Frequency and impact of disease symptoms experienced by patients with systemic sclerosis from five European countries

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ABSTRACT

Objective. *Knowledge about the nature and impact of symptoms faced by patients with systemic sclerosis (SSc) is needed to identify targets for research and treatment. The aim of this study was to assess and compare the frequency and impact on everyday activities of SSc symptoms among patients from five European countries.*

Methods. *European patients with SSc were invited through announcements by patient associations to complete an online survey. The survey included items assessing the frequency of 40 SSc symptoms and the impact on daily activities, if present. Chi-square tests were utilised to assess the differences in frequency and impact of symptoms across countries.*

Results. *In total, 537 patients were included from France (n=111), the Netherlands (n=229), Spain (n=61), Switzerland (n=50), and the United Kingdom (n=86). Symptoms experienced by ≥70% of patients in all countries were fatigue, Raynaud's phenomenon, joint pain, and muscle pain. Twenty symptoms were experienced by ≥50% of patients in all countries. Thirty symptoms had an impact on daily activities in ≥50% of patients who reported that the symptom was present in all countries. There were significant differences among countries in the prevalence of 17 out of 40 symptoms. Furthermore, in 24 out of 40 symptoms significant differences in the proportion of patients reporting impact of a specific symptom on everyday activities were observed.*

Conclusion. *European patients with SSc experience a broad range of symptoms that have an impact on everyday activities. International research initiatives should target common SSc symptoms cooperatively. Further research is needed to better understand the differences in SSc symptoms among countries.*

Introduction

Systemic sclerosis (SSc, or scleroderma) is a rare, clinically heterogeneous, autoimmune connective tissue disease. The disease is characterised by thickening and fibrosis of the skin, fibrosis of internal organs, and vascular damage (1). SSc has an important impact on physical functioning and health-related quality of life (2-16).

Several studies have used qualitative or survey methods to identify the most frequently experienced and impactful physical and emotional symptoms in patients with SSc, including pain, fatigue, functional limitations, stiffness of joints, concerns with physical appearance, and uncertainty about future outcomes (17-19). These studies generally assessed only a relatively narrow range of potential problems, even though SSc is a highly heterogeneous disease with a wide range of potentially problematic symptoms that vary across patients (20). Only two studies have examined a broader range of symptoms and their impact on daily functioning (3, 21). A Canadian study, in which 464 SSc patients participated, assessed the frequency and impact on daily activities of 69 possible symptoms of SSc and showed that fatigue, Raynaud's phenomenon, stiffness of hands, joint pain, and difficulty sleeping were the most frequently present symptoms, and that these symptoms impacted the ability to carry out everyday activities in the vast majority of patients (3). The authors also identified symptoms that had an important role in patients' daily lives, but that have been overlooked in research, including, for instance, sleep problems. Among 128 Brazilian SSc patients, using the same survey as the Canadian study, the five most commonly reported symptoms were joint pain, skin tightening, heartburn, difficulty concentrating, and difficulty with memory (21).

No studies have examined the frequency and impact of a broad range of SSc symptoms in Europe. Patient-oriented research that involves international collaboration, however, depends on understanding the frequency and impact of problems faced by patients with SSc in order to prioritise problems for future research and intervention. Geographic and national differences in disease severity and manifestation have been reported (22), but the frequency and impact of problems faced by patients have not been compared across countries.

The aim of this study was to describe similarities and differences in prevalence of symptoms and their impact on everyday activities among patients with SSc from five European countries: France, the Netherlands, Spain, Switzerland, and the United Kingdom (UK).

Table I. Demographics and disease characteristics of 537 patients with systemic sclerosis per country.

Characteristics	France (n=111)	Netherlands (n=229)	Spain (n=61)	Switzerland (n=50)	UK (n=86)
Female, %*	96.4	83.8	80.3	88.0	89.5
Age, years; median (IQR)*	55 (45-62)	60 (51-66)	49 (43-56)	56.5 (49-67)	57.5 (48-63)
> 12 years education, %*	53.8	46.3	62.3	38.0	34.9
Living with partner, %	67.3	72.6	65.6	64.0	72.1
Paid employment, %*	33.6	20.7	52.5	42.0	37.2
Disease subtype, %*					
Limited	52.3	63.8	52.4	30.0	54.7
Diffuse	35.1	32.3	27.9	62.0	37.2
Subtype unknown	12.6	3.9	19.7	8.0	8.1
Time since diagnosis, years; median (IQR)*	8 (4-15)	9 (4-15)	8 (3-13)	5 (3-11)	6 (3-12)
Number of symptoms, median (IQR)*	24 (18-29)	22 (18-27)	18 (13-25)	21 (16-29)	26 (19-31)
Number of symptoms with impact if present, median (IQR)*	20 (12-23)[a]	14 (8-18)[b]	14 (11-21)[c]	14 (9-21)[d]	18 (11-26)[e]

UK: United Kingdom; IQR: interquartile range; *$p<0.05$; [a] n=102; [b] n=225; [c] n=35; [d] n=30; [e] n=78.

