HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2016 October ; 68(10): 1554–1559. doi:10.1002/acr.22859.

Anti-centromere antibodies are associated with more severe exocrine glandular dysfunction in Sjögren's syndrome: Analysis of the Sjögren's International Collaborative Clinical Alliance cohort

Alan N. Baer[1], **Leah Medrano**[1], **Mara McAdams-DeMarco**[2], and **Thomas J. Gniadek**[3]

[1]Division of Rheumatology, Department of Medicine, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[3]Department of Pathology, Johns Hopkins University School of Medicine, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Abstract

Objectives—Anti-centromere antibodies (ACA) define a subset of primary Sjögren's syndrome (SS) with a unique phenotype, including features of limited cutaneous systemic sclerosis and a lower frequency of anti-SSA/-SSB antibodies. We sought to determine whether ACA are associated with more severe exocrine glandular dysfunction in a large cohort of primary SS subjects.

Methods—We performed a cross-sectional analysis of 1361 subjects with primary SS from the Sjögren's International Collaborative Clinical Alliance (SICCA) registry, stratified by the presence or absence of ACA. ACA were assayed by immunofluorescence staining on HEp-2 cells.

Results—ACA were present in 82 (6%) of the 1361 SS subjects and were associated with older age, female gender, and lower frequencies of anti-SSA/-SSB, rheumatoid factor, and hyperglobulinemia. Among ACA (+) vs ACA (−) subjects, there was a higher frequency of focus

Address for reprint requests and correspondence: Alan N. Baer, MD, Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD 21224, Tel: (410) 550-2042, Fax: (410) 550-6255, alanbaer@jhmi.edu.

Dr. Baer has received consulting fees from Glenmark and Bristol Myers Squibb Pharmaceutical Companies (less than $10,000 each).
Ms. Medrano has no relevant disclosures.
Dr. McAdams-DeMarco has no relevant disclosures
Dr. Gniadek has no relevant disclosures.

Author contributions
Dr. Baer: 1 a,b,c, 2, 3
Ms. Medrano: 1c, 2, 3
Dr. McAdams-DeMarco: 1a, b, 2, 3
Dr. Gniadek: 1 a, b, c, 2, 3

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content and all authors approved the final version to be submitted for publication. Dr. Alan Baer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design: Baer, McAdams-DeMarco, Gniadek
Acquisition of data: Baer, Gniadek
Analysis and interpretation of data: Baer, Medrano, McAdams-DeMarco, Gniadek

score ≥2 (71 vs 53%, p=0.002), higher median focus score (2.8 vs 2.5, p=0.0440) and greater exocrine gland dysfunction: Schirmer's test value: median 4 vs 5 mm/5 min, p=0.0003; unstimulated whole saliva (UWS) flow rate: median 0.08 vs 0.37 ml/5 min, p<0.0001. ACA (+) subjects had an increased risk of UWS<0.1 ml/min [OR=12.24 (95% CI, 4.91–41.02)] and Schirmer value <5 mm/5 min [OR=2.52 (95% CI, 1.50–4.36)] after correcting for age, gender, anti-SSA/-SSB, and focus score. Labial gland fibrosis was not different between the two groups.

Conclusions—In a large international registry of SS, ACA had an independent association with more severe exocrine glandular dysfunction. This dysfunction was associated with more pronounced labial salivary glandular inflammation but not fibrosis.

Keywords

anti-centromere antibodies; Sjögren's syndrome; salivary gland dysfunction

Anti-centromere antibodies (ACA) are present in 1–13% of patients with primary Sjögren's syndrome (SS) in recently-defined cohorts (1–5) and mark those who have more frequent Raynaud's phenomenon and less frequent anti-SSA and anti-SSB antibodies, hyperglobulinemia, rheumatoid factor, and leucopenia (2, 5, 6). These SS patients have a higher frequency of primary biliary cirrhosis and limited scleroderma and may be at higher risk of developing lymphoma or scleroderma (2–4). There are conflicting data with respect to several phenotypic features of these patients, including their average age (2, 5, 6), glandular dysfunction (3, 5), and extent of glandular fibrosis (5, 6). This relates in part to the small size of previously published cohorts of ACA-positive SS patients.

