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Clinical associations of anti-Smith antibodies in PROFILE: a multi-ethnic lupus cohort

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Abstract

The aim of this study was to determine the association of anti-Sm antibodies with clinical manifestations, comorbidities, and disease damage in a large multi-ethnic SLE cohort. SLE patients (per American College of Rheumatology criteria), age ≥ 16 years, disease duration ≥ 10 years at enrollment, and defined ethnicity (African American, Hispanic or Caucasian), from a longitudinal US cohort were studied. Socioeconomic-demographic features, cumulative clinical manifestations, comorbidities, and disease damage (as per the Systemic Lupus International Collaborating Clinics Damage Index [SDI]) were determined. The association of anti-Sm antibodies with clinical features was examined using multivariable logistic regression analyses adjusting for age, gender, ethnicity, disease duration, level of education, health insurance, and smoking. A total of 2322 SLE patients were studied. The mean (standard deviation, SD) age at diagnosis was 34.4 (12.8) years and the mean (SD) disease duration was 9.0(7.9)years; 2127 (91.6 %) were women. Anti-Sm antibodies were present in 579 (24.9 %) patients. In the multivariable

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analysis, anti-Sm antibodies were significantly associated with serositis, renal involvement, psychosis, vasculitis, Raynaud's phenomenon, hemolytic anemia, leukopenia, lymphopenia, and arterial hypertension. No significant association was found for damage accrual. In this cohort of SLE patients, anti-Sm antibodies were associated with several clinical features including serious manifestations such as renal, neurologic, and hematologic disorders as well as vasculitis.

Keywords

Anti-Smith antibodies; Clinical manifestations; Disease damage; Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a wide range of clinical manifestations and the presence of multiple autoantibodies. Some of these autoantibodies are used in clinical practice for diagnosis and to monitor disease activity [1]. Anti-Smith (anti-Sm) antibodies are highly specific for SLE and have an important value in the classification of this disease [2, 3]. Their frequency in SLE has been reported between 9 and 49 % depending on the demographic and ethnic characteristics of the study populations [3–12]. Several authors have described associations of anti-Sm antibodies with specific subsets of organ/system involvement and disease activity [2, 4, 7, 8, 10, 12–19]. However, most studies used to evaluate these associations are relatively small, differ on study designs, or are limited to specific ethnic populations. In this study, we sought to determine the association between anti-Sm antibodies and clinical manifestations, comorbidities, and damage accrual in a large multi-center cohort of SLE patients with diverse ancestry backgrounds enrolled from the continental USA and Puerto Rico.

Patients and methods

The Genetic Profile Predicting the Phenotype (PROFILE) is a well-characterized multi-ethnic cohort of SLE patients constituted in 1998 from existing cohorts at the University of Alabama at Birmingham, Johns Hopkins University, Northwestern University, the University of Texas Health Science Center at Houston, and the University of Puerto Rico Medical Sciences Campus [20]. The Institutional Review Board of each institution approved this study, and written informed consent was obtained from all participating subjects according to the Declaration of Helsinki.

PROFILE patients meet the 1997 American College of Rheumatology (ACR) revised criteria [21], are 16 years of age or older, and have disease duration ≥ 10 years at the time of enrollment. They are of defined ethnicity (Hispanic of Mexican ancestry [residing and enrolled in Texas, hence Texan Hispanics], Hispanic of Puerto Rican ancestry [residing and enrolled in Puerto Rico, hence Puerto Rican Hispanics], African American, and Caucasian), having reported all four grandparents to be of the same ethnic background. At the time of this analysis, a total of 2322 SLE patients are followed longitudinally in PROFILE.

Variables

The combined PROFILE cohort includes data variables common to the individual cohorts identified after data harmonization [20]. As previously described, combined cohort includes variables from the socioeconomic-demographic, clinical, immunological, and genetic domains. Only the variables included in this study will be described. Socioeconomic-demographic variables evaluated included age at SLE diagnosis, age at last study visit, gender, ethnicity, years of education, health insurance, and smoking status. Time of SLE diagnosis was defined as the date at which a patient met at least four revised ACR criteria for SLE [21]. Disease duration was defined as the time between SLE diagnosis and last study visit.

