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Clinical peculiarities of patients with scleroderma exposed to silica: A systematic review of the literature

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ABSTRACT

Objective: There are few data regarding the existence of clinical differences between patients with systemic sclerosis (scleroderma) exposed to silica (SSc-si) and "idiopathic" cases (SSc-id). Our goal is to describe the clinical characteristics of patients with SSc-si and see if they differ from the SSc-id cases.
Methods: We performed a systematic review of the literature by searching the MEDLINE, EMBASE and Web of Science databases. We also included our own series of patients diagnosed with SSc-si and SSc-id controls at the "Complejo Hospitalario Universitario de Vigo (CHUVI)" from 1985 to January 2013.
Results: The review of the literature disclosed 32 published series, with clinical data of 254 SSc-si patients (96% males). SSc-si represented 37.5–86% of the scleroderma males and 0–2.7% of the scleroderma females. Globally, more than expected proportion of diffuse forms (61%) and interstitial lung disease (81%) were observed in exposed patients. In the present series, the diagnosis of SSc exposure to silica was recorded in nine patients (9.5%), showing predominance of the diffuse form (77%, $p = 0.001$), positivity for anti-Scl70 (55%, $p = 0.001$), presence of ILD (78%, $p = 0.048$) and lower survival (9.2 versus 15.1, $p = 0.023$). Diffuse variant remained more prevalent analysing exposed versus non-exposed women (50% versus 8%, $p = 0{,}000$) and exposed versus non-exposed men (85.8% versus 50%, $p = 0{,}000$).
Conclusion: Silica exposure is a predominant risk factor in male SSc populations. The review of the literature is consistent with an association of SSc-si and diffuse scleroderma. A trend toward lower survival was observed in our series in SSc-si group.

Introduction

Although systemic sclerosis or scleroderma (SSc) has unknown aetiology, it is associated with a number of environmental factors. These factors include silica or organic solvents, which can act as a trigger in genetically predisposed individuals [1]. The association between silica exposure, with or without silicosis, and SSc, was named "Erasmus syndrome" after the publication by L.D. Erasmus in 1957 of a series of South African male miners with scleroderma [2]. Recently, the name "Erasmus syndrome" was dropped since Byrom Bramwell had already shown increased frequency of SSc in stone masons in 1914 [3]. References in the medical literature to this association often point out that patients with SSc exposed to silica (SSc-si) and the "idiopathic" (SSc-id) cases do not show clinical differences. Nonetheless, the clinical descriptions on which they are based are isolated cases or small series and are mostly without a control group of patients with SSc-id. Moreover, it is frequent to publish cases of SSc exposed to various toxins together, or of patients exposed to silica with various autoimmune diseases, without specifying the clinical features of each subgroup.

The objective of this study is to describe the clinical characteristics of patients with SSc-si and analyse if there are differences with the SSc-id patients. We carried out a systematic literature review focused on the collection of the clinical features of the patients described up to now with this association. In addition, we added patients from our own series.

Methods

Literature review

A systematic review of the literature was performed by searching through the MEDLINE [source: PubMed (1950 to Feb 2015)],

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EMBASE (1974 to Feb 2015) and Web of Science (1900 to Feb 2015) databases. The following terms were used: scleroderma, systemic sclerosis, silicon dioxide and silica, combining Mesh terms and text words, without language restrictions. We also checked bibliographic references of articles that were previously retrieved on these topics. We used the EPPI-Reviewer software for reference management, extraction and data storage. Two researchers independently performed the data extraction. Disagreements were resolved by consensus among the researchers. Studies were deemed eligible when it was possible to obtain the full-text article and when the study included enough clinical data of patients with SSc and documented silica exposure. With articles describing cases with various autoimmune diseases or exposure to several toxins, we only included those articles where the clinical characteristics of SSc patients exposed to silica could be differentiated. To avoid misclassification resulting from the changes in nomenclature over the past 100 years, we individually reviewed the cases described in the literature and classified them into subtypes on the basis of the clinical description.

