CLINICAL AND SOCIODEMOGRAPHIC FEATURES OF PUERTO RICANS WITH SYSTEMIC SCLEROSIS

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Introduction: Systemic sclerosis is an autoimmune disease of unknown etiology characterized by fibrotic changes in the skin, blood vessels, and various internal organs. The disease has a wide spectrum of presentation and a variable clinical course that includes limited skin involvement to life-threatening disease. Clinical manifestations and disease severity differs among ethnic groups. The objective of this study is to describe the clinical and sociodemographic features of patients with well-characterized systemic sclerosis from Puerto Rico.

Methods: A structured questionnaire was completed for each patient to gather information about demographic factors, clinical manifestations, laboratory findings, diagnostic studies, and pharmacologic treatments.

Results: Of the 24 patients with systemic sclerosis, 96% were females, 83% had Raynaud's phenomenon, 67% had gastrointestinal involvement, 63% had skin hypopigmentation, 50% had digital pitting scars, 46% had arterial hypertension, 11% had pulmonary hypertension, and 4.8% had renal involvement. The overall median modified Rodnan skin score was 24.5 (inter-quartile range 16.0–31.3). Pulmonary function tests resulted in abnormal in 60% of 14 patients, of which 57% had restrictive lung disease (FVC<70%) and 42.9% had decreased diffusion capacity. Serologically, 66.7% were positive for antinuclear antibody and 62.5% were positive for anti-centromere.

Conclusions: In this study, the predominant clinical features of Puerto Ricans with systemic sclerosis were gastrointestinal involvement, Raynaud's phenomenon, digital pitting scars, and lung disease. Patients had a moderate severity of skin disease. The presence of renal involvement and pulmonary hypertension were low in our group. No significant differences were found between systemic sclerosis disease subsets. (*Ethn Dis*. 2010;20[Suppl 1]:S1-185–S1-190)

Key Words: Systemic Sclerosis, Scleroderma, Hispanics

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INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrotic changes in the skin, blood vessels, and various internal organs.[1–4] SSc is classified into two major groups of limited (lcSSc) and diffuse (dcSSc) cutaneous disease, which are defined by the extent of skin involvement.[1] Patients with dcSSc are at a greater risk of developing rapid progression of both skin thickening and visceral involvement than those with lcSSc.[2,3] The condition is more prevalent in women than in men, with a female to male ratio ranging from 3:1 to 6:1.[1–6]

Racial differences are apparent in the incidence and clinical presentation of this disease. African-Americans and Hispanics are more likely to have dcSSc. In addition, African-Americans have an earlier onset, as well as a higher frequency of pulmonary disease and an overall worse prognosis than Caucasian patients.[4–6] Limited data of Hispanics of Mexican ancestry suggest that the occurrence and the clinical manifestations of SSc are more severe in this ethnic group than in Whites.[7,8]

The presence of autoantibodies is a characteristic trait of autoimmune disorders and was one of the first immune-serological abnormalities observed in SSc patients. Approximately 90% to 95% of individuals diagnosed with SSc test positive for antinuclear antibodies.[1–6] Anticentromere antibodies (ACA) and anti-Scl 70 antibodies are considered specific for SSc and correlate with lcSSc and dcSSc, respectively. Anticentromere antibodies are associated with a better prognosis of the disease and increased survival, while anti-Scl 70 is associated with pulmonary involvement and an increased mortality rate.[5,6] In addition, the frequency of certain autoantibodies subsets varies among different racial groups. Caucasians with SSc have the highest frequency of anticentromere antibodies (associated with limited skin involvement and less pulmonary fibrosis), whereas African Americans have a higher frequency of anti-Scl 70, anti-ribonucleoprotein, and fibrillarin autoantibodies.[7,8] Reveille et al reported a lower presence of anti-Scl 70 antibodies in Hispanic groups in comparison with African Americans. To our knowledge no previous studies that evaluate the clinical manifestations of Puerto Ricans with SSc have been conducted. Therefore, we conducted this study to describe the clinical and sociodemographic features of these patients.

