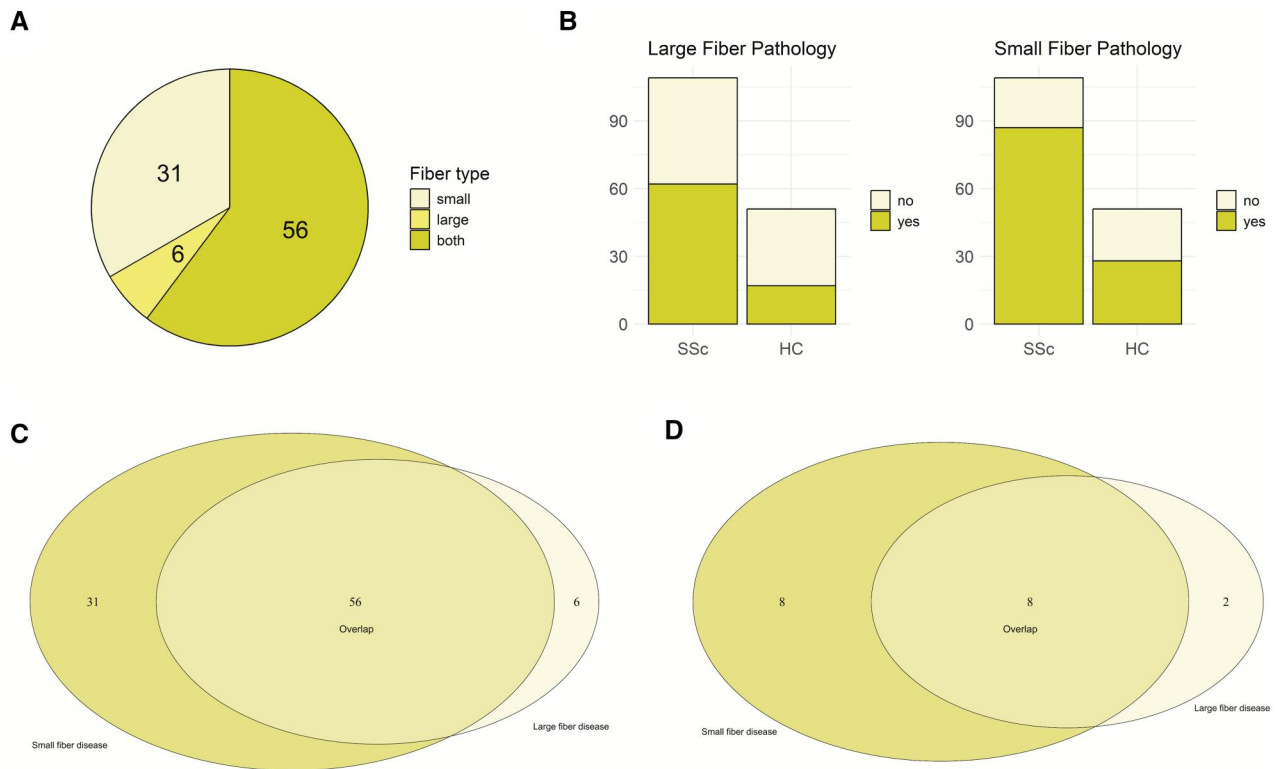
Figure 2. Distribution of small and large fiber neuropathy in the study population. (A) Distribution of fiber type neuropathy in SSc cohort (*n* = 109). (B) Prevalence of large and small fiber neuropathy across SSc and HC cohorts. (C) Overlap of small and large fiber neuropathy across SSc patients presenting at least one type of nerve pathology (*n* = 93). (D) Overlap of small and large fiber neuropathy in asymptomatic SSc patients presenting at least one type of nerve pathology (*n* = 18)

