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BRIEF REPORT

High prevalence of occupational exposure to solvents or silica in male systemic sclerosis patients: a Belgian cohort analysis

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Abstract

Increasing evidence supports a relation of some occupational exposures to systemic sclerosis pathogenesis. We aimed to evaluate occupational exposure and clinical characteristics in male patients with systemic sclerosis followed in two Belgian academic hospitals. One hundred and three male patients, included in the Belgian Systemic Sclerosis Cohort, were identified. An expert in occupational medicine reviewed the occupational history and allocated the patients to one of the following groups: probable exposure to crystalline silica, probable exposure to solvents, probable exposure to other toxins, or no suspected occupational exposure. Clinical characteristics were extracted from the Belgian Systemic Sclerosis Cohort database. Sufficient data were available for 96/103 patients. Most of these male patients (70/96, 72.9%) had a history of occupational exposure, 55 patients were likely exposed to crystalline silica, 11 patients to solvents, 2 patients to both silica and solvents, and 2 patients to asbestos. Only 26 patients had no suspected occupational exposure (27.1%). We noticed a significant difference in smoking status between exposed and non-exposed patients, with the highest percentage of ever smokers in the group with solvent exposure ($p = 0.011$). We found no significant differences in disease phenotype between exposed and non-exposed patients. However, we noted a trend to a higher prevalence of anti-Scl70 antibodies, cardiac dysfunction, and higher disease activity score in patients with occupational exposure. We observed a strikingly high prevalence of occupational exposure to both silica and solvents in male systemic sclerosis patients. Occupational exposure to silica or solvents is highly prevalent in male systemic sclerosis patients.

Keywords Crystalline silica · Environment · Occupational exposure · Solvents · Systemic sclerosis

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Introduction

Both genetic and environmental factors are thought to play a role in the pathogenesis of systemic sclerosis (SSc) [1, 2]. SSc is a rare autoimmune connective tissue disease with high morbidity and mortality. It has a variable disease expression but is consistently characterized by autoantibody production, small-vessel vasculopathy, and increased fibrogenesis affecting the skin and/or internal organs [3]. Pulmonary (interstitial lung disease and pulmonary arterial hypertension) and cardiac involvement are leading causes of death in SSc [4, 5].

Increasing evidence supports a role of occupational exposure to crystalline silica or solvents and this association appears to be stronger in males [6–11]. Reported data on occupational exposure in male systemic sclerosis patients are

limited in sample size due to the natural sex imbalance in disease occurrence. SSc predominantly affects women with a reported sex ratio of 4–9/1 [12, 13]. In males, an independent association with the diffuse cutaneous subtype, pulmonary hypertension, and heart involvement has been reported, all associated with a more severe disease course and impaired prognosis [14]. Here, we aimed to evaluate occupational exposure and clinical characteristics in a substantial number of male systemic sclerosis patients followed in two Belgian academic hospitals.

Methods

Patients

The Belgian Systemic Sclerosis Cohort (BSSC), initiated in 2006, is a multicenter prospective cohort including patients fulfilling ACR 1980 systemic sclerosis criteria [15, 16]. This registry was approved by each institution's ethical committee review board. All patients signed a written informed consent. For this study, we evaluated male patients included in the BSSC that were under care at the rheumatology and general internal medicine departments at the University Hospital of Leuven and the Cliniques Universitaires Saint-Luc (Université Catholique de Louvain), between 2006 and 2015.

Assessment of exposure

Patients included in the BSSC are routinely scheduled for follow-up visits at baseline, at 6 months, and yearly thereafter. Every visit includes detailed history and clinical examination, laboratory testing, and the following technical investigations: electrocardiogram (ECG), chest X-ray, pulmonary function test (PFT), and Doppler echocardiography. Baseline visit includes a high-resolution computed tomography (HRCT), which is repeated upon clinical indication. Baseline assessment includes an occupational history. An expert in occupational medicine and toxicology (BN) reviewed the detailed history and identified four groups: probable occupational exposure to crystalline silica, probable occupational exposure to solvents, probable occupational exposure to asbestos, or no occupational exposure. Probable silica exposure was suspected in patients with construction-related occupations (electricians, joiners, masons, tilers, plumbers, and pipefitters) or an occupation in glass industry, concrete, sandblasting, foundry metal work, or the mining industry. Probable solvent exposure was suspected in patients working in paint industry or in patients with occupational exposure to white spirit, trichloroethylene, or petroleum. Smoking status was dichotomized between ever smokers (past smokers, current smokers) and never smokers.

