Racial Variation in Clinical and Immunological Manifestations of Systemic Sclerosis

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ABSTRACT. ***Objective.*** To clarify which racial differences in disease manifestations can be attributed to differences in other factors such as gender, education, disease classification, and disease duration.

Methods. The study included white and black patients with systemic sclerosis (SSc) treated at a university hospital rheumatology clinic between November 1997 and April 2003. Demographic, clinical, and immunological measurements were obtained on each subject. Using multivariable statistical techniques we assessed differences in disease manifestations between white and black patients after adjusting for gender and classification and duration of disease.

Results. Two hundred sixty-three patients (199 whites, 64 blacks) were enrolled in the study. Blacks experienced an earlier age at disease onset than whites and were significantly more likely to have diffuse disease, digital ulcers, digital pitting, impaired lung function, and anti-RNP, and anti-Ro antibodies. Whites were significantly more likely to have anti-centromere antibodies.

Conclusion. After adjusting for gender, disease classification, and disease duration, whites and blacks with SSc differ in some clinical and immunological manifestations of disease. Whether these differences can be attributed to genetic or environmental factors remains unknown. (J Rheumatol 2006;33:263–8)

Key Indexing Terms:
SCLERODERMA   CONTINENTAL POPULATION GROUPS   RACIAL DISPARITIES
AUTOANTIBODIES   DEMOGRAPHICS   CLINICAL MANIFESTATIONS

Systemic sclerosis (SSc) is an autoimmune disease characterized by skin thickening, microvascular injury, and organ disruption, primarily due to an abnormal fibrosing process. Several authors have noted significant racial/ethnic variation in the clinical characteristics and course of this disease[1-7] as well as differences in serologic[7,8], immunologic[4,5,7,9], and genetic characteristics[9,10]. However, many of these studies comprised small samples or failed to account for differences in disease duration or distribution of limited versus diffuse cutaneous involvement, the 2 primary classifications in which this disease is manifested. This distinction is vital

since, on average, the prognosis for patients with diffuse disease is much worse than that for patients with limited disease[11].

Previous studies noted an association between race/ethnicity and the manifestations of SSc, as well as the presence of certain antibodies and specific symptoms. For example, one study found that blacks with SSc were more likely than whites with SSc to test positive for antibodies to topoisomerase I, which are associated with increased likelihood of lung disease, and were more likely to exhibit lower forced vital capacity than their white counterparts, signifying worse lung function[5]. The authors concluded that both race and the presence of certain antibodies are independent predictors for SSc lung disease and that race directly influenced the manifestations of SSc. Similar results were found in a biracial study investigating the presence of several antibodies[4], in which whites were found to be less likely than blacks to have anti-topoisomerase I autoantibodies and more likely to have a higher frequency of anti-centromere autoantibodies.

Further support that SSc disease burden is greater among blacks than whites derives from studies of hospital admissions and emergency room visits[1,2]. In these studies, blacks presented at a younger age (about 10 years younger, on average), another indication of more severe disease in the black population.

The current literature suggests that more severe disease is found among populations of African descent, including

higher mortality rates, more compromised lung function, as well as a greater prevalence of anti-topoisomerase I antibodies. In concordance with the Healthy People 2010 Goals of identifying and better understanding racial disparities in healthcare[12], we determined if there are alternate explanations for the racial disparities by utilizing a large sample of patients with SSc from a major university hospital rheumatology clinic.

MATERIALS AND METHODS

Patient sample. Our study population was drawn from a cohort of patients whose first visit to the Medical University of South Carolina's (MUSC) rheumatology clinic occurred between November 1997 and April 2003. All consenting patients meeting the American College of Rheumatology clinical criteria for SSc were included in the study[13]. Patients who could not be classified with either limited (lcSSc) or diffuse cutaneous SSc (dcSSc) were not included in the analyses. The study was approved by the MUSC institutional review board.

