Prevalence and clinical manifestations of Erasmus syndrome in systemic sclerosis: a cross-sectional study

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ABSTRACT

Introduction: Erasmus syndrome (ErS) is a rare entity in which Systemic Sclerosis (SSc) develops following exposure to silica, with or without associated silicosis. The objectives of this study were: 1) to evaluate the prevalence of ErS in our SSc cohort; 2) to characterize the cases; 3) to evaluate the clinical and laboratory characteristics of SSc in patients with (Ers) or without silica exposure.

Methods: Cross-sectional study. Sociodemographic, clinical and laboratory data were collected from all patients with SSc diagnosed in our department according to ACR / EULAR criteria. Data on professional activity and possible exposure to silica were obtained by phone interview.

Results: Among 48 patients with SSc, the prevalence of ErS was 16.7% (8/48). All cases identified were male, corresponding to 72.7% of men with SSc followed at our department. There was a statistically significant association between ErS and male gender ($p<0.001$), initial pulmonary manifestation ($p=0.005$), history of digital ulcers ($p=0.014$) and smoking ($p=0.047$). A lower risk of gastrointestinal involvement was found in ErS cases ($p=0.008$). All patients with ErS had positive autoantibodies (mainly anti-Scl70 and anti-centromere) with higher titters than those with SSc with no silica exposition, although this difference was not statistically significant. Although with no statistical significance, we found that pulmonary artery systolic pressure (PASP) estimated by echocardiogram was higher in patients with ErS.

Conclusion: In our study, prevalence of ErS was higher than that reported on previous studies. For a more accurate ErS diagnosis it is necessary to be aware of silica exposure, even if for short periods, which may have occurred many years before diagnosis. Significant clinical differences were found between ErS and SSc patients without silica exposure, which can have a relevant impact on diagnosis, treatment and prognosis.

Keywords: Occupational disease; Disease parameters; Systemic sclerosis; Silicosis; Erasmus Syndrome

INTRODUCTION

Erasmus syndrome (ErS) was defined in 1957 as the association of exposure to silica with the subsequent development of systemic sclerosis (SSc), with or without associated silicosis[1,2].

SSc is a rare immune-mediated connective tissue disease characterized by vasculopathy and fibrosis[3]. Diffuse cutaneous SSc, interstitial lung disease (ILD), and pulmonary arterial hypertension (PAH) have been associated with higher mortality in patients with SSc[3,4,5].

Understanding the link between environmental risk factors and the development of SSc is challenging. This may be due to the phenotypic and pathogenic heterogeneity of patients and disease and also to the poor capability to quantify environmental exposure and to assess the role of the gene-environment interactions in this disease[6]. The most credible theory explaining this association is the dysregulation of T lymphocytes by exposure to silica[4,7]. The frequency of occupational exposure to silica dust as a generator of occupational disease has been underestimated, even though it is recognized as a risk factor for many others systemic autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus and small-vessel vasculitis with renal involvement[8,9]. There are a few cases of ErS reported in the literature and most refer to miners, although there are other professions that may lead

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to silica exposure in varying degrees[10,11].

Only a few series have compared features of SSc in patients with ErS and without exposure to crystalline silica[12,13,14]. To date, no major clinical or laboratory differences between the two groups have been reported[13]. However, there are some evidence that patients exposed to crystalline silica can present with different characteristics, such as more frequently diffuse scleroderma and more extensive pulmonary involvement[14].

The objectives of this study were: 1) to evaluate the prevalence of ErS in our SSc cohort; 2) to characterize the cases; 3) to evaluate the clinical and laboratory characteristics of SSc in patients with ErS or without silica exposure.

METHODS

A cross-sectional study was conducted. Demographic, clinical and laboratory data were collected from all patients with SSc diagnosed in our department according to ACR / EULAR criteria[15]. Data on professional activity and possible exposure to silica were obtained by phone interview. Informed consent was firstly obtained from all patients.

Forty-eight patients with SSc were identified.