The clinical variables included cumulative SLE-related clinical manifestations, autoantibodies, comorbidities, and disease damage assessed with the Systemic Lupus International Collaborating Clinics Damage Index (SDI) [22]. Clinical manifestations were examined as per the revised ACR classification criteria [21] as well as other selected clinical manifestations such as vasculitis and Raynaud's phenomenon. Antinuclear, anti-dsDNA, anti-Smith, and anti-phospholipid antibodies were locally measured at each study site using standard clinical laboratory protocols. Selected comorbidities were recorded including arterial hypertension, coronary artery disease, cerebrovascular events, peripheral artery disease, venous thromboembolism, pulmonary hypertension, and hypothyroidism. Hypertension was defined as systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg on two or more occasions, and/or patient self-reported intake of antihypertensive medication. Coronary artery disease was defined as classic or unstable angina and/or history of myocardial infarction documented by electrocardiogram changes and/or elevation of cardiac enzymes and/or myocardial stress test, myocardial perfusion imaging, or coronary angiogram with evidence of coronary atherosclerosis. Cerebrovascular events included transient ischemic attacks (TIA), ischemic or embolic stroke, subarachnoid or intraparenchymal hemorrhage ascertained by history and/or physical examination, and the corresponding lesion on computed tomography (CT) or magnetic resonance imaging (MRI), except for TIA. Peripheral arterial disease was defined as claudication, rest pain, presence of non-healing ulcer or wound, or gangrene and confirmation by Doppler flow studies or angiogram. Venous thromboembolism was defined as peripheral and/or visceral thrombosis documented by noninvasive (impedance plethysmography, compression ultrasonography, magnetic resonance venography, or CT angiogram) or invasive studies (contrast venography). Pulmonary hypertension was defined by mean pulmonary pressure exceeding 25 mmHg at rest or 30 mmHg with exercise, ascertained by a right ventricular heave or a loud pulmonary component on cardiac physical examination and/or right ventricular prominence on chest radiograph and/or by echocardiography and/or right heart catheterization. Lastly, hypothyroidism was defined as high serum thyroid-stimulating hormone and/or clinical symptoms and/or pharmacologic treatment for hypothyroidism.

Statistical analyses

Using a cross-sectional case-only approach, descriptive analyses were performed to compare the socioeconomic-demographic features, cumulative clinical variables, and disease damage

in SLE patients with and without anti-Sm antibodies. The relationship between variables was examined by Student's *t* tests or chi-square tests, as appropriate. The association of anti-Sm antibodies with clinical manifestations and disease damage was examined using multivariable logistic regression adjusted for age, gender, ethnicity, disease duration, years of education, health insurance, and smoking. Variables with a *p* < 0.05 in these analyses were considered to be significant. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

Results

At the time of the analysis, 2322 patients enrolled in PROFILE were included. The mean (standard deviation [SD]) age at diagnosis was 34.4(12.8)years and the mean (SD) disease duration was 9.0(7.9)years. Ninety-one percent were women. The distribution of ethnic populations was as follows: 42.6 % were Caucasians, 35.7 % were African American, 10.2 % Texan Hispanics, 9.8 % Puerto Rican Hispanics, and other ethnic groups represented 1.6 % of the cohort. Anti-Sm antibodies were observed in 579 (24.9 %) of SLE patients.

Table 1 shows the socioeconomic and demographic features in SLE patients with and without anti-Sm antibodies. Anti-Sm antibodies were more common in African Americans (49.4 %), followed by Caucasians (26.8 %), Texan Hispanics (11.6 %), and Puerto Rican Hispanics (10.7 %) (*p*<0.001). Patients with anti-Sm antibodies were more likely to be diagnosed with SLE at a younger age (32.3 [±11.5] vs. 35.0[±13.2]years, *p*<0.001) and have shorter disease duration (7.4 [±6.8] vs. 9.6[±8.2]years, *p*<0.001) compared to SLE patients without anti-Sm antibodies. No significant differences were observed for years of education, health insurance, or current tobacco use.

