Antifibrillarin Antibodies Are Associated with Native North American Ethnicity and Poorer Survival in Systemic Sclerosis

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J Rheumatol 2017;44;799-805
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*The Journal of Rheumatology* is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
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ABSTRACT. Objective. To examine the clinical correlates and survival in patients with antifibrillarin antibodies (AFA) in a large international study population consisting of well-characterized systemic sclerosis (SSc) cohorts from Canada, Australia, and the United States.

Methods. Baseline clinical data from the prospective cohorts (Canadian Scleroderma Research Group, the Australian Scleroderma Cohort Study, and the American Genetics versus Environment in Scleroderma Outcome Study) were investigated. Clinical variables were harmonized and sera were tested for AFA using a commercially available SSc profile line immunoassay, regardless of the immunofluorescence staining pattern. Association of demographic and clinical features with AFA was investigated by logistic or linear regression. Further, a survival analysis was performed by Cox regression analysis.

Results. A total of 1506 patients with SSc with complete serological profiles were included in the study. Fifty-two patients (3.5%) had antibodies detected against fibrillarin. Patients of African descent and Native North American ethnicity were more likely to be AFA-positive compared with other ethnicities. After adjustment for demographic factors, diffuse involvement, and intestinal bacterial overgrowth requiring antibiotics, gastrointestinal reflux disease showed a trend for association with AFA. Further, AFA positivity was associated with shorter survival independently of demographic factors and disease type (HR 1.76, 95% CI 1.11–2.79, p = 0.016).

Conclusion. In this large multinational SSc cohort, AFA was associated with Native American ethnicity and was an independent predictor of mortality. (First Release April 1 2017; J Rheumatol 2017;44:799–805; doi:10.3899/jrheum.160574)

Key Indexing Terms: SYSTEMIC SCLEROSIS AUTOIMMUNITY ANTIFIBRILLARIN ANTIBODIES

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Accepted for publication February 21, 2017.
Systemic sclerosis (SSc) is a multisystem rheumatic disease characterized by immune dysregulation, endothelial damage, and fibrosis. It is broadly divided into limited cutaneous and diffuse cutaneous SSc (lcSSc and dcSSc). According to available data, its prevalence can range from 50 to 300 cases per 1 million persons and its incidence from 2.3 to 22.8 cases per 1 million persons per year. Women are at higher risk for SSc than men, and a slightly increased susceptibility to SSc among blacks has been reported.

Most patients with SSc have detectable circulating antibodies against intracellular proteins and their presence is generally associated with different organ system involvement, natural history, and survival among patients with SSc.

Antifibrillarin (U3-RNP) antibodies (AFA) are relatively specific biomarker for SSc. AFA are directed against a 35-kDa protein component of a nucleolar ribonucleoprotein called fibrillarin. It has been previously reported to occur in 5%-8% of patients with SSc. AFA, characterized as a “clumpy” nucleolar indirect immunofluorescence pattern, have been detected by a variety of immunoassays including immunoprecipitation of native or in vitro translated proteins, ELISA, and line immunoassays (LIA). Despite variances in these immunoassays, there is general consensus that the frequency of AFA differs across ethnic groups; previous studies have indicated a higher prevalence of AFA among American and white individuals, African Americans, and Japanese patients. AFA was reported to be protective against interstitial lung disease (ILD).

Internal organ involvement in association with AFA varies across studies. AFA has been reported to be associated with pulmonary arterial hypertension (PAH), skeletal muscle, and gastrointestinal (GI) involvement. Among African American and Japanese patients, AFA was reported to be protective against idiopathic pulmonary fibrosis. It is broadly divided into limited cutaneous and diffuse cutaneous SSc (lcSSc and dcSSc).

There are conflicting reports on the association of AFA with survival. Some authors have identified a decreased survival among patients with SSc with AFA as determined by LIA (regardless of immunofluorescence staining pattern) in a large international study population consisting of well-characterized patients with SSc from Canada, Australia, and the United States.

MATERIALS AND METHODS

The cohort consists of patients with SSc enrolled in the Canadian Scleroderma Research Group (CSRG), the Australian Scleroderma Cohort Study (ASCS), and the American Genetics versus Environment in Scleroderma Outcome Study (GENISOS) cohorts. Ethics committee approval for this study was obtained at the University of Texas Health Science Center at Houston, Texas, USA, and at all participating CSRG, ASCS, and GENISOS study sites. All patients provided informed written consent to participate in the study.

