Autoimmune Diseases in Systemic Sclerosis Patients and Their Relatives: Data from a Single Center

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ABSTRACT: **Background:** The aggregation of autoimmune diseases in relatives (AID-R) of patients with systemic sclerosis (SSc) has been reported.

Objectives: To analyze the prevalence of autoimmune diseases in SSc relatives and to compare their features to those of SSc patients without AID-R (controls).

Methods: A case-control analysis compared SSc patients with AID-R to those without AID-R (25 patients) with similar disease duration.

Results: Among 322 patients, 25 (7.7%; 21 females, 41.4 ± 15.6 years of age, disease duration 11 ± 8.6 years) had AID-R (21 had a first-degree relative, 4 had a second-degree relative, and 2 had both). Fourteen patients (56%) and five controls (20%) had an additional autoimmune disease ($P < 0.009$). Diffuse SSc (48% vs. 24%) and arthritis (72% vs. 28%) were more frequent among the patients with AID-R than the controls ($P < 0.05$). No significant differences were found regarding lung, heart, vascular, and digestive system involvement. The mean number of additional autoimmune diseases was 0.84 ± 0.94 in AID-R vs. 0.24 ± 0.52 in controls ($P < 0.038$). The mean number of autoantibodies was 2.8 ± 1.5 and 2.2 ± 0.9 ($P < 0.047$). Five patients died during follow-up, four of whom had AID-R. Relatives of SSc patients had diverse autoimmune diseases; the prevalence of SSc in scleroderma relatives was 1.86% (2 in first-degree and 6 in second-degree relatives). SSc patients with AID-R had an obvious tendency to polyautoimmunity.

Conclusion: A precise family history is an important clue in prognosis and prediction of autoimmune diseases in SSc patients and their relatives.

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KEY WORDS: autoimmune diseases, family predisposition, polyautoimmunity, scleroderma in relatives, systemic sclerosis (SSc)

Systemic sclerosis (SSc) is a chronic rheumatic autoimmune disease affecting skin (scleroderma) and internal organs. The estimated prevalence of SSc in the United States is about 24.2 cases in 100,000 adults in the general population [1,2]. In the course of SSc, combined pathogenetic processes are common and include microvasculature insult and injury (Raynaud's phenomenon, digital ulcers and ischemic skin ulcers, scleroderma renal crisis and progressive renal failure, telangiectasia, gastric antral vascular ectasia, primary pulmonary hypertension), inflammation (early stage of diffuse skin involvement, arthritis, tenosynovitis, myositis, myocarditis, serositis [pericarditis and/or pleuritis]), fibrosis (skin fibrosis, interstitial lung disease and pulmonary fibrosis, joint contractures and sclerodactyly, muscle atrophy, gastrointestinal involvement with progressive motility problems, cardiomyopathy, and fibrosis of lacrimal and salivary glands), and autoimmune alterations (appearance of antinuclear antibodies and specific antibodies such as anticentromere, anti-topoisomerase I, anti-RNA polymerase III) [3].

SSc is characterized by diverse and variable clinical features; nevertheless, some more apparent clinical patterns in SSc presentation are based on the stage of the disease (early or late), degree and spread of skin involvement (limited or diffuse), and autoantibody profile. SSc is often part of an overlap syndrome; that is, scleroderma appears simultaneously or at different points with another autoimmune rheumatic disease. Common combinations include SSc with inflammatory myopathies (polymyositis or dermatomyositis), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and/or anti-phospholipid syndrome (APS) [4]. In addition, patients with SSc frequently have another organ-targeted autoimmune disease, such as autoimmune thyroid disease (AITD, mainly hypothyroidism as a result of Hashimoto's thyroiditis or Grave's disease), celiac disease, pernicious anemia, type I diabetes mellitus, and primary biliary cirrhosis. The polyautoimmunity and increased incidence in families may attract the kaleidoscope of autoimmunity concept in this pathology [5].