The association of anti-Sm antibodies with clinical manifestations, immunologic features, and damage accrual is shown in Table 2. In the crude and adjusted analyses, anti-Sm antibodies were positively associated with serositis, renal disease, neurologic disorder (per ACR Clinical Classification of CNS lupus) [21], psychosis, hemolytic anemia, leukopenia, lymphopenia, vasculitis, Raynaud's phenomenon, ANA, and anti-dsDNA antibodies. Anti-Sm antibodies were also positively associated with seizures, thrombocytopenia, and lupus anticoagulant in the crude analysis but did not retain statistical significance in the multivariable model. Anti-Sm antibodies were negatively associated with photosensitivity in the crude analysis but did not remain statistically significant in the multivariable analysis. We did not observe a significant association between anti-Sm antibodies and SDI score.

Table 3 shows the association of anti-Sm antibodies with comorbidities frequently seen in SLE patients. Anti-Sm antibodies were positively associated with hypertension both in the crude and adjusted analyses. No significant associations were found between anti-Sm antibodies and coronary artery disease, cerebrovascular events, peripheral arterial disease, venous thrombosis, pulmonary hypertension, and hypothyroidism.

Discussion

In this large multi-ethnic longitudinal cohort of SLE patients, we studied the association of anti-Sm antibodies with the presence of clinical manifestations, comorbidities, and damage

accrual. We found that anti-Sm antibodies were associated with serious complications such as renal disease, central nervous system involvement, vasculitis, and hemolytic anemia. In addition, patients with anti-Sm antibodies were more likely to have serositis, Raynaud's phenomenon, leukopenia, lymphopenia, and arterial hypertension.

The frequency of anti-Sm antibodies in our cohort was 24.9 %, comparable with other ethnic populations [23, 24]. However, the seroprevalence was higher than that reported for European cohorts [6, 8, 9] but lower than in GLADEL, a large multi-ethnic Latin American cohort study [25]. We also noted significant variations between ethnic groups in our study. African Americans (49.4 %) had higher seroprevalence of anti-Sm antibodies when compared to Caucasians (26.8 %) and Hispanics from Texas (11.6 %) and Puerto Rico (10.7 %). The higher frequency of anti-Sm antibodies in African American SLE patients has been described in previous studies [7, 26].

Associations between autoantibodies and renal involvement have been extensively studied; however, only the relationship between anti-dsDNA antibodies and lupus nephritis has been consistently established [2, 4, 13]. We found that anti-Sm antibodies were significantly associated with renal involvement. Previous data regarding this association have been inconsistent [4–10, 12–17, 23, 24, 27–34]. A prospective cohort study of 201 Puerto Rican patients showed associations of anti-Sm antibodies with proteinuria, hematuria, urinary cellular casts, nephrotic syndrome, renal insufficiency, and end-stage renal disease [4]. Also, in a case-control study, Alba et al. found that anti-Sm antibodies were linked with biopsy-proven lupus nephritis [13]. Similar associations have also been depicted in several cross-sectional studies [14–16, 23, 24, 27–30]. Moreover, other authors have described relationships between anti-Sm antibodies and mild forms of lupus nephritis as well as late-onset proteinuria [14, 23, 24, 26–31]. More recently, anti-Sm antibodies were identified as predictors of silent lupus nephritis [35]. In contrast, several studies have not found associations between anti-Sm antibodies and renal involvement [5–10]. Variability in study design, number of patients evaluated, and differences in ethnic backgrounds could explain these inconsistencies.

