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Polyautoimmunity and familial autoimmunity in systemic sclerosis

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ABSTRACT

Characterization of the extent to which particular combinations of autoimmune diseases occur in excess of that expected by chance may offer new insights into possible common pathophysiological mechanisms. The goal of this study was to investigate the spectrum of polyautoimmunity (i.e. autoimmune diseases co-occurring within patients) and familial autoimmunity (i.e. diverse autoimmune diseases co-occurring within families) in patients with systemic sclerosis (SSc). A cross-sectional study of two convenience samples of patients with SSc, one in Canada and the other in Colombia, was performed. History of other autoimmune diseases in the SSc patients as well as a family history of autoimmunity was obtained. Of 719 patients, 273 (38%) had at least one other autoimmune disease. A total of 366 autoimmune diseases were reported, of which the most frequent were autoimmune thyroid disease (AITD, 38%), rheumatoid arthritis (RA, 21%), Sjögren's syndrome (18%), and primary biliary cirrhosis (4%). There were 260 (36%) patients with first-degree relatives with at least one autoimmune disease, of which the most frequent were RA (18%) and AITD (9%). Having at least one first-degree relative with autoimmune disease was a significant predictor of polyautoimmunity in SSc patients. No significant differences in polyautoimmunity or familial autoimmunity were noted between diffuse and limited subsets of disease. Our results indicate that polyautoimmunity is frequent in patients with SSc and autoimmune diseases cluster within families of these patients. Clinically different autoimmune phenotypes might share common susceptibility variants, which acting in epistatic pleiotropy may represent risk factors for autoimmunity.

1. Introduction

Autoimmune diseases (ADs) are a heterogeneous group of diseases characterized by the loss of immunological tolerance to self-antigens and multiple alterations in the immune system resulting in a spectrum of syndromes that either target specific organs or affect the body systemically [1]. Although their etiology remains poorly understood, common features and a plausible background for shared autoimmunity are being increasingly recognized [2].

Systemic sclerosis (SSc) is an unusual systemic autoimmune disease characterized by microvasculopathy with destruction or functional damage of small blood vessels, fibroblast activation and excessive production of collagen [3]. SSc is clinically characterized by different degrees of skin fibrosis and visceral organ involvement and the presence of specific autoantibodies [4,5], which could be one of the factors that sustain the profibrotic phenotype of fibroblasts.

The term kaleidoscope of autoimmunity describes the fact that more than one distinct autoimmune disease may coexist in a single patient (polyautoimmunity) or in the same nuclear family (familial autoimmunity) [6,7]. Characterization of the extent to which particular combinations of ADs occur in excess of that expected by chance in the same individual or within a family may offer new

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insights into shared pathophysiological mechanisms of autoimmune diseases. The goal of this study was thus to investigate the spectrum of the kaleidoscope of autoimmunity (i.e. polyautoimmunity and familial autoimmunity) in patients with SSc.

2. Patients and methods

2.1. Study subjects

This was a cross-sectional study of two convenience samples of patients with SSc, one in Canada and the other in Colombia. The Canadian study subjects consisted of those enrolled in the Canadian Scleroderma Research Group Registry. Patients in this Registry are recruited from 15 centers across Canada [4]. They must have a diagnosis of SSc made by the referring rheumatologist (whether they fulfill the 1980 American College of Rheumatology (ACR) preliminary criteria for SSc or not), be >18 years of age and be fluent in English or French. The patients included in this study were those whose baseline visit was between August 2004 and August 2007 and fulfilled the ACR preliminary criteria for SSc [8]. Patients recruited into the Registry undergo an extensive standardized evaluation including a history, physical evaluation and laboratory investigations. In the detailed case report forms, physicians report whether patients have other co-existing autoimmune diseases, namely rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyositis/dermatomyositis (PMDM), Sjögren's syndrome (SjS) and mixed connective tissue disease (MCTD). Physicians also record the patient's medications, including thyroid supplements. This was taken as a surrogate marker of autoimmune thyroid disease (AITD). Patients are asked to self-report on family history of SSc and other autoimmune diseases in their parents and siblings (as well as children, grandparents, aunts, uncles and cousins).

The Colombian patients were assessed at five rheumatology units [9]. Information on patient demographics and cumulative clinical and laboratory manifestations over the course of the disease was obtained either by verification during discussion with the patient or by chart review [9]. History of polyautoimmunity and family history of SSc and other ADs was obtained by discussion with the patients and, in most of the cases, by clinical evaluation of the affected family members as previously reported [10]. All Colombian patients fulfilled the 1980 ACR preliminary criteria for SSc [8].