The Sjögren's International Collaborative Clinical Alliance (SICCA) is an NIH-funded international registry of over 3500 participants with signs and symptoms suggestive of SS, each of whom underwent a systematic and extensive assessment, including minor salivary gland biopsy (7). In the current study, we analyzed data from SICCA in order to define the phenotypic features of 82 primary SS patients with ACA, the largest cohort available to date. We sought to determine if these patients had more severe glandular dysfunction and corresponding glandular histopathologic alterations.

PATIENTS and Methods

SICCA registry

The SICCA project was implemented in 2003 by investigators at the University of California, San Francisco to establish a large registry of participants who had symptoms or signs indicating they may have or develop SS (7). Nine worldwide research sites contributed to the registry. To be eligible, participants must have been at least 21 years old and have had one of the following: 1) dry eye or mouth symptoms; 2) bilateral parotid enlargement; 3) recent increase in dental caries; 4) previous SS diagnosis; or 5) elevated titers of antinuclear antibodies (ANA), rheumatoid factor (RF), and/or anti-SSA or anti-SSB. These broad inclusion criteria resulted in a cohort of individuals with a wide range of SS symptoms and signs. Subjects with known rheumatoid arthritis (RA) or systemic lupus (SLE) were eligible for SICCA, while those with other autoimmune rheumatic diseases were excluded. Additional exclusion criteria included: known diagnoses of hepatitis C, HIV infection,

sarcoidosis, amyloidosis, active tuberculosis, graft versus host disease; past head and neck radiation treatment; current treatment with daily eye drops for glaucoma; cosmetic eyelid surgery or vision-corrective corneal surgery in the last 5 years; or a physical or mental condition interfering with successful study participation. Informed consent was obtained from all participants in compliance with the Helsinki Declaration.

SICCA study procedures

Every participant underwent a systematic and extensive assessment of SS symptoms and signs, the details of which may be found at: http://sicca.ucsf.edu/. Uniform protocol-driven data collection methods were used for the completion of questionnaires, recording of findings from detailed rheumatologic, ocular, and oral examinations, and biospecimen acquisition. Each participant underwent a minor salivary gland biopsy, and the biopsy slides were independently read by two histopathologists calibrated in this assessment (7).

SICCA laboratory testing

Apart from the complete blood count, all testing was performed by a central commercial laboratory, Quest Diagnostics (Madison, NJ). ANA testing was performed with an immunofluorescent staining assay on HEp-2 cells with screening at a 1:40 serum dilution. Positive tests were titrated to a maximum dilution of 1:1280 and the pattern of staining at the end dilution was reported. The presence of ACA was defined by a centromere pattern of immunofluorescent staining.

Study subjects

There were 3514 SICCA participants enrolled as of September 6, 2013. We excluded 1) 217 for whom data were lacking on at least one of the three objective criteria for SS, as defined by the American College of Rheumatology (ACR) classification set (8); 2) 241 participants who had a diagnosis of an underlying systemic rheumatic disease, including RA (n=174), SLE (n=62), scleroderma (n=2), and undifferentiated (n=3), and 3) 1695 participants who had features suggestive of SS but did not fulfill ACR criteria (8). This left 1361 participants with SS for the current cross-sectional analysis.