In addition to renal involvement, we found that anti-Sm antibodies were linked with other severe SLE manifestations, including vasculitis and neuropsychiatric manifestations, specifically psychosis. Other authors have confirmed these associations [4, 15, 17, 24, 31, 36–39]. A retrospective cross-sectional study of 111 South African black patients described an association between anti-Sm antibodies and psychosis [17]. Additionally, a longitudinal study of SLE patients found increased anti-Sm IgG titers preceding the onset of neurologic disease [36]. More recently, Hiroata et al. noted associations between cerebrospinal fluid anti-Sm antibodies and acute confusional state in SLE patients [39]. In contrast, Borowoy et al. reported that anti-Sm antibodies were negatively associated with neuropsychiatric lupus in a cohort of 1417 SLE patients in Canada [40]. With regard to the association between anti-Sm antibodies and vasculitis, other reports have also described this relationship, in particular for cutaneous vasculitis [24, 31].

Anti-Sm antibodies were found to be associated with hemolytic anemia. Prior studies have linked anti-Sm antibodies with anemia [4]; but, to the best of our knowledge, this is the first

to specifically establish an association with hemolytic anemia. With regard to other hematological abnormalities, we confirmed the association of anti-Sm antibodies with leukopenia and neutropenia [4, 5, 30, 34, 41]. We also found a relationship with thrombocytopenia; however, after multivariable analysis, this did not remain statistically significant.

We found that anti-Sm antibodies were linked with other clinical SLE manifestations. Our patients with anti-Sm antibodies had a significantly higher frequency of Raynaud's phenomenon. This observation has been previously reported, especially with the coexistence of anti-ribonucleoprotein (RNP) antibodies [11, 14, 18, 30, 42]. Serositis was also associated with the presence of anti-Sm antibodies in our cohort. Similarly, prior reports have linked anti-Sm antibodies with organ-specific serositis such as pericarditis [36, 41]. Conversely, we found no associations with arthritis or muco-cutaneous manifestations such as malar rash, photosensitivity, or discoid lupus as previously noted by other authors [4, 6, 9, 10, 24, 30, 41]. The presence of anti-Sm antibodies was significantly associated with positive anti-dsDNA antibodies. Other authors have noted this relationship [16], while others have found a potential synergistic effect between them [15, 32]. Janwityanuchit et al. found that patients with anti-dsDNA and anti-Sm antibodies had higher prevalence of renal disease in a group of 131 Thai SLE patients [14]. Furthermore, a study in 51 SLE Mexican patients found that those with both auto-antibodies had higher levels of disease activity [33]. These synergistic associations have also been described for other autoantibodies. For instance, the coexistence of anti-C1q and anti-dsDNA antibodies was recently linked to renal disease [43].

Even though anti-Sm antibodies were linked with multiple complications of SLE, we did not find an association between anti-Sm antibodies and cumulative organ damage. Findings with respect to this association have been inconsistent [4, 19]. A longitudinal cohort of Puerto Rican SLE patients found that anti-Sm antibodies were associated with greater damage accrual [4]. Conversely, Prasad et al. found that anti-Sm antibodies did not predict organ damage in a Canadian SLE cohort [19]. Disease activity is a major predictor of disease damage [44]. In fact, some authors have reported the relationship between anti-Sm antibodies and disease activity [23, 33, 42]. Unfortunately, we could not explore this association systematically in our combined population as not all study sites use the same instruments to measure disease activity, thereby minimizing our ability to harmonize these data into a single metric for disease activity.

The role of anti-Sm antibodies in SLE pathogenesis is not well known. These autoantibodies are directed against a group of core proteins (Sm) that, together with RNP, make up the RNA-protein complex called small nuclear RNP (snRNP) [1]. The snRNP complex is involved in the splicing of messenger RNA prior to its translation into proteins. Whether or not antibodies against these proteins have an impact in the potential mechanisms of disease (direct action, immune complex deposition, etc.) remain uncertain. Interestingly, Mannik et al. isolated anti-Sm antibody immune complexes from the glomeruli of patients with lupus nephritis [45]. These findings are notable, and even though they suggest a causal role for anti-Sm antibodies in SLE, additional studies are needed.