Assessment of disease characteristics

The following data were recorded in the BSSC registry: death, age, disease duration (defined as time of onset of first non-Raynaud phenomenon), subset (diffuse cutaneous SSc (dcSSc) or limited cutaneous SSc (lcSSc), according to criteria by LeRoy et al., upper gastro-intestinal (GI) symptoms (dysphagia, heartburn, early satiety, bloating, vomiting), lower gastro-intestinal symptoms (diarrhea, constipation, intestinal distention), telangiectasia, digital ulcers, modified Rodnan skin score (mRSS), arthritis, biochemical tests: antinuclear antibodies (ANA) assessed by indirect immunofluorescence and extractable nuclear antigens (ENA), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatinine kinase (CK) (positive when higher than upper limit of normal), and disease activity score (DAS) according to the European Scleroderma Study Group [17, 18]. Heart involvement was evaluated by the last recorded electrocardiogram and echocardiography, assessing ejection fraction (EF), diastolic function, and pulmonary arterial pressure (PAP) [19]. Conduction defect was defined as left or right bundle branch block or left anterior hemiblock. Arrhythmia was defined as sinus arrhythmia, atrial fibrillation, atrial flutter, atrioventricular block, or ventricular arrhythmia. Presence of a pacemaker was recorded. High-resolution computed tomography findings included adenopathies and interstitial pulmonary changes (honeycombing, ground glass opacities, and fibrosis). Pulmonary function tests assessed forced vital capacity (FVC), forced expiratory volume (FEV1), and diffusing capacity for carbon monoxide (DLCO).

Statistical analysis

For a two-group comparison involving binary data, we used the Fisher exact test. Comparisons involving continuous data were performed using Student's t test when distribution of variables was normal and Mann-Whitney test in other cases. For three-group comparisons involving binary data, we used the chi-square test. Comparisons involving continuous data were performed using one-way ANOVA when distribution of variables was normal and the Kruskal-Wallis test in other cases. $P < 0.05$ was considered significant.

Results

Patient population

We identified 103 male systemic sclerosis patients, included in the BSSC registry. All were white Europeans. Patient characteristics are described in Table 1.

Table 1 Clinical and serological characteristics of the total population

	Total population $N = 103$
Death (*n*, %)	18 (17.5)
Median age (*n*, range)	57.1 (25–81)
Subtype (*n*, %)	
dcSSc	45 (43.7)
lcSSc	58 (56.3)
ANA (*n*, %)	
Scl70	39 (37.9)
Anti-centromere	25 (24.3)
U1RNP	2 (1.9)
Fibrillarin	1 (1.0)
Th/To	1 (1.0)
SSA	10 (9.7)
Pm/Scl	2 (1.9)
SSB	1 (1.0)

Scl70 topoisomerase 1, *U1RNP* U1 ribonucleoprotein, *SSA* anti-Sjögren's syndrome-related antigen A/Ro60, *Pm/Scl* polymyositis/scleroderma, *SSB* anti-Sjögren's syndrome-related antigen A/La

Occupational exposure

After review of available data on occupational history, seven patients were excluded from further analysis because of insufficient information to allow for a proper allocation to one of the groups. Expert review identified 55 patients with probable occupational exposure to crystalline silica (57.3%), 11 patients with probable occupational exposure to solvents (11.5%), 2 patients with combined silica and solvent exposure (2.1%), and 2 patients with probable asbestos exposure (blue-collar jobs). Only 26 patients (27.1%) were considered to have so-called white-collar jobs, without occupational exposure. Hence, as many as 72.9% (70/96) of male systemic sclerosis patients have a history of occupational exposure.