Selection of study patients and harmonization of clinical variables between the study cohorts has been described. Briefly, over 98% of the CSRG subjects and all GENISOS subjects meet the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism classification criteria for SSc. Subjects in the ASCS cohort fulfilled either the ACR criteria for classification of SSc, or the LeRoy and Medsger criteria for SSc.

Clinical variables. Patients recruited into these prospective cohorts underwent standardized medical evaluation including medical history, physical examination, and laboratory investigations. Demographic information regarding age, sex, and ethnicity was collected by subject self-report.

Disease duration was recorded as the interval between the onset of the first non-Raynaud phenomenon symptom attributable to SSc and baseline study visit as determined by the study physician.

Skin involvement was assessed using the modified Rodnan skin score. lcSSc and dcSSc were defined as previously described. A history of inflammatory myositis, calcinosis, telangiectasia, digital tip ulcers or pits, scleroderma renal crisis, malignancy, overlap with rheumatoid arthritis, and gastric antral vascular ectasia was recorded by a study physician. To assess GI involvement, presence of gastroesophageal reflux disease (GERD), use of antibiotics for bacterial overgrowth, or hyperalimentation was identified by the treating physician. The presence of ILD was determined using a published clinical decision rule. Using this algorithm, ILD was considered present if a high-resolution computed tomography (HRCT) scan of the lung was interpreted by an experienced radiologist as showing ILD, or in the case where no HRCT was available, if a chest radiograph was reported as showing either increased interstitial markings (not thought to be because of congestive heart failure) or fibrosis, and/or if a study physician reported the presence of typical “Velcro-like crackles” on physical examination. Pulmonary hypertension (HTN) was defined as an estimated systolic pulmonary artery pressure (sPAP) > 45 mmHg measured using the Doppler flow measurement of the tricuspid regurgitant jet on cardiac echocardiography (an estimate that correlates strongly with right heart catheter studies) for CSR-GISOS subjects, or mean pulmonary artery pressure > 25 mmHg with a pulmonary capillary wedge pressure < 15 mmHg on right heart catheterization for ASCS patients. Forced vital capacity as percentage of predicted, hemoglobin, and C-reactive protein were recorded as continuous variables.

Serology. Autoantibody analyses of the CSR-GISOS cohorts were performed in a central laboratory, Mitogen Advanced Diagnostics Laboratory, University of Calgary, Calgary, Alberta, Canada, and the ASCS analyses were performed in Australia using an identical immunoassay kit and protocol. Antibodies against fibrillarin (U3-RNP) and other SSc-related autoantibodies were detected and digitally quantified by the Euroline systemic sclerosis profile LIA (Euroimmun), according to the manufacturer’s instructions. Patients with positive AFA results by LIA regardless of the immunofluorescence HEP-2 staining pattern were considered as having AFA. The co-occurrence of AFA with other SSc-related antibodies as determined by the above LIA was also investigated.

Statistical analysis. Descriptive statistics were used to compare demographic characteristics of 1506 patients with SSc according to their cohort of origin. First, logistic regression was used to examine the association of demographic variables with AFA (dependent variable) at the baseline visit. Then, logistic or linear regression was used to examine the association of AFA with clinical features (dependent variable) after adjustment for baseline age, sex, and ethnicity.

Cox regression analysis was used to investigate the predictive significance of AFA for all-cause mortality after adjusting for age at enrollment.
sex, study site, and ethnicity. The starting point of the survival analysis was time of the first non-Raynaud phenomenon symptom. Kaplan-Meier analysis and Cox proportional hazard models were used to compare survival between AFA-positive versus -negative patients. P values < 0.05 were considered statistically significant for the latter analysis. All statistical analyses were performed with Stata version 13.1 (StataCorp). An adjustment for multiple comparison was not performed for our study.