Quantification of glandular fibrosis in minor labial salivary gland biopsies

Glandular fibrosis was quantified in minor salivary gland biopsy specimens from 18 SICCA participants, including: 1) six with ACA; 2) six with anti-SSA and/or anti-SSB and lacking ACA and 3) six lacking anti-SSA, anti-SSB, and ACA. Microscopic sections of each specimen were stained with Masson trichrome stain and glandular fibrosis was quantified with image analysis software. For each case, all tissue fragments on a particular section were imaged. Large tissue fragments were imaged in an overlapping grid at 2x magnification using an Olympus DP-73 color camera (resolution: 2.2 μ/pixel). Overlapping images were combined into one using FIJI Image Stitching (9). Pixels corresponding to non-salivary gland tissue (e.g. skeletal muscle, skin, and nerve) as well as background pixels were cleared to white by manual cropping. The remaining pixels, representing manually selected salivary gland tissue, were quantified to determine total glandular surface area. A custom-written Java program was then used to quantify the percent fibrosis in the glandular tissue, using

HSB color space segmentation. Fibrosis was defined as pixels with a hue from 174 to 274 degrees, corresponding to blue staining with Masson trichrome.

Statistical analyses

Descriptive statistics were used to describe the demographic features. We utilized a cross-sectional study design to investigate the correlation of ACA status with SS phenotype. Differences in categorical variables were assessed using a Fisher's exact test, and in continuous variables by a Wilcoxon rank sum test. Given the limited number of hypotheses tested, no formal adjustment was made for multiple hypothesis testing. However, we note that reported p-values of ≤0.0017 would still retain significance at the 5% level for as many as 30 independent tests using the very conservative Bonferroni procedure. Thus, reported results with p-values in this range would also be deemed significant even under fairly stringent control of the family-wise type 1 error rate (likelihood of incorrectly rejecting a null hypothesis).

We hypothesized that greater exocrine glandular dysfunction in ACA-positive SS patients was an independent feature of this disease subset. We thus performed simple and multivariable logistic regression analyses to explore the association of key SS phenotypic features in relation to the outcomes of high versus low unstimulated whole saliva (UWS) flow and minimum Schirmer <5 mm/5 min vs ≥5 mm/5 min. Covariates examined included the following demographic, histologic, serologic and clinical features that would be expected to influence salivary gland function based on existing literature: age, gender, focus score, positive anti-SSA and/or SSB, and ACA status.

All statistical analyses were performed using JMP (Cary, NC) and STATA version 13 (College Station, TX) software.

RESULTS

Sociodemographic features

Most of the 1361 registrants with SS were women (93%) and had a median age of 53 years (range 21–89). Caucasians comprised 44% and Asians 38%.

Features of SS participants with ACA

ACA were present in 82 (6%) of the SS participants. Table 1 shows the demographic and phenotypic features of these participants, stratified by the presence or absence of ACA. The ACA-positive participants were significantly older (median 59 vs. 52 years; p-value <0.0001), more likely to be female (99 vs. 93%; p-value 0.0379) and less likely to be Caucasian (30 vs 45%, p=0.0077). There were no significant differences in terms of their symptoms or signs, with similar percentages of dry mouth and dry eye symptoms and parotid gland enlargement by ACA status. In the ACA-positive group, all had an ANA ≥1:320, in contrast to only 56% in the ACA-negative group (p-value <0.0001). ACA-positive participants were less likely to have anti-SSA or anti-SSB (29 vs. 82%; p-value <0.0001), rheumatoid factor (39 vs. 60%; p-value 0.0003), and hyperglobulinemia

(IgG>1445 mg/dL; 30 vs. 58%; p-value <0.0001). However, the prevalence of hypocomplementemia and leucopenia did not differ between the two groups.

ACA-positive participants had worse exocrine glandular function, evidenced by higher maximum OSS (median 9.5 vs. 8.0; p-value 0.0122), lower minimum Schirmer values (median 4 vs. 5 mm/5 min; p-value = 0.0003), and lower UWS flow (median 0.08 vs. 0.37 ml/5 min; p-value <0.0001). The median focus score on labial gland biopsy was higher in the ACA-positive group (2.8 vs. 2.5; p-value 0.0440). Additionally, a focus score ≥2 was more prevalent in the ACA-positive group (71 vs 53%, p=0.002). The prevalence of histopathologic patterns indicative of greater glandular fibrosis, namely biopsies interpreted as focal sclerosing/lymphocytic or sclerosing chronic sialadenitis, was not different between the two groups.

