Systemic Sclerosis in Canada's North American Native Population: Assessment of Clinical and Serological Manifestations

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ABSTRACT. ***Objective.*** Certain North American Native (NAN) populations are known to have higher rates of systemic sclerosis (SSc) compared to non-NAN; however, little is known of the specific disease characteristics in this population in Canada. This study compares the clinical and serological manifestations of SSc in NAN and white patients.

Methods. This cross-sectional, multicenter study included subjects enrolled in the Canadian Scleroderma Research Group registry between September 2004 and June 2012. Subjects were evaluated with complete medical histories, physical examinations, and self-questionnaires. Ethnicity was defined by self-report. Disease characteristics were compared between NAN and white patients and multivariate analyses were performed to determine the independent association between ethnicity and various clinical manifestations.

Results. Of 1278 patients, 1038 (81%) were white, 71 (6%) were NAN, and 169 (13%) were classified as non-white/non-NAN. There were important differences between NAN and white subjects with SSc. In multivariate analysis adjusting for socioeconomic differences and smoking status, NAN ethnicity was an independent risk factor for the severity of Raynaud phenomenon and more gastrointestinal symptoms, and was associated with a nonsignificant increase in the presence of digital ulcers.

Conclusion. NAN patients with SSc have a distinct clinical phenotype. Our study provides a strong rationale to pursue further research into genetic and environmental determinants of SSc. (First Release May 15 2013; J Rheumatol 2013;40:1121–6; doi:10.3899/jrheum.121212)

Key Indexing Terms:
SCLERODERMA   SYSTEMIC SCLEROSIS
DISEASE SEVERITY   NORTH AMERICAN NATIVE

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Systemic sclerosis (SSc) is a connective tissue disease characterized by cutaneous and visceral fibrosis, microvascular alterations, and abnormal humoral and cellular immunity[1]. SSc affects between 50,000 and 100,000 North Americans, with a female-male ratio of 8:2[2,3]. While the etiology of SSc is unclear, genetic and environmental factors are believed to play a significant role[4]. The prevalence and clinical manifestations of SSc vary among different ethnic groups. African Americans are known to have a higher incidence of SSc, an earlier age of onset, and a greater frequency of interstitial lung disease (ILD) and pulmonary hypertension compared to whites[5,6]. Choctaw Native Americans living in southeastern Oklahoma have the highest prevalence of SSc found in any population, with a prevalence of 469 cases per 100,000 compared with 1.2–25.6 per 100,000 in non-Natives and even compared with other Native tribes residing in Oklahoma[7]. Clinical characteristics of the Oklahoma SSc Choctaw Natives included diffuse cutaneous involvement, pulmonary fibrosis, and high prevalence of antitopoisomerase I

(anti-topo I) antibodies. These clinical findings may be explained in part by genetic variation; the Amerindian HLA haplotype, HLA-DRB1*1602, DQB1*0301, and DQA1*0501, was strongly associated with SSc in this population[7].

Beyond studies of Choctaw Indians, the influence of North American Native (NAN) ancestry on clinical presentation and phenotype of SSc remains unknown. In Canada, 3.5% of the population identified themselves as NAN in 2006 and to date there have been few studies on SSc in this population[8]. Thus, using the cohort from the Canadian Scleroderma Research Group (CSRG) registry, we set out to determine whether baseline clinical and serological characteristics of SSc in NAN differ from those of whites in Canada.

MATERIALS AND METHODS

Study cohort. The study subjects consisted of patients enrolled in the CSRG registry whose baseline visit was between September 2004 and June 2012. The CSRG registry consists of over 1200 patients with SSc from 15 academic centers across Canada, which includes English or French-speaking adults (age > 18 years) with a diagnosis of SSc by a recruiting rheumatologist. All patients within the registry undergo yearly evaluations including a complete medical history, physical examination, and laboratory investigations. Information on demographics, lifestyle factors, comorbid conditions, and disease characteristics are obtained through standardized clinical visits and patient-administered questionnaires. Additionally, patients undergo yearly pulmonary function tests (PFT), chest radiographs, and cardiac echocardiograms. Upon clinical suspicion of ILD, patients also undergo a high-resolution computed tomography (HRCT) scan of the chest.

