



Prevalence of polyneuropathies among systemic sclerosis patients and impact on health-related quality of life

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ABSTRACT

Introduction. Systemic sclerosis (SSc) is a chronic rheumatic disease that affects multiple organ systems, including the peripheral nervous system. However, studies into the involvement of polyneuropathies (PNP) have shown inconsistent results. The aim of this study was to determine the prevalence of small (SFN) and large (LFN) fibre neuropathy among SSc patients and the impact on health-related quality of life (HRQoL).

Material and methods. The study enrolled 67 patients with diagnosed SSc. The severity of neuropathic symptoms was evaluated using shortened and revised total neuropathy scoring criteria. Nerve conduction studies were used for LFN, and quantitative sensory testing was used to evaluate SFN. Neuropathic pain was evaluated using a Douleur Neuropathique en 4 questionnaire, and the severity of anxiety symptoms was assessed using a Generalised Anxiety Disorder-7 scale. The Health Assessment Questionnaire-Disability Index was used to assess HRQoL. Previous data on antinuclear autoantibodies (ANA) test results was obtained. Statistical analysis was performed using SPSS software.

Results. LFN was diagnosed in 47.8% (n = 32/67) and SFN in 40.3% (n = 27/67) of the subjects. ANA positivity was not associated with the presence of LFN/SFN. The severity of neuropathic pain had a significant correlation with anxiety symptoms (r = 0.61, p < 0.001), the severity of neuropathy symptoms (r = 0.51, p < 0.001) and HRQoL (r = 0.45, p < 0.001). The severity of neuropathy symptoms correlated with HRQoL (r = 0.39, p = 0.001).

Conclusions. We demonstrated that PNP are found in almost all SSc patients. Also, SFN is as common as LFN. Additionally, we found that the severity of neuropathy symptoms and neuropathic pain are both associated with a worse HRQoL.

Key words: systemic sclerosis, large fibre neuropathy, small fibre neuropathy, neuropathic pain, anxiety, health-related quality of life
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Introduction

Systemic sclerosis (SSc), also known as scleroderma, is a rare chronic rheumatic disease characterised by immune activation, widespread vascular damage, and progressive fibrosis [1, 2]. The hallmark of this disease is thickening and hardening of the skin, but other organ systems are also commonly affected, leading to considerable morbidity

and mortality. Many patients complain about one or more symptoms of gastroesophageal reflux disease, but more severe upper and lower gastrointestinal tract involvement can be associated with malnutrition. Restricted joint mobility, arthritis, renal failure, heart and pulmonary complications are the main causes of morbidity and mortality in the course of SSc [2]. Additionally, the peripheral nervous system can also be affected [3]. Neurological involvement includes both

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compression (e.g. trigeminal neuropathy, carpal tunnel syndrome, ulnar nerve entrapment) and non-compression (e.g. sensorimotor neuropathy, sensory ataxic neuropathy, multiple mononeuropathies) neuropathies [4].

Neuropathy was previously thought to be a less common SSc finding [5]. However, recent studies have shown that neurological involvement is fairly common. The prevalence of peripheral neuropathy in SSc ranges from 17% [6] to 40% [7], with a pooled prevalence close to 30% [3, 4]. Probably due to the rarity of the disease, the methods used in these studies and the characteristics of the study groups, the results differ and the extent of peripheral nervous system involvement remains unclear. Moreover, there are only a few studies on polyneuropathy that have differentiated small (SFN) from large fibres (LFN). To the best of our knowledge, no nationwide study of peripheral nervous system disorders among SSc patients has previously been carried out in the Baltic countries.

As a chronic systemic disease, SSc affects patients' health-related quality of life (HRQoL), with a number of problems associated with decreased functional status and increased disability [8, 9]. It is unclear whether HRQoL has a direct association with SSc or nervous system involvement, as other factors such as anxiety and neuropathic pain can worsen patients' HRQoL.