To analyze this further, we used image analysis software to quantify fibrosis in the labial salivary gland biopsies of 18 SICCA subjects, six with ACA, six with anti-SSA and or -SSB antibodies, and six with negative testing for ACA and anti-SSA/SSB (Supplementary Material). The three groups of biopsies were matched closely in terms of age, histopathologic pattern and focus score. No differences in the extent of intraglandular fibrosis were observed.

The ACA-positive group had more features of systemic sclerosis, including higher rates of Raynaud's phenomenon (62 vs. 28%; p-value <0.0001), sclerodactyly (16 vs. 1%; p-value <0.0001), dilated capillary loops (20 vs. 5%; p-value <0.0001), matted telangiectasia (11 vs. 5%; p-value 0.0390) and oral mucosal telangiectasia (15 vs. 6%; p-value 0.0113). Although individuals with systemic sclerosis were excluded from SICCA at the time of registration, 14 of the 82 (17%) ACA-positive participants fulfilled the 2013 ACR/European League Against Rheumatism (EULAR) classification criteria for systemic sclerosis when these were applied retrospectively (10). When the ACA-positive group was stratified by the presence or absence of anti-SSA/SSB, there were no significant inter-group differences in the prevalence of systemic sclerosis clinical features, focus score ≥2, and germinal centers or sclerosis in the biopsy (data not shown).

Multivariate analyses

A multivariate model was used to assess the explanatory role of ACA and other selected phenotypic features of SS in relation to the outcome "UWS flow <0.1 ml/min vs. ≥0.1 ml/min." We did not include duration of dry mouth and dry eyes since these values were not significantly different between the ACA-positive and ACA-negative groups and missing data limited these analyses. Shown in table 2A, we found that older age (OR 2.12; 95% CI: 1.64–2.77), female gender (OR 1.92; 95% CI: 1.23–3.02), and focus score ≥2 (OR 2.50; 95% CI: 1.98–3.15) were each independently associated with low UWS. The greatest risk factor was ACA (OR 12.24; 95% CI: 4.91–41.02). We found similar results in relation to the outcome "Schirmer's <5 mm/5 min vs ≥5 mm/5 min." Shown in table 2B, older age (OR 1.46; 95% CI: 1.14–1.86), anti-SSA/SSB (OR 1.55; 95% CI: 1.17–2.07), and focus score ≥2 (OR 1.97; 95% CI: 1.58–2.46) were independently associated with poor tear production. Again, ACA was significantly associated and had the highest OR (OR 2.52; 95% CI: 1.50–4.36).

DISCUSSION

ACA are most commonly associated with systemic sclerosis, defining a subset with limited cutaneous disease, matted telangiectasia, slower disease progression, and lower risk for renal crisis or interstitial pulmonary fibrosis (11). They have also been reported in SS, primary biliary cirrhosis, primary Raynaud's phenomenon, SLE, RA, and malignancies (12). The antibodies recognize different centromere proteins, although those reactive with CENP-A, -B, and -C are the primary ones in the systemic autoimmune diseases. Anti-CENP-A, -B, -C, -D, -E, and -O have been linked to systemic sclerosis, while anti-CENP-B, -C and -H are linked to SS and anti-CENP-F to malignancy (12, 13). Dual antibody reactivity to CENP-B and -C is more frequent in systemic sclerosis than SS (13).

ACA can be detected by a distinctive pattern of immunofluorescent staining of HEp-2 cells, and their specificity confirmed by solid-phase immunoassays using recombinant centromere proteins. ELISA has greater sensitivity than the immunofluorescent staining assay for detection of antibodies to CENP-A, -B, and -C, but the clinical associations of ACA detected only by ELISA have not been established (11). All ACA were present in high titer (≥1:320) among the SICCA subjects with SS.