with age ($P < 0.001$; $\rho = 0.569$). A multivariate analysis confirmed the association of all these variables with vibration sensitivity (B = 2.16, $P = 0.006$ for smoking habit; B = 8.87, $P < 0.001$ for history of foot ulcers; B = 0.12, $P < 0.001$ for age). Warm sensitivity threshold was significantly associated with smoking habit ($P = 0.01$) and treatment with corticosteroids ($P = 0.009$). Moreover, a direct weak correlation was found with age ($P = 0.003$; $\rho = 0.279$) and disease duration ($P = 0.04$; $\rho = 0.219$). After a multivariate analysis, only corticosteroids and age were confirmed significantly associated with warm sensitivity threshold (B = 1.53, $P = 0.04$ and B = 0.06, $P = 0.01$, respectively). On the other hand, the only correlation found for cold sensitivity threshold was with age ($P = 0.006$; $\rho = -0.261$). As a result, warm–cold threshold range was significantly associated with smoking history ($P = 0.01$), corticosteroids treatment ($P = 0.04$) and weak correlated with age ($P = 0.001$; $\rho = 0.298$). In the multivariate analysis for warm–cold threshold range, only age was confirmed (b = 0.13, $P = 0.006$). Lastly, heat pain threshold was found in a direct weak correlation with age ($P = 0.007$; $\rho = 0.253$) and disease duration ($P = 0.03$; $\rho = 0.210$), both confirmed at a multivariate analysis (B = 0.04, $P = 0.01$ and B = 0.05, $P = 0.04$, respectively). Notably, other associations or correlations between QST results and age, disease duration, smoking habit, history of foot ulcers and corticosteroids use were not significant. Moreover, no associations were found between SSc sensory neuronal results and gender, autoantibody positivity, skin subset and treatment with immunosuppressants or vasoactive drugs.

When considering the presence of large and small fiber neuropathy in SSc cohort, patients affected were found to be significantly older ($P < 0.001$ and $P = 0.004$, respectively), especially when the two conditions co-existed ($P < 0.001$). Small fiber neuropathy was more frequent in patients with lcSSc and ACA positivity ($P = 0.03$ for both). No other relevant associations were found between the presence of large and/or small fiber neuropathy and epidemiological or disease-specific characteristics.

Impact on physical function and QoL

The relationship between PSN and physical function and QoL was then evaluated by different PROMS. SSc-HAQ revealed a median score of 1.25 (IQR 0.54–1.76). Subgroup analysis showed that SSc-HAQ was significantly higher in patients complaining of neuropathic symptoms such as paraesthesia (1.47 [IQR 0.95–1.89] *vs* 0.74 [IQR 0.46–1.38]; $P = 0.003$), numbness (1.47 [IQR 0.88–1.90] *vs* 0.70 [IQR 0.45–1.38]; $P < 0.001$) and stabbing pain (1.42 [IQR 0.75–1.86] *vs* 1.07 [IQR 0.45–1.73]; $P = 0.02$). Similar results were obtained for MFPDI that yielded a median score of 20 (IQR 8–26) and was significantly higher in patients complaining of paraesthesia (22 [IQR 14–28] *vs* 18 [IQR 4–22]; $P = 0.01$). Interestingly, according to MFPDI, 82 (75.2%) patients were affected by disabling foot pain (MFPDI > 4), and these patients were complaining more often of paraesthesia ($P = 0.007$), numbness ($P = 0.006$) and stabbing pain ($P = 0.04$). SScQoL showed a median score of 16 (IQR 8–22) and was significantly higher in patients complaining of paraesthesia (21 [IQR 11–24] *vs* 12 [IQR 6–20]; $P = 0.009$), numbness (21 [IQR 11–24] *vs* 11 [IQR 5–19]; $P = 0.003$) and stabbing pain (21 [IQR 12–23] *vs* 12 [IQR 5–21]; $P = 0.008$). SScQoL also presented a weak negative correlation

with cold sensitivity threshold ($P = 0.008$; $\rho = -0.249$). Apart from this, no other associations were found between PROMs and QST results or the presence of large/small fiber neuropathy.

Discussion

Peripheral neuropathy and foot involvement are two under-recognized aspects of SSc, but both are actually more frequent than previously thought [4, 11]. Moreover, they are both able to independently determine disability in SSc [13, 25]. The aim of our work was therefore to characterize PSN in SSc foot, then explore any association with disease-specific characteristics and assess its impact on physical disability and QoL.