Patients and methods

Patients and procedure

An anonymous survey was distributed through patient organisations in 16 European countries (Belgium, Cyprus, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Portugal, Spain, Switzerland, and the UK). The current study included data from the five countries with at least 50 respondents (France, the Netherlands, Spain, Switzerland, and the UK). Data were collected between December 2010 and November 2011. Two different methods were used for the recruitment of SSc patients. In the Netherlands, the Dutch organisation for patients with systemic autoimmune diseases (Nationale Vereniging voor Lupus, APS, Sclerodermie en MCTD; NVLE) mailed members with SSc an invitation to complete the survey. Patients in the other European countries were invited to participate through the Federation of European Scleroderma Associations and national scleroderma associations, which advertised the survey on their websites, in their newsletters and via information e-mailed to their members. The survey was administered via the internet in all countries, and patients in the Netherlands and Switzerland also had the opportunity to receive a paper version on request.

To be included in the current study, survey respondents had to be 18 years or older and diagnosed with SSc by a physician (self-report). Possible duplicate surveys, based on matching demographic data, were removed, and patients who did not complete ≥10% of the survey items on symptom frequency and impact (8 of 80 items) were excluded.

Patients did not provide signed informed consent due to the anonymous nature of the survey. Ethical approval was obtained from the local medical ethics board of the Radboud University Medical Center for the Dutch part of the study (CMO 2011/203), and from the ethics committee of the Centre for Research in Psychology at the University of Minho in Portugal for the other European countries.

Questionnaire

The English and French versions of the Canadian Scleroderma Patient Survey of Health Concerns and Research Priorities (3) were provided by the Canadian research group. The survey was translated into Spanish, German, and Dutch by qualified translators. For each translation, patient representatives from the given country reviewed the survey to ensure that items were understandable, unambiguous, and acceptable.

Demographic variables included sex, age, education, marital status, current employment status, self-reported disease subtype and time since diagnosis. Of the 69 symptoms included in the Canadian survey (3), the 30 most frequently experienced symptoms and the 30 symptoms with the highest impact in that study were included in the European survey (33 items), as well as 7 additional items (persistent coughing, dilated face vessels, nausea, medication side effects, difficulty opening mouth, open sores, weight loss). Patients rated each symptom on frequency, "How frequently have you experienced (*insert symptom*) in the past year?" with the response options *never*, *rarely*, *sometimes*, *most of the time*, *always*. If a symptom was at least rarely present, the impact on daily activities was assessed: "Please specify the degree of impact that (*insert symptom*) has had on your ability to carry out everyday activities in the past year." with the response options *no impact*, *minimal*, *moderate*, *severe*, *extremely severe*.

Statistical analysis

Differences in demographic and disease characteristics across countries were assessed using the chi-square statistic for categorical variables and the Kruskal-Wallis test for continuous variables.

Symptom frequency and impact were recoded into dichotomous variables,

with 'never or rarely' *versus* 'sometimes, most of the time, or always' for frequency and 'no impact or minimal impact' versus 'moderate, severe, or extremely severe impact' for impact (3). The proportion of patients reporting that a symptom was present was calculated, as well as the proportion of patients reporting an impact on everyday activities (only for those patients reporting the given symptom was present). Responses on the items for vaginal dryness and erectile dysfunction were included only from women and men, respectively.

We used the chi-square statistic to assess possible differences in frequency and impact across countries for each symptom. We used α=0.05 and the Benjamini-Hochberg method to adjust for multiple tests since there were 40 frequency analyses and 40 impact analyses. We did not conduct post-hoc tests within symptoms to attempt to identify specific differences between countries, given the number of potential tests this would involve, beyond the 80 tests already conducted. As a sensitivity-analysis to examine the robustness of the differences in frequency and impact of symptoms, differences in median scores were also assessed with the Kruskal-Wallis test, similarly adjusting with the Benjamini-Hochberg method. Finally, we tested for differences across countries in the median number of symptoms and the median number of symptoms with an impact per patient using the Kruskal-Wallis test. All statistical analyses were conducted using Stata/IC 10.1 software (StataCorp LP, College Station, TX).