RESULTS

Study population, disease, and autoantibody characteristics. As shown in Table 1, a total of 1506 patients with SSc with complete serological profiles from the cohorts was included in our study, 714 from the CSRG, 493 from the ASCS, and 299 from the GENISOS group. The mean age (± SD) of patients at enrollment was 55 years (12.8), and the majority of patients were women (1292, 86%) and of white ethnicity (1249, 83%). The distribution of other ethnicities was 5% of African descent, 6% Latino, 3% Asian, 2.6% Native North American, and 1.6% Australian Aboriginal. At enrollment, 588 patients with SSc (or 40%) were diagnosed with diffuse cutaneous involvement. The mean disease duration (± SD), defined as the interval between the onset of the first non-Raynaud disease manifestation and baseline study visit was 9.5 years (9.2) for the overall cohort.

Of the 1506 patients with SSc, 52 (3.5%) were AFA-positive [31 (4%) from the CSRG, 6 (1.2%) from the ASCS, and 15 (5%) from the GENISOS cohorts], while the comparison group (AFA-negative group) consisted of 1454 patients. Among 52 AFA-positive patients, anticentromere B, anti-Scl70, anti-RNA polymerase III, and Th/To antibodies were present in 9, 6, 11, and 1 cases, respectively, while 27 AFA patients (51.7%) did not have any of the aforementioned antibodies.

The mean (± SD) age at enrollment was 51.7 years (± 15.5) for AFA-positive patients and 55.1 years (± 12.7) for AFA-negative participants (p = 0.14, 95% CI –1.09 to 7.72). The mean disease duration (± SD) was 9.9 years (± 8.9) and 9.5 (± 9.2) for AFA-positive and AFA-negative patients, respectively, with no significant difference between the 2 groups (p = 0.72).

Demographic correlates of AFA. In logistic regression analysis, patients of Native North American ethnicity were more likely to be AFA-positive compared with other ethnicities (OR 3.85, 95% CI 1.30–11.41, p = 0.01; Table 2). Consistent with previously published data, patients of African descent showed a trend for higher frequency of AFA (p = 0.06). Of the 8 Australian Aboriginal patients, none had AFA.

Table 1. Demographic characteristics of the patients with SSc in the 3 cohorts at the baseline visit. Values are n (%) unless otherwise specified.

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>CSRG, n = 714</th>
<th>ASCS, n = 493</th>
<th>GENISOS, n = 299</th>
<th>Total, n = 1506</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>615 (86.1)</td>
<td>429 (87)</td>
<td>248 (82.9)</td>
<td>1292 (85.8)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>644 (90.2)</td>
<td>464 (94.1)</td>
<td>141 (47.2)</td>
<td>1249 (82.9)</td>
</tr>
<tr>
<td>African descent</td>
<td>10 (1.4)</td>
<td>0</td>
<td>61 (20.4)</td>
<td>71 (4.7)</td>
</tr>
<tr>
<td>Latino</td>
<td>3 (0.4)</td>
<td>1 (0.2)</td>
<td>86 (28.8)</td>
<td>90 (6)</td>
</tr>
<tr>
<td>Asian</td>
<td>17 (2.4)</td>
<td>20 (4.1)</td>
<td>10 (3.3)</td>
<td>47 (3.1)</td>
</tr>
<tr>
<td>Native North American</td>
<td>38 (5.3)</td>
<td>0</td>
<td>1 (0.3)</td>
<td>39 (2.6)</td>
</tr>
<tr>
<td>Australian aboriginal</td>
<td>0</td>
<td>8 (1.6)</td>
<td>0</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.3)</td>
<td>0</td>
<td>0</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Diffuse involvement</td>
<td>286 (40.1)</td>
<td>127 (26.7)</td>
<td>175 (58.5)</td>
<td>588 (39.5)</td>
</tr>
<tr>
<td>Age at enrollment, yrs, mean (± SD)</td>
<td>55.6 (12.1)</td>
<td>57.8 (12.4)</td>
<td>48.7 (12.8)</td>
<td>54.9 (12.8)</td>
</tr>
<tr>
<td>Disease duration, yrs, mean (± SD)</td>
<td>10.7 (9.0)</td>
<td>11.9 (10.0)</td>
<td>2.5 (1.6)</td>
<td>9.5 (9.2)</td>
</tr>
<tr>
<td>Anti-Scl70</td>
<td>128 (17.9)</td>
<td>93 (18.9)</td>
<td>45 (15)</td>
<td>266 (17.7)</td>
</tr>
<tr>
<td>Anticentromere B</td>
<td>248 (34.7)</td>
<td>42 (14.1)</td>
<td>200 (40.8)</td>
<td>490 (32.6)</td>
</tr>
<tr>
<td>Anti-RNA polymerase III</td>
<td>126 (17.6)</td>
<td>62 (12.6)</td>
<td>41 (13.7)</td>
<td>229 (15.2)</td>
</tr>
<tr>
<td>Th/To</td>
<td>10 (1.4)</td>
<td>9 (1.8)</td>
<td>5 (1.7)</td>
<td>24 (1.6)</td>
</tr>
</tbody>
</table>