METHODS

A cross sectional study was performed among a group of adult patients with SSc, as defined by the 1980 American College of Rheumatology (ACR) criteria, that were being seen at the rheumatology clinics of the Puerto Rico School of Medicine from September 2004 to August 2007.[9]

A questionnaire was designed and completed for each patient to gather information about demographic factors, clinical manifestations, laboratory tests, diagnostic studies, and pharmacologic treatments. Enrollment includes a retrospective abstraction of the clinical and laboratory data from the medical record and a patient interview.

Included variables from the demographic domain were age, sex, education, and toxic habits (smoking, alcohol or illicit drug use). Clinical variables included were age at diagnosis, disease duration, clinical manifestations, diagnostic studies,

laboratory findings, and therapy. Age at diagnosis was defined as the age at which the patient fulfilled the diagnosis of SSc by the 1980 ACR classification criteria. Duration of disease was defined as the time elapsing from the date when the patient completed the ACR criteria for SSc (diagnosis date) to the date of the baseline visit.

Clinical manifestations in all organ systems were ascertained by history, physical examination, and medical record review. The following manifestations were identified: Raynaud's phenomenon, sclerodactyly, Sicca syndrome, digital pitting scars, digital ulcers, digital gangrene, calcinosis, flexion contractures, hypopigmentation, proximal muscle weakness, arthritis, dysphagia, gastrointestinal reflux, diarrhea, constipation, systemic arterial hypertension, and congestive heart failure. The extent of skin involvement was evaluated using the modified Rodnan skin score that assesses the skin thickness by palpation of 17 body areas on a scale of 0–3. The maximum score for this scale is 51.[10]

The results of pulmonary function tests (PFT's), chest X-rays, high resolution CT scans, and echocardiogram were reported and evaluated. Abnormal PFT was defined by impairments of carbon monoxide diffusion capacity (DLCO) with <70% of the predictive values and/or the forced vital capacity (FVC) <70%. Pulmonary interstitial fibrosis was defined as SSc associated fibrosis confirmed by chest X-ray and/or high resolution CT scan. Pulmonary hypertension was defined by an estimated right ventricular systolic pressure (RVSP) >40 mm Hg as determined by echocardiogram. No cardiac catheterization was reported.

Reported laboratory tests (most recent to last visit) were serum creatinine, hemoglobin, sedimentation rate, fasting blood sugar, urine protein, complement levels (C3, C4), antinuclear antibodies and scleroderma associated autoantibodies (anti-Scl70, anticentromere, anti U1-RNP).

The study evaluated the use of prednisone, cyclophosphamide, D-penicillamine, methotrexate, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and statins after the diagnosis of SSc.

Patients were classified in 2 subsets, limited (lcSSc) or diffuse (dcSSc), according to the extension of skin thickening as suggested by LeRoy.[1] The lcSSc subset was defined by skin involvement of extremities distal to the knee and elbow joints and facial skin. The dcSSc subset was defined as a progressive form with an involvement of trunk, face, proximal and distal extremities.

This study was approved by the University of Puerto Rico Medical Sciences Campus (UPR MSC) Institutional Review Board. All patients were enrolled after informed consent was obtained.

STATISTICS

The Statistical Package of Social Sciences (SPSS, Inc Chicago) version 12.0 was used to perform univariate and bivariate analyses. Univariate analysis describes the frequencies of the demographic parameters, clinical manifestations, laboratories, diagnostic tests, and treatments. Differences between patient groups were analyzed with the Chi-square or Fisher exact test, and non-parametric Mann-Whitney U test were used to evaluate median differences and interquartile ranges (IQR). The P value used to determine statistical significance was $<.05$.

RESULTS

A total of 24 patients were evaluated during the study period. Table 1 shows the distribution of baseline demographic parameters. As expected, the majority of the enrolled patients was female (95.8%). The median (IQR) age of the patients at the study entry was 52.0 (39.0–59.0) and the median (IQR) disease duration from onset time to study entry was 6.5 years (3.0–11.5) The prevalence of unhealthy habits in this group was low, only 4% reported alcohol use and 12.5% cigarette smoking.