The aggregation of autoimmune diseases in families reflects the higher rate of appearance of these diseases than in the general population. Several studies on single cohorts (Taiwan, Australia, and Texas, USA), combined cohorts (Texas–Texas–Michigan, USA), and comparative cohorts (Canada and Columbia) have demonstrated a higher prevalence of SSc in families of scleroderma patients and a high prevalence of autoimmune diseases in SSc relatives [6-10]. Our aim was to analyze the prevalence of autoimmune diseases in first-degree relatives (FDR) and second-degree relatives (SDR) of SSc patients and

to compare their features with data of SSc patients without a relative with an autoimmune disease (AID-R).

PATIENTS AND METHODS

The Shine Rheumatology Institute at Rambam Health Care Campus is affiliated with the European League Against Rheumatism (EULAR) and the EULAR Scleroderma Trials and Research Group (EUSTAR). We manage a consecutive prospective patient registry using the main SSc demographic and clinical data set. Additional data on family history (including autoimmune diseases), concomitant diseases, and treatments are documented in patient medical records.

A retrospective case-control analysis of SSc patients who visited our center from 2004 to 2016 was performed. Data on SSc patients with AID-R (probands) were extracted. A control group comprised SSc patients without AID-R but with similar disease duration (n=25). Data on the family history of SSs probands were retrieved from medical files. In uncertain cases, additional interviews with patients or relatives was performed. The prevalence of autoimmune diseases in both groups was compared, as was the clinical presentation and outcome of the disease.

Statistical analysis included Student's paired *t*-test and chi-square analyses. $P < 0.05$ signified statistical significance.

Table 1. Demographic data of patients with and without AID-R

Variables	All patients (N=50)	Patients with AID-R (N=25)	Patients without AID-R (N=25)	*P* value
Age at diagnosis, years	43.4 ± 15.2	41.4 ± 15.6	45.4 ± 15.2	NS
Female (%)	41 (82)	21 (84)	20 (75)	NS
Disease duration diagnosis, years	11.5 ± 8.5	11.0 ± 8.5	11.9 ± 8.8	NS
Diffuse SSc (%)	19 (38)	13 (52)	6 (24)	*P* < 0.043
Antibodies status				
ANA (%)	46 (92)	22 (88)	24 (96)	NS
ACA (%)	15 (30)	7 (28)	9 (36)	NS
ATA (%)	24 (48)	10 (40)	10 (40)	NS
RNAP (%)	5 (10)	2 (8)	3 (12)	NS
No. of SSc patients with more than 2 autoantibodies (%)	22 (44)	15 (60)	7 (28)	NS (All vs. AID-R) NS (All vs. non-AID-R) *P* < 0.024 (AID-R vs. non-AID-R)
Mean no. of autoantibodies ± SD	2.5 ± 1.3	2.8 ± 1.5	2.2 ± 0.9	NS (All vs. AID-R) NS (All vs. non-AID-R) *P* < 0.047 (AID-R vs. non-AID-R)
No. of SSc patients with additional autoimmune diseases (%)	19 (38)	14 (56)	5 (20)	NS (All vs. AID-R) NS (All vs. non-AID-R) *P* < 0.0094 (AID-R vs. non-AID-R)
Mean no. of autoimmune diseases ± SD	0.54 ± 0.81	0.84 ± 0.94	0.24 ± 0.52	NS (All vs. AID-R) *P* < 0.049 (All vs. non-AID-R) *P* < 0.0038 (AID-R vs. non-AID-R)

Bold signifies significance

ACA = anticentromere antibodies, AID-R = relatives with AID, ANA = antinuclear antibodies, ATA = anti-topoisomerase I antibodies, NS = not significant, RNAP = anti-RNA polymerase III antibodies, SD = standard deviation, SSc = systemic sclerosis

RESULTS

Of the 322 SSc patients registered in our center's database, 25 (7.7%) had at least one AID-R. The control group comprised 25 SSc patients without a family history of autoimmune diseases but with a similar disease duration. Demographic data on the entire group of patients, including subgroups with and without AID-R, are presented in Table 1.