Table II. Frequency of 40 symptoms experienced by patients with systemic sclerosis in Europe (n=537).

Symptoms[1]	France (n=111) %	Netherlands (n=229) %	Spain (n=61) %	Switzerland (n=50) %	UK (n=86) %
Fatigue*	96	95	76	85	93
Raynaud's phenomenon	85	90	84	83	98
Joint pain	84	80	81	83	92
Stiffness of hands*	76	83	59	73	91
Muscle pain	74	70	76	79	86
Skin tightening	68	75	73	79	79
Erectile dysfunction	75	75	50	100	100
Difficulty sleeping	76	69	71	80	84
Shortness of breath*	73	65	86	84	76
Tender joints*	77	71	49	69	79
Difficulty holding objects*	70	72	51	63	85
Dry mouth	74	69	55	69	79
Difficulty climbing stairs	69	68	62	73	68
Heartburn*	71	59	73	74	76
Difficulty making fist*	63	67	41	49	76
Difficulty concentrating*	61	55	75	77	75
Dry eyes	62	62	53	66	67
Difficulty walking	56	61	60	66	63
Skin color change*	55	59	78	40	73
Vaginal dryness	68	53	62	76	58
Difficulty swallowing*	53	56	56	77	70
Dilated hand vessels*	66	55	49	44	74
Difficulty remembering*	59	49	62	79	70
Swollen joints*	68	48	70	57	65
Itching*	61	48	70	69	67
Diarrhoea	54	56	53	60	67
Numbness	60	52	69	63	54
Skin pain	53	58	45	53	58
Difficulty opening hand	54	51	40	41	60
Constipation*	52	42	54	65	64
Difficulty in/out car	42	51	49	61	59
Persistent coughing*	49	37	76	73	45
Nausea	44	46	34	55	47
Dilated face vessels	49	42	45	24	48
Side effects	49	41	43	41	41
Difficulty opening mouth	39	44	40	39	44
Difficulty dressing*	41	32	56	41	55
Finger ulcers	36	37	56	50	37
Open sores	22	31	40	39	35
Weight loss	26	28	31	37	25

[1]Symptoms are ordered in the table by the overall frequency among all patients from the five countries; UK: United Kingdom; *p<0.05 for differences in proportion of patients among countries based on chi-square test with Benjamini-Hochberg correction.

Results

Sample characteristics

In total, 537 European patients with SSc were included, from France (n=111), the Netherlands (n=229), Spain (n=61), Switzerland (n=50), and the UK (n=86). Demographics and disease characteristics for each country are displayed in Table I. In total, 68 men and 469 women were included, with a median age of 57 (interquartile range [IQR] = 48–64) years. About half of the respondents completed more than 12 years of education, and approximately 70% were married or living as married. The majority of the patients (55%) had limited SSc, 36% had diffuse SSc, and 9% did not know their disease subtype. The mean time since diagnosis was 8 (IQR=4–14) years.

There were some notable differences in sample characteristics between countries. The percentage of female participants was highest in France (96%) and lowest in Spain (80%). Patients in the Netherlands were the oldest (median age=60, IQR=51–66 years) and least likely to be employed (21%), whereas patients in Spain were the youngest (median age=49, IQR=43–56 years) and most likely to report paid employment (53%). The median time since diagnosis ranged from 5 (IQR=3–11) years in Switzerland to 9 (IQR=4–15) years in the Netherlands. Overall, approximately half of the patients were diagnosed with limited SSc and one-third of the patients with diffuse SSc, except in Switzerland where 30% reported having limited SSc and 62% diffuse SSc. The proportion of patients with more than 12 years of education ranged from 35% in the UK to 62% in Spain.

Table III. Impact on everyday activities of 40 systemic sclerosis symptoms if present.