Eighty-eight percent of patients enrolled in our study fulfilled the American College of Rheumatology (ACR; formerly the American Rheumatism Association) criteria for SSc[9], which are known to be poorly sensitive in particular to subjects with limited SSc[10]. Ethnicity was self-reported using a survey where patients were asked to identify with 1 (or more) of the following groups: NAN (Amerindian, Metis, Inuit), white, French Canadian (defined as having 4 grandparents born in the province of Quebec), Chinese, South Asian (e.g., East Indian, Pakistani, Sri Lankan), black, Filipino, Latin American, Southeast Asian (e.g., Cambodian, Indonesian, Loatian, Vietnamese), Arab, West Asian, (e.g., Afghan, Iranian), Japanese, Korean, or none of the above. We defined the NAN group as any subject who identified as NAN. Of note, 22 NAN subjects also identified as white and 1 as black. White subjects were those who self-identified as only white or as French Canadian. Subjects who did not identify as white only, French Canadian, or NAN were grouped in the "non-white/non-NAN" category. The ethnic groups in our study thus were mutually exclusive.

Ethics committee approval for the Canadian Scleroderma Research Group registry and for our study was obtained at McGill University, Montreal, Quebec, and at each study site. Informed written consent was obtained from each subject.

Study measures. Baseline characteristics including age, sex, smoking status (current, past, or never smoker), education (above or below high school), and level of income were obtained by self-report. Postal codes were used to determine rural or urban residence. Duration of disease was measured from the onset of the first non-Raynaud disease manifestation to cohort entry.

Clinical characteristics of organ system involvement including skin, joints, gastrointestinal (GI), pulmonary, and renal involvement were obtained from physician reports and patient questionnaires. Patients were classified into diffuse (dcSSc) or limited cutaneous systemic sclerosis (lcSSc) disease according to the definition proposed by LeRoy, *et al*[11]. Classification of patients having "sine scleroderma" required a clinical diagnosis of SSc with no skin thickening[12]. Skin thickness was measured using the modified Rodnan skin score[13]. The presence of digital ulcers and inflammatory arthritis was based on physician report. Severity of Raynaud phenomenon (RP) was assessed using the Scleroderma-Health Assessment Questionnaire (S-HAQ)[14]. The S-HAQ contains the HAQ-Disability Index (HAQ-DI) and items to quantify symptoms specific for SSc: overall disease severity, RP, finger ulcers, breathlessness, and GI symptoms, as described[14]. Unlike the visual analog scales used in the original S-HAQ, our study used numerical rating scales ranging from 0 to 10.

Severity of GI symptoms was obtained using the S-HAQ[14]. To assess the number of GI symptoms, patients answered yes/no to a series of 14 questions concerning appetite loss, difficulty swallowing, acid reflux, nocturnal choking, heartburn, early satiety, abdominal bloating, nausea and vomiting, constipation, diarrhea, need for antibiotics for diarrhea, greasy stools, fecal incontinence, and need for parenteral nutrition[15]. Lower GI dysmotility was defined as the presence of malabsorption, hyperalimentation, and/or pseudoobstruction based on physician report. Malabsorption was determined by asking the patient specific questions regarding stool consistency and the presence of specific markers of malabsorption on laboratory investigations as described[16]. Esophageal dysmotility was based on the physician's clinical history and physical examination as well as imaging studies if performed (barium radiography and/or abdominal radiography).

For lung involvement, pulmonary hypertension was defined as a right ventricular systolic pressure > 45 mm Hg measured by echocardiography (an estimate that has been found to correlate strongly with right heart catheter findings of pulmonary arterial hypertension[17]). ILD was considered present according to a recently published algorithm based on radiographic abnormalities compatible with ILD on HRCT or, if HRCT was not available, by chest radiograph and/or the presence of "Velcro" crackles on examination[18].

History of scleroderma renal crisis and inflammatory myositis was obtained by physician report. Subjects were classified as having overlap disease if the recruiting rheumatologist reported that they also had rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyositis or dermatomyositis (PM/DM), Sjögren syndrome, and/or mixed connective tissue disease.

Subjects had serum tested for antibodies against centromere (ACA) by immunofluorescence and topo I (also known as anti-Scl70), RNA polymerase III, and PM/Scl as per standard laboratory protocols[19,20].

