
Systemic sclerosis in Argentina: evaluation of a large cohort from a single centre and comparison with other international series

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ABSTRACT

Objective. Prevalence of systemic sclerosis (SSc) and different clinical subsets varies across the world. Few data have been published on SSc patients in Latin America. Our objective was to describe a SSc cohort in Argentina and to compare clinical findings, disease subsets and antibodies with other international SSc populations.

Methods. Patients with SSc (n=234) seen at the Rheumatology section of the Hospital Italiano de Buenos Aires between 2000–2011 were retrospectively analysed. Data on clinical manifestations, disease subsets and antibodies were obtained. Patients were classified into diffuse cutaneous (dc) and limited cutaneous (lc) subsets. Comparison with other cohorts (France, United States, Germany, Italy, Mexico, EUSTAR and Brazil) was made based on published information.

Results. A higher female:male ratio (12:1) and a higher limited subset prevalence (76.1%) was found in this Argentine cohort comparing with others. We also found a lower prevalence of diffuse disease, anti Scl-70 (antitopoisomerase) and nucleolar pattern antinuclear antibodies. Within each subset, clinical findings were similar with other SSc populations except for a very low prevalence in renal crisis (0.02% of dc SS).

Conclusion. With slight variations perhaps due to genetic, environmental or referral factors, SSc in this cohort appears to be similar to that described in other parts of the world.

Introduction

Systemic sclerosis (SSc) is a disease characterised by inflammatory, fibrotic and degenerative changes in skin, blood vessels and major internal organs. Patients' clinical manifestations, natural history and survival are highly variable

and in general are related to the disease subset (limited vs. diffuse) and presence of different autoantibodies.

Prevalence of the disease varies according to gender, geographic location and ethnic background. For example, Afroamerican patients develop disease earlier and have a higher proportion of the diffuse variant (1). SSc affects mainly women (3:1 in Great Britain; 6:1 in Europe overall, 6.2:1 in Hungary and 14:1 in Japan) (1–2). Taking into account that this female preponderance is greater in the limited subtype of the disease, gender distribution variations may be due to different proportion of disease subsets in these populations (1). In Europe the incidence and prevalence of SSc is lower (10 and 50 cases per million adults) than in the US (19.3 and 242 per million adults, respectively) (3–4). In Argentina, SSc prevalence has been reported to be 296 per million people (CI 95% 193–434) and incidence density was of 6.1 per million-people-year (CI 95% 2.3–14.5) for diffuse subset and 15.2 per million-people-year (CI 95% 2–28) for limited disease (5).

Classical textbooks mention that the usual proportion between diffuse and limited forms seen at tertiary centres is around 40% for diffuse *versus* 60% for limited. However, this differs greatly in different series, perhaps reflecting referral patterns to the research centre involved. Indeed, the EUSTAR registry (1), which may “dilute” this referral bias, due to the numbers of patients and the different countries involved, has approximately the above mentioned proportion. There is scarce data on clinical characteristics in SSc patients in Latin America and particularly in Argentina. A recent large series from Brazil (6) has described causes of death but with limited details on subsets and antibody profiles, and there are two previous re-

Competing interests: none declared.

ports from Argentina, but with smaller numbers of patients (7-8).

Our objective was to describe clinical manifestations, disease subsets and autoantibody profile in an Argentine SSc cohort taken from our Hospital registry over ten years, and to compare this with data published from other international SSc populations.

Materials and methods

Patients

Patients registered in the Hospital Italiano de Buenos Aires electronic databases between 2000 and 2011. *Case ascertainment:* a) patients included in Rheumatology Section databases, b) patients with the problem scleroderma, SSc or CREST in the computer-based Patient Record System, c) patients with ICD 9 code 710.1 (systemic sclerosis) on admission to Hospital, and d) patients with anti Scl-70, anticentromere or anti nucleolar antibodies in the laboratory database. Medical records of all patients were reviewed and only cases fulfilling ACR 1980 criteria (or considered to be SSc by authors in spite of incomplete criteria) were included. They were classified as diffuse cutaneous (dc) or limited cutaneous (lc) according to LeRoy's criteria (skin involvement proximal or distal to elbows or knees respectively) (9).