The aim of this study was to define the prevalence of SFN and LFN among patients with SSc, based on a population-wide cohort in Latvia, and to identify factors associated with LFN or SFN development. Additionally, we aimed to identify the effects of LFN and SFN, the severity of neuropathic pain, and anxiety symptoms related to HRQoL.

Material and methods

Materials

This study was performed on Latvian patients diagnosed with SSc in accordance with the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) criteria [10] who were diagnosed or consulted in the period from 1 January 2016 to 30 September 2021 at either of Latvia's adult university hospitals: Riga Eastern Clinical University Hospital and Pauls Stradins Clinical University Hospital. In total, 109 SSc patients were assessed for participation and 67 (54 women and 13 men, age range 23 to 83 years) were enrolled in the study.

Methods

According to the ACR/EULAR criteria [10], patients were assessed for skin thickening on the fingers, fingertip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), Raynaud phenomenon (RP), and SSc-related autoantibodies. Disease duration was determined based on the occurrence of the first non-Raynaud's phenomenon symptom. The general severity of cutaneous involvement was assessed using

the modified Rodnan skin score (mRSS) [11]. Additionally, all subjects were asked regarding specific therapy use (e.g. cyclophosphamides) and common health conditions (e.g. diabetes, thyroid diseases) that are known to be causative for peripheral neuropathy. Previous data on antinuclear autoantibody (ANA) test results was obtained. ANA tests were performed on peripheral blood serum by indirect immunofluorescence using HEP-2 ANA indirect fluorescent antibody (IFA) assays [12].

Enrolled subjects underwent a uniform evaluation of the peripheral nervous system. Firstly, patients were screened using the shortened and revised total neuropathy scoring criteria (srTNS) [13], which consists of three symptom extension components (numbness, tingling, and neuropathic pain) and two objective testing components (tendon reflex and vibration sensibility). Next, the patients were examined using nerve conduction studies (NSC) by a certified neurophysiology expert. Nerve conduction studies were performed on both motor and sensory conduction according to the polyneuropathic examination protocol. Each patient underwent bilateral upper extremities NCS (motor and sensory components of ulnar and median nerves) and bilateral lower extremities NCS (motor component of peroneal and tibial nerves and sensory components of a sural nerve) for nerve conduction latency, amplitude, and velocity. Those subjects who had abnormal NCS results according to the normal values used in Latvian clinical practice [14, 15] in more than one attribute in two separate nerves were diagnosed as having large fibre polyneuropathy. Quantitative sensory testing (QST) was performed in the subjects with normal NSC results in order to evaluate small fibre function for possible abnormalities [16]. Thermal (warm, cold, painful warm/painful cold) sensations were checked. Stimuli were applied to the thenar region of the hands and the dorsal surface of the feet. QST results were compared to normative data, and those subjects who had abnormal values in two separate extremities were diagnosed as having small fibre polyneuropathy.

Additionally, all enrolled subjects completed the Latvian version of the Douleur Neuropathique en 4 (DN4) [17] questionnaire to assess neuropathic pain, the Generalised Anxiety Disorder-7 (GAD-7) [18] scale to assess anxiety symptoms, and the Health Assessment Questionnaire-Disability Index (HAQ-DI) [19] to assess HRQoL. Those patients scoring four or more points on the DN4 questionnaire were defined as having neuropathic pain. More than four points on the GAD-7 questionnaire indicates an increased risk of generalised anxiety. The eight scores of the eight sections of the HAQ-DI were added together and divided by eight to provide the functional disability index.

Statistical analysis

Statistical analysis was performed using SPSS 27.0 software (SPSS Inc., Chicago, IL, USA). Data normality was assessed using histograms and the Kolmogorov-Smirnov test.