ASSESSMENT OF SSC FEATURES

Sociodemographic (age, gender, occupation, duration of possible silica exposure), clinical (disease duration, presence of silicosis, smoking status, onset of symptoms of SSc, type of organ involvement, other comorbidities and treatments) and laboratorial data (antibody profile along with patients nailfold capillaroscopy pattern according to current classifications proposed to define SSc microvascular involvement[16] and last echocardiogram) were collected. The extent of cutaneous disease was classified according to the two subtypes defined by Le Roy EC *et al*: limited and diffuse scleroderma[17]. Oesophageal dysfunction was assessed by oesophageal manometry and endoscopy. Lower gastrointestinal tract involvement was assessed by patients' symptoms and colonoscopy results. Pulmonary involvement was assessed with pulmonary function tests and chest high resolution computed tomography[18]. PAH was diagnosed in the presence of a mean pulmonary arterial pressure (PAP) ≥ 25 mmHg with a pulmonary capillary wedge pressure ≤ 15 mm Hg on right heart catheterization[19]. Silicosis diagnosis was established by a pneumologist.

ASSESSMENT OF SILICA EXPOSURE

A phone interview was made to all patients in order to confirm and detail professional activity and evaluate possible silica exposure.

The telephone interview start with the question: "What is your job?", if patient' profession was include in following industry sectors: stonemasonry, quarrying, marble working, brickworks and tile manufacture, house-building or miner working we proceed with questionnaire. The next question were to assess daily exposure to products containing silica. "Do you work every day with any of the following materials?" Rocks that contain an elevated concentration of silica, such as quartz, or with materials that contain particles of silica like in surfacing or cement finishing bricklaying or in demolition work. And finally we ask to patient "Do you work every day with airway protection material?" Exposure was assumed when patient worked daily with products containing silica and at least sometimes with no protection equipment.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 24. Descriptive statistical analysis included the evaluation of absolute and relative frequencies for categorical variables and calculation of the mean, median and standard deviation for continuous variables. *A Kolmogorov-Smirnov* (KS) *test* and *Shapiro-Wilk test* (SW) were used to determine the distribution of continuous variables. In the comparison of means between groups, the *Student t Test* (t) was applied for the variables with normal distribution. In the case of binary independent variables, the *Mann-Whitney U test* (U) was used for variables with 2 categories, and the *Kruskal-wallis H test* (H) if there were more than 2 categories. In the case of dependent variables, the *Wilcoxon test* (W) was used. For the evaluation of the relationship between two categorical variables, the *Chi-square test* ($\chi 2$) was performed, and if its assumptions were not assured, a *Fisher's Exact Test* was used. Statistical significance was defined as 2-sided $p < 0.05$.

RESULTS

ERS: UNCOMMON OR UNDERDIAGNOSED?

Forty-eight patients with SSc were included. In the overall sample, most patients were female (77.1%). The mean age at the study date was 60.1 years old

(SD=12.3), with a minimum of 29 and a maximum of 84 years old. The diagnosis was established, on average, 3.0 years after symptoms onset (SD=4.9), with a mean age of 51.9 years old (SD=13.3). The mean disease duration was 11.0 years (SD=6.9) with a minimum of two and a maximum of 33 years. The prevalence of ErS was 16.7% (8/48), corresponding to 72.7% (8/11) of the SSc male patients' cohort. All patients with ErS were male.

ERS PATIENT'S CHARACTERISTICS

In eight ErS patients, three had a prior diagnosis of silicosis. Mean silica exposure was 30.1 years (SD=8.0), with a minimum of 20 years and a maximum of 45 years.

SSc presented as a limited cutaneous form in 100% (8/8) patients with ErS and 87.5% (35/40) of SSc patients without silica exposure.

Pulmonary involvement was the presenting manifestation in 50.0% (4/8) of ErS patients, with the other half having a cutaneous manifestation as the first symptom. In non-ErS patients the initial involvement was cutaneous in 85.0% (34/40) cases, pulmonary in 5.0% (2/40), articular in 5.0% (2/40) and gastrointestinal in 5.0% (2/40).

At the time of the study, three ErS patients had a previous smoke exposure and one was an active smoker. In non-ErS patients, five had a previous smoke exposition and one was still smoker.

Digital ulcers history was present in all patients with ErS and 20/40 of SSc without silica exposure.

With respect to treatment, six ErS patients were treated with calcium channel blockers and/or angiotensin antagonists and four of the patients had already been treated with intravenous prostacyclins. Four patients were treated with hydroxychloroquine, one with mycophenolate mofetil and one with methotrexate.

The clinical and laboratory characteristics of ErS patients are shown in Table I.

ERS AND SSC WITHOUT EXPOSURE TO SILICA: DIFFERENT CLINICAL MANIFESTATIONS?

Eight of 48 SSc patients fulfilled the criteria for ErS.

