Autoimmunity Reviews 13 (2014) 151–156

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature

I. Marie [a,b,*], J.-F. Gehanno [c], M. Bubenheim [d], A.-B. Duval-Modeste [e], P. Joly [e], S. Dominique [f], P. Bravard [g], D. Noël [h], A.-F. Cailleux [i], J. Weber [i], P. Lagoutte [d], J. Benichou [j], H. Levesque [a,b]

[a] Department of Internal Medicine, CHU Rouen, Rouen, France
[b] INSERM U 905, University of Rouen IFRMP, Institute for Biochemical Research, Rouen, France
[c] Department of Occupational Medicine, CHU Rouen, Rouen, France
[d] Department of Biostatistics, CHU Rouen, Rouen, France
[e] Department of Dermatology, CHU Rouen, Rouen, France
[f] Department of Pneumology, CHU Rouen, Rouen, France
[g] Department of Dermatology, CHG Le Havre, Le Havre, France
[h] Department of Internal Medicine, CHG Elbeuf, Elbeuf, France
[i] Clinical Investigation Center, CIC 0204-INSERM, Institute for Biomedical Research, CHU Rouen, Rouen, France
[j] Department of Epidemiology, CHU Rouen, Rouen, France

ARTICLE INFO

Article history:
Received 1 October 2013
Accepted 8 October 2013
Available online 12 October 2013

Keywords:
Systemic sclerosis
Occupational factors
Crystalline silica
Solvents
Ketones
Welding fumes

ABSTRACT

Introduction: Systemic sclerosis (SSc) has complex pathogenesis and likely multifactorial causes. Environmental exposures have been suggested to play a role in SSc pathogenesis, including occupational exposure to pollutants and chemicals as well as use of drugs leading to modulation of immune response. Thus, this case–control study aimed to assess: the relationship between SSc and occupational exposure; and the risk of SSc related to occupational exposure in male and female patients.

Methods: From 2005 to 2008, 100 patients with a definite diagnosis of SSc were included in the study; 3 age, gender, and smoking habits matched controls were selected for each patient. A committee of experts evaluated blindly occupational exposure to crystalline silica, white spirit, organic solvents, ketones, welding fumes, epoxy resins, and pesticides; an occupational exposure score was calculated for all subjects. Our findings were compared with previous data in the literature.

Results: Increased ORs for SSc were found for: crystalline silica ($p < 0.0001$), white spirit ($p < 0.0001$), aromatic solvents ($p = 0.0002$), chlorinated solvents ($p = 0.014$), trichlorethylene ($p = 0.044$), ketones ($p = 0.002$) and welding fumes ($p = 0.021$). Elevated risk associated with high final cumulative score in SSc was observed for: crystalline silica, white spirit, chlorinated solvents, trichlorethylene, aromatic solvents, any type of solvents, ketones and welding fumes. A marked association between SSc and occupational exposure was further found for: 1) crystalline silica, chlorinated solvents, trichloroethylene, white spirit, ketones and welding fumes in male patients; and 2) white spirit, aromatic solvents, any type of solvent and ketones in female patients. Finally, we did not find an association between SSc and: 1) the use of drugs that have been speculated to play a role in SSc onset (anorexigens, pentazocine, bromocriptine, L-tryptophan); 2) implants — that are prosthesis, silicone implants, and contact lenses; and 3) dyeing hair. In the literature, SSc has been associated with occupational exposure to silica and solvents, while the association between SSc and specific organic solvents and welding fumes has been anecdotally reported.

Conclusion: The following occupational factors have an impact in the development of SSc: crystalline silica, white spirit, aromatic solvents, chlorinated solvents, trichlorethylene, ketones and welding fumes. The risk of SSc appears to be markedly associated with high cumulative exposure. Finally, the association between SSc and occupational exposure may be variable according to gender.

Contents

* Corresponding author at: Département de Médecine Interne, CHU Rouen 76031 Rouen Cedex, France. Tel.: +33 2 32 88 90 03; fax: +33 2 32 88 90 26.
E-mail address: isabelle.marie@chu-rouen.fr (I. Marie).