Table 1. Clinical characteristics of SSc subjects with and without peripheral neuropathy

Characteristic	No neuropathy (n = 8; 11.9%)	Large fibre neuropathy (n = 32; 47.8%)	Small fibre neuropathy (n = 27; 40.3%)
Median age	62.5 (IQR, 9.25)	66.5 (IQR, 10.50)	57.0 (IQR, 17.50)
Female sex	8 (100%)	24 (75%)	22 (81.5%)
Male sex	0	8 (25%)	5 (18.5%)
Age at scleroderma onset	46.5 ± 15.4	51.0 ± 13.8	40.7 ± 17.4
Median duration of SSc	15.0 (IQR, 13.50)	19.5 (IQR, 17.25)	12.0 (IQR, 13.50)
Scleroderma subtype			
Limited	5 (62.5%)	23 (71.9%)	22 (81.5%)
Diffuse	3 (37.5%)	9 (28.1%)	5 (18.5%)
Median Rodnan score	11.0 (IQR, 14.50)	6.0 (IQR, 10.0)	4.0 (IQR, 10.0)
Antinuclear antibodies	7 (87.5%)	26 (81.3%)	21 (77.8%)
Anti-centromere		<i>Data not shown</i>	
Anti-SCL70		<i>Data not shown</i>	
Speckled		<i>Data not shown</i>	
Nucleolar		<i>Data not shown</i>	
Homogenous		<i>Data not shown</i>	
Median TNS	2.0 (IQR, 3.50)	7.0 (IQR, 5.25)	0 (IQR, 3.50)
Median DN4 score	3.0 (IQR, 3.50)	4.0 (IQR, 6.0)	3.0 (IQR, 7.5)
Median GAD-7 score	8.0 (IQR, 13.0)	4.5 (IQR, 10.25)	5.0 (IQR, 7.50)
Median HAQDI score	0.81 (IQR, 1.47)	1.63 (IQR, 1.72)	0.63 (IQR, 1.56)
Without risk factors	5 (62.5%)	18 (56.3%)	20 (74.1%)
With risk factors	3 (37.5%)	14 (43.8%)	7 (25.9%)
Treatment with cyclophosphamide	1 (12.5%)	9 (28.1%)	6 (22.2%)
Treatment with chemotherapy	2 (25%)	2 (25%)	0
Diabetes mellitus	0	0	1 (3.7%)
Thyroid diseases	0	3 (9.4%)	2 (3.7%)
Chronic renal diseases	0	4 (12.5%)	3 (3.7%)

TNS — total neuropathy score; DN4 — douleur neuropathique 4; GAD-7 — general anxiety disorder-7; HAQDI — Health Assessment Questionnaire Disability Index

For comparison between groups, the Kruskal-Wallis H test, Spearman's rank-order correlation and Fisher's exact tests were used. P values < 0.05 were considered significant.

Ethical approval

This study was approved by the Ethics Committee of Riga Stradiņš University [Nr. 22-2/481/2021]. All subjects were informed about the rationale and goals of the study, signed an informed consent form, and gave their permission for anonymised publication of their clinical information.

Results

The median age of the study group was 64 years (IQR, 12.0). Out of 67 enrolled patients, 54 (80.6%) were female and 13 (19.4%) were male. The median age at the onset of SSc

was 47 (IQR, 19.5) years and the median duration of disease was 16 (IQR, 15.0) years. 52.2% of subjects had the limited subtype of SSc (n = 35/67), while 47.8% had the diffuse type (n = 32/67). A description of the SSc groups divided by the presence of polyneuropathy and its type is set out in Table 1.

Based on the NCS evaluation, LFN was identified in almost half of the SSc individuals (47.8%, n = 32/67). Furthermore, the majority of individuals who did not have LFN showed signs of SFN, evaluated by QST (40.3%, n = 27/67); only 11.9% (n = 8/67) of the subjects did not fulfil any criterion for SFN or LFN. A comparison of the clinical features, as well as neuropathy risk factors between these three groups, is set out in Table 1.

To identify the aetiology of the peripheral nervous system involvement in SSc, we analysed the prevalence of neuropathy risk factors among the SSc patients. Neuropathy risk factors as

a possible secondary cause were defined in 35.8% of subjects ($n = 21/59$). These included treatment with cyclophosphamides, chemotherapy, diagnosed diabetes mellitus, thyroid disorders, and chronic renal disease [20–22]. However, the same risk factors were present in 37.5% ($n = 3/8$) of individuals without neuropathy and there was no difference in risk factor prevalence among the subjects with LFN, with SFN, or without neuropathy ($p > 0.05$). Because we understood that the small number of SSc patients without polyneuropathy affected the statistical power of the given result, we further analysed other factors that could explain the presence of LFN or SFN.