SSt: systemic sclerosis; CSRG: Canadian Scleroderma Research Group; ASCS: Australian Scleroderma Cohort Study; GENISOS: Genetics versus Environment in Scleroderma Outcome Study.
It is noteworthy that 10% (4/39) of patients of Native North American descent had AFA positivity. Appendix 2 shows the frequency of AFA among investigated ethnic groups.

Clinical correlates of AFA. There were more AFA-positive patients classified as having dcSSc (56%) than lcSSc (44%), although there were some differences according to ethnicity (within the African descent subgroup, all 5 patients had dcSSc and within the Native North American ethnicity subgroup, 3 of the 4 patients had dcSSc, whereas only 50% of white patients had dcSSc). In multivariable regression analysis after adjustment for age, sex, and ethnicity (Table 3), these characteristics showed trends for association with AFA positivity: dcSSc (p = 0.057), bacterial overgrowth requiring antibiotics (p = 0.053), and GERD (p = 0.076). No association was demonstrated between the other clinical variables, including myositis or digital ulcers, and AFA positivity.

AFA is associated with decreased survival. In unadjusted survival analysis, AFA-positive patients had decreased survival compared with AFA-negative patients (HR 2.02, p = 0.002; Figure 1). In the multivariable model, AFA positivity was still a significant predictor of mortality even after adjusting for sex, ethnicity, age at enrollment, and site (HR 1.88, 95% CI 1.19–2.97, p = 0.007; Table 4).

After adjusting for differences in baseline demographic characteristics, site, and diffuse disease subtype, AFA-positive patients still had decreased survival compared with AFA-negative patients (HR 1.76, 95% CI 1.11–2.79, p = 0.016).

Among the 21 deaths occurring in the AFA group, information on the cause of death was available for only 8 patients. The cause of death in these 8 patients was as follows: 3 non-SSc–related, 2 combined severe ILD and PAH, 1 PAH, 1 scleroderma gut involvement, and 1 scleroderma renal crisis.

DISCUSSION

The overall prevalence of AFA in this large tri-nation SSc cohort was 3.5%, relatively lower than in other cohorts in which prevalence has been reported to be 5%–8%6,7,8,9,10,11. However, if separated by cohorts, the prevalence of AFA was 5% for GENISOS. It is possible that this can be attributed to the sensitivity of the LIA. In our study, we confirm the previously reported association of AFA with African descent and report for the first time an association of these antibodies with Native North American ethnicity. We also observed a strong association between AFA and decreased survival, which was independent of demographic factors, site, and disease type. AFA also showed a trend for association with SSc GI manifestations.

Prior studies have indicated a higher prevalence of AFA among African American patients6,13,14, but little was known to date regarding the prevalence of AFA among Native North American patients. The relatively high prevalence of AFA among the latter is a novel observation. This finding also contributes to the higher frequency of AFA in the CSRG compared with the ASCS cohort, even though these 2 cohorts have similar clinical characteristics (e.g., disease duration).

The association of internal organ manifestations in previous studies has been summarized in Table 5A–6,9,11,15,17,25,26. Overall, AFA have been more consistently associated with dcSSc, pulmonary HTN, and GI tract involvement. In agreement with previous studies4,15, we observed that the majority of AFA-positive patients had dcSSc. AFA was also associated with SSc GI manifestations (in particular bacterial overgrowth requiring antibiotics and GI reflux disease).