Data collection. The following types of data on patient characteristics were collected at the visit: demographic information (age, race, sex, number of years of formal education, and smoking history), disease classification (limited, diffuse, other), Rodnan total skin score, age at Raynaud's disease onset and first onset of non-Raynaud's symptoms (used in calculation of disease duration), modified Scleroderma Health Assessment Questionnaire (SHAQ) score[14], organ involvement (skin, joint, muscular, cardiac, gastrointestinal, pulmonary, renal) and other clinical manifestations (e.g. alveolitis, digital tip ulcers), and immunologic involvement. Data were obtained by a rheumatologist during the patient evaluation. Diffuse cutaneous SSc (dcSSc) was defined as the presence of any skin involvement proximal to the patient's elbows and/or knees; however, facial involvement did not determine diffuse involvement as it can be present in dcSSc or lcSSc. Patients not meeting the criteria for dcSSc were classified as having lcSSc. For patients with dcSSc, age at onset was defined as the age of first onset of non-Raynaud's symptoms, while for patients with lcSSc, age at onset was defined as the age of first onset of Raynaud's or non-Raynaud's disease symptoms. Joint involvement was defined as joint swelling noted on physical examination, and muscular involvement was defined as proximal muscle weakness on physical examination. Cardiac involvement included the presence of pericarditis, congestive heart failure, arrhythmias, myocarditis, or any cardiac symptom deemed related to the patient's disease. Gastrointestinal (GI) tract involvement was indicated if the patient reported GI symptoms during the physical examination and/or if there was radiographic or endoscopic evidence of GI involvement (100%, 11%, and 29% of patients with GI tract involvement, respectively); thus a patient could be classified as having GI tract involvement simply by his/her complaint of heartburn with no objective findings of esophageal scleroderma. Pulmonary fibrosis was determined by chest radiograph and/or CT scan (50% and 75% of pulmonary fibrosis patients, respectively). Pulmonary hypertension was defined as having a PA pressure = 45 mm Hg (as recommended by Mukerjee, *et al*[15]) by echocardiogram and/or a mean PA = 25 mm Hg by cardiac catheterization (96% and 5% of patients with pulmonary hypertension, respectively). Renal involvement was defined via patient history, abnormal blood urea nitrogen (> 20 mg/dl), and/or elevated creatinine (> 1.4 mg/dl) (25%, 50%, and 75% of patients with renal involvement, respectively). For renal involvement, non-SSc causes of renal disease (e.g. elevated serum creatinine from diabetes mellitus) were considered exclusions. Alveolitis was diagnosed if there was evidence of ground glass opacity on high resolution computed tomography (CT) scan and/or by bronchoalveolar lavage (71% and 43% of patients with alveolitis, respectively). Serologic involvement included the presence (i.e. titer ≥ 1:80) of any of a number of antibodies, including antinuclear (ANA), anti-centromere, anti-SCL 70, anti-Smith, anti-ribonucleoprotein (anti-RNP), anti-Ro/SSA, and anti-La/SSB.

Statistical analysis. Initially t tests, chi-square tests, and non-parametric Wilcoxon rank sum tests, as appropriate were used to make unadjusted comparisons in the distribution of patient characteristics and clinical and immunological manifestations of disease between whites and blacks. Subsequently, in order to understand the extent to which the racial differences in disease manifestations could be explained by other patient characteristics, a series of multivariable analyses were undertaken using linear (for continuous dependent variables, e.g. Rodnan skin score), logistic (for binary dependent variables, e.g., autoantibody presence), and log-linear [for smoking status, since it has a trichotomous response (current, former, never)] regression models. Each of these disease manifestations was a dependent variable in a regression model. In all of these models, race was the primary independent variable of interest, and education, gender, disease classification, and disease duration were included as covariates. Models for pulmonary outcomes also included current smoking status as a covariate. Contrasting the associations involving race and disease manifestations between the unadjusted and adjusted (multivariable) analyses helped to better understand the influence of a patient's race on the disease manifestations of interest.

RESULTS

The study included 263 patients (160 white women, 39 white men, 47 black women, 17 black men) who met the ACR criteria for systemic sclerosis and who were categorized as having limited or diffuse cutaneous SSc. Less than 5% of patients eligible for inclusion in the clinical database declined to participate and were therefore excluded from all analyses.

Of the 3 variables used as covariates in the multivariable analyses, 2 were found to be statistically different between white and black patients in bivariate analyses. Blacks were significantly more likely than whites to have dcSSc (68.8% vs 43.2%), and on average they had significantly shorter disease duration (3.9 ± 5.0 vs 16.4 ± 7.3 yrs). More black patients with SSc were male (26.6% vs 19.6%), although this finding was not statistically significant.