Twenty-one patients (84% of AID-R) had an FDR with an autoimmune disease. Four patients had an SDR and two patients had both an FDR and an SDR. There were no significant differences between patients with and without AID-R in terms of age at disease onset, gender, and main SSc-specific antibodies (anticentromere, anti-topoisomerase I, anti-RNA polymerase III). In the AID-R group, 13 patients (52%) had diffuse SSc compared to 6 patients (24%), $P < 0.043$, in the control group. Fifteen AID-R patients (60%) had more than two autoantibodies compared to seven patients without AID-R (28%), $P < 0.024$. Five patients (20%) with AID-R and three (12%) patients (P = NS) in the control group had more than three autoantibodies (rheumatoid factor, anti-citrullinated peptide antibodies, antibodies to cardiolipin, anti-mitochondrial antibodies, and anti-DNA antibodies).

The mean number of autoantibodies in compared groups was 2.8 ± 1.5 and 2.2 ± 0.9, respectively ($P < 0.047$). Data on AID-R patients are presented in Table 2. In 10 AID-R patients, autoimmune diseases were spread in a horizontal pathway (sister or brother). In 11 patients the disease appeared in the mother–children (vertical) direction. Two patients had AID-R in both directions.

Fourteen patients (56%) with AID-R had an additional autoimmune disease compared to five patients (20%) in the control group ($P < 0.0094$). The mean number of additional autoimmune diseases was significantly higher in AID-R patients, compared to patients without AID-R (0.84 ± 0.94 vs. 0.24 ± 0.52, $P < 0.0038$). Among additional autoimmune diseases in the AID-R group were five cases of SLE, four of RA, four of inflammatory myopathies, two of ulcerative colitis, two of clinical APS, and one each of Sjögren's syndrome, polychondritis, and vasculitis. AITD was registered in three AID-R patients. In the control group, two patients had AITD, one had RA, one had myositis and sarcoidosis, and one had primary biliary cirrhosis. Prominent skin involvement showing a modified Rodnan skin score above 15 was reported in 13 AID-R patients (52%) and 6 controls (24%), $P < 0.043$. Arthritis was noted significantly more often in patients with AID-R than in controls (72% vs. 28%, $P < 0.002$). There were no differences in other clinical SSc features in the studied groups: myositis (24% vs. 16%, P = NS), lung involvement (48% vs. 46%, P = NS), heart disease and/or pulmonary hypertension (36% vs. 32%, P = NS), digital ulcers or critical ischemia (76% vs. 72%, P = NS), scleroderma renal crisis (12% vs. 8%, P = NS), digestive system involvement

Table 2. Clinical data of SSc patients with relatives diagnosed with autoimmune diseases