Data analysis. Descriptive statistics were used to summarize the demographic and clinical characteristics, as well as the serological profiles, of the study cohort according to ethnicity (white, NAN, non-white/non-NAN). Continuous variables were expressed as mean ± SD and categorical variables were expressed as total number with percentiles. Any variables with > 10% of missing patient data were noted. Comparison of clinical and serological features between white and NAN patients was performed using ANOVA and logistic regression, as appropriate. Multivariate linear and logistic regressions were performed to show the relationship between ethnicity and selected clinical characteristics found to be either clinically or significantly different between NAN and whites in univariate analysis, adjusted for age, education, income, rural versus urban residence, smoking status (current vs noncurrent), and disease subset (diffuse vs limited). P values < 0.05 were considered statistically significant. Further statistical analysis was not performed because of the exploratory intention of our study. Statistical analyses were performed using SAS 9.2 (SAS Institute).

RESULTS

Population characteristics. Of 1278 patients with SSc, 81% were white (n = 1038), 6% were NAN (n = 71), and 13% were classified as non-white/non-NAN (n = 169). Of the NAN population, 65% identified as Amerindian (n = 46), 32% as Metis (n = 23), and 3% as Inuit (n = 2). Baseline characteristics of white, NAN, and non-white/non-NAN are

presented in Table 1 and clinical and serological profiles in Table 2.

Baseline characteristics of NAN compared to white SSc subjects. As shown in Table 1, there were important demographic and socioeconomic differences between NAN and white subjects. There were fewer NAN patients with an education level above high school (31.4%, n = 22, vs 47.1%, n = 487; p = 0.012), more NAN patients with a yearly

Table 1. General characteristics of white, North American Native (NAN), and non-white/non-NAN subjects with systemic sclerosis (SSc).

Characteristics	White, n = 1038	NAN, n = 71	Non-white/ non-NAN, n = 169	p*
Mean age, yrs ± SD	56.2 ± 11.7	50.9 ± 11.8	54.0 ± 14.2	0.0003
Female, n (%)	899 (86.6)	61 (85.9)	141 (83.4)	0.8684
Disease duration, yrs ± SD	11.0 ± 9.6	9.9 ± 7.2	10.2 ± 9.2	0.3671
Age at disease onset, yrs ± SD	45.3 ± 13.3	41.0 ± 12.8	43.7 ± 14.7	0.0092
Cutaneous subtype, n (%)				
lcSSc	619 (60.4)	38 (53.5)	91 (55.5)	0.2546
dcSSc	365 (35.6)	33 (46.5)	69 (42.1)	0.0674
Sine sclerosis	41 (4.0)	0 (0)	4 (2.4)	0.9751
Never smoker, n (%)	394 (38.1)	13 (18.3)	90 (53.9)	0.0013
Current smoker, n (%)	154 (14.9)	20 (28.2)	12 (7.2)	0.0036
Past smoker, n (%)	487 (47.1)	38 (53.5)	65 (38.9)	0.2922
Education (> high school), n (%)	487 (47.1)	22 (31.4)	99 (60.0)	0.012
Income < $50,000/year, n (%)	454 (48.8)	49 (76.6)	74 (49.0)	< 0.0001
Rural residence, n (%)	223 (21.6)	34 (48.6)	18 (10.7)	< 0.0001

* White vs NAN. lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc.

Table 2. Disease manifestations and serological profiles of white, North American Native (NAN), and non-white/non-NAN subjects with systemic sclerosis (SSc).