Definition of organ involvement

SSc clinical manifestations were considered to be present if predefined criteria were met during the course of the illness. Involvement of skin: the maximum extension of skin involvement at any one time during course of the disease was considered to define subsets (limited vs. diffuse). Organ involvement definitions were the following: a) Upper gastrointestinal tract: manometry with esophageal dysmotility, esophagram with gastroesophageal reflux or upper endoscopy with esophagitis, b) Pulmonary hypertension (PH): echocardiogram with estimated pulmonary systolic artery pressure greater than 40 mmHg or right heart catheterisation with mean pulmonary artery pressure at rest over 25 mm Hg, c) Interstitial lung disease (ILD): pulmonary interstitial disease observed in high resolution computerised tomography (HRCT) or pulmonary function

Table I. General characteristics.

Type of systemic sclerosis	Limited (n=178)	Diffuse (n=56)	p-value (limited vs. diffuse)
Females, n (%)	167 (93.8)	49 (87.5)	0.13
Age at diagnosis, years, mean (SD)	55 (16.2)	53 (18.3)	0.038
Duration of Raynaud before diagnosis, years, median	2.4	0.8	0.008

Table II. Clinical and serological features in this Argentine SSc cohort.

Type of systemic sclerosis	Limited (n=178)	Diffuse (n=56)	p-value (limited vs. diffuse)
Anti Scl-70, %	11.8	43.9	<0.001
Anticentromere, %	71.6	4.8	<0.001
Nucleolar ANA, %	5.3	20.9	0.001
Other autoantibodies, %	25.7	25.9	0.76
GI involvement, %	68.2	64.3	0.45
Interstitial lung disease, %	21.9	65.3	<0.001
Pulmonary hypertension with ILD, %	4.6	15.4	0.03
Pulmonary hypertension (without ILD), %	8.4	2.6	0.39
Echocardiographic abnormalities (other than PH), %	5.6	10	0.26
Digital ulcers, %	28.2	32.1	0.86
Renal crisis, n	0	1	
Follow-up: patient-year	543.2	144.8	
Currently followed, %	57.9	46.4	
Died under our care, n	13	4	

Scl-70: anti-topoisomerase I; ANA: antinuclear antibodies; GI: gastrointestinal; ILD: interstitial lung disease; PH: pulmonary arterial hypertension.

Table III. Comparison of this series and two previous ones from Argentina regarding disease subset and autoantibody profile.

Type of systemic sclerosis	This series (n=234)		Catoggio <i>et al.</i> (1990) (7) (n=33)		Laborde <i>et al.</i> (2000) (8) (n=189)	
	Limited cutaneous	Diffuse cutaneous	Limited cutaneous	Diffuse cutaneous	Limited cutaneous	Diffuse cutaneous
	26%	74%	45%	55%	47%	53%
Anti centromere	68%	5%	73%	0	63%	0
Anti Scl-70	11%	44%	13%	39%	1%	48%
Antinucleolar	5 %	21%	20%	72%	NA	NA

Scl-70: anti-topoisomerase I; NA: not assessed.

tests with vital forced capacity (VFC) lower than 70% of expected and/or carbon monoxide lung diffusion (DLCO) test under 80% of expected, d) Echocardiographic alterations: left or right ventricular diastolic dysfunction in absence of arterial hypertension or pulmonary hypertension respectively, or pericardial effusion, e) digital ulcers: active digital ulcers or pitting scars confirmed by a physician, f) Renal involvement: history of scleroderma renal crisis (abrupt onset of accelerated arterial hypertension and/or rapidly progressive renal failure).

Autoantibodies

Laboratory detection methods were indirect immunofluorescence on HEP-

2 cells (antinuclear antibodies, antinucleolar and anticentromere). ANA dilutions greater or equal to 1/80 were considered positive. ELISA was used for antitopoisomerase I (anti Scl-70).

Statistical analysis

Chi-square analysis was used to determine significant differences between sets of categorical data, and Fisher's exact test when appropriate. A *p*-value <0.05 was considered statistically significant. Kaplan-Meier survival curve was used for survival analysis. Incomplete data was analysed as missing data.

Comparison with other cohorts

We conducted a Pubmed review in or-

Table IV. Clinical findings in different cohorts according to disease subset.