Patient initials	Age at diagnosis, years	Gender	Disease duration, years	Autoantibodies	SSc subset	Additional autoimmune diseases	Treatment	Main clinical features	Relatives (diagnosis)
AA	30	M	2	ATA, ANA	Diffuse		CS, MMF, Iloprost, bosentan, IVIG, PPI	ILD, arthritis, DU, muscles, GIT, joint contractures, RP	Sister (RA)
AS	16	F	14	ANA	Diffuse		CS, iloprost, CCB, AZA, PPI	Arthritis, DU, GIT, sclerodactyly, calcinosis, RP, joint contractures	Mother (Sjögren's syndrome and myositis), 2 aunts (RA)
AV	37	F	27	ATA, ANA, SSA	Diffuse		CS, AZA, bosentan, iloprost, sildenafil, warfarin, PPI	DU, GIT, sclerodactyly, calcinosis, RP, gangrene, joint contractures, telangiectasia	Daughter (SLE), brother (SLE)
AB	30	M	2	ATA, ANA, SSA, RNP	Diffuse		CS, AZA, iloprost, sildenafil, PPI	ILD, arthritis, DU, muscles, GIT, sclerodactyly, RP	Sister (SLE)
BhC	34	F	24	ACA, RF, ACPA, ANA	Limited	RA	MTX, HCQ, PPI	Arthritis, RP, sclerodactyly	Son (RA)
BsP	73	F	4	RNAP, ANA, SSA	Limited		PPI, CCB	ILD, PAH, calcinosis, RP	Daughter (SLE)
DY	64	F	4	ACA, ANA, AMA	Limited		CCB, PPI	RP, puffy fingers, breast carcinoma	Daughter (RA)
DL	27	F	29	ATA, ANCA, ANA	Diffuse		HCQ, AZA, iloprost, bosentan	ILD, arthritis, DU, sclerodactyly, GIT, RP, joint contractures, telangiectasia	Sister (SLE)
GT	41	F	24	ACA, ANA	Limited	Colitis	PPI, CCB	DU, RP, calcinosis, sclerodactyly, telangiectasia	Daughter (SLE)
GoT	31	F	7	ATA, ANCA, ANA	Diffuse	RA	CS, CYC, AZA, rituximab, abatacept, iloprost, PPI	ILD, arthritis, cardiomyopathy, DU, muscles, GIT, RP, joint contractures	Brother (vasculitis)
HS	40	F	8	ACA, ACL, ANA, RNP, SMITH, DNA	Limited	SLE, APLA	PPI, warfarin, iloprost, CS	ILD, arthritis, DU, gangrene, RP, sclerodactyly	Sister (SLE, catastrophic APS)
HN	26	F	11	ANA, Smith, SSA	Limited	SLE	CS, CYC, AZA, iloprost, bosentan	ILD, arthritis, RP, gangrene	Cousin (ITP), cousin (RA)
KE	57	F	17	ANA, ATA	Diffuse	Colitis, AITD	Bosentan, PPI	ILD, PAH, calcinosis, RP, death from lung carcinoma	Daughter (Crohn's disease)
NH	65	F	9	ANA, ATA, RF	Diffuse		CS, MTX, HCQ, iloprost, CCB, beta-blockers, aspirin, TAVI and pacemaker implantation	Cardiomyopathy, RP, GIT, puffy fingers, arthritis, AS, compete AVB	Cousin (SSc), son (Crohn's disease, RA)
SY	69	M	5	Negative	Diffuse		CYC, rituximab, MMF, bosentan, PPI	ILD, arthritis, RP, DU, GIT, telangiectasia	Two cousins (SLE, SSc)
SA	24	F	13	ANA, ACA	Limited		Bosentan, sildenafil, PPI	DU, gangrene, anal incontinence, telangiectasia	Cousin (SSc)
SR	53	F	3	ANA, ATA	Diffuse	Myositis	CS, CYC, AZA, iloprost, IVIG, diuretics, oxygen	ILD, PAH, tamponade, CHF, DU, RP, myositis, joint contractures; death from CHF	Cousin (SSc), nephew (Crohn's disease, RA)
VH	35	F	9	ANA,DNA, SSA	Limited	SLE, myositis, AITD	CS, AZA, PPI, IVIG	RP, myositis, arthritis, GIT, calcinosis, telangiectasia	Sister (SSc, myositis)
WMG	36	F	8	ANA, ATA, ACL, ANCA, AGP-I, JO1	Diffuse	SLE, APLA, myositis	CS, AZA, iloprost, colchicine, macitentan, ACE, aspirin	Arthritis, RP, DU, gangrene, myositis, calcinosis, SRC, joint contractures, telangiectasia	Sister (polycondritis, colitis)
YV	31	F	7	RNAP, ANA, SSB	Diffuse	Myositis, AITD	CS, CYC, MTX, rituximab, PPI, bosentan	Arthritis, RP, DU, gangrene, myositis, calcinosis, SRC, joint contractures, GIT, telangiectasia	Sister (SSc, myositis, SLE)
CR	35	F	1	ANA	Diffuse		CS, bosentan, PPI	Arthritis, PAH, RP	Daughter (SLE)
AvB	29	M	3	ATA, ANA, SSA, RNP	Limited	RA	AZA, iloprost, sildenafil, PPI	ILD, arthritis, DU, muscles, GIT, sclerodactyly, RP	Sister (SLE)
HN	46	F	5	ACA, RNP, RF, SSA, ANA	Limited	Sjögren's syndrome	HCQ, MTX, iloprost	Arthritis, DU, RP, GIT	Mother (RA), 2 brothers (RA), 1 sister (RA)
HV	61	F	19	ACA, ACL, ANA	Limited		Bosentan, PPI, diuretics, aspirin, colchicine	ILD, PAH, DU, GIT, calcinosis, sclerodactyly, telangiectasia, breast carcinoma; death from PAH	Daughter (RA)
NZ	46	F	20	ANA	Limited	SLE	HCQ, diuretics, iloprost, PPI, oxygen	ILD, arthritis, CHF, PAH, DU, GIT, sclerodacrtyly, calcinosis, RP, death from CHF	Mother (SLE and morphea)