Unadjusted and adjusted comparisons between the white and black patients are listed in Table 1. A number of demographic, clinical, and immunologic characteristics were associated with race in both the unadjusted and adjusted analyses. Black patients with SSc presented at their first clinic visit at a significantly younger age (43.8 ± 13.4 yrs) than white patients (55.4 ± 13.9 yrs). Although disease duration was significantly (p < 0.05) longer among whites than blacks, this was due to differences noted among patients with dcSSc (whites: 10.9 ± 9.7 yrs; blacks: 5.5 ± 7.0 yrs, p < 0.05), but not patients with lcSSc. Black patients also reported significantly lower levels of education (13.4 ± 3.0 vs 14.3 ± 2.9 yrs). Although fewer blacks reported ever to have smoked (34.4% vs 49.7%), those blacks who did ever smoke were significantly less likely than whites to have quit. Black patients reported significantly earlier onset than white patients (39.8 ± 13.1 vs 49.0 ± 14.2 yrs), and they reported higher rates of digital ulcers (26.6% vs 15.6%) and digital pitting (57.8% vs 39.9%) than whites. On several measures of lung function, including those involving forced vital capacity (FVC) and carbon monoxide diffusing capac-

Table 1. Unadjusted and multivariable (adjusted) comparisons between white and black patients with SSc. Multivariable analyses were adjusted for the following covariates: gender, years of education, disease classification (lcSSc vs dcSSc), disease duration, and smoking status (pulmonary outcomes only). No multivariable adjustment was performed when the characteristic was one of the 5 covariates in the multivariable analyses. Age at disease onset was defined by the age at onset of first non-Raynaud's phenomenon symptom.

Characteristic	White Patients (n = 199)	Black Patients (n = 64)	p Compared to Whites Unadjusted	p Compared to Whites Multivariable
Demographic characteristics				
Age at first clinic visit, mean ± SD	55.4 ± 13.9	43.8 ± 13.4	< 0.001	0.001
Education yrs, mean ± SD	14.3 ± 2.9	13.4 ± 3.0	< 0.05	
Gender, % male	19.6	26.6		
Smoking status (%)				
Current	9.6	18.8	< 0.001	
Former	40.2	15.6	< 0.001	
Never	50.3	65.6	< 0.001	
Clinical characteristics				
Modified SHAQ score	1.1 ± 0.8 (available n = 106)	1.4 ± 1.0 (available n = 32)		
Family history of autoimmune disease, %	53.9	49.2		
Age at disease onset, mean ± SD	47.6 ± 14.6	39.6 ± 13.0	< 0.001	< 0.001
Duration of disease, yrs, mean ± SD				
All patients	7.8 ± 8.7	4.2 ± 5.6	< 0.05	
Patients with dcSSc	3.6 ± 4.7	3.6 ± 4.7	< 0.05	
Patients with lcSSc	10.9 ± 9.7	5.5 ± 7.0	< 0.05	
Systolic blood pressure, mean ± SD	123.4 ± 21.9	123.8 ± 23.9		
Diastolic blood pressure, mean ± SD	69.1 ± 11.1	71.2 ± 10.5		
Disease classification, % diffuse	43.2	68.8	< 0.001	
Active pattern on nailfold capillaroscopy, %	51.4 (available n = 109)	76.3 (available n = 38)		
Raynaud's phenomenon, %	93.0	85.9		
Ulcer over PIP, MCL, elbow, %	10.6	14.3		
Digital/upper extremity amputation, %	4.0	1.6		
Digital/lower extremity amputation, %	2.5	0.0		
Lower extremity ulcer, %	3.0	3.1		
Cancer, %	9.7	3.2		
Organ involvement				
Skin involvement. %	95.9	98.9		
Total skin score, mean ± SD	13.3 ± 0.8	16.9 ± 1.32	< 0.05	
Any joint involvement, %	51.8	57.8		
Joint contracture, %	33.9	41.3		
Digital gangrene, %	1.0	4.7		
Digital tip ulcers, %	15.6	26.6	< 0.05	< 0.05
Digital tip pitting, %	39.9	57.8	< 0.05	< 0.05
Proximal muscle weakness, %	10.9	21.3	< 0.05	
Any pulmonary involvement, %	58.3	68.3		
Pulmonary hypertension, %	7.0	12.5		
Pulmonary fibrosis, %	24.6	34.4		
Alveolitis, %	12.1	10.9		
Pulmonary function				
Forced vital capacity, mean ± SD	82.2 ± 17.8 (available n = 153)	73.7 ± 20.1 (available n = 52)	< 0.01	< 0.01
Forced vital capacity, proportion < 70%	25.5 (available n = 153)	42.3 (available n = 52)	< 0.05	< 0.05
DLCO, mean ± SD	70.4 ± 23.6 (available n = 133)	60.5 ± 25.7 (available n = 47)	< 0.05	< 0.05
DLCO, proportion < 80%	63.2 (available n = 133)	76.6 (available n = 47)		
Renal involvement, %	4.4	1.7		
Cardiac involvement, %	13.0	9.8		
Gastrointestinal tract involvement, %	81.1	70.3		< 0.05