Some limitations of the present study should be addressed. First, serum antibodies were not determined using a central laboratory; hence, variations in the assay sensitivity may exist [30, 46]. Second, not all anti-Sm antibodies were ascertained at SLE diagnosis; therefore, we were not able to examine their positive predictive value for developing specific clinical manifestations. Third, the fluctuation of anti-Sm antibodies' levels was not studied, as serial measurements were not obtained for all patients. Nonetheless, some studies have shown that seropositivity of anti-Sm antibodies remains stable during the disease course despite treatment effects [5, 47–50]. Finally, we did not evaluate the clinical associations of the coexistence of anti-Sm antibodies with other autoantibodies commonly seen in SLE. Future studies that include systematically evaluated autoantibody profiles conducted over time in a similarly large, well-characterized ancestry diverse population will be required to improve our understanding of autoantibody signatures in aggregate as biomarkers, which may be used to predict disease progression as well as to provide new insight into the biological mechanism underlying serious clinical manifestations among patients with SLE.

In summary, to our knowledge, this is the largest prospective multi-center and multi-ethnic SLE study used to evaluate the relationship between anti-Sm antibodies and several clinical manifestations. Our results suggest that anti-Sm antibodies are associated with major clinical manifestations, such as renal involvement, psychosis, hemolytic anemia, and vasculitis. These findings highlight the importance of recognizing the value of anti-Sm antibodies not only as a classification criterion for SLE but also as a surrogate marker for major organ involvement and clinically relevant SLE manifestations.

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Table 1

Association of anti-Smith antibodies with socioeconomic-demographic features

Clinical and demographic feature	Anti-Sm positive (<i>n</i> =579)	Anti-Sm negative (<i>n</i> =1743)	<i>p</i> value
Age at diagnosis, mean (SD) years	32.3 (11.5)	35.0 (13.2)	<0.001
Gender, <i>n</i> (%) female	517 (89.3)	1610 (92.4)	0.021
Ethnicity, <i>n</i> (%)			
African American	286 (49.4)	543 (31.2)	<0.001
European American	155 (26.8)	835 (47.9)	
Hispanic, Puerto Rico	62 (10.7)	166 (9.5)	
Hispanic, Texas	67 (11.6)	170 (9.75)	
Other	9 (1.6)	29 (1.7)	
Disease duration, mean (SD) years	7.4 (6.8)	9.6 (8.2)	<0.001
Years of education, mean (SD) years	13.7 (2.9)	13.8 (3.0)	0.361
Health insurance, <i>n</i> (%) having it	429 (74.1)	1319 (75.7)	0.445
Current smoking, <i>n</i> (%)	83 (14.3)	275 (15.8)	0.405

Anti-Sm anti-Smith, *SD* standard deviation

Table 2

Association of anti-Smith antibodies with clinical manifestations and damage accrual