There was a significant association between ErS and male gender (OR=3.67 [CI 95%: 1.40-9.62], p<0.001), initial pulmonary manifestation (OR=19.0 [CI 95%: 2.61-138.4], p=0.005), history of digital ulcers (OR=1.400 [CI 95%: 1.11-1.77], p=0.014) and smoking history (OR= 5.7 [CI 95%: 1.1-29.1], p=0.047). On the other hand, in ErS cases, a significantly lower risk of gastrointestinal involvement was found (p=0.008, OR=0.097 [CI 95%: 0.017-0.565]).

All patients with ErS had positive autoantibodies (mainly anti-Scl70 and anti-centromere) with higher titters compared with patients without ErS, although with no statistical significance. Also, it was found that pulmonary artery systolic pressure (PASP) estimated by echocardiogram was higher in ErS patients, but again, without statistically significant differences (42.6 mmHg (SD=17.4) *vs* 29.6 mmHg (SD=7.6)).

Clinical and laboratory data and respective differences between patients are shown in Table II.

DISCUSSION

SSc is characterized by microvascular abnormalities, immune activation with autoimmunity and then fibroblastic proliferation leading to fibrosis[20]. In our study, and accordingly with previous studies, SSc was more common in women (3 to 4:1 compared with male gender) with a mean age of approximately 50 years suggesting that our sample is representative of SSc patients and results may be reproduced in larger studies[3].

Prevalence of ErS in our cohort (16.7%) and specifically in the male patients (72.7%) was much higher than that described in the literature (0.3 to 0.9% of overall SSc and 43% of male SSc)[21,22]. This may be due to the high number of granite quarries in our hospital area of influence which are rich in quartz (made of silica crystals)[23] and the manufacturing industry and house-building employ a large percentage of the working population[24].

Other fact that can contribute for this high prevalence was that, in contrast with other studies, less intense exposures to silica have also been considered, as in house-builders[21,22]. However, there is some evidence that these lower dose exposures are also associated with the development of SSc[7].

Studies suggested that small inhaled particles of quartz contacting with lungs are probably responsible for immunological changes, such as stimulation of macrophages and interleukin-1, platelet derived growth factor and fibronectin production[4,7]. In our study, only one case of ErS occurred in a miner worker and another one in a granite worker, suggesting that other patients were exposed in a lesser degree. Most of the cases described in the literature occurred in patients with occupations that involve an intense exposure to

TABLE I. CLINICAL AND LABORATORY CHARACTERISTICS OF PATIENTS WITH ERASMUS SYNDROME

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age (years)	59	50	61	39	51	84	77	38
Sex	Male	Male	Male	Male	Male	Male	Male	Male
Profession	Marble worker	House-builder	Bricklayer	House-builder	House-builder	Bricklayer	Miner	House-builder
Time (years) sílica exposure	35	30	30	20	31	45	30	20
Silicosis	Yes	No	Yes	No	No	No	Yes	No
Time (years) since symptom onset to diagnosis	1	2	3	1	0,5	1	4	1
Age at diagnosis	56	48	58	37	49	73	74	29
First organ manifestation	Pulmonary	Cutaneous	Pulmonary	Cutaneous	Cutaneous	Pulmonary	Pulmonary	Cutaneous
SSc type	Limited	Limited	Limited	Limited	Limited	Limited	Limited	Limited
Antibody	Anti-Scl70	Anti-RNP	Anti-SSA and Anti-SSB	Anti--centromere	Anti-SSA and Anti-SSB	Anti-Scl70	Anti--centromere	Anti--centromere
Pattern and titles	Speckled pattern 1/640	Speckled pattern 1/160	Speckled pattern 1/320	Anticentromere pattern 1/640	Speckled pattern 1/640	Speckled pattern 1/160	Anticentromere pattern 1/640	Anticentromere pattern 1/320
Capillaroscopy (escleroderma pattern)	Yes	Yes	Yes	Yes	Not performed	Not performed	Not performed	Not performed
PAH	No	No	Yes	No	No	Yes	Yes	No
ILD	Yes	No	Yes	No	No	No	Yes	No
Gastrointestinal involvement	No	No	Yes	No	No	No	No	Yes
Digital ulcers	Yes	Yes	Yes					
	Yes	Yes	Yes	Yes	Yes			
Calcinosis	No	No	No	No	No	No	Yes	Yes
Last echocardiogram	Mild AI and MI	Normal	Mild MI, Mild TI, Mild dilation of RV, PASP: 52	Normal	Mild MI and TI, PASP: 26	Dilation of RV, LA e RA, Mild MI and TI, PASP: 41	Dilation of LA, Moderate MS and AS, Mild MI, PASP: 67	Mild TI, PASP: 27
Smoking	Past	No	Past	No	Yes	No	No	Past
Treatment	HCQ, Nefedipine, prostacyclins	HCQ, Nefedipine, prostacyclins	Losartan	HCQ, Nefedipine, prostacyclins	Metotrexate	Nefedipine	Losartan	HCQ, MMF, prostacyclins