Table 1. Continued.

Characteristic	White Patients (n = 199)	Black Patients (n = 64)	p Compared to Whites Unadjusted	Multivariable
Immunologic characteristics				
Positive ANA	96.4	95.9		
	(available n = 168)	(available n = 49)		
Nucleolar pattern	30.4	44.9		
Speckled pattern	36.9	28.6		< 0.05
Centromere pattern	25.6	4.1		
Anti-topoisomerase (Scl-70)	23.1	39.1	< 0.05	< 0.01
	(available n = 121)	(available n = 46)		
Anti-Smith	2.5	7.7		
	(available n = 122)	(available n = 39)		
Anti-RNP	7.4	21.6	< 0.05	< 0.01
	(available n = 121)	(available n = 37)		
Anti-Ro/SSA	7.6	23.5	< 0.01	< 0.01
	(available n = 119)	(available n = 34)	< 0.01	< 0.01
Anti-La/SSB	5.9	5.9		
	(available n = 118)	(available n = 34)		
> 1 of the above autoantibodies	16.6	40.6	< 0.001	< 0.001

SHAQ: Scleroderma Health Assessment Questionnaire; DLCO: diffusing capacity carbon monoxide; ANA: antinuclear antibody.

ity, black patients had decreased function as compared to whites, even after adjusting for gender, disease duration, disease classification, and smoking status. There were no racial differences in the frequency of pulmonary hypertension. Of the 22 cases with pulmonary hypertension, 12 were considered "intrinsic" and not secondary to interstitial lung disease (forced vital capacity < 70%, n = 9) or heart failure (left ventricular ejection fraction < 30%, n = 1). There were no significant racial differences in the proportion of patients with intrinsic pulmonary hypertension. With respect to serological markers, blacks were significantly more likely to have anti-topoisomerase (39.1% vs 23.1%), anti-RNP (21.6% vs 7.4%), and anti-Ro antibodies (23.5% vs 7.6%). Black patients were also significantly more likely to have more than one autoantibody present (40.6% vs 16.6%). The most common pairwise combinations of autoantibodies in the cohort were ANA and anti-topoisomerase (whites: 12.6%, blacks: 28.1%, p < 0.01), ANA and RNP (whites: 4.5%, blacks 12.5%, p < 0.05), and ANA and anti-SSA (whites: 4.0%, blacks 12.5%, p < 0.05).

Some disease characteristics were associated with race in the in the unadjusted analyses but the association diminished after multivariable adjustment and *vice versa*. Blacks were significantly more likely than whites to have an active pattern on nailfold capillaroscopy (76.3% vs 51.4%) and to have proximal muscle weakness (21.3% vs 10.9%). Likewise, the Rodnan skin scores were also significantly higher among blacks compared to whites (16.9 ± 1.32 vs 13.3 ± 0.8) in the unadjusted analysis. However, after multivariable adjustment, associations with these variables and race were not detected, primarily because of the strong association of disease classification with nailfold capillaroscopy pattern and Rodnan skin score, and between gender and proximal muscle weakness (females: 25.5%; males: 10.1%). In unadjusted analyses, no significant racial differences were noted in ANA patterns; however, in a multivariate model whites were significantly more likely to have a speckled ANA pattern (36.9% vs 28.6%).

DISCUSSION
Our results indicate that there are several key differences between white and black patients with SSc that remain even after adjusting for gender, education, disease classification, and disease duration. Black patients had earlier disease onset; more digital ulcers and digital pitting; worse lung function; more GI tract involvement; higher rates of anti-topoisomerase, anti-RNP, and anti-Ro antibodies; and lower rates of speckled ANA patterns.