In the current study, the prevalence of ACA in our cohort of primary SS was 6%, commensurate with other recent studies (1–5). Our cohort of SS with ACA is the largest reported to date. We confirmed previous observations that ACA mark SS patients with distinctive phenotypic features, including a lower frequency of anti-SSA and anti-SSB, rheumatoid factor, and hyperglobulinemia. Our ACA-positive subjects were significantly older, a finding replicated in only one previous study (6), and included a significantly higher prevalence of women, a finding not previously observed. As noted in other studies, our ACA-positive subjects had a higher frequency of clinical features commonly seen in limited cutaneous systemic sclerosis, including Raynaud's phenomenon, dilated nailfold capillary loops, and matted and oral mucosal telangiectasia. Individuals with systemic sclerosis were excluded from participation in SICCA, and this assessment was made utilizing the 1980 ACR (formerly American Rheumatism Association) preliminary criteria for the classification of systemic sclerosis extant at the time that recruitment was active (14). A new set of classification criteria for systemic sclerosis was approved by the ACR and EULAR in 2013 and differed from the earlier one by including patients with Raynaud's phenomenon, ACA and one or more cutaneous features of systemic sclerosis other than scleroderma or sclerodactyly (10). With the application of these new criteria, only 17% of the ACA-positive SS subjects would be classified with systemic sclerosis, substantiating the classification of these subjects as primary SS.

The presence of ACA was associated with significantly worse exocrine glandular function, as evidenced by lower Schirmer and salivary flow results. Similar observations were made by Salliot et al and Kitagawa et al (3, 15). ACA-positive subjects, when compared with ACA-negative ones, had a significantly higher median focus score and prevalence of focus score ≥2. This finding contrasts with that of Nakamura et al, who found the focus score to be lower in SS patients with ACA (5). In a multivariate logistic regression analysis, we found

the association of diminished tear and salivary flow rates with ACA to be independent of age, gender, focus score, and anti-SSA/-SSB.

Labial gland histopathology has been reported to show greater degrees of fibrosis in ACA-positive as opposed to ACA-negative SS patients, despite comparable mean ages (5). This finding mirrors those in patients with established systemic sclerosis, where perilobular and intraglandular fibrosis and glandular atrophy have been reported to be a histopathologic feature of minor salivary glands (16). In the current study, we did not observe any increase in prevalence of histopathologic patterns marked by increased glandular fibrosis, namely sclerosing chronic and focal/sclerosing lymphocytic sialadenitis, among the SS patients with ACA versus those without. Additionally, glandular fibrosis was not increased in ACA-positive SS participants when quantified with the aid of image analysis software in a study of 18 subjects. These findings suggest that the exocrine glandular dysfunction in ACA-positive SS patients may relate more to extensive glandular inflammation than glandular fibrosis.

Our study is limited by our reliance on an immunofluorescence staining assay for the detection of ACA. It is known that the immunofluorescent ANA test is less sensitive than ELISA for the detection of anti-CENP-B and may not detect antibodies to other centromere proteins (e.g. CENP-C) which can occur in SS. This is a limitation shared by most other previous studies. In those studies where an ELISA was utilized to detect ACA, the testing was restricted to the detection of anti-CENP-B. Since all SICCA participants underwent labial gland biopsy, our cohort included a broader spectrum of ACA-positive SS than might be seen in clinical practice, where such biopsies are not uniformly performed. The strengths of our study include the size of our cohort, constituting the largest studied to date in this regard, its global composition, and the characterization of each member utilizing a standardized and uniformly applied protocol, including labial gland biopsy.

In summary, ACA in primary SS define patients who are older, have more severe salivary and lacrimal gland dysfunction, and higher labial gland focus scores. They have a significantly higher frequency of clinical findings seen in systemic sclerosis, including Raynaud’s phenomenon, sclerodactyly, and matted, nailfold capillary and oral mucosal telangiectasia. Anti-SSA and anti-SSB and their common correlates, hyperglobulinemia and rheumatoid factor, are present in a minority of these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by a contract from the NIH/NIDCR NO1-DE-32636 and the Jerome L. Greene Foundation. Dr. Baer was supported by NIH R01 DE12354-15A1 and Dr. McAdams-DeMarco by NIH K01AG043501. Data and specimens used in this manuscript are from the Sjögren’s International Collaborative Clinical Alliance (SICCA) Biorepository, funded under contract #HHSN26S201300057C by the National Institute of Dental and Craniofacial Research. This manuscript was prepared using a publicly available SICCA data set and does not necessarily reflect the opinions or views of the SICCA investigators, the NIH or NIDCR.