ANA = antinuclear antibodies, ACA = anticentromere antibodies, ACE = angiotensin-converting enzymes inhibitors, AITD = autoimmune thyroid disease, APS = antiphospholipid syndrome, AS = aortic stenosis, ATA = anti-topoisomerase I antibodies, AVB = atrioventricular block, AZA = azathioprime, CCB = calcium channel blockers, CHF = congestive heart failure, CS = corticosteroids, CYC = cyclophosphamide, DU = digital ulcers, GIT = gastrointestinal tract, HCQ = hydroxychloroquin, ILD = interstitial lung disease, ITP = idiopathic thrombocytopenic purpura, IVIG = immunoglobulins, MMF = micophenolate mofetil, MTX = methotrexate, PAH = pulmonary arterial hypertension, PPI = proton pump inhibitors, RA = rheumatoid arthritis, RNAP = anti-RNA polymerase III antibodies, RP = Raynaud's phenomenon, SLE = systemic lupus erythematosus, SRC = scleroderma renal crisis, SSc = systemic sclerosis, TAVI = transthoracic aortic valve insertion

(68% vs. 60%, *P* = NS), and sclerodactyly/calcinosis 68% vs. 56% (*P* = NS).

Seventeen AID-R patients and 12 patients in the control group received immunosuppressant therapies (68% and 48%, *P* = NS). Additional autoimmune diseases developed in five AID-R patients despite treatment with immunosuppression (cyclophosphamide, methotrexate, azathioprine, or mycophenolate mofetil). Four patients with AID-R and two patients in the control group had malignancy (breast, lung, lymphoma, colon). Five patients died during follow-up, four of whom had relatives with autoimmune diseases.

The list of autoimmune diseases in relatives of SSc patients was diverse. Seven relatives had RA, 10 had SLE, one had discoid lupus (all FDR), 6 had SSc (2 FDR), 4 had inflammatory bowel disease (3 FDR), and 3 had polymyositis (all FDR). One each had polychondritis, APS, thrombotic thrombocytopenic purpura, vasculitis, and Sjögren's syndrome (all FDR).

We analyzed and compared those patients who had FDR or SDR with SSc and those whose relatives had other autoimmune diseases. There were no differences in patient age and gender. The number of relatives with autoimmune diseases was not significantly higher among AID-R with SSc relatives (2.0 ± 0.63) compared to SSc patients whose relatives had another autoimmune disease (1.36 ± 0.84), $P < 0.067$. Patients who had relatives with SSc had significantly fewer autoantibodies (1.8) [1,2] than those whose relatives had another autoimmune disease (3.1), $P < 0.03$ [1,5], but had more autoimmune diseases (12 diseases in 6 patients) compared to AID-R who had no SSc relatives (26 diseases in 19 patients), $P < 0.039$. AID-R with SSc had more autoimmune diseases (1.35 ± 1.22) compared to AID-R whose relatives had another autoimmune disease (1.56 ± 0.91), $P < 0.006$. There was no difference in the need for immunosuppression between those with SSc relatives and those with non-SSc autoimmune diseases in relatives (82.3% vs. 63.2%, *P* = 0.4).