AI: Aortic insufficiency; AS: Aortic stenosis; ILD: Interstitial lung disease; HCQ: hydroxychloroquine; LA: Left atrium; MI: Mitral insufficiency; MMF: Mycophenolate mofetil; MS: Mitral stenosis; PAH: Pulmonary arterial hypertension; PASP: Pulmonary artery systolic pressure (mmHg); RA: Right atrium; RV: Right ventricle; TI: Tricuspid Insufficiency;

TABLE II. CLINICAL AND LABORATORY CHARACTERISTICS OF PATIENTS WITH SYSTEMIC SCLEROSIS AND SYSTEMIC SCLEROSIS WITHOUT EXPOSURE TO SILICA, AND THEIR COMPARISON

	SSc without exposure to silica	Erasmus syndrome	Comparation
Age (years)	60.6 (SD=11.4)	57.4 (SD=16.6)	p=0.503*
Sex	Male: 3/40 Female: 37/40	Male: 8/8 Female: 0/8	p<0.001 † OR=3.67 [CI 95%: 1.40-9.62]
Age at diagnosis	51.7 (SD=13.0)	53.0 (SD=11.4)	p=0.807*
Time (years) since symptom onset to diagnosis	3.3 (SD=5.3)	1.7 (SD=1.2)	p=0.393*
First organ manifestation	Cutaneous: 34/40 Pulmonary: 4/40 Articular: 2/40 Gastrointestinal: 2/40	Cutaneous: 4/8 Pulmonary: 4/8 Articular: 0/8 Gastrointestinal: 0/8	p=0.025 †
SSc type	Limited: 35/40 Diffuse: 5/40	Limited: 8/8 Diffuse: 0/8	p=0.573 †
Antibodies	Anti-Scl70: 7/40 Anti-centromere: 20/40 Anti-RNP: 0/40 Anti-SSA: 2/40 Only ANAs: 4/40 Anti-PM75: 1/40 Anti-centromere and SSA: 2/40 Anti-SSA and SSB: 0/40 Anti-RNP, SSA and SSB: 1/40 Negative: 2/40	Anti-Scl70: 2/8 Anti-centromere: 3/8 Anti-RNP: 1/8 Anti-SSA: 0/8 Only ANAs: 1/8 Anti-PM75: 0/8 Anti-centromere and SSA: 0/40 Anti-SSA and SSB: 1/8 Anti-RNP, SSA and SSB: 0/8 Negative: 0/8	p=0.418 †
Pattern	Anti-centromere: 22/40 Speckled: 12/40 Fine granular: 1/40 Homogeneous: 1/40 Nucleolar: 1/40 Speckled and nucleolar: 1/40	Anti-centromere: 3/8 Speckled: 5/8 Fine granular: 0/8 Homogeneous: 0/8 Nucleolar: 0/8 Speckled and nucleolar: 0/8	p=0.677†
Titles	1/160: 8/40 1/320: 18/40 1/640: 9/40	1/160: 2/8 1/320: 2/8 1/640: 4/8	p=0.313 †
PAH	8/40	3/8	p=0.361 ‡
ILD	16/40	3/8	p=0.999 ‡
Gastrointestinal involvement	31/40	2/8	p=0.008 ‡ OR=0,097 [CI 95%: 0.017-0.565]
Digital ulcers	20/40	8/8	p=0.014 † OR= 1.4 [CI 95%: 1.11-1.77]
Calcinosis	17/40	2/8	p=0.451 ‡
Dilation of LA	10/40	2/8	p=0.999†
Dilation of RA and/or RV	2/40	2/8	p=0.124 ‡
LV hypertrophy	3/40	0/8	p=0.999 †

continues on the next page

TABLE II. CONTINUATION

	SSc without exposure to silica	Erasmus syndrome	Comparation
Valvular insufficiency	35/40	6/8	p=0.583 ‡
Valvular stenosis	6/40	1/8	p=1.000 ‡
PASP	29.6 (SD=7.6)	42.6 (SD=17.4)	p=0.122 #
Smoking (pasto or present)	4/40	6/8	p=0.047 ‡ OR= 5.7 [CI 95%: 1.1-29.1]