Organ-specific Manifestations	White, n = 1038	NAN, n = 71	Non-white/ non-NAN, n = 169	p*
Skin/vascular/joint severity				
mRSS, mean ± SD	9.7 ± 9.6	10.4 ± 8.7	10.1 ± 9.8	0.5801
Patient-reported RP severity (range 0–10; mean ± SD)	2.8 ± 2.9	3.9 ± 3.2	3.1 ± 3.1	0.0029
Digital ulcers, n (%)	537 (52.1)	45 (63.4)	92 (55.4)	0.0672
Inflammatory polyarthritis, n (%)	305 (30.5)	30 (44.8)	46 (28.9)	0.0161
Gastrointestinal (GI) involvement				
No. GI symptoms (range 0–14; mean ± SD)	4.1 ± 3.1	5.8 ± 3.2	4.1 ± 3.2	< 0.0001
Lower GI dysmotility, n (%)	152 (14.8)	26 (36.6)	21 (12.7)	< 0.0001
Severity of GI symptoms (range 0–10; mean ± SD)	1.7 ± 2.5	2.9 ± 3.2	2.2 ± 2.7	< 0.0001
Esophageal dysmotility, n (%)	680 (71.7)	47 (74.6)	90 (62.5)	0.6235
Lung involvement				
Pulmonary hypertension**, n (%)	98 (11.0)	5 (8.5)	17 (11.7)	0.5407
Interstitial lung disease, n (%)	340 (33.7)	21 (29.6)	59 (36.2)	0.4775
Inflammatory myositis, n (%)	107 (10.4)	9 (12.7)	18 (10.8)	0.5501
Scleroderma renal crisis, n (%)	40 (3.9)	3 (4.3)	9 (5.5)	0.8552
Any disease overlap	151 (14.9)	17 (24.3)	27 (16.5)	0.0385
SSc autoantibodies, n (%)				
Anticentromere**	315 (35.1)	20 (36.4)	42 (29.6)	0.8510
Topoisomerase-1 (Scl70)**	117 (13.0)	8 (14.5)	40 (28.4)	0.7490
RNA pol III**	122 (19.6)	9 (23.1)	14 (13.5)	0.5923
PM/Scl**	44 (7.2)	2 (5.1)	7 (6.9)	0.6204

** Over 10% of patient data missing. * White vs NAN. mRSS: mean Rodnan Skin Score; PM: polymyositis; RP: Raynaud phenomenon; RNA pol III: RNA polymerase III antibody.

income under $50,000 (76.6%, n = 49, vs 48.8%, n = 454; p < 0.0001), and more NAN patients lived in rural areas (48.6%, n = 34, vs 21.6%, n = 223; p < 0.0001) compared to whites. There was a greater proportion of current smokers (28.2%, n = 20, vs 14.9%, n = 154; p = 0.0036) among NAN than whites and a smaller proportion of NAN who were never smokers compared to white patients (18.3%, n = 13, vs 38.1%, n = 394; p = 0.0013).

Clinical and serological profiles of NAN compared to white SSc subjects. NAN patients were younger at age of disease onset (41.0 ± 12.8 yrs vs 45.3 ± 13.3 yrs; p = 0.0092), but had similar disease duration compared to whites (9.9 ± 7.2 yrs vs 11.0 ± 9.6 yrs). There was a trend toward more diffuse disease in NAN patients compared to whites (46.5%, n = 33, vs 35.6%, n = 365; p = 0.0674). As shown in Table 2, compared to white patients, NAN reported more severe RP symptoms (3.9 ± 3.2 vs 2.8 ± 2.9; p = 0.0029) and higher rates of inflammatory polyarthritis (44.8%, n = 30, vs 30.5%, n = 305; p = 0.0161). Additionally, a trend toward a greater burden of digital ulcers was observed in NAN compared to whites (63.4%, n = 45, vs 52.1%, n = 537; p = 0.0672).

NAN patients had significantly more GI involvement than white patients. On a 14-item checklist, they had more GI symptoms (5.8 ± 3.2 vs 4.1 ± 3.1; p < 0.0001), more frequent lower GI dysmotility (36.6%, n = 26, vs 14.8%, n = 152; p < 0.0001), and rated their GI symptoms as more severe on a 10-point rating scale (2.9 ± 3.2 vs 1.7 ± 2.5; p < 0.0001) compared to whites. In addition, the median score for GI severity in NAN was higher (2, range 0–5) compared to white patients (0, range 0–3; data not shown). Conversely, NAN and white patients had similar frequencies of esophageal dysmotility (74.6%, n = 47, vs 71.7%, n = 680).

NAN patients had significantly higher rates of overlap disease compared to whites (24.3%, n = 17, vs 14.9%, n = 151; p = 0.0385).