Disease characteristics

We observed a significant difference in smoking status as a substantially higher proportion of patients with blue-collar jobs had a history of past or current smoking habits ($p = 0.003$) (Table 2). None of the other assessed clinical characteristics were significantly different between both groups. We note a numerical difference in the prevalence of anti-Scl70 antibodies (34/70 patients with blue-collar jobs versus 7/26 patients with white-collar jobs, $p = 0.067$). Patients with occupational exposure to silica or solvents tended to have a higher disease activity score (mean 2.5 versus 1.5, $p = 0.055$) and a trend to increased prevalence of diastolic dysfunction (32/70 patients with blue-collar jobs versus 6/26 patients with white-collar jobs, $p = 0.060$). In our work, we did not observe significant differences in cardiopulmonary involvement between individuals with or without suspected occupational exposure.

Clinical characteristics in specific occupational exposure groups

Due to the low number ($n = 2$), patients with probable occupational exposure to asbestos were not included in further subanalysis. When comparing clinical characteristics across the different types of exposure groups, we note a high prevalence of past or current smokers in the solvent-exposed group (90.9%) versus the silica-exposed (81.8%) and no exposure groups (53.8%) ($p = 0.011$) (Table 2). We did not find significant associations between specific exposure and disease characteristics such as cardiopulmonary involvement. We did observe a significant difference in the age of solvent-exposed patients. They were older than patients in both other groups (mean age of 62, versus 57 and 58 in the silica-exposed and no exposure groups, respectively, $p = 0.045$).

Discussion

This study demonstrates that male patients with SSc have a high prevalence of occupational exposure to silica or solvents. Systemic sclerosis has a multifactorial etiology and develops in patients with a susceptible genetic background, upon exposure to specific, at present largely unknown, environmental triggers. Twin concordance for SSc is remarkably low (4.7%), indicating that environmental and acquired (e.g., epigenetic) genetic factors strongly dominate inherited genetics in disease development [1].

Chemical exposure has long been proposed to play an important role in SSc. However, small sample sizes and wide variation in the assessment of exposure, as well as differences in analysis methods, result in an unclear view on this relation. Increasing data support the existence of a correlation between crystalline silica exposure and SSc. In 1957, Erasmus was the first to describe the co-occurrence of silicosis and systemic sclerosis in gold miners and the number of reports linking so-called blue-collar jobs to the occurrence of autoimmune diseases, including systemic sclerosis, has been increasing ever since [19–21]. Crystalline silica is released in sandblasting, granite cutting, sand factory work, concrete work, construction work, and bricklaying, among others [2]. In 2008, Smith et al. demonstrated that the prevalence of construction-related professions in males with SSc was tenfold higher than in the general working population (50 versus 5%). Interestingly, when applying a broader definition of construction-related occupations, as much as 75% of men with SSc were considered to have a construction-related occupation [10]. Of note, in this study, only 20 male patients were

Table 2 Clinical and biochemical features in male patients with systemic sclerosis and occupational exposure to crystalline silica, solvents, or asbestos compared with those without occupational exposure