References

1. Collins K, Mitchell S, Griffiths B, Bowman SJ, Ng WF, United Kingdom Primary Sjögren's Syndrome Registry. Potential diagnostic utility of anti-centromere antibody in primary Sjögren's syndrome in the UK. Clin Rheumatol. 2012 Jul; 31(7):1147–8. [PubMed: 22648094]
2. Bournia VK, Diamanti KD, Vlachoyiannopoulos PG, Moutsopoulos HM. Anticentromere antibody positive Sjögren's Syndrome: a retrospective descriptive analysis. Arthritis Res Ther. 2010; 12(2):R47. [PubMed: 20302639]
3. Salliot C, Gottenberg JE, Bengoufa D, Desmoulins F, Miceli-Richard C, Mariette X. Anticentromere antibodies identify patients with Sjögren's syndrome and autoimmune overlap syndrome. J Rheumatol. 2007 Nov; 34(11):2253–8. [PubMed: 17937465]
4. Baldini C, Mosca M, Della Rossa A, Pepe P, Notarstefano C, Ferro F, et al. Overlap of ACA-positive systemic sclerosis and Sjögren's syndrome: a distinct clinical entity with mild organ involvement but at high risk of lymphoma. Clin Exp Rheumatol. 2013 Mar-Apr;31(2):272–80. [PubMed: 23343785]
5. Nakamura H, Kawakami A, Hayashi T, Iwamoto N, Okada A, Tamai M, et al. Anti-centromere antibody-seropositive Sjögren's syndrome differs from conventional subgroup in clinical and pathological study. BMC Musculoskelet Disord. 2010 Jul 1.11 140,2474-11-140.
6. Katano K, Kawano M, Koni I, Sugai S, Muro Y. Clinical and laboratory features of anticentromere antibody positive primary Sjögren's syndrome. J Rheumatol. 2001 Oct; 28(10):2238–44. [PubMed: 11669163]
7. Daniels TE, Cox D, Shiboski CH, Schiodt M, Wu A, Lanfranchi H, et al. Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren's syndrome among 1,726 registry participants. Arthritis Rheum. 2011 Jul; 63(7):2021–30. [PubMed: 21480190]
8. Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, et al. American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken). 2012 Apr; 64(4):475–87. [PubMed: 22563590]
9. Schindelin J, Arganda-Carreras I, Frise E, Kaynig V, Longair M, Pietzsch T, et al. Fiji: an open-source platform for biological-image analysis. Nature Methods. 2012; 9:676–682. [PubMed: 22743772]
10. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. Classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013 Nov; 65(11):2737–47. 2013. [PubMed: 24122180]
11. Mahler M, You D, Baron M, Taillefer SS, Hudson M, Canadian Scleroderma Research Group (CSRG). et al. Anti-centromere antibodies in a large cohort of systemic sclerosis patients: comparison between immunofluorescence, CENP-A and CENP-B ELISA. Clin Chim Acta. 2011 Oct 9; 412(21–22):1937–43. [PubMed: 21756890]
12. Fritzler MJ, Rattner JB, Luft LM, Edworthy SM, Casiano CA, Peebles C, et al. Historical perspectives on the discovery and elucidation of autoantibodies to centromere proteins (CENP) and the emerging importance of antibodies to CENP-F. Autoimmun Rev. 2011 Feb; 10(4):194–200. [PubMed: 20933614]
13. Gelber AC, Pillemer SR, Baum BJ, Wigley FM, Hummers LK, Morris S, et al. Distinct recognition of antibodies to centromere proteins in primary Sjögren's syndrome compared with limited scleroderma. Ann Rheum Dis. 2006 Aug; 65(8):1028–32. [PubMed: 16414973]
14. Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum. 1980 May; 23(5):581–90. [PubMed: 7378088]
15. Kitagawa T, Shibasaki K, Toya S. Clinical significance and diagnostic usefulness of anti-centromere antibody in Sjögren's syndrome. Clin Rheumatol. 2012 Jan; 31(1):105–12. [PubMed: 21670951]