In our cohort of 322 patients, two FDG relatives with SSc were found (0.62%). The prevalence of relatives with SSc (FDR and SDR) among SSc patients (six relatives) was 1.86% in our cohort.

Overlap syndrome was often observed in our patient groups [Table 3]. To assess polyautoimmunity, we divided all patients into two subgroups: those with more than one autoimmune disease (17 patients with a mean number of autoimmune diseases 2.65 ± 0.79) and 33 patients with SSc only. There was no difference between SSc patients with overlap syndrome compared to SSc alone in terms of age of onset, gender, diffuse or limited SSc subsets, positivity to main SSc autoantibodies (anticentromere, anti-topoisomerase I, anti-RNA polymerase III), and mean number of relatives with autoimmune diseases. There was a significant difference among these subgroups in the mean number of any autoantibodies (2.94 ± 1.52 and 2.21 ± 0.99, respectively, $P < 0.023$). Skin (diffuse vs. limited skin involvement) and non-skin clinical features such as lung, heart, kidney, gastrointestinal involvement, calcinosis/sclerodactyly, need for immunosuppression, and death were not different in SSc patients with and without an additional autoimmune disease. Joint involvement was more often seen in patients with overlap syndrome (82.4% and 36.2%, respectively, $P < 0.023$). Relatives of patients with overlap syndrome had more autoimmune diseases (1.29 ± 1.26 and 0.59 ± 0.91, respectively, $P < 0.015$).

Table 3. Demographic and clinical data of SSc patients with and without additional autoimmune diseases (polyautoimmunity)

Variables	Patients with additional autoimmune diseases (N=17)	Patients without additional autoimmune diseases (N=33)	*P* value
Age at diagnosis, years ± SD	43.9 ± 14.0	43.2 ± 16.2	NS
Female (%)	15 (88.2)	26 (78.8)	NS
Disease subsets			
Diffuse SSc (%)	5 (29.4)	14 (42.4)	NS
Limited SSc (%)	12 (70.6)	19 (57.6)	NS
Antibodies status			
ACA (%)	7 (41.5)	9 (27.3)	NS
ATA (%)	5 (29.4)	14 (45.5)	NS
RNAP (%)	1 (5.9)	4 (12.1)	NS
No. of antibodies, mean ± SD	2.94 ± 1.52	2.21 ± 0.99	**< 0.023**
No. of relatives with autoimmune diseases, mean ± SD	1.31 ± 0.95)	1.06 ± 0.83	NS

Bold signifies significance

ACA = anticentromere antibodies, ANA = antinuclear antibodies, ATA = anti-topoisomerase I antibodies, RNAP = anti-RNA polymerase III antibodies, SD = standard deviation, SSc = systemic sclerosis

DISCUSSION

Autoimmunity is one major factor in SSc pathogenesis. It is reflected by a high positivity to autoantibodies, such as antinuclear antibodies, and the presence of specific autoantibodies, such as anti-topoisomerase I, anticentromere, and anti RNA polymerase III. SSc is a rare disease in the general population (0.026%). Epidemiological data demonstrated a higher incidence of SSc in twins (monozygotic and dizygotic, 4.7%) [11] and family members of patients with SSc, SLE, and Sjögren's syndrome.

Several studies have assessed the family aggregation of SSc patients. An Australian study on 710 families calculated the prevalence of SSc in families at 1.4% with a risk ratio (RR) of 11.0 compared to the general population [7]. A similar prevalence was reported in a combined American cohort (two cohorts from Texas [190 and 175 patients] and one from Michigan [338 patients]). Arnett et al. [8] found that a positive family history is the main risk factor for developing SSc, with a RR of 13.0 for family members and 15.0 in siblings [8]. In our study, the risk for SSc was 1.6% (RR 3.5) in FDR.

Hudson and colleagues [10] analyzed a Canadian cohort (429 SSc patients) and a Columbian cohort (210 SSc patients);

36% of SSc patients in this combined cohort had an FDR with autoimmune diseases, mainly RA and AITD. In the Canadian cohort, the rate of SSc in FDR was 2.8% and in all relatives 5.6%. Among the Columbian patients, the rate of SSc in FDR was 2.1% and in all relatives 3.1% (no significant difference in the two populations).