In our cohort, SSc patients presented a significant alteration of all the sensory parameters examined in comparison with HC. Schady *et al.* [6] were among the first to look for peripheral neuropathy in SSc: they performed a complete QST in the hands and feet of 29 patients but found convincing signs of neuropathic impairment only for tactile and thermal sensitivity. More recently, Frech *et al.*[8] showed in 20 SSc patients a significant foot vibratory alteration when compared with HC and a trend for tactile impairment, which instead was found significant in the hands of 15 SSc subjects [26]. To the best of our knowledge, this is the largest SSc cohort undergoing a complete neuropathic assessment for small fiber and large fiber neuropathy of the foot, and our results confirm the presence of PSN already suggested in smaller cohorts. Our results highlight that PSN in SSc often affects small fibres, thus corroborating the several works that have reported a pathological impairment in thermal and nociceptive sensitivity, as well as in autonomic dysfunction [3, 7, 17]. Moreover, the co-presence of large and small fibre neuropathy was even more frequent, thus strengthening the relevance and the potential severity of PSN in SSc. Large fiber neuropathy also has been previously reported in symptomatic and asymptomatic SSc patients [9]. When symptomatic, the most prevalent complain in our cohort was numbness and paraesthesia, two symptoms commonly reported in clinic. It is also interesting to note that clinically asymptomatic patients were often affected by large and/or small fiber neuropathy so that subclinical PSN might be suspected even in SSc subjects not complaining of paraesthesia, numbness, stabbing or burning pain. Finally, in view of some reports suggesting an association between peripheral neuropathy and gastrointestinal motility disorders, which are expression of an autonomic dysfunction, it would be interesting to investigate whether in SSc patients PSN could potentially represent a surrogate marker for autonomic dysfunction, especially for gastrointestinal involvement [27, 28].

When evaluating associations with disease characteristics, age was the most impactful variable for almost all neurosensory parameters examined. These findings are in line with the well-recognized role of age in peripheral sensitivity [29]. While disease duration, smoking, history of foot ulceration and corticosterois use were significantly associated with one of the six sensory tests. We believe the significant association of smoking history and history of foot ulcers with vibratory sensitivity and the corelation with thermal sensitivity offers an interesting glimpse into the potential direct relationship between peripheral vasculopathy and neuropathy, re-purposing a pathogenetic model of interrelation already present in diabetes

[30]. Furthermore, the association with corticosteroid treatment could be related to animal findings that prolonged exposure to glucocorticoids often leads to maladaptive neuronal and glial plasticity consisting of both structural and functional changes, particularly regarding mechanical allodynia and thermal hyperalgesia, associated with the development of neuropathic pain [31, 32]. On the other hand, we observed an association between small fiber neuropathy and both lcSSc and anti-centromere positivity, not confirmed for large fiber neuropathy or their co-presence. In this context, there are contrasting results in the literature. In fact, there are studies that identify dcSSc and anti-centromere positivity as major risk factors for peripheral neuropathy [4, 33], whereas others found a significant association with lcSSc and positivity for anti-topoisomerase I and anti-U1-RNP [9, 34]. However, there are also studies that have not highlighted a particular influence of cutaneous involvement or autoantibody profile [6, 35]. In this regard, larger cohort, multicentre studies are needed to confirm association with specific disease characteristics.

From the evaluation of different PROMs, it clearly emerged that neuropathic symptoms as paraesthesia, numbness and stabbing pain are associated with worse physical disability and QoL. These findings confirm, expand and enrich those by Ivanova *et al.* [25], who observed that the severity of neuropathic symptoms is associated with a worse physical disability. On the other hand, the lack of significant associations between PROMs and QST results can be explained by the fact that PROMs are designed to reliably return the picture of subjective symptoms, while they may perform less well in capturing objectifiable instrumental alterations. However, it should be noted that MFPDI showed that three quarters of the SSc cohort is affected by disabling foot pain, and when compared with those without disabling foot pain the predominant neuropathy symptoms where parasthesia, numbness and stabbing pain.

The main limitation of our work is the absence of nerve conduction studies to corroborate large fiber neuropathy, and skin biopsies to corroborate small fiber neuropathy and obtain a histologic evaluation. Nonetheless, QST is recommended as a battery of tests to assess small fiber neuropathy [36]. The lack of use of the clinical total neuropathy score limits the comparison of our results with those of other similar studies that applied this assessment tool. Additionally, other underlying diseases or causes that could contribute to the PSN, for example, haematologic abnormalities, vitamin B12, B1 and B6 deficiency were not assessed. Moreover, the exclusion of patients with active ulcers and those with diabetes may have led to an underestimation of the true prevalence of PSN in SSc. Finally, given the cross-sectional design of this study, it is not possible to infer causality when speculating on the pathophysiological mechanisms.