16. Osial TA Jr, Whiteside TL, Buckingham RB, Singh G, Barnes EL, Pierce JM, et al. Clinical and serologic study of Sjögren's syndrome in patients with progressive systemic sclerosis. Arthritis Rheum. 1983 Apr; 26(4):500–8. [PubMed: 6838673]

Significance and Innovations

- Anti-centromere antibodies (ACA) define a subset of primary Sjögren's syndrome (SS) with a unique phenotype, including features of limited cutaneous systemic sclerosis and a lower frequency of anti-SSA/-SSB antibodies.
- ACA were present in 82 (6%) of the 1361 primary SS subjects in the Sjögren's International Collaborative Clinical Alliance (SICCA) registry. This is the largest series of ACA-positive SS patients studied to date.
- We demonstrate that exocrine gland disease is more severe in ACA-positive as compared to ACA-negative primary SS subjects, as indicated by greater degrees of labial gland biopsy inflammation and worse excretory function.

Table 1

Demographic and phenotypic features of SICCA participants classified with primary Sjögren's syndrome, stratified by presence or absence of anti-centromere antibodies

Feature	SS by ACR		
	ACA positive (n=82)	ACA negative (n=1279)	p-value[1]
Categorical variables[2]	**N (%)**	**N (%)**	
Female	80 (99)	1189 (93)	0.0379
Caucasian	24 (30)	576 (45)	0.0077
Dry mouth symptoms	77 (95)	1145 (90)	0.1289
Dry eye symptoms	74 (91)	1071 (84)	0.0826
Parotid gland enlargement on exam	18 (22)	245 (19)	0.5635
Joint pain or swelling	37 (45)	689 (54)	0.1380
ANA≥1:320	82 (100)	715 (56)	<0.0001
Anti-SSA or -SSB	24 (29)	1047 (82)	<0.0001
Rheumatoid factor	32 (39)	768 (60)	0.0003
IgG>1445 mg/dL	25 (30)	738 (58)	<0.0001
C4< 16 mg/dL	10 (12)	232 (18)	0.2321
WBC≤4000/mm^3	13 (16)	288 (23)	0.1715
Schirmer's ≤5 mm/5 min	58 (71)	657 (52)	0.0013
UWS <0.1 ml/min	78 (95)	757 (59)	<0.0001
Focus score ≥2	58 (71)	681 (53)	0.0020
F/SLS or SCS	34 (42)	455 (36)	0.2871
History of Raynaud's	51 (62)	359 (28)	<0.0001
Sclerodactyly	13 (16)	14 (1)	<0.0001
Dilated capillary loops	16 (20)	64 (5)	<0.0001
Matted telangiectasia	9 (11)	66 (5)	0.0390
Oral mucosal telangiectasia	12 (15)	83 (6)	0.0113
Continuous variables	**Median [25th, 75th percentile]**	**Median [25th, 75th percentile]**	
Age	59 [52,67]	52 [42,62]	<0.0001
Dry mouth duration	4.0 [1.8,10.3]	3.6 [1.3,8.9]	0.1886
Dry eye duration	5.6 (1.9,13.9)	4.3 [1.6,9.3]	0.1526
Maximum OSS	9.5 [6,11]	8.0 [5,11]	0.0122
Minimum Schirmer value	4 [2,6]	5 [3,9]	0.0003
UWS, ml/min	0.08 [0–0.29]	0.37 [0.09,0.81]	<0.0001
Focus score	2.8 [2.0,4.9]	2.5 [1.4,4.3]	0.0440

[1] Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables

[2] Denominators may vary due to missing observations for some variables.

Abbreviations: ACA: anti-centromere antibodies; ANA: antinuclear antