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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.

Table 2
Number of SSc patients who reported ADs in relatives

	SSc		SLE		RA		SjS		AITD		Others	
	Col	Can	Col	Can	Col	Can	Col	Can	Col	Can	Col	Can
First-degree relative	6 (2.1)	12 (2.8)	2 (0.7)	21 (4.9)	10 (3.4)	123 (28.7)	1 (0.3)	3 (0.7)	4 (1.4)	60 (14.0)	8 (2.8)	10 (2.3)
All relatives[a]	9 (3.1)	24 (5.6)	11 (3.8)	35 (8.2)	16 (5.5)	162 (37.8)	1 (0.3)	5 (1.2)	6 (2.1)	80 (18.7)	15 (5.1)	12 (2.8)

Col, Colombia; Can, Canada; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SjS, Sjögren's syndrome; AITD, autoimmune thyroid disease. Others includes at least one of the following: primary biliary cirrhosis, vitiligo, multiple sclerosis, mixed connective tissue disease, polymyositis/dermatomyositis, autoimmune hepatitis, and inflammatory bowel disease.

[a] All relatives include first-degree relatives and at least one of the following: children, grandparents, aunts, uncles, or cousins.

cohorts. The rates of SSc in FDR were similar in both cohorts (2.1% in the Colombian and 2.8% in the Canadian cohorts). There were more FDR with SLE, RA and AITD in the Canadian patients compared to the Colombian patients. Finally, although SjS was a common AD in cases of polyautoimmunity, the frequency of SjS in FDR was very low in both cohorts. Details of the reported ADs in the relatives of patients with SSc are shown in Table 3. Of note, the findings for familial autoimmunity were not different in patients with either diffuse or limited subsets of disease (data not shown).

4. Discussion

The high prevalence of polyautoimmunity and familial autoimmunity in SSc patients in this study strongly suggests that clinically different autoimmune phenotypes might share common susceptibility variants, which acting in epistatic pleiotropy may represent risk factors for autoimmunity. The factors that determine whether someone with this predisposition will develop one specific disease or another may then depend upon the presence of either other genetic factors or specific environmental triggers.

The most frequent ADs observed in patients with SSc in this study were AITD, RA, SjS, and PBC, all of which have been previously reported to be associated with SSc [11–18]. Moreover, in this study a family history of AD (FDR) was a significant predictor of polyautoimmunity.

The rate of familial SSc has been previously reported only infrequently. In three US cohorts with a total of 703 SSc patients, Arnett et al. found that the rate of SSc among parents and siblings of SSc patients was 1.6% [19]. In a retrospective cohort study conducted in Sydney, Australia, Englert reported that SSc affected first-degree relatives in 10 of 710 (1.4%) families [20]. In our study, 2.8% of the Canadian patients and 2.1% of the Colombian patients reported having a parent and/or sibling affected by SSc. This result is thus consistent with previous reports. In addition, we described for the first time a high rate of familial autoimmunity in patients with SSc (36%), of which the most frequent were RA (18%) and AITD (9%). Familial autoimmunity in patients with other ADs have been reported, most commonly AITD, SSc, RA and SLE, and somewhat less frequently multiple sclerosis (MS), PBC, celiac disease, vitiligo, type 1 diabetes mellitus (T1D) and antiphospholipid syndrome [5,7,9,21].

We hypothesize that differences in the frequency of polyautoimmunity and familial autoimmunity between the Canadian and Colombian SSc patients found in this study may be due to a latitudinal gradient effect in which the influence of ethnic and genetic differences as well as environmental factors may be critical. It is well known that genetic variants in complex diseases such as SSc might vary according to ethnicity and admixture [5,22]. The 'complex genetic trait' term defines those phenotypes not fitting patterns of Mendelian segregation, but showing a preferential familial clustering that cannot be exclusively explained by cultural or environmental effects. Possible causes underlying this departure from Mendelian laws are the presence of genetic heterogeneity, unknown or unmeasurable contributions of low-penetrance common alleles and environmental factors [5,22]. Among the latter, solvents have been associated with SSc by several rigorous case-control studies that suggest a causal role, as reviewed elsewhere [23]. Other toxic agents (epoxy resins, vibrations, welding fumes) have also been identified as possible environmental triggers but data do not currently justify firm conclusions about their role in SSc [23]. Infectious agents are important in the pathogenesis of autoimmune diseases as they are believed to be a major part of the environmental trigger of autoimmunity. A negative relationship between latitude and presence of various infectious disease species has been suggested [24,] and latitudinal differences in prevalences of antibodies to various infectious agents have been reported [25]. However, whether infection, as an environmental factor, plays a role in SSc remains a matter of further study [26,27].

The common variants/multiple disease (CV/MD) hypothesis has been invoked to underlie the pathogenesis of several complex disease states [28,29]. This hypothesis states that "complex phenotypes are not unique entities but are mosaics of common disease specific alleles and non-disease specific modifying alleles in the population influenced by a vast array of environmental factors" [28]. Supporting the tenets of this hypothesis, findings from the Multiple Autoimmune Disease Genetics Consortium (MADGC) indicated that clinically distinct autoimmune phenotypes such as RA, SLE, T1D and Hashimoto thyroiditis can share a common susceptibility allele (e.g., R620W allele of the intracellular tyrosine phosphatase PTPN22 gene) [30]. Further supporting the CV/MD hypothesis, we confirm results of the MADGC [31], and additionally observed that TNF2 and *STAT4* rs7574865 T alleles [32,33] as well as *BAK1* rs513349G-rs561276C-rs5745582A (GCA) haplotype [34] affects susceptibility for acquiring diverse ADs in a same and homogeneous population of Northwestern Colombians. The high familial aggregation of ADs observed in the current study together

Table 3
Reported autoimmune diseases in the families of patients with SSc

	SSc		SLE		RA		SS		AITD		Others	
	Col	Can	Col	Can	Col	Can	Col	Can	Col	Can	Col	Can
Mother	2	5	0	9	8	78	0	2	1	38	3	4
Father	2	0	0	2	0	33	0	0	0	4	1	0
Siblings	2	9	5	13	2	68	1	1	3	47	4	9
Other relatives	3	16	9	24	8	162	0	2	2	93	7	18

See Table 2 for abbreviations.

with the high rate of polyautoimmunity registered in patients with SSc indicate that several phenotypes might be related to a single genotype and provide evidence to support the common origin of ADs concept [2,7,22]. As mentioned, familial autoimmunity has been reported in patients with MS, T1D, RA, SLE, primary SjS, idiopathic inflammatory myopathy, and PBC among others [5,7,9,21,35,36].

This study has limitations. First, the information on family history in the Canadian cohort was obtained by patient self-reports, and was not independently confirmed by physicians or chart review. This may lead to over-estimation of autoimmune diseases. For example, the high rates of RA found could be due, at least in part, to patients mistakenly reporting osteoarthritis in family members. On the other hand, self-report may also lead to underestimation of disease such as a SSc patient believing that family members have only Raynaud's phenomenon when in fact they have SSc. Independent confirmation of diagnoses could provide more reliable estimates. Nevertheless, self-reported family histories are commonly reported in the literature. In addition, the confirmation rate of ADs reported by patients and relatives of patients with ADs is about 80%, ranging from 40% to 98%, as has been shown and discussed [37].

In conclusion, although this study remains hypothesis-generating it provides rationale for further research to identify genetic and environmental determinants of autoimmunity. This research may, in time, dramatically change the way autoimmune diseases are classified, provide insight into the pathogenesis of these diseases, and lead to new targets for therapeutic interventions.

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