In conclusion, we showed that foot peripheral neuropathy is a common clinical entity and represents a tangible burden on physical disability and QoL. However, routine screening for peripheral neuropathy is often not mentioned in best clinical practice guidelines [37]. Moreover, despite SSc patients have a relatively high prevalence of self-reported foot problems, their foot health care and information are usually inadequate [38]. These concerns are even more important when considering that SSc patients often present with a postural imbalance and a consequent increased risk of falls [39]. Therefore, the screening for PSN is something that should be taken into account during SSc workup, assessing the potential

presence of both small and large fiber neuropathy. Moreover, further longitudinal studies are required to determine whether the subclinical PSN is an early manifestation that will evolve into an overt clinical feature or just a mild manifestation that remains below clinical significance.

Conclusion

Foot PSN presents as common and disabling manifestation in patients with SSc, involving both large and small fibers, often co-existing. Clinically, the presence of neuropathic symptoms is associated with poorer physical function and QoL. Additionally, almost one in five patients with sensory testing proven PSN do not recognize their symptoms, supporting the role of PSN assessment as a valuable tool in SSc management.

Data availability

All data relevant to the study are included in the article. Further data are available from the corresponding author upon reasonable request.

Contribution statement

Conceptualization: B.A.-P., A.C.R., A.-M. K., M.B.; investigation: B.A.-P.; statistical analysis: M.D.B., S.D.D.; data curation: B.A.P., M.D.B., S.D.D.; writing—original draft preparation: M.D.B.; writing—review and editing: B.A.P., M.D.B., S.D.D., F.D.G.; visualization: B.A.P., M.D.B., A.C.R., A.-M.K., S.D.D., M.B., F.D.G.; supervision: F.D.G.

Funding

References

1. Di Battista M, Barsotti S, Orlandi M *et al.* One year in review 2021: systemic sclerosis. Clin Exp Rheumatol 2021;39(Suppl 131):3–12.
2. Amaral TN, Peres FA, Lapa AT, Marques-Neto JF, Appenzeller S. Neurologic involvement in scleroderma: a systematic review. Semin Arthritis Rheum 2013;43:335–47.
3. Di Battista M, Wasson CW, Alcacer-Pitarch B, Del Galdo F. Autonomic dysfunction in systemic sclerosis: a scoping review. Semin Arthritis Rheum 2023;63:152268.
4. Almehmadi BA, To FZ, Anderson MA, Johnson SR. Epidemiology and treatment of peripheral neuropathy in systemic sclerosis. J Rheumatol 2021;48:1839–49.
5. Di Trapani G, Tulli A, La Cara A *et al.* Peripheral neuropathy in course of progressive systemic sclerosis—light and ultrastructural study. Acta Neuropathol 1986;72:103–10.
6. Schady W, Sheard A, Hassell A *et al.* Peripheral nerve dysfunction in scleroderma. Q J Med 1991;80:661–75.
7. Poncelet AN, Connolly MK. Peripheral neuropathy in scleroderma. Muscle Nerve 2003;28:330–5.
8. Frech TM, Smith G, Reily M *et al.* Peripheral neuropathy: a complication of systemic sclerosis. Clin Rheumatol 2013;32:885–8.
9. Paik JJ, Mammen AL, Wigley FM *et al.* Symptomatic and electrodiagnostic features of peripheral neuropathy in scleroderma. Arthritis Care Res 2016;68:1150–7.
10. Dyck PJB, Hunder GG, Dyck PJ. A case-control and nerve biopsy study of CREST multiple mononeuropathy. Neurology 1997;49:1641–5.
11. Sari-Kouzel H, Hutchinson CE, Middleton A *et al.* Foot problems in patients with systemic sclerosis. Rheumatology 2001;40:410–3.
12. La Montagna G, Baruffo A, Tirri R, Buono G, Valentini G. Foot involvement in systemic sclerosis: a longitudinal study of 100 patients. Semin Arthritis Rheum 2002;31:248–55.
13. Bongi SM, Ravenni G, Ciampi B, Rosso AD, Aoufy KE. Biomechanical podiatric evaluation in an Italian cohort of patients with systemic sclerosis: a pilot study. Eur J Rheumatol 2016;3:169–74.
14. van den Hoogen F, Khanna D, Fransen J *et al.* 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis 2013;72:1747–55.
15. Zhong C, Cockburn M, Cozen W *et al.* Evaluating the use of friend or family controls in epidemiologic case-control studies. Cancer Epidemiol 2017;46:9–13.
16. LeRoy EC, Black C, Fleischmajer R *et al.* Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202–5.
17. Bajocchi G, Terlizzi R, Zanigni S *et al.* Evidence of a selective nociceptive impairment in systemic sclerosis. Clin Exp Rheumatol 2009;27:9–14.
18. Olaleye D, Perkins BA, Bril V. Evaluation of three screening tests and a risk assessment model for diagnosing peripheral neuropathy in the diabetes clinic. Diabetes Res Clin Pract 2001;54:115–28.
19. Santos TRM, Melo JV, Leite NC, Salles GF, Cardoso CRL. Usefulness of the vibration perception thresholds measurement as a diagnostic method for diabetic peripheral neuropathy: results from the Rio de Janeiro type 2 diabetes cohort study. J Diabetes Complications 2018;32:770–6.
20. Rolke R, Baron R, Maier C *et al.* Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006;123:231–43.
21. Steen VD, Medsger TA. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997;40:1984–91.
22. Garrow AP, Papageorgiou AC, Silman AJ *et al.* Development and validation of a questionnaire to assess disabling foot pain. Pain 2000;85:107–13.
23. Roddy E, Muller S, Thomas E. Defining disabling foot pain in older adults: further examination of the Manchester foot pain and disability index. Rheumatology 2009;48:992–6.
24. Ndosi M, Alcacer-Pitarch B, Allanore Y *et al.* Common measure of quality of life for people with systemic sclerosis across seven European countries: a cross-sectional study. Ann Rheum Dis 2018;77:1032–8.
25. Ivanova K, Žukovs D, Možeitoviča E *et al.* Prevalence of polyneuropathies among systemic sclerosis patients and impact on health-related quality of life. Neurol Neurochir Pol 2023;57:206–11.
26. Silva PG, Jones A, Araujo PMP, Natour J. Assessment of light touch sensation in the hands of systemic sclerosis patients. Clinics 2014;69:585–8.
27. Camilleri M. Gastrointestinal motility disorders in neurologic disease. J Clin Invest 2021;131:e143771.
28. Moors VJ, Graveran KD, Shahsavari D, Parkman HP. A cross-sectional study describing peripheral neuropathy in patients with symptoms of gastroparesis: associations with etiology, gastrointestinal symptoms, and gastric emptying. BMC Gastroenterol 2022;22:315.
29. Kenshalo DR. Somesthetic sensitivity in young and elderly humans. J Gerontol 1986;41:732–42.
30. Xia N, Morteza A, Yang F, Cao H, Wang A. Review of the role of cigarette smoking in diabetic foot. J Diabetes Investig 2019;10:202–15.
31. Takasaki I, Kurihara T, Saegusa H, Zong S, Tanabe T. Effects of glucocorticoid receptor antagonists on allodynia and hyperalgesia in mouse model of neuropathic pain. Eur J Pharmacol 2005;524:80–3.