Case series

The "Complejo Hospitalario Universitario de Vigo" (CHUVI) is the reference centre for a population of 437,181 inhabitants from both urban and rural areas. The vast majority are of Caucasian origin. The study design is a retrospective case–control. We performed a review of the medical histories of patients diagnosed with SSc after hospital admission from 1985 until January 2013 using the Medical Record Department file. We also included patients with scleroderma diagnosis that were followed-up from 2008 to January 2013 in our systemic autoimmune diseases outpatient service. We reviewed age, sex, clinical features and autoantibodies profile. We tested exposure to silica as follows: we looked in the medical history for information about profession or contact to silica and, if the medical history did not give this information, we carried out a personal survey. The survey was designed according to the Spanish Health Surveillance Protocol "Silicosis and other pneumoconiosis" (Annex 1). It contained the following variables: patient's personal data, occupational history, job title, category, date of starting work, description of tasks performed, availability and use of personal protective equipment, materials handled, machinery and tools used and environmental protection systems in the workplace [4]. They were also asked whether they were exposed to other toxins (tobacco, alcohol, organic solvents and vinyl chloride) and SSc family history.

The patients or relatives gave informed consent. The local ethics committee approved the study.

Definitions

SSc

We used the 2013 ACR/EULAR classification for SSc [5] to select patients. We used an adaptation of the classification proposed by LeRoy and Medsger [6] for classifying patients into four subgroups: diffuse cutaneous systemic sclerosis (dcSSc), limited cutaneous systemic sclerosis (lcSSc), systemic sclerosis sine scleroderma (ssSSc) and pre-scleroderma (pre-SSc).

Disease onset

Age at which the first SSc manifestation (Raynaud's or non-Raynaud) began.

Risk of environmental exposure to silica dust: Industries listed in "annex 5" from the European multi-sector "Agreement on Workers Health Protection through the Good Handling and Use of Crystalline Silica and Products containing it" [7].

Group 1 (cases)

Patients diagnosed of SSc and environmental exposure to silica dust.

Group 2 (controls)

Three patients for each patient from Group1, in which the risk of silica exposure was excluded as described above.

ILD

Defined by interstitial pattern x-ray or CT and forced vital capacity (FVC) $< 80\%$ and/or diagnostic lung biopsy (the latter not essential).

Statistical analysis

An association between qualitative covariates was evaluated using the chi-square test. Kaplan–Meier survival curve was used to assess the differences between groups in survival rates. Analyses were performed using SPSS software version 21.0.

Results

Case series

The diagnosis of SSc was confirmed in 94 patients in the CHUVI from 1985 until January 2013. This represents an annual incidence of 0.82 per 100,000 population. This incidence rate is similar to that previously reported in our geographical area [8].

Table 1
Epidemiological data of group 1

Case	Age	Sex	Activity	Employment	Resource	Length[a]	Latency[b]	Other toxic[c]
1	42	M	Stone quarry	Cutter	Granite, marble, quartz compounds[d]	23	20	Smoking
2	62	M	Stone quarry	Cutter	Granite	33	50	Smoking
3	52	M	Tunnels	Shotfirer	–	1	30	Smoking
4	25	M	Stone quarry	Shotfirer	Granite	25	10	Smoking
5	59	F	Ceramics	Decoration	–	–	–	Perchlorethylene
6	29	M	Stone quarry		Granite	–	–	Smoking
7	45	M	Mill	Milling	Granite	30	28	No
8	39	M	Stone quarry	Shotfirer	Granite	8	23	No
9	44	F	Ceramics		Kaolin	–	–	No

M: male; F: female.

[a] Years of exposure to silica.
[b] Years since the beginning of silica exposure to onset of symptoms of scleroderma.
[c] Tobacco, alcohol, vinyl chloride and organic solvents.
[d] Silestone®.