Ethics committee approval for this study was obtained at each site and each patient provided informed written consent to participate in this study.

Disease duration was calculated since the onset of the first non-Raynaud's disease manifestation in the Canadian cohort and the onset of the first sign or symptom compatible with the disease in the Colombian cohort. First-degree relatives (FDR) were defined as parents and siblings.

2.2. Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the patients. Data were managed and stored using the SPSS program (V15 for Windows, Chicago, IL). The familial rates of ADs were computed by individual, such that a patient who reported a disease in several family members was nevertheless counted only once. However, if a patient reported several AD in the same family member this was counted separately as different cases corresponding to each AD. In addition, the frequency of reports of AD in several family members when counted separately was also computed. We attempted to identify predictors of polyautoimmunity using a logistic regression analysis adjusting for age and duration of SSc. Adjusted odds ratios (AORs) were calculated with 95% confidence intervals (CIs). A p value of less than 0.05 was considered significant.

3. Results

3.1. General characteristics of patients

This study included 719 patients with SSc of whom 429 were enrolled in Canada and 290 in Colombia. The majority of patients were women (86% in the Canadian cohort and 91% in the Colombian cohort) with a mean age of 55 (standard deviation (SD) 13) years in the Canadian cohort and 54 (SD 13) years in the Colombian cohort. Mean disease duration was 11 (SD 9) years in the Canadian cohort and 7 (SD 6) years in the Colombian cohort. The Canadian cohort was composed mainly of whites (89%) while the Colombian cohort was composed of mestizo individuals (100%). All of the patients included into this study fulfilled the 1980 ACR preliminary criteria for SSc and 46% of the Canadian cohort and 21% of the Colombian cohort had diffuse disease.

3.2. Polyautoimmunity

First we examined the prevalence of other ADs in the SSc patients themselves. In the combined cohort, there were 273 (38%) patients with at least one other AD (Table 1). A total of 366 ADs were reported, of which the most frequent were autoimmune thyroid disease (AITD, $N = 139$, 38%), RA ($N = 75$, 21%), SjS ($N = 67$, 18%), and primary biliary cirrhosis (PBC, $N = 15$, 4%). Results did not differ in patients with either limited or diffuse skin involvement.

In the Colombian cohort, 118 (41%) patients presented at least one other AD, including 90 (31%) with one, 18 (6%) with two, 9 (3%) with three and one with four ADs (0.3%) in addition to their SSc. The first, second and third most frequent AD encountered were AITD ($N = 67$, 23%), SjS ($N = 43$, 15%) and PBC ($N = 15$, 5%), respectively.

In the Canadian cohort, 155 (36%) patients presented at least one other AD, including 114 (27%) with one, 31 (7%) with two, 7 (2%) with three and 3 (0.7%) with four ADs in addition to their SSc. The first, second and third most frequent AD encountered were RA ($N = 75$, 17.5%), AITD ($N = 72$, 17%), and SjS ($N = 24$, 6%).

Comparisons between SSc patients with and without polyautoimmunity are shown in Table 1. Having at least one FDR with AD was a predictor of polyautoimmunity in the Canadian (AOR: 1.25, 95% CI: 1.07–1.45, $p < 0.001$) and Colombian (AOR: 2.62, 95% CI 1.24–5.54, $p = 0.01$) cohorts. In addition, female sex was a strong predictor of polyautoimmunity in the Colombian cohort (AOR: 9.08, 95% CI: 2.09–39.30, $p = 0.003$).

3.3. Familial autoimmunity

We examined the prevalence of SSc patients within each cohort who had relatives with ADs. In the combined cohort, there were 260 (36%) patients with FDR with at least one AD (Table 2). There were similarities and differences in the frequencies of AD in FDR in the two

Table 1
Polyautoimmunity in patients with SSc

	Canadian cohort		Colombian cohort	
	SSc/other AD	SSc/no other AD	SSc/other AD	SSc/no other AD
	$N = 155$	$N = 274$	$N = 118$	$N = 172$
Mean age (SD)	57 (12)	54 (13)	55 (13)	54 (13)
Duration of SSc in years (SD)	11 (9)	10.4 (9)	6 (6)	7 (6)
Women (%)	137 (88)	232 (85)	113 (96)	148 (86)
No. with first-degree relative with AD[a] (%)	86 (56)	118 (43)	20 (17)	13 (8)

AD, autoimmune disease.
[a] Patients who reported an AD in several first-degree relatives were nevertheless counted only once.