Although race/ethnicity has not necessarily been shown to be a causal factor for SSc, the incidence of SSc has been shown to be higher in blacks compared to whites[16]. Race/ethnicity has also been previously identified as a determinant of both the severity of the disease and patients' symptomatology. For example, a study conducted on several minority groups (black, Japanese, and Native American Choctaw) of SSc patients along with a white cohort showed that the white population exhibited higher cumulative survival when compared with black and Japanese patients[7]. Whites also had a lower frequency of SSc-associated lung involvement in comparison to the minority groups. The rate of FVC decline was greater in blacks than in whites, and the mortality rate was lower in whites than in black and Japanese patients. Ethnicity affected almost every statistical comparison we performed supporting the theory that ethnicity is an independent predictor for many manifestations and symptoms of SSc. Similar poor lung function outcomes

were associated with black race in a separate study, which also controlled for important covariates[5].

Our study is not the first to note significant racial/ethnic differences in antibody prevalence patterns. Kuwana, *et al* found significant ethnic differences in the prevalence of anti-RNA polymerase II and anti-SSA (Ro) antibodies[7]. Greidinger, *et al* showed that American blacks have higher levels of anti-SCL70 and anti-RNA polymerase II antibodies than American whites[5]. The nature of the association between race, autoantibody prevalence, and disease progression warrants further study.

Genetic predispositions for SSc were shown to exist in a study conducted on 3 cohorts in the US[17], in which it was shown that families with members who already have SSc are more likely to have subsequent development of SSc among other relatives than families without previous diagnoses. This study provides evidence for the existence of a genetic predisposition to the development of SSc for family members of an SSc patient. A Japanese study looked at haplotype frequencies of single nucleotide polymorphisms (SNP) of the *ILIA* gene in patients with SSc and controls[18]. The CTG haplotype of the *ILIA* gene was found to be present in all patients with interstitial lung disease, and this haplotype was found in 95% of all SSc patients in the study population. The authors concluded that the CTG haplotype might be an important marker for SSc development as well as a possible predictor of disease severity, again illustrating a potential existence for a genetic predisposition in the development of SSc.

Because our study was restricted to patients satisfying ACR criteria for SSc, it is important to note that our results may have been different had we used less stringent criteria for entry into this study. During the study time period, there were 25 white patients and 9 black patients who did not meet the ACR criteria for SSc but who were labeled with SSc. Typically these patients had a positive ANA, Raynaud's phenomenon, and sclerodactyly. Had these patients been included and labeled as lcSSc, the racial difference in disease classification would have been slightly altered. A total of 38.4% (instead of 43.2%) of white patients and 60.3% (instead of 68.8%) of black patients would then have been classified with dcSSc.

It is important to note that while we observed significant racial differences among SSc patients, we do not have a clear understanding as to whether these differences may be attributable to genetic or environmental differences. The pathogenesis of this disease is not fully understood, and the sufficient and necessary causes of SSc have yet to be identified. It is evident, however, from our study as well as previous analyses, that many factors work together to influence both the etiology and progression of SSc. These possible causes warrant further investigation, with special attention paid to racial and ethnic backgrounds.

There are a few limitations of our study that should be considered. It was largely an analysis of a referral population, which may not be fully representative of the black SSc population, and certain biases may have been introduced that could have impacted our findings. For example, it has been shown that there are likely to be many black patients with SSc that are not referred to MUSC[2], so some of the noted differences between the white and the black populations may be due to the study population being an under-representation of blacks with a less-severe form of SSc. However, by adjusting for disease classification we minimized the effect that such a bias may have had on our results. Also, since the number of black men in the study was relatively small, it was difficult to note whether there were any race by gender interactions present. In other words, it remains unclear whether the significant racial differences that we noted were stronger among women than men or *vice versa*.

Further study of the racial and ethnic disparities of SSc will undoubtedly result in the scientific community gaining a more thorough understanding of what factors associated with the patient, his/her treatment, and the healthcare system in general contribute to the development and progression of the disease. It would be ideal to be able to determine if there are ways to improve the quality of primary or specialty care that would result in improved prognosis for SSc patients, or if the majority of poor outcomes can be attributed to genetics. Such knowledge will ultimately improve the outlook for all patients with this disease.

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