Cumulative clinical features are also shown in table 1. The median (IQR) skin score (mRSS) was 24.5 (16.0–31.3). The most frequent features in this group were Raynaud's phenomenon (83.3%), sclerodactyly (58.3%), digital pitting scars (50%), hypopigmentation (62.5%), and gastroesophageal reflux (66.7%). Pulmonary disease was a prominent feature in this group. Sixty percent (60%) of patients presented abnormal Pulmonary Function tests ($n=14$); 57% had restrictive lung disease (FVC<70%); and 42.9% presented decreased diffusion capacity (predicted DLCO <70%). Otherwise, only 30% of patients presented pulmonary fibrosis of CT scan. There were no significant differences of the clinical features between the two disease subsets.

For the 24 study patients, only 16 were evaluated for antinuclear antibodies (ANA's) with 62.5% showing positive. Less than 30% of patients presented scleroderma associated autoantibodies (anti-Scl70, anti-centromere, anti U1-RNP). Median (IQR) sedimentation rate was 23.0 (11.0–57.0). The median (IQR) hemoglobin value was 12.8 (12.1–13.7). The presence of proteinuria was low (4.8%). Complement was evaluated in 18 patients and all had normal complement C3 and C4 levels. No significant statistical difference was identified between the two subsets.

Pharmacological therapies are also shown in Table 1. The most common medications were prednisone (62.5%), d-penicillamine (50%), and calcium channel blockers (54.2%). All patients received dihidropyridine type calcium channel blockers. The median dose of prednisone ($n=10$) was 10.00 (IQR: 6.76–13.81). No renal crisis was identified in these patients. No significant therapeutic difference was identified between the two subsets.

Table 1. Demographic parameters, cumulative clinical manifestations, laboratory findings and pharmacological treatment

	Limited *N*=12	Diffuse *N*=12	Total *N*=24	*P* value
Demographics				
Gender, women %	91.7	100.0	95.8	1.000
Age at diagnosis, median years (IQR*)	37.5(26.3–48.8)	43.0(36.5–51.3)	43(29.3–49.8)	.340
Age at last visit, median years (IQR)	47.5(32.3–54)	53.5 (42.5–60.0)	52 (39.0–59.0)	.148
Disease duration, median years (IQR)	6.5 (3.0–10.0	6.5(1.5–13.5)	6.5(3.0–11.5)	.932
Smoking, %	8.3	16.7	12.5	1.000
Alcohol use, %	8.2	0.0	4.2	1.000
Clinical manifestations				
Skin score median (IQR)	18.5(16.0–25.8)	27.5(15.8–34.3)	24.5(16.0–31.3)	.133
Raynaud's phenomenon, %	66.7	100.0	83.3	.093
Sclerodactyly, %	50.0	66.7	58.3	.680
Digital pitting scars, %	33.3	66.7	50.0	.220
Digital ulcers, %	25.0	33.3	29.2	1.000
Calcinosis, %	41.7	33.3	37.5	1.000
Hypopigmentation, %	66.7	58.3	62.5	1.000
Dysphagia, %	33.3	25.0	29.2	1.000
Gastroesophageal reflux, %	66.7	66.7	66.7	1.000
Diarrhea, %	16.7	8.3	12.5	1.000
Arthritis, %	0	16.7	8.3	.478
Proximal weakness, %	8.3	0	4.2	1.000
Flexion contractures, %	25.0	25.0	25.0	1.000
Sicca syndrome, %	41.7	50.0	45.8	1.000
Abnormal pulmonary function test, %	57.1	62.5	60.0	1.000
Pulmonary hypertension, %	0	18.2	11.1	.497
Laboratory findings				
Antinuclear antibody, % (*n*=16)	57.1	66.7	62.5	1.000
Anticentromere ab, % (*n*=15)	37.5	28.6	33.3	1.000
Anti Scl 70 ab, % (*n*=22)	8.3	30.0	18.2	.293
Anti-RNP ab, %(*n*=23)	12.5	25.0	18.0	1.000
Hemoglobin, median (IQR*), *n*=23	13.0(12.1–13.7)	12.7(11.9–13.8)	12.8(12.1–13.7)	.600
Sedimentation ratemedian (IQR), *n*=19	17.0(9.0–48.5)	26.5(10.5–60.3)	23.0(11.0–57.0)	.744
Proteinuria, % *n*=21	10	0	4.8	.303
Pharmacological treatment				
Prednisone, %	66.7	58.3	62.5	1.000
D-penicillamine, %	41.7	58.3	50.0	.685
Methotrexate, %	16.7	8.3	12.5	1.000
Cyclophosphamide, %	0.0	8.3	4.2	1.000
ACE inhibitors, %	16.7	41.7	29.2	.371
Calcium channel blockers, %	50.0	58.3	54.2	1.000
HMG-CoA reductase inhibitors, %	8.3	25.0	16.7	.590