Horimoto et al. [12] reported on 60 patients with SSc who had relatives with autoimmune diseases. In their population, 53.8% of patients presented with AITD, 35.8% had Sjögren's syndrome, and 11.5% had inflammatory myopathy. Analysis of relatives of the patients revealed AITD in 32.3%, and 22.6% in both RA and SLE.

In a Taiwanese study of a cohort population (23,658,577 people), researchers analyzed data based on National Health Insurance catastrophic illness certificate reports (years 1996–2010) and found 1891 cases of SSc. Those SSc patients had 3081 relatives with SSc. Relatives of SSc patients who had SSc themselves were significantly older (46.4 vs. 37.5 years), were more often male (53.6% vs. 49.6%), and were more often living in urban areas (63.7% vs. 58.9%) than the general population. The prevalence of SSc among SSc relatives was significantly higher than in the general population: 0.08% vs. 0.008% ($P < 0.001$) [6]. The authors concluded that having a relative with SSc is associated with a high risk of developing SSc. The estimated risk of developing SSc was 13.23: 81.22 for siblings and 9.17 for offspring. Despite a higher prevalence of SSc in family members, only 15.9% of all SSc cases were non-sporadic [6].

In another large cohort, 1071 SSc patients (probands), their 4612 FDR, and 637 controls completed a questionnaire on the history of one autoimmune disease (mainly RA, AITD, or SLE). In 10.8% of scleroderma patients, at least one autoimmune disease was reported in an FDR, while 13.5% had several autoimmune diseases simultaneously. Patients with limited SSc had relatives with autoimmune diseases more often (odds ratio [OR] 1.31, 95% confidence interval [95%CI] 1.01–1.69, $P = 0.041$) as well as patients with anticentromere positivity (OR 1.39, 95%CI 1.05–1.84, $P = 0.022$), in contrast to patients with anti-topoisomerase I positivity who had lower incidence of autoimmune diseases (OR 0.688, 95%CI 0.498–0.949, $P = 0.021$) [13].

In the Assassi series [9], 18/710 SSc families (2.5%) had at least one confirmed SSc case, with 37 cases in the SSc group and 38 cases in the FDR group. In families of SSc patients with polyautoimmunity, there was a higher proportion of males ($P = 0.033$, OR 2.06, 95%CI 1.00–4.25). These families included a smaller proportion of African-American and Hispanic families. The authors showed vertical (mother–daughter or mother–son) and horizontal (sister–sister, sister–brother, twins, and multiple sisters) propagation of the disease. Patients with AID-R had mainly limited SSc, but showed interstitial lung diseases, gastrointestinal involvement, and myositis more often. Patients with SSc and their relatives exhibited similar antibody profiles [9].

In a French cohort of 373 SSc patients' families, about one-third had at least one additional autoimmune disease or one FDR with autoimmune diseases, including AITD (4.9%), RA (4.1%), psoriasis (3.9%), and type 1 diabetes mellitus (2.9%). Compared to control families, more autoimmune diseases (AITD, SSc, SLE, and Sjögren's syndrome) appeared in families with SSc but not in those with inflammatory bowel disease. SSc patients with additional autoimmune diseases had more FDR with autoimmune diseases [14].

Interesting results were obtained in a study conducted in Utah on 1037 SSc patients and 50 SSc-associated families (risk ratio 2–17 for SSc in these families). The incidence of SSc was about 2.8–3.3: in FDR it was 3.08, in SDR 3.8, and in third-degree relatives 2.14. In this study, a high familial incidence of Raynaud's phenomenon presented as a population-attributing risk of 6.38. Interstitial lung disease (risk ratio of 1.53) and any autoimmune diseases (risk ratio 2.49) was demonstrated among relatives of SSc patients. A less prominent but still significantly higher incidence of these features was seen in SDR and third-degree relatives [15].