	White-collar jobs ($n = 26$)	Blue-collar jobs ($n = 70$)	p value	Occupational exposure to silica ($n = 55$)	Occupational exposure to solvents ($n = 11$)	p value
Age (mean, range)	58 (25–80)	57 (37–81)	0.717	57 (37–81)	62 (42–76)	0.045
Death (n, %)	2 (7.7)	9 (12.9)	0.722	9 (16.4)	5 (45.5)	0.070
Age at death (mean, range)	57 (49–63)	62 (47–74)	0.311	59 (47–71)	69 (60–74)	0.032
Ever smoker (n, %)	14 (53.8)	59 (84.4)	0.003	45 (81.8)	10 (90.9)	0.011
Disease duration (mean, range)	10 (0.5–34)	9 (1–34)	0.540	9 (1–35)	8 (3–13)	0.137
Disease duration at death (mean, range)	12 (2–40)	6 (1–18)	0.742	6 (1–13)	6 (1–18)	0.858
SSc subtype (n, %)						
lcSSc	16 (61.5)	38 (54.4)	0.645	27 (49.1)	4 (36.4)	0.337
dcSSc	10 (38.5)	32 (45.7)	0.645	28 (50.9)	7 (63.6)	0.337
History (n, %)						
Upper GI symptoms	13 (50.0)	40 (57.1)	0.645	29 (52.7)	8 (72.7)	0.416
Lower GI symptoms	8 (30.8)	20 (28.6)	0.807	15 (27.3)	4 (36.4)	0.819
Cardiac symptoms	5 (19.2)	22 (31.4)	0.311	18 (32.7)	3 (27.3)	0.451
Dyspnea	8 (30.8)	40 (57.1)	0.246	34 (61.8)	7 (63.6)	0.375
Cough	10 (38.5)	25 (35.7)	1	21 (38.2)	3 (27.3)	0.778
Clinical examination						
Digital ulcers (n, %)	17 (65.4)	39 (51.4)	0.645	33 (60.0)	5 (45.5)	0.527
Telangiectasia (n, %)	12 (46.3)	28 (40.0)	0.487	23 (41.8)	4 (36.4)	0.851
mRSS (mean, range)	9 (0–35)	10 (0–37)	0.313	11 (0–11)	7 (0–18)	0.334
Tendon friction rubs (n, %)	2 (7.7)	12 (17.1)	0.338	11 (20.0)	9 (81.8)	0.119
Arthritis (n, %)	5 (19.2)	18 (25.7)	0.599	12 (21.8)	5 (45.5)	0.197
Biochemistry						
Scl70 (n, %)	7 (26.9)	34 (48.6)	0.067	25 (45.5)	4 (36.4)	0.275
Elevated CK levels (n, %)	9 (34.6)	24 (34.3)	1	17 (30.9)	7 (63.6)	0.117
ESR (mm/h, mean and range)	18 (2–83)	19 (2–60)	0.423	18 (2–60)	14 (2–34)	0.160
CRP (mg/l, mean and range)	8.4 (0.0–169.0)	3.9 (0.0–43.3)	0.137	7.0 (0.0–43.3)	3.0 (0.3–8.4)	0.255
DAS (mean, range)	1.5 (0–5)	2.5 (0–8)	0.055	2.5 (0.0–7.5)	3.0 (0.0–8.0)	0.128
Electrocardiogram (n, %)						
Conduction defect	5 (19.2)	15 (21.4)	1	13 (23.6)	2 (18.2)	0.863
Arrhythmia	1 (3.8)	8 (11.4)	0.4363	8 (14.5)	0 (0.0)	0.162
Pacemaker	2 (8.7)	1 (1.4)	0.177	1 (0.0)	0 (0.0)	0.309
Echocardiography						
Ejection fraction (mean, range)	61 (30–80)	60 (17–82)	0.797	61 (34–82)	57 (17–79)	0.681
PAP (mmHg) (mean, range)	30 (12.0–63)	34 (13–88)	0.355	32 (13–82)	42 (15–88)	0.396
Diastolic dysfunction (n, %)	6 (23.1)	32 (45.7)	0.060	25 (45.5)	6 (54.5)	0.093
PFT (% predicted, mean, range)						
FEV1	84 (50–114)	86 (36–133)	0.708	84 (36–133)	97 (68–125)	0.177
FVC	90 (47–139)	92 (29–140)	0.637	91 (29–140)	98 (76–118)	0.151
TLC	91 (61–138)	89 (46–144)	0.666	90 (46–144)	88 (67–108)	0.355
DLCO	53 (14–100)	56 (14–101)	0.563	57 (14–101)	48 (20–96)	0.521
HRCT (n, %)						
Adenopathy	11 (42.3)	33 (47.1)	0.649	28 (50.9)	3 (27.3)	0.328
Ground glass opacities	11 (42.3)	25 (35.7)	0.637	18 (32.7)	5 (45.5)	0.582
Fibrotic changes	7 (26.9)	9 (12.9)	0.126	8 (14.5)	1 (9.1)	0.289