There were no associations between the presence of LFN or SFN and sex ($p = 0.32$), age ($p = 0.63$), disease duration ($p = 0.64$), severity of cutaneous involvement ($p = 0.19$), subtype of SSc ($p = 0.73$), or ANA positivity ($p = 0.91$), nor with any specific subtype of ANA ($p = 0.93$) (ANA subtype data not shown).

LFN patients had higher TNS scores [median TNS = 7.0 (IQR, 5.25)] than SFN patients [median TNS = 0 (IQR, 3.5)] and also higher than subjects without neuropathy [median TNS = 2.0 (IQR, 3.5)], but the difference was not statistically significant ($p = 0.37$).

There were no significant differences between LFN/SFN and the severity of neuropathic pain ($p = 0.46$), anxiety symptoms ($p = 0.75$), or HRQoL ($p = 0.68$). However, the severity of neuropathic pain had a significant correlation with anxiety symptoms ($r = 0.61$, $p < 0.001$), the severity of neuropathy symptoms ($r = 0.51$, $p < 0.001$), and HRQoL ($r = 0.45$, $p < 0.001$). Additionally, the severity of neuropathy symptoms had a moderately strong correlation with HRQoL ($r = 0.39$, $p = 0.001$).

Discussion

In this study, we performed a detailed evaluation of large and small fibre polyneuropathy in a large cohort of SSc patients from Latvia. By systematically analysing both LFN and SFN, we identified that the prevalence of peripheral neuropathy in SSc patients is very high, affecting ~90% of patients. Even though some subjects had possible secondary causes (risk factors) for their neuropathy, we did not find any significant differences between individuals with polyneuropathy and those without, although the second group of patients was not big enough to make a firm conclusion of neuropathy to be developed independently of known risk factors.

Additionally, we found that neuropathic pain is common among SSc patients and that neuropathic pain has a significant correlation with the total neuropathic score and the severity of anxiety symptoms. While the presence of LFN or SFN did not reach statistical significance, neuropathy-related symptoms (both neuropathic pain and severity assessed by the TNS) affected SSc patients' HRQoL.

Our study revealed a higher prevalence of polyneuropathy in SSc than has been found in other studies, but only a few studies have performed as detailed and targeted an evaluation of the peripheral nervous system as we have. Furthermore, the

materials and methods used in those studies provide a large range of results. A recent systematic review of 113 studies [4] showed a pooled prevalence of neuropathy involvement in 27.37% of cases, including 26% ($n = 556/2,143$) with SFN and 10.8% ($n = 231/2,143$) with LFN when neuropathies were assessed based on small and large fibres.

However, the titles and abstracts were not selected according to strict criteria regarding evaluated neuropathies, including all works where peripheral neuropathy was reported by symptoms and clinical examination, nerve conduction studies or other detection tools. LFN was observed in many studies on isolated or multiple mononeuropathies [23–30], and confirmatory diagnostic tests differed depending on the design of the study. Some studies performed electrophysiological examinations [27, 28, 31], while others used imaging techniques [23, 26, 32], biopsy [26, 30] or other methods. Only a few studies showed similar results to our study. One study on the role of ultrasound imaging in the evaluation of peripheral nerves in SSc [32] showed sensory disturbances revealed by clinical examination in 40% ($n = 10/25$) of subjects, but the imaging modalities used (ultrasound, computer tomography, magnetic resonance) revealed abnormalities in 7/10 patients. However, a peripheral nervous system examination was performed only on median and ulnar nerves, observing compression neuropathies. We believe that the high prevalence of LFN can be explained by the fact that we were working with a relatively large study group and that all subjects were evaluated using both clinical symptoms and electrophysiological methods, where motor and sensory components were studied on several nerves of each extremity.