1568-9972/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.autrev.2013.10.002

1. Introduction

Systemic sclerosis (SSc) is a systemic inflammatory disorder affecting the skin and other organs [1–3]. The condition is characterized by 3 histopathologic features: (i) both structural and functional vascular lesions; (ii) perivascular and tissue infiltration of mononuclear inflammatory cells; and (iii) increased synthesis and excessive deposition of extracellular matrix, resulting in fibrotic destruction of internal organs during the course of SSc [4–12]. SSc has complex pathogenesis and likely multifactorial causes [4–12]. Recently, environmental exposures have been suggested to play a role in SSc pathogenesis, including occupational exposure to pollutants and chemicals as well as use of drugs; such environmental exposure may result in the production of auto-reactive T cells and autoantibodies, the stimulation of pro-inflammatory cytokines and target end-organ damage [13–18]. However, to date, studies of occupational exposure, especially to specific organic solvents (i.e.: chlorinated, trichlorethylene, toluene, xylene, aromatic, ketones, any type), welding fumes, epoxy resins and pesticides have received limited attention in SSc.

These data prompted us to conduct this prospective case–control study, in order to assess the risk of SSc related to occupational exposure in 100 patients with SSc and 300 controls. Furthermore, we have evaluated the risk of SSc related to occupational exposure in male and female patients.

2. Patients and methods

2.1. Patients

From 2005 to 2008, 100 consecutive patients with a definite diagnosis of systemic sclerosis (SSc) were included in the study; only 2 patients refused to participate to the study. SSc patients were seen, as either inpatients or outpatients, in 3 medical centers (Departments of Internal Medicine, Dermatology and Pneumology of Rouen, Elbeuf and Le Havre). The criteria used for the diagnosis of SSc were based on the American College of Rheumatology preliminary classification [19]. The study cohort consisted of 22 men and 78 women with a median age of 52 years (IQR: 45–61 years). There were Caucasian (n = 98), African (n = 1) and Asian (n = 1) patients. The median duration of the disease, considered from the onset of the first non-Raynaud's phenomenon clinical manifestations was 2 years (IQR: 0.1–7 years). Patients were grouped into disease subsets according to the criteria of LeRoy et al. [20] with 33 patients having diffuse cutaneous SSc (dcSSc) and 67 as having limited cutaneous SSc (lcSSc). In our population, autoantibody profile was as follows: antinuclear antibodies (n = 100), anti-centromere (n = 42) and anti-Scl70 (n = 26) antibodies. None of the patients with SSc had other connective tissue disorders (systemic lupus erythematosus, Sjögren's syndrome, polymyositis, dermatomyositis) or systemic vasculitis.

2.2. Controls

From 2005 to 2008, 3 age (±5 years), gender, and smoking habits matched controls were also selected for each patient. There were Caucasian (n = 299) and African (n = 1) subjects.

These matched controls: 1) were healthy controls, being recruited using local: print media, TV-channel and radio networks; or 2) suffered from chronic conditions (e.g.: arterial hypertension, angor pectoris, diabetes) as well as acute diseases (e.g.: erysipela, urinary or pulmonary infection). Controls were excluded from the study if they exhibited a previous history of: connective tissue disease, systemic vasculitis, as well as other autoimmune systemic disorder, neoplasia or chronic interstitial lung disease.

Finally, controls came from the same geographical region than patients with SSc, i.e. from Normandy (consisting of 5 departments in the North-western area) in France.

The study was approved by the local Medical Research Ethics Committee (CPP de Haute—Normandie, France). Written informed consent was obtained from all patients with SSc and controls prior to inclusion in the study.

2.3. General characteristics and occupational exposure

All SSc patients and controls were systematically interviewed by a trained investigator using a standardized questionnaire, in which they were asked about: 1) socioeconomic features; 2) smoking habits. Regarding smoking habits, both patients and controls were dichotomized into 2 groups: 1) smokers and former smokers if disruption of tobacco consumption was ≤5 years; and 2) non-smokers and former smokers if disruption of tobacco consumption was >5 years; 3) previous use of the following drugs that have been incriminated in the onset of scleroderma-like syndrome: anorexigens, pentazocine, bromocriptine, taxanes and L-tryptophan; 4) previous history of: prosthesis (e.g.: hip, knee), contact lenses, cosmetic surgery (paraffin, processed petrolatum jelly, silicone implants) and dyeing hair; and 5) occupational history.

Regarding patients' and controls' occupational histories, particular attention was paid to exposure to: crystalline silica, white spirit, solvents (chlorinated, trichlorethylene, toluene, xylene, aromatic, ketones, any type), welding fumes, epoxy resins, pesticides, as well as vinyl chloride.