* IQR= Inter-quartile ranges

COMPARISON WITH OTHER ETHNIC GROUPS

Table 2 shows the clinical and serologic findings of our study and other SSc ethnic groups. Specifically, we compared our findings with studies from Europe,[2] South Africa,[9] Colombia[10] and United States.[7] The age of diagnosis was lower in our group and in South Africans. Puerto Ricans exhibited the highest female predominance at 96%. The distribution of diffuse and limited subtype was different in all groups. The limited skin disease subtype was predominant in the Germans[2] and Colombians[10] in contrast to the South Africans[9] and Mexicans from Texas.[7] Our group showed equal distribution between both subtypes. Raynaud's phenomenon was a prominent feature in all groups. Digital ulcers were presented less frequently on the Caucasians.[2] Puerto Ricans showed a more affected skin with high prevalence of hypopigmentation and higher skin scores. Pulmonary fibrosis and decreased DLCO were prominent features in the South Africa group.[10] Puerto Ricans exhibited the lowest presence of Pulmonary Hypertension (PAH) and kidney disease. Antinuclear antibodies were prominent in all groups. The Colombians presented the highest percent of anticentromere pattern.[10]

Table 2. Comparison with other ethnic groups

Feature	Humelmann *N*=1483 Caucasians Germany	Tager *N*=230 Black South Africans	Coral-Alvarado *N*=349 Hispanics Colombian	Revielle *N*=54 Mexicans Texas, US	Ríos *N*=24 Hispanics Puerto Rico
Demographic					
Age at onset, yrs	55.7	36.1	54.5	—	39.7
Female, %	83	83	92	93	96
SSc subtype, %					
Diffuse	32.7	41	23.5	61	50
Limited	45.5	18	76.5	39	50
Clinical features					
Raynaud phenomenon, %	94.4	90	92	93	83
Digital ulcers, %	24.4	46	—	61	50
Hypopigmentation, %	—	—	—	59	62
Pulmonary fibrosis, %	34.5	56	12.9	22	30
Decreased DLCO, %	24.8	86	50.0	—	60
PAH, %	15.8	13	17	6	11
Kidney, %	10.5	12	5.7	—	4.8
Skin score, mean	9.2	—	—	15.0	23.1
Antibodies, %					
ANA	90.4	98	97	85	62.5
Anticentromere	36.4	—	93	13	33.3
Anti-topoisomerase I	27.6	—	25	34	18.2

DISCUSSION

In this study, we analyzed the demographics, clinical features, laboratory tests, and treatment of 24 Puerto Rican patients with SSc that are being treated in Puerto Rico. These data represent the first study about SSc in a Caribbean group. As in previous studies, SSc occurred more commonly in females. Of our patients, 96% were female, with a female/male ratio of 24:1, much higher than the one reported by other studies. For example, the group of Huzzelman et al reported a female to male ratio of approximately 5:1.[2]

In our study, a similar proportion of subjects suffered the limited as well as the diffuse skin involvement. Reveille et al reported a higher frequency of diffuse disease in another comparison between a Hispanic group and North American Whites.[7] Another Hispanic group from Columbia presented more as a limited disease, similar to Caucasians from Germany.[2]

Different from previous studies, the present study did not detect significant clinical, laboratory, or therapeutic differences between the two cutaneous subsets, lcSSc and dcSSc. As expected, the most frequent clinical features in our group were Raynaud's phenomenon, digital pitting scars, sclerodactyly, hypopigmentation, and gastroesophageal reflux.