The GI tract has been reported to be the most frequently involved internal organ in SSc, affecting more than 90% of patients, with the esophagus being the most frequent GI organ involved27. The proposed pathophysiology of GI involvement in SSc includes vasculopathy, neural dysfunction, smooth muscle atrophy, and tissue fibrosis28. Small intestinal bacterial overgrowth has been reported to affect 33% to 43% of the patients with SSc29 and is considered to be the main cause of malabsorption. Malabsorption is a poor prognostic factor, with a 50% mortality rate at 8.5 years30,31. Further, gastroesophageal disease has been suggested to be a risk factor for the development of ILD32. Although the high prevalence of GI tract involvement in SSc is well recognized,
and the association with AFA positivity has been described, there are no studies investigating the pathogenic involvement (if any) of AFA in GI involvement in SSc.

There was a strong association between AFA and decreased survival in our present study, which was independent of demographic factors, site, and disease type. The observed associations with pulmonary HTN and GI manifestations might explain this finding. PAH was the most common cause of death among AFA-positive patients in a single center study by Aggarwal, et al. Severe GI tract involvement has also been associated with disease-related mortality.

The main strength of our study is its large sample size and the inclusion of patients from 3 countries from a wide geographic area. Further, all the antibody determinations were performed using the same platform and protocol. Nevertheless, our study has some limitations. Causes of death were not available for the patients in the GENISOS cohort. Therefore, our analysis focused on all-cause mortality. Further, right heart catheterization results were not available from patients with pulmonary HTN in the CSRG and GENISOS cohorts. Nevertheless, the sPAP cutoff of > 45 mmHg on cardiac echo used in our study has been reported to correlate strongly with right heart catheter studies.

Another limitation of our present study is that we did not validate the LIA results in comparison to the immunoprecipitation assays because our goal was to investigate the demographic and clinical correlates of AFA by LIA, a widely used method that has received CE (Conformité Européenne) approval for clinical use. A previous study has shown that the performance of LIA is comparable to the gold standard method, immunoprecipitation of radiolabeled proteins, although in that study only samples were investigated that had a positive nucleolar immunofluorescence pattern and lacked the other SSc-specific antibodies.

AFA was strongly associated with bacterial overgrowth requiring antibiotics and was an independent predictor of mortality in this large multinational SSc cohort. Further, we confirmed the association of AFA with African descent and reported for the first time an association with the Native North American ethnicity. The association of AFA with GI manifestations and decreased survival supports the value of this antibody as a clinically useful biomarker.

**ACKNOWLEDGMENT**

We thank Dr. Suman Murthy for assistance in obtaining the 2013 American College of Rheumatology/European League Against Rheumatism classification.
APPENDIX 1.

List of study collaborators. The Australian Scleroderma Cohort Study (ASCs): C. Hill, Adelaide, South Australia; S. Lester, Adelaide, South Australia; P. Nash, Sunshine Coast, Queensland; M. Nikpour, Melbourne, Victoria; J. Roddy, Perth, Western Australia; K. Patterson, Adelaide, South Australia; S. Proudnick, Adelaide, South Australia; S. Rischmueller, Adelaide, South Australia; J. Sahhar, Melbourne, Victoria; W. Stevens, Melbourne, Victoria; J. Walker, Adelaide, South Australia; J. Zochling, Hobart, Tasmania.

The Canadian Scleroderma Research Group (CSRG): M. Baron, Montreal, Quebec; M. Hudson, Montreal, Quebec; G. Gyger, Montreal, Quebec; J. Pope, London, Ontario; M. Larché, Hamilton, Ontario; N. Khalidi, Hamilton, Ontario; A. Masetto, Sherbrooke, Quebec; E. Sutton, Halifax, Nova Scotia; D. Robinson, Winnipeg, Manitoba; T.S. Rodriguez-Reyna, Mexico City, Mexico; D. Smith, Ottawa, Ontario; C. Thorne, Newmarket, Ontario; P.R. Fortin, Quebec, Quebec; M. Fritzler, Mitogen Advanced Diagnostics Laboratory, Cumming School of Medicine, Calgary, Alberta.

REFERENCES


APPENDIX 2. Frequency of AFA among investigated ethnic groups.

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Total Patients, n</th>
<th>Patients with AFA, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1249</td>
<td>36 (2.9)</td>
</tr>
<tr>
<td>African descent</td>
<td>71</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Latino</td>
<td>90</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>47</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Native North American</td>
<td>39</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>Australian aboriginal</td>
<td>8</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

AFA: antifibrillarin antibodies.