	Anti-Sm positive (n=579)	Anti-Sm negative (n=1743)	Crude OR (95 % CI)	p value	Adjusted OR (95 % CI) [*]	p value
ACR criteria for SLE, %						
Malar rash	315 (54.4)	983 (56.4)	0.92 (0.76-1.11)	0.403	1.06 (0.87-1.30)	0.565
Photosensitivity	304 (52.5)	1109 (63.6)	0.63 (0.52-0.76)	<0.001	0.82 (0.67-1.01)	0.058
Oral ulcers	281 (48.5)	905 (51.9)	0.87 (0.72-1.05)	0.158	1.07 (0.88-1.31)	0.483
Arthritis	482 (83.2)	1450 (83.2)	1.00 (0.78-1.29)	0.975	1.14 (0.88-1.49)	0.326
Serositis	299 (51.6)	713 (40.9)	1.54 (1.28-1.86)	<0.001	1.51 (1.23-1.84)	<.001
Renal disorder	254 (43.9)	541 (31.0)	1.74 (1.43-2.11)	<0.001	1.33 (1.08-1.64)	0.008
Neurologic disorder	81 (14.0)	160 (9.2)	1.61 (1.21-2.14)	0.001	1.51 (1.12-2.04)	0.007
Seizures	54 (9.3)	116 (6.7)	1.44 (1.03-2.02)	0.033	1.40 (0.98-1.99)	0.065
Psychosis	33 (5.7)	56 (3.2)	1.82 (1.17-2.83)	0.008	1.60 (1.01-2.53)	0.045
Hematologic disorder						
Hemolytic anemia	81 (14.0)	138 (7.9)	1.89 (1.41-2.53)	<0.001	1.73 (1.28-2.35)	<.001
Leukopenia	291 (50.3)	682 (39.1)	1.57 (1.30-1.90)	<0.001	1.56 (1.28-1.91)	<.001
Lymphopenia	308 (53.2)	678 (38.9)	1.79 (1.48-2.16)	<0.001	1.76 (1.43-2.16)	<.001
Thrombocytopenia	125 (21.6)	304 (17.4)	1.30 (1.03-1.65)	0.026	1.23 (0.96-1.56)	0.101
Immunologic disorder						
ANA	571 (98.6)	1677 (96.2)	2.81 (1.34-5.89)	0.006	2.62 (1.23-5.56)	0.012
Anti-dsDNA	404 (69.8)	948 (54.4)	1.94 (1.58-2.37)	<0.001	1.87 (1.51-2.32)	<.001
Lupus anticoagulant	84 (14.5)	318 (18.2)	0.76 (0.59-0.99)	0.040	0.81 (0.62-1.07)	0.139
Other SLE manifestations						
Vasculitis	115 (19.9)	259 (14.9)	1.42 (1.11-1.81)	0.005	1.50 (1.17-1.94)	0.002
Raynaud's phenomenon	294 (50.8)	742 (42.6)	1.39 (1.15-1.68)	<0.001	1.64 (1.34-2.00)	<.001
Transverse myelitis	4 (0.7)	12 (0.7)	1.00 (0.32-3.12)	0.995	1.15 (0.36-3.69)	0.817
SDI score, mean (SD)	1.7 (2.03)	1.7 (2.07)	1.00 (0.95-1.04)	0.909	1.01 (0.96-1.07)	0.602

Anti-Sm anti-Smith, *OR* odds ratio, *CI* confidence interval, *ACR* American College of Rheumatology, *SLE* systemic lupus erythematosus, *ANA* antinuclear antibody, *SDI* Systemic Lupus International Collaborating Clinics Damage Index, *SD* standard deviation

* Adjusted for age, gender, ethnicity, disease duration, years of education, health insurance, and smoking

Table 3

Association of anti-Smith antibodies with selected comorbidities

	Anti-Sm positive (n=579)	Anti-Sm negative (n=1743)	Crude OR (95 % CI)	p value	Adjusted OR (95 % CI) [*]	p value
Comorbidities						
Hypertension	246 (42.5)	625 (35.9)	1.32 (1.09-1.60)	0.004	1.32 (1.07-1.62)	0.010
Coronary artery disease	14 (2.4)	68 (3.9)	0.61 (0.34-1.09)	0.097	0.86 (0.47-1.58)	0.624
Stroke	30 (5.2)	68 (3.9)	1.35 (0.87-2.09)	0.186	1.38 (0.88-2.19)	0.162
Peripheral artery disease	19 (3.3)	79 (4.5)	0.71 (0.43-1.19)	0.197	0.89 (0.53-1.52)	0.676
Venous thrombosis	49 (8.5)	145 (8.3)	1.02 (0.73-1.43)	0.913	1.09 (0.77-1.55)	0.627
Pulmonary hypertension	24 (4.1)	53 (3.0)	1.38 (0.84-2.25)	0.200	1.59 (0.95-2.65)	0.079
Hypothyroidism	51 (8.8)	190 (10.9)	0.79 (0.57-1.09)	0.154	1.03 (0.73-1.44)	0.877

Anti-Sm anti-Smith, *OR* odds ratio, *CI* confidence interval, *SD* standard deviation^{*} Adjusted for age, gender, ethnicity, disease duration, years of education, health insurance, and smoking