Our study suggests that small fibre abnormalities are common in SSc, and that neurological events appear in almost all SSc patients, with the predominant involvement of small fibres, although there are limitations on assessing small fibre function. As mentioned above, in a recent systematic review of peripheral neuropathy in SSc [4], the prevalence of SFN was more than double that of LFN. In our study, SFN was less prevalent than LFN; even so, of those subjects who did not show abnormalities by NCS, only eight had normal QST results. The high prevalence of SFN may be associated with skin changes due to SSc, but there was not a significant difference between the severity of cutaneous involvement and the presence of SFN.

The diagnosis of SFN can be challenging because the diagnostic criteria for SFN are not yet fully established. This lack of standardised diagnostic criteria for SFN may indeed have implications on our research in terms of the definition of SFN, since our study subjects were defined to have SFN solely based on their QST results [33, 34]. We did not detect specific gene mutations for transthyretin familial amyloid polyneuropathy as a rarer underlying cause of SFN and LFN [35, 36]. Neither were autoantibodies in SFN tested, for example antisulfatide and anti-plexin antibodies, which could be specific for small fibre neuropathies and may be a key pointer towards explaining the high frequency of small fibre polyneuropathies in our study [37].

We speculate that the autoimmune nature of polyneuropathy could justify immunomodulatory therapy use such as plasma exchange for those SSc patients who show neuropathic symptoms [38, 39]. Thus more specific examinations of possible autoantibodies should be performed as the next stage of research.

Our study assessed neuropathic pain in SSc patients and showed that LFN and SFN subjects have a tendency towards higher DN4 scores, with no direct association with the severity of neuropathic pain, but a significant association between neuropathic pain and the severity of neuropathy symptoms where both affect SSc patients' HRQoL. Neuropathic pain occurs in many rheumatic diseases and neuropathic pain is thought to be more prevalent in these patients than in the general population [40]. A Danish nationwide cross-sectional registry survey (DANBIO) on pain and pain mechanisms in patients with inflammatory arthritis showed neuropathic pain in 20% of rheumatic arthritis patients, 28% of psoriatic arthritis patients, and 21% of spondylarthritis patients [41]. The prevalence and severity of neuropathic pain in SSc patients is not well-studied and is not yet established. One cross-sectional study on neuropathic pain in SSc patients showed that neuropathic pain was significantly higher in SSc patients compared to control subjects (56.2% vs. 13.3%) [42]. In our study, we assessed the severity of neuropathic pain by the DQ4 in all study participants. Only 18 subjects (26.87%) scored zero points on the DQ4. We found neuropathic pain to have an important impact on SSc patients' HRQoL, but it is unclear whether neuropathic pain affects HRQoL independently of, or in relation with, a higher severity of neuropathy symptoms. Moreover, our study supports the concept of neuropathic pain being associated with the severity of anxiety symptoms, showing significance between the DN4 and GAD-7 scores [43].

The main limitation of this study was the size of our study group. Although we enrolled 67 out of 109 SSc patients who were examined at Latvia's university hospitals over the course of 5.75 years, we believe that more statistical significance would be found with a larger study group. The small number of SSc patients is explained by the rarity of the disease and Latvia's small population. Another limitation was the small fibre function being assessed by QST only. To clarify the involvement of SFN, a skin punch biopsy should be performed to measure epidermal nerve fibre density (ENFD), since the results of such a biopsy can provide more objective diagnostic data for defining SFN.

Conclusions

We demonstrated an unexpectedly high prevalence of polyneuropathy in Latvian SSc patients, showing that the peripheral nervous system is affected in almost all patients. Moreover, we found SFN to be as common as LFN. Another important finding in our study is that the severity of neuropathy symptoms and neuropathic pain were both associated

with a higher health-related disability index, indicating worse HRQoL. The presence of polyneuropathy was not associated with known risk factors. Therefore it is necessary to seek other reasons for the presence of SFN and LFN in SSc patients, possibly associated with specific antibodies.

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