$P < 0.05$ was considered significant

included. In 2014, Marie et al. evaluated 100 SSc patients (22 males) and 300 controls matched for age, gender, and smoking habits. In that study, crystalline silica, white spirit, aromatic solvents, chlorinated solvents, TCE, ketones, and welding fumes were associated with SSc, with increased risk in exposed males [8]. Overall, silica exposure has been repeatedly suggested to be a risk factor predominantly in the male SSc population [11]. The mechanism by which silica exposure leads to autoimmunity is largely unknown, but increasing literature could in time shed a light, as elegantly reviewed by Pollard [22]. Likewise, correlations between exposure to organic solvents and SSc have been observed in case-control studies, with a meta-analytic risk estimate of 2.4, higher in men (OR 3.0) than women (OR 1.8) [6]. Two recent meta-analyses further strengthened the ever-increasing evidence and noted an overall OR of 2.81 of silica and an overall OR 2.00 of solvent exposure in in SSc patients [23]. Separate analyses for specific solvent subtypes indicated that SSc was associated with aromatic solvents (OR, 2.72; 95% CI, 1.21–6.09), trichloroethylene (OR, 2.07; 95% CI, 1.34–3.17), halogenated solvents (OR, 1.49; 95% CI, 1.12–1.99), and ketones (OR, 4.20; 95% CI, 2.19–8.06) [24].

The abovementioned studies share a limitation: although male sex is typically dominant in the exposure groups, the overall ratio between males and females in SSc results in very small sample sizes. It is well established that SSc predominantly affects females [12]. The increasing evidence for occupational exposure in SSc development in males, notably affected by a more severe disease course and largely underrepresented in the available case-control studies, motivated our group to perform an exploratory study evaluating occupational exposure and clinical characteristics in a larger group of male SSc patients. In our cohort, we note a history of occupational exposure (combined silica, solvents, and asbestos) in as many as 72.9% of male patients. The majority was exposed to silica in construction-related occupations. This finding firmly strengthens the accumulating evidence resulting from diverse series and urges the scientific community to continue research into the role of occupational exposure in SSc pathogenesis.

Previous reports observed differences in disease characteristics between exposed and non-exposed patients. Marie et al. noted that exposed SSc patients (83.3% males in silica-exposed group) were more frequently suffering from the diffuse SSc subset, interstitial lung disease, and macroangiopathy [9]. A recent systematic review showed that silica-exposed SSc patients more often suffered from the diffuse disease subset, with increased frequency of ILD [11]. We could not confirm these findings in our cohort of male patients. We did observe a trend to higher percentage of anti-Scl70 antibodies, higher disease activity score, and increased prevalence of diastolic dysfunction, all associated with a severe disease phenotype, but not reaching statistical significance. We did observe a significant difference in the age of solvent-exposed patients. They were older than patients in both other groups. The relevance of this is unclear, as the numerical difference is low, as well as the number of solvent-exposed patients. This finding does not appear to result from reduced mortality rates, or increased disease duration at time of death in the solvent-exposed group.

In this study, we observe a remarkable difference in smoking status between the groups with occupational exposure, compared to white-collar professions. The highest percentage of smokers is found in the group with suspected solvent exposure and by far exceeds the reported smoking behavior in the Belgian adult population (overall percentage of current smokers 23% in 2016) (http://www.who.int/tobacco/surveillance/policy/country_profile/bel.pdf). Smoking status could be a confounding factor in our findings. However, a large case control study performed in 2011 found no evidence to support the notion that smoking confers a risk for development of SSc, although it may impact disease severity [25]. This finding, however, merits further investigation, as both additive as synergistic mechanisms between the different toxins might be in play eventually necessitating further prevention.

Our study has clear limitations. First, occupational exposure was not evaluated by a standardized questionnaire with detailed assessment of the nature, probability, intensity, frequency, and duration of exposure, precluding calculation of an exposure score. Secondly, there is no control group in our study. However, we do think it is highly unlikely that the proportion of construction-related occupations would be higher than that observed in our cohort. Furthermore, the difference in smoking status is a possible confounding factor in our study, but may well reflect a true synergistic pathogenic mechanism. The strength of our study lies in the large number of male patients, confirming the preliminary presumption of a significant role of occupational exposure in the subgroup of male patients. High quality epidemiological research is urgently needed, investigating the role of smoking and occupational exposure in SSc disease development. In doing so, the choice of adequate controls and high-quality assessment of exposure and potential confounders is crucial. Providing support for this hypothesis will not only lead to better epidemiological insights into SSc but also suggest that prevention can have an impact on disease incidence.

In conclusion, we firmly believe that our work adds to the presented ever-increasing scientific evidence that occupational exposure plays a crucial role in systemic sclerosis, especially in male subjects.

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Compliance with ethical standards

Disclosures None.

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