Clinical finding	DIFFUSE SYSTEMIC SCLEROSIS							
	United States (11) (n=119)	France (11) (n=30)	Germany (13) (n=484)	Italy (12) (n=177)	Mexico (10) (n=60)	EUSTAR (1) (n=1349)	Spain (14) (n= 243)	Argentina (n=56)
Esophageal dysmotility, %	67	79	69.3	69	69***	68.2	71.2	64.3
ILD, %	30	57	56.1	71**	47	53.4	70	65.3
Isolated PH, %	2	12	18.5	NR	30 [§]	5.9	13.7	2.6
Renal crisis, %	17	7	15.9	12	0	4.2	7.8	0.02
Digital ulcers, %	NR	NR	34.4	51	NR	42.7	63.8	32.1
Calcinosis, %	23	16	NR	20	NR	NR	23.5	NR
Echocardiographic abnormalities, %	20	15	23 [‡]	32 [‡]	16 [‡]	23.8	32.5 [‡]	10 ^{§§}
Arrhythmias and/or conduction blocks in EKG, %	11	10				12.7	10.3	NR

Clinical finding	LIMITED SYSTEMIC SCLEROSIS							
	United States (11) (n=128)	France (11) (n=97)	Germany (13) (n=674)	Italy (12) (n=565)	Mexico (10) (n=79)	EUSTAR (1) (n=2101)	Spain (14) (n= 568)	Argentina (n=178)
Esophageal dysmotility, %	67	63	59.2	55	63***	66.8	57.3	64.5
ILD, %	37	30	20.8	53***	36	34.7	39.3	26.7
Isolated PH, %	31	9	14.9	NR	34 [§]	9.2	8.8	7.3
Renal crisis, %	2	0	9.1	6	2.5	1.1	0.7	0
Digital ulcers, %	NR	NR	23.8	43	NR	32.9	39	28.1
Calcinosis, %	42	36	NR	22	NR	NR	19.8	NR
Echocardiographic abnormalities, %	6	12	12 [‡]	23 [‡]	7 [‡]	20.4	31.1 [‡]	10 ^{§§}
Arrhythmias and/or conduction blocks in EKG, %	19	14				10.4	11.9	NR

ILD: interstitial lung disease; PH: pulmonary hypertension; EKG: electrocardiogram; NR: not reported.

** : patients with isolated PH were included in this group; ***: patients with small bowel hypomotility, wide-mouth colonic sacculations, or malabsorption syndrome were also included in this group; [§]: patients with primary or secondary PH were included; [‡]: this group included cardiac involvement in general (pericardial effusion, diastolic dysfunction, heart failure, arrhythmias, conduction disturbances); ^{§§}: patients with diastolic dysfunction and history of PH or arterial hypertension were excluded.

der to find SSc cohorts with clear data published regarding visceral involvement, autoantibodies and disease subsets' classification. For comparisons, we chose the limited data from Argentina (7-8) and that published from Brazil (6), the EULAR Scleroderma Trials and Research (EUSTAR)(1) cohort and cohorts from Mexico (10), US and France (11), Italy (12), Germany (Registry of the German Network for Systemic Sclerosis)(13) and Spain (14).

Results

From year 2000, 234 patients (216 females) with SSc had been evaluated at the Rheumatology section of the Hospital Italiano de Buenos Aires. Table I shows the general characteristics of our population. Female:male ratio was 12:1. Fifty six patients (23.9%) had dc SS and 178 (76.1%) the limited form. Total follow up was 688 patients-years. Over half (55.1%) are still under our care. Seventeen have died in our hospital during this period. Ten-year survival rate was 80% for limited and 70% for diffuse

variants respectively (HR: 0.88 95% CI: 0.7–1.1). Table II shows the clinical and serological profile of this cohort.

Digital ulcers and gastrointestinal involvement occurred similarly in dc and lc, Interstitial lung disease in 65.3% of diffuse and 21.9% of limited ($p<0.001$). Renal crisis was only seen in one patient with diffuse disease.

Anti Scl-70 was present in 16.2% of overall patients, anticentromere in 52.9% and nucleolar ANA in 7.3% (insufficient laboratory data from 18.4% of patients).

Anticentromere antibodies were associated with pulmonary hypertension with an OR of 8.25 (95% CI 1.9–35.7). On the other hand, ILD was less frequent in patients with this antibody (OR 0.18, 95% CI 0.11–0.29). As expected they were also associated with limited disease with an OR of 34.4 (95% CI 10.2–116.6). On the other hand, anti Scl-70 was associated with ILD (OR 12.7, 95% CI 6.9–23.3) and diffuse clinical subset (OR 5.9, 95% CI 2.7–12.8). Nucleolar ANA was also

related to diffuse disease (OR 4.7, 95% CI 1.7–12.8).

Comparison with previous Argentine cohorts

Table III shows comparison of the current cohort with other groups of patients reported by us in one case and by another centre. In both cases, and as opposed to our current data, the proportion of limited *versus* diffuse was almost half and half. These differences may in part reflect the reporting of consecutive cases seen *versus* the complete search of the hospital registry for patients with the disease. Prevalence of anticentromere and anti Scl-70 was similar to our current data.