Familial clustering for SSc is often associated with multiple autoimmunity. SSc is one of the diseases with a prominent tendency toward polyautoimmunity. We reported previously on a high incidence of overlap syndrome in SSc patients, especially with inflammatory myopathies, Sjögren's syndrome, RA, and SLE [4]. Elhai and co-authors [16] performed a meta-analysis of 20 studies on polyautoimmunity (at least one additional autoimmune disease) and multi-autoimmunity (two or more additional autoimmune diseases) in SSc patients and found that polyautoimmunity ranged from 10.9% to 43.9% (~26%) in various reports. The prevalence of polyautoimmunity was 25.7% and multi-autoimmunity 3.9%. Patients with additional autoimmune diseases were mostly female and had a limited subset of SSc. The list of associated autoimmune diseases was as follows: AITD (10.4%), Sjögren's syndrome (7.7%), inflammatory myopathies (5.6%), RA (4.2%), primary biliary cirrhosis (3%), and SLE (2.6%). The authors suggested common genetic and environmental mechanisms for polyautoimmunity in SSc. According to their results, patients with polyautoimmunity conditions had better outcomes. The authors speculated that this finding could be due to concurrent relationships in multiple autoantibodies [16]. Polyautoimmunity with AITD, APLA, Sjögren's syndrome, and scleroderma was reported in SLE patients as well [17]. Our study analyzed polyautoimmunity in a subgroup of patients with AID-R and in an artificially constructed control group. Similar to other studies, we calculated a rate of 34% for additional autoimmune diseases.

One possible explanation for the familial appearance of autoimmune diseases is the existence of a common susceptibility locus, such as the *PTPN22* gene known for its connection with a variety of autoimmune diseases, such as RA,

SLE, type I diabetes mellitus, multiple sclerosis, and AITD, as well as its significant association with anticentromere and anti-topoisomerase I positivity in different ethnic populations in the United States [18]. Similar results were obtained with the *STAT4* gene, which may be involved in the pathogenesis of several autoimmune diseases (SLE, RA, and Sjögren's syndrome) and a predisposition to limited SSc in Spanish and several other European SSc populations [19]. Anaya et al. [20] reported a genetic association between non-synonymous single nucleous polymorphism (SNP, rs1143679) in patients with SLE and SSc.

Our results correspond with those from other cohorts. The assumed prevalence of SSc in a family in our cohort was 1.86%. Patients with AID-R had more severe skin and joint involvement. They also had significantly more autoimmune diseases. In our cohort, there was no association with routinely assessed autoantibodies. SSc patients with FDR and SDR diagnosed with scleroderma did not have significantly more relatives with autoimmune diseases but did have significantly more concomitant autoimmune diseases. Relatives of patients with SSc and additional autoimmune diseases also had significantly more autoimmune diseases. Our group was too small to draw conclusions on the severity of the disease in AID-R patients or on the outcome.

CONCLUSIONS

There is a family predisposition to SSc and autoimmune diseases in scleroderma patients, and such patients have a tendency to carry multiple autoantibodies. They are prone to poly- and multi-autoimmunity. The same tendency is obvious in relatives of patients with SSc (more autoantibodies and higher occurrence of autoimmune diseases). There were no differences in main SSc features between familial and sporadic SSc, except for more severe skin and joint disease.

A detailed familial history is important, as it might help in diagnosing familial cases of SSc and preclude the appearance of additional autoimmune diseases in SSc patients. In addition, the prevalence may provide a different perspective when consulting with family members. The high incidence of polyautoimmunity in our patients supports the hypothesis of shared pathogenetic mechanisms in different autoimmune conditions and provides data on features of scleroderma and related conditions when they appear as a part of the overlap syndrome. Knowledge of polyautoimmunity could be reflected in the management of the assessment and treatment SSc patients and provide information to their family members.

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"To sit in the shade on a fine day and look upon verdure is the most perfect refreshment"

Jane Austen (1775–1817), English novelist known primarily for her six major novels, which interpret, critique and comment upon the British landed gentry at the end of the 18th century