No significant differences in the rates of pulmonary hypertension (8.5%, n = 5, vs 11.9%, n = 98) or ILD (29.6%, n = 21, vs 33.7%, n = 340) were noted between NAN and white patients. Similarly, there were no differences in the rates of scleroderma renal crisis and inflammatory myositis in the 2 groups.

SSc-specific autoantibodies had a comparable distribution in NAN and white patients. ACA was the most prevalent SSc-specific autoantibody in both groups (36.4%, n = 20, and 35.1%, n = 315), followed by RNA polymerase III (23.1%, n = 9, and 19.6%, n = 122), topo I (14.5%, n = 8, and 13.0%, n = 117), and PM/Scl antibodies (5.1%, n = 2, and 7.2%, n = 44).

Multivariate regression analyses. Multiple linear and logistic regressions were performed to determine the independent effect of NAN ethnicity on 4 selected outcomes, namely, severity of RP, presence of digital ulcers, skin scores, and number of GI symptoms, after adjustment for socioeconomic differences and smoking status (Table 3). The differences with regard to worse severity of RP and more GI symptoms in NAN compared to whites persisted even after adjustment. There were no meaningful differences in skin scores between NAN and whites after adjustments. Although not statistically significant, NAN were 30% more likely than whites to have digital ulcers, after adjustment for socioeconomic status and smoking. Of note, smoking appeared to be an independent risk factor for worse RP severity, worse GI symptoms, and better skin scores, and there was a strong trend for smoking to be associated with more digital ulcers, consistent with previous reports[15,21].

Posthoc analyses. The analyses were repeated excluding patients who did not meet the 1980 ACR criteria for SSc. The results were consistently unchanged (data not shown). An additional analysis was performed to compare disease duration at time of diagnosis by ethnicity and residence (rural/urban). There were no statistical or clinically important differences (data not shown).

DISCUSSION
In this study of 71 NAN and 1038 white patients with SSc, we found NAN had an earlier disease onset, a trend to more diffuse disease, greater burden of GI symptoms, greater severity of RP, a trend to a higher burden of digital ulcers, increased rates of inflammatory polyarthritis, and increased rates of overlap disease compared to white patients. In multivariate analyses adjusting for differences in socioeconomic and smoking status, NAN were significantly more likely to have worse RP severity and more GI symptoms, and although this was not statistically significant, NAN were 30% more likely to have digital ulcers.

Although no previous studies have examined onset of SSc in Canadian NAN, studies of other rheumatic diseases such as RA[22,23,24] and SLE[23,25] have shown that NAN patients have earlier disease onset compared to whites. Studies of Choctaw Indians in southeastern Oklahoma found 65% of Choctaw patients had dcSSc[7], suggesting that NAN patients may have a predisposition to more diffuse disease. In addition, NAN with other rheumatic diseases (RA, SLE) have more severe disease[22,23,25,26]. Our findings are consistent with these observations.

In our study, NAN patients had significantly more GI symptoms, lower GI dysmotility, and rated their GI symptoms as more severe compared to whites. Our study is the first to describe this observation in NAN. GI involvement affects 90% of patients with SSc, making it the most frequent internal complication; it occurs in those with limited or diffuse SSc[27,28]. Studies have shown that severe GI involvement, defined as malabsorption, multiple episodes of pseudoobstruction, and/or severe problems requiring hyperalimentation, occurs in 8% of patients with SSc, and is associated with high mortality (15% of patients survive after 9 years)[29]. Additionally, malabsorption alone

Table 3. Multivariate linear and logistic regressions showing the association between ethnicity, severity of Raynaud phenomenon (RP), number of gastro-intestinal (GI) symptoms, skin scores, and digital ulcers. Positive beta values indicate the variable is associated with higher severity of RP, more GI symptoms, and higher skin scores. Negative beta values are associated with lower severity of RP, number of GI symptoms, and skin scores. OR > 1 indicates that the variable is associated with more digital ulcers and < 1 with fewer digital ulcers.