* Statistically significant differences are underlined
CI: Confidence Interval; ILD: Interstitial lung disease; LA: Left atrium; LV: Left ventricle; OR: Odds Ratio; PAH: Pulmonary arterial hypertension; PASP: Pulmonary artery systolic pressure (mmHg); RA: Right atrium; RV: Right ventricle; SD= Standard deviation;
* test T student; † Fisher's exact test; ‡ Chi-square test; # Mann-Whitney U test

silica dust [25,26]. However, our findings, consistent with others studies, suggest that less intense exposures may also play a role in ErS development[7].

None of our female patients with SSc had a previous silica exposure and none developed ErS. Our findings can help to corroborate that the low prevalence of ErS in the female sex can be explained by occupational factors and not by different susceptibility[14,27].

The relevance of considering ErS as an occupational disease is of paramount importance due to possible economic, social and professional implications.

We found an association between ErS and pulmonary involvement as the presenting manifestation of the disease, smoking exposition and history of digital ulcers. The relevance of this association was proved in the EUSTAR registry, in a multivariable analysis adjusted for age, gender and all parameters considered potentially significant. In this registry, a history of digital ulcers was the strongest predictor of new digital ulcers, elevated PASP on heart echocardiogram, cardiovascular event and death[28].

Magnant *et al*, in a study with 105 patients with SSc, reported that patients exposed to crystalline silica may have different characteristics when compared with patients with no exposure[14]. In that study, patients exposed to silica more often exhibited: diffuse cutaneous SSc, presence of digital ulcers, interstitial lung disease, myocardial dysfunction and cancer[14]. In our study, all patients with ErS had limited cutaneous SSc and no statistically significant differences were found between SSc with or without silica exposition. In our SSc population (48 patients) only five (10.4%) had the diffuse type of disease, whilst literature reports an incidence between 26 and 44.2%[29]. It was not possible to evaluate cancer outcome due to the reduced sample.

We found an inverse association between silica exposure and gastrointestinal involvement. Although gastrointestinal complications can be the most frequent internal complications of SSc[30], we did not find studies evaluating the association of gastrointestinal involvement with exposure to silica. However, silica particles appear to be capable of inhibiting bacterial adhesion and are currently being studied in nanoparticles for the treatment of infections[31].

Rustin *et al.* report that 16 of 17 patients exposed to silica who developed SSc (ErS) had bibasilar pulmonary fibrosis on chest radiographs[12]. In our study, ILD was not more common in patients with exposure to silica than in those not exposed. This may be due to the fact that Rustin et al followed underground coal or uranium workers, therefore patients with very intense exposure to silica crystals[12]. Studies in mice indicate that intense silica exposures lead to the development of progressive pulmonary inflammation and ultimately fibrosis, while inflammation caused by less intense exposures may be reversible[32].

Some studies have shown a relationship between silica exposure and positivity of anti-Scl70 (anti-topoisomerase I) antibodies, while others have shown a lower prevalence of anti-centromere antibodies[14,27,33]. However, in our study, no relationship was found between positive anti-Scl70 or anti-centromere and toxic exposure, as described in Czirjak and Kumánovic's study[34].

This study has some potential limitations. Firstly, our sample is relatively small and would be desirable to collect data from larger samples and other centers. Given the differences in mineral composition among Portuguese territory it would be advisable to include patients from different regions to obtain more reliable data. Secondly, silica exposition was self-reported and

not quantified in a standardized manner, so high/low exposure was not defined and its definitive role in SSc development is very hard to assure. Finally, this is a cross-sectional study with patients from different backgrounds and disease duration, so some patients' features can change over the time.

CONCLUSION

The prevalence of ErS may be higher than previously described in silica-rich rocks regions. For a more accurate ErS diagnosis it is necessary to be aware and actively investigate silica exposures.

In our study, ErS patients presented pulmonary involvement as initial manifestation of the disease more frenquently than non-exposed patients, more digital ulcers and a higher exposure to tobacco. The gastrointestinal involvement was found less frequently in ErS cases.

The fact that subjects' exposure to silica dust could develop SSc, a rare but potencially severe disease, is a call for awareness regarding the identification of workers at risk, and should prompt the implementation of effective protection measures and screnning strategies. Further studies with bigger samples are warranted to understand if these differences may influence the diagnosis, treatment and prognosis of patients with SSc with ErS and without silica expose.

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