Symptoms[1]	France %	Netherlands %	Spain %	Switzerland %	UK %
Difficulty walking	92	83	96	79	84
Fatigue*	94	84	76	63	92
Swollen joints*	96	74	83	81	85
Finger ulcers*	46	86	96	76†	97
Stiffness of hands*	94	82	96	63	75
Joint pain*	95	74	85	80	81
Raynaud's phenomenon*	91	79	78	62	78
Difficulty holding objects	89	76	87†	74	75
Muscle pain*	91	70	94	71	78
Difficulty climbing stairs*	88	73	86	63	78
Difficulty sleeping*	89	70	81	62	81
Difficulty opening hand*	89	66	83†	83†	80
Difficulty making fist*	94	65	94†	67†	81
Open sores*	96†	70	55†	57†	90
Erectile dysfunction	67†	67†	83†	100†	89†
Tender joints*	88	66	81†	70	75
Side effects	87	65	77†	80†	71
Skin tightening*	85	63	81	63	83
Shortness of breath	NA	76	55	71†	69
Difficulty concentrating	85	66	64	64	70
Heartburn*	87	52	97	73	67
Difficulty swallowing	79	65	72†	53	73
Difficulty dressing	76	67	75†	71†	56
Skin pain	73	60	89†	65†	73
Diarrhoea*	86	56	64†	52†	77
Vaginal dryness*	83	58	62†	61†	65
Difficulty in/out car*	87	58	86†	52	60
Difficulty opening mouth	84	60	67†	50†	61
Dry eyes*	84	50	88†	68	64
Numbness*	77	47	70	74	67
Difficulty remembering	71	58	72	51	61
Constipation*	81	47	62	36†	76
Nausea	71	52	53†	56†	66
Dilated hand vessels*	85	39	57†	50†	61
Weight loss	79	47	43†	58†	62†
Dry mouth	69	50	64†	46	53
Persistent coughing	NA	50	52†	42†	68
Itching*	55	25	87	41	41
Skin colour change	39	34	53	38†	50
Dilated face vessels*	52	23	70†	20†	43

[1]Symptoms are ordered in the table by the overall impact among all patients from the five countries; UK: United Kingdom; *$p<0.05$ for differences in proportion of patients among countries based on chi-square test with Benjamini-Hochberg correction; NA: not administered in the French version of the survey due to technical failure; †based on ≤25 respondents.

Comparisons among countries

Frequency

The percentages of patients in each country who experienced each symptom are shown in Table II (detailed country-level results in Appendices 1–5). The symptoms fatigue, Raynaud's phenomenon, joint pain, and muscle pain were experienced by ≥70% of the patients in each country. In the five countries, each of the 40 symptoms was experienced by at least 22% of the patients and 20 of 40 symptoms were experienced by at least half of the patients in all countries.

Statistically significant differences across countries were found for 17 of the 40 symptoms. Of these 17 symptoms there were very large differences (>30%) in reported symptoms between countries for persistent coughing (37% in the Netherlands *vs*. 76% in Spain), skin color change (40% in Switzerland *vs*. 78% in Spain), difficulty making a fist (41% in Spain *vs*. 76% in the UK), difficulty holding objects (51% in Spain *vs*. 85% in the UK), and stiffness of hands (59% in Spain *vs*. 91% in the UK). When ordinal item data were compared across countries, there were differences in Raynaud's phenomenon, dry mouth, dilated face vessels, difficulty with sleeping, difficulty fully opening the hand, and erectile dysfunction, in addition to the 17 items identified via analysis of dichotomous data.

Impact

As shown in Table III (see also Appendices 1–5 in the online Supplementary data file for detailed country-level results), in each country all 40 symptoms, when present, had an impact on daily functioning for ≥20% of the patients and 30 out of 40 symptoms had an impact ≥50% of patients in all countries. Difficulty walking, swollen joints, joint pain, difficulty holding objects, and muscle pain impacted daily functioning for ≥70% of the patients in all countries. In addition, symptoms related to decreased hand function, including difficulty opening hand (66%–89%), difficulty making a fist (65%–94%), stiffness of hands (63%–96%), and Raynaud's phenomenon (62%–91%) impacted the ability to carry out everyday activities in the majority of patients.