Comparison with other international cohorts

Eight different SSc populations have been chosen for comparison with our patients based on published data: United States (n=247) (11), France (n=127) (11), Italy (n=1012) (12), Germany (n=1483) (13), Mexico (n=139) (10),

Table V. Frequency of disease subsets and autoantibody profiles in different SS cohorts.

	United States (11)* (n=247)	France (11)* (n=127)	Germany (13)** (n=1483)	Italy (12)*** (n=1012)	Mexico (10) (n=139)	EUSTAR (1)* (n= 3656)	Brazil (6)**** (n=947)	Spain (14) (n= 916)*****	Argentina (n=234)
Limited cutaneous, %	42	54	45.5	64	56.8	57.5	56.4	61.8	76.1
Diffuse cutaneous, %	47	19	32.7	14	43.1	36.9	31	26.5	23.9
Scl-70, %	22	35	27.6	36	28.1	35.9	16.1	21.7	16.2
Anticentromere, %	21	18	36.4	39	29.5	29	22.1	44.1	52.9
Nucleolar ANA, %	35 [†]	15 [‡]	32.5 [‡]	20	20.1 [€]	NR	NR	NR	7.3

Scl-70: anti-topoisomerase I; ANA: antinuclear antibodies; NR: not reported; *: patients were classified into limited cutaneous, diffuse cutaneous and overlap syndromes; **: patients were classified into limited cutaneous, diffuse cutaneous, overlap syndromes, sclerosis sine scleroderma and undifferentiated systemic sclerosis; ***: patients were classified into limited cutaneous, intermediate cutaneous and diffuse cutaneous systemic sclerosis; ****: patients were classified into limited cutaneous, diffuse cutaneous, overlap syndromes and sclerosis sine scleroderma; *****: patients were classified into limited cutaneous, diffuse cutaneous, prescleroderma and sclerosis sine scleroderma; †: we include for analysis as nucleolar ANA antibodies anti Th/To, anti-U3RNP, anti-PM-Scl, antiKu and anti RNA polymerase III; ‡: reported in this cohort as systemic sclerosis associated antibodies; €: we include for analysis as nucleolar ANA antibodies anti Pm-Scl, Anti RNA pol III and anti-Ku.

EULAR Scleroderma Trials and Research (EUSTAR) (1) cohort (n=3656), Spain (n=916) (14) and one from Brazil (n=947) (6). Frequencies of visceral involvement in diffuse and limited forms are shown in Table IV, proportion of disease subsets and autoantibody profile in Table V.

In the current, larger Argentine cohort, we found a greater female preponderance (12:1) comparing with other countries. This may be also due to the increased proportion of limited subset (76.1%) versus diffuse subset (23.9%) in relation with other SSc populations. Anticentromere was the main antibody present in our patients (52.9%). Prevalence of diffuse subset, Scl-70 and nucleolar ANA was lower than reported elsewhere. Within each disease subset, clinical manifestations were quite similar to other cohorts except for a very low prevalence for renal crisis. We believe that different referral patterns in different institutions may be in part responsible for these differences, aside from different genetic and or environmental backgrounds.

As previously reported in other series, anticentromere antibodies were associated with pulmonary isolated hypertension (OR 8.25) and with limited disease (OR 34.4) and anti Scl-70 antibodies with interstitial lung disease (OR 12.7) and diffuse cutaneous involvement (OR 5.9) (13-14).

There were some limitations when comparing subsets and clinical data with other SSc populations. First of all, patients were not homogeneously classified in different cohorts: in the US (11),

France (11) and EUSTAR (1) they included patients with overlap syndromes; in the German cohort (13) patients were classified into limited cutaneous, diffuse cutaneous, overlap syndromes, sclerosis sine scleroderma and undifferentiated systemic sclerosis; Italian patients (12) were classified into limited cutaneous, intermediate cutaneous and diffuse cutaneous systemic sclerosis. Analysis of antibodies was also different. We were not able to determine other SSc-related autoantibodies (*i.e.* RNAP III, U3RNP, etc) besides ANA, Scl-70 and anticentromere. Organ involvement was not defined similarly in all the cohorts as it is shown in Table II. Therefore, these limitations may also account for some of the differences we found.

In spite of these possible differences, data shown here support the clinical and serologic characteristics found in SSc patients worldwide. Disease-related autoantibodies showed an intimate relationship with disease subsets and visceral involvement as described elsewhere.

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