Factor	Severity of RP			No. GI Symptoms			Skin Scores			Digital Ulcers		
	ß	(95% CI)	p	ß	(95% CI)	p	ß	(95% CI)	p	OR	(95% CI)	p
Age	–0.04	(–0.05, –0.02)	< 0.0001	–0.01	(–0.03, 0.00)	0.0823	–0.12	(–0.17, –0.07)	< 0.0001	0.98	(0.97, 0.99)	0.0008
Current vs noncurrent smoker	0.94	(0.46, 1.43)	0.0002	0.94	(0.41, 1.46)	0.0005	–1.88	(–3.55, –0.20)	0.0279	1.42	(1.00, 2.03)	0.0528
Diffuse vs limited disease	0.43	(0.08, 0.78)	0.0164	0.19	(–0.19, 0.57)	0.3366	—	—	—	1.57	(1.22, 2.03)	0.0005
Education (greater vs less than high school)	–0.18	(–0.54, 0.18)	0.3277	–0.06	(–0.45, 0.33)	0.7576	–1.08	(–2.32, 0.17)	0.0893	1.27	(0.98, 1.65)	0.0746
Income (less vs greater than $50,000/yr)	0.59	(0.24, 0.95)	0.0012	0.52	(0.13, 0.90)	0.0091	0.21	(–1.02, 1.44)	0.7381	1.44	(1.11, 1.87)	0.0057
Rural vs urban	–0.09	(–0.51, 0.32)	0.6673	0.19	(–0.26, 0.64)	0.4075	–0.23	(–1.64, 1.18)	0.7498	1.08	(0.80, 1.45)	0.6243
NAN vs white	0.92	(0.16, 1.67)	0.0170	1.36	(0.55, 2.16)	0.0010	0.34	(–2.20, 2.89)	0.7907	1.31	(0.75, 2.29)	0.3404
Non-white/Non-NAN vs white	0.36	(–0.15, 0.88)	0.1612	0.12	(–0.43, 0.67)	0.6628	–0.03	(–1.76, 1.71)	0.9762	1.07	(0.74, 1.54)	0.7311

NAN: North American Native.

has a poor prognosis, with a 50% mortality rate at 8.5 years[30]. GI manifestations of SSc affect not only mortality but also severely influence quality of life[31]. Therefore, higher rates and worse GI symptoms in NAN with SSc are of great concern and should be aggressively managed.

NAN had higher rates of overlap disease (9.9%, n = 7, vs 1.9%, n = 19). High rates of overlap syndromes with RA, SLE, SSc, and PM have been described in Nuu-Chah-Nulth Indians[24]. This observation has implications for diagnosis, treatment, and prognosis of SSc in NAN and may also point to genetic and environmental determinants of SSc.

Unlike the study of Choctaw Indians[7], we did not find high rates of ILD or topo I antibodies in NAN patients with SSc. The previous study of Choctaw Indians with SSc from southeastern Oklahoma found high rates of ILD (88%) and anti-topo I antibodies (71%)[7], but included only 12 subjects. We found a lower rate of ILD (29.6%) and anti-topo I positivity (14.5%) among 71 NAN.

We recognize potential limitations of this research including our definition of NAN, which incorporates various subgroups (Amerindian, Metis, Inuit). It is known that Inuit and Amerindian Natives share different genetic markers when it comes to certain rheumatologic diseases[32,33,34,35,36,37], and Amerindians are more susceptible to seropositive connective tissue diseases such as RA[22,26,38,39,40], SLE[25,41,42], and SSc[37,41]. Because of our small sample size, we were unable to analyze the clinical and serological manifestations of SSc of each separate indigenous group within our NAN population. However, a focus on such factors among such specific indigenous groups, as well as genetic and environmental data, would be of considerable interest in future studies of SSc among NAN.

The strength of our study is that, although other studies have described rheumatologic diseases in NAN people[22,25,37,40,43], this is the largest to focus on the manifestations of SSc in NAN patients to date, to our knowledge. Our data begin to fill knowledge gaps, provide insight into the determinants of SSc, and may lead to improved diagnosis and prognosis of this segment of the population. This is especially important because Canada's NAN population is growing at a faster rate than the total population: by 2017, Canada's NAN population is estimated to account for 4.1% of the total population[44].

Our findings suggest that NAN people with SSc have a distinct clinical phenotype. This observation provides a strong rationale to pursue further research into genetic and environmental determinants of SSc. New insights into the pathogenesis may lead to new targets for intervention for this as-yet incurable disease.

Appendix 1.

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