32. Madalena KM, Lerch JK. The effect of glucocorticoid and glucocorticoid receptor interactions on brain, spinal cord, and glial cell plasticity. Neural Plast 2017;2017:8640970.

33. Manneschi LI, Del Rosso A, Milia AF *et al.* Damage of cutaneous peripheral nervous system evolves differently according to the disease phase and subset of systemic sclerosis. Rheumatology 2005; 44:607–13.

34. Hietarinta M, Lassila O, Hietaharju A. Association of anti-U1RNP-and anti-Scl-70-antibodies with neurological manifestations in systemic sclerosis (scleroderma). Scand J Rheumatol 1994; 23:64–7.

35. Raja J, Balaikerisnan T, Ramanaidu LP, Goh KJ. Large fiber peripheral neuropathy in systemic sclerosis: a prospective study using clinical and electrophysiological definition. Int J Rheum Dis 2021; 24:347–54.

36. Cascio MA, Mukhdomi T. Small fiber neuropathy. In: Primer on the autonomic nervous system, 4th edn. Treasure Island, Florida, USA: StatPearls Publishing, 2022: 565–8.

37. Smith V, Scirè CA, Talarico R *et al.* Systemic sclerosis: state of the art on clinical practice guidelines. RMD Open 2018;4:e000782.

38. Alcacer-Pitarch B, Siddle HJ, Buch MH *et al.* Foot health needs in people with systemic sclerosis: an audit of foot health care provision. Clin Rheumatol 2011;30:1611–5.

39. Yakut H, Özalevli S, Birlik AM. Postural balance and fall risk in patients with systemic sclerosis: a cross-sectional study. Arch Rheumatol 2021;36:167–75.