The median skin score (mRSS) was 24.5 (16.0–31.3). According to a disease severity scale proposed by Medsger et al, our group had moderate skin disease.[11] Recently, the European Scleroderma Study Group established that a score of more than 14 represents an active skin disease, and is a predictive severity factor.[12–14]

Pulmonary disease was also a prominent feature in our group. Sixty percent of patients presented abnormal findings in their lung function tests. However, the prevalence of pulmonary fibrosis in radiological studies of this study group was low. This difference could be explained because a high resolution CT scan was not available for every study patient. In a recent study, a group of Hispanic patients were intermediate between White and African American patients in the presence of pulmonary fibrosis and abnormal pulmonary function tests (decreased predicted FVC and FEV1).[8]

Similarly, cardiovascular conditions, including pulmonary hypertension, were less commonly detected in this group than in previously reported studies.[2,8] This finding can be a result of poor access of our patients to a cardiovascular specialist, echocardiogram, and cardiac catheterization.

The presence of antinuclear antibodies was lower than what has been reported in other groups (62.5% versus 90%).[2,5,7] The present study found a similar percentage (33%) of anticentromere antibodies to that of Caucasians with SSc in the United States and Germany.[2,7] Reveille et al reported that North American Caucasians have higher frequency of anticentromere (24%) antibodies and a lower frequency of anti-topoisomerase antibodies (9%) compared to North American Blacks that reported 4% and 18%, respectively.[7] A Hispanic group from Colombia showed the highest frequency of anticentromere (93%) antibodies compared to other SSc groups. McNeilage et al reported a high frequency (76%) of anti-Scl 70 antibodies in non-white Thais with diffuse disease, in contrast to high frequency (51%) of ACA in white Australians.[15]

With respect to therapeutic management, the majority of the study patients were being treated only symptomatically with corticosteroids (62.5%) and calcium channel blockers (54.2%). It is remarkable that few (50%) of the patients received a disease-modifying drug, especially d-Penicillamine. Other disease-modifying drugs, such as cyclophosphamide or methotrexate were used in less than 12% of the patients, despite the high pulmonary involvement. New SSc clinical studies suggest the benefit of aggressive therapy with cyclophosphamide in SSc patients with lung involvement.[16,17]

In conclusion, the predominant clinical features of Puerto Ricans with SSc were gastrointestinal involvement, Raynaud's phenomenon, and digital pitting scars. Pulmonary disease was a prominent feature in our group, with impairment in diffusion capacity. Currently, lung disease is the principal cause of death in SSc patients.[4,18,19] This problem encourages our group to establish a standard surveillance protocol to diagnose and treat lung disease as early as possible in our SSc patients.

The study had two important limitations. First, the study sample was small with all the analytical limitations that implies, specifically small sample size may contribute to conservative bias, type II error, in the application of the statistical test. Also, the sample size is not sufficient to register a difference above the statistical significance threshold. Therefore, evaluations may wrongly conclude that there are not significant group differences. On the other hand, a larger sample size can compensate variable variations. Secondly, the study has missing data that could affect the study findings and conclusion as the missing data would reduce the sample size, increasing this study limitation. The more prevalent missing data was in the pulmonary function measurements and laboratory findings. The missing laboratory data was distributed similarly in both study groups. However, the missing data in the pulmonary hypertension evaluation was higher in the group of limited SSc than in the diffuse group (41.6 % vs 8.3%). This finding may explain the low presence of pulmonary hypertension in our group. Usually, pulmonary hypertension is common in limited SSc.

IMPLICATIONS FOR IMPROVING HEALTH DISPARITIES

This study found a disparity between the SSc clinical presentation and management that needs to be addressed. Pulmonary disease was a predominant problem in our group. New SSc clinical studies suggest the benefit of aggressive therapy with cyclophosphamide in SSc patients with lung involvement. The majority of the study patients were being treated only symptomatically and cyclophosphamide was used in less than 12% of the patients, despite the high pulmonary involvement.

According to the findings of our study, we need to establish standard guidelines to assure the access of our patients to pulmonary function testing, chest CT scan, echocardiograms and cardiac catheterization. This will permit the diagnosis and early treatment of SSc lung disease.

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