Statistically significant differences among countries in the proportion of patients who reported an impact on everyday activities once a symptom was present were found in 24 out of 40 symptoms (Table III). Of these 24 symptoms, symptoms with at least 25 respondents with differences of >30% between countries included itching (25% in the Netherlands *vs*. 87% in Spain), dilated hand vessels (39% in the Netherlands *vs*. 85% in France), finger ulcers (46% in France *vs*. 97% in the UK), constipation (47% in the Netherlands *vs*. 81% in France), dry eyes (50% in the Netherlands *vs*. 84% in France), heartburn (52% in the Netherlands *vs*. 97% in Spain), difficulty getting in/out a car (52% in Switzerland *vs*. 87% in France), stiffness of hands (63% in Switzerland *vs*. 96% in Spain), and fatigue (63% in Switzerland *vs*. 94% in France). When ordinal item data were compared across countries, there were also differences in weight loss, difficulty opening the mouth, dry mouth, and difficulty swallowing. However, there were eight symptoms (stiffness of hands, joint pain, difficulty sleeping, Raynaud's phenomenon, tender joints, difficulty opening the hand, difficulty

climbing stairs, vaginal dryness) not significantly different compared to the analysis of dichotomous data.

Number of symptoms

The median number of symptoms experienced in the past year differed significantly across countries ($\chi^2(4)=28.5$, $p<0.05$), and ranged from 18 in Spain to 26 in the UK (Table I). The median number of symptoms with an impact on the ability to carry out everyday activities in the past year also differed significantly across countries ($\chi^2(4)=23.3$, $p<0.05$), and ranged from 14 in the Netherlands, Spain, and Switzerland to 20 in France.

Discussion

This was the first study that examined the frequency and impact of a broad range of symptoms experienced by patients with SSc in Europe. Overall, European patients with SSc experienced many different symptoms, often simultaneously. Fatigue, Raynaud's phenomenon, joint pain, and muscle pain were experienced by at least 70% of patients in all five countries. These symptoms also frequently had an impact on the ability to carry out everyday activities.

The results of our study confirm findings among Canadian and Brazilian patients regarding the high prevalence of symptoms faced by patients with scleroderma (3, 21). In line with these studies, fatigue and symptoms related to hand function were highly prevalent in our sample, and had an impact on daily functioning in the majority of patients.

Although fatigue and problems related to functional disabilities in SSc are increasingly recognised in the literature (3, 12, 13, 23-26), non-pharmacological interventions targeting these symptoms in SSc are scarce (27). There have been studies that have evaluated interventions to improve hand function in patients with SSc, but none have included a sufficiently large number of patients to robustly assess the effectiveness of these interventions (28-32). Beyond hand function, at least 80% of the patients in each country reported difficulty walking, which commonly impacted the ability to carry out everyday activities. Currently, however, there are no studies that describe interventions to address problems with walking in patients with SSc. Consistent with this, authors of recent EULAR guidelines for the treatment of SSc indicated that no recommendations could be made for or against non-pharmacological interventions that address functional problems because of a lack of evidence, despite the potential of these interventions to help patients (33). Thus, there is an urgent need to develop and rigorously test non-pharmacological interventions that focus on reducing fatigue and improving hand function and mobility in SSc.

In addition, differences across countries in the frequency and the impact of SSc symptoms were identified as well. Further research is warranted to better understand and explain these differences, since it is not clear whether differences may be attributed to different disease profiles or to different access to services, such as physical or occupational therapy, or assistive devices.

In a rare disease context, international collaborations play an important role, and large international consortia will be needed to better understand the nature and impact of symptoms in SSc and to develop and test interventions addressing these symptoms. Currently, multiple international consortia, including the Scleroderma Patient-centered Intervention Network (27, 34) and the EULAR Scleroderma Health Professionals Network (EUSHNet) (35) have been established to address this important care gap.

This study has limitations that should be considered when interpreting the results. First, the generalisability of our results may be limited because the study was conducted in a convenience sample, and the survey was distributed through patient associations. As a consequence, it was not possible to verify the patient-reported diagnosis and medical information. However, patients rarely report a diagnosis that is incompatible with their clinical diagnosis (36). Second, it is unclear to what extent the observed differences in the frequency and impact of SSc symptoms reflect actual differences in disease presentation, or whether it is a consequence of sampling differences, differences in climate, culture, or the management of SSc. Finally, the survey did not include mental health problems in the symptom list, and was limited by single-item assessment of symptoms and the lack of open-ended response options for symptoms that were not listed.

In conclusion, European patients with SSc experienced a broad range of symptoms, many of which had an impact on the ability to carry out everyday activities. Differences as well as similarities in disease presentation exist among European patients with SSc. International research initiatives should target common symptoms of SSc cooperatively, for instance to develop and evaluate non-pharmacological interventions to reduce fatigue, limitations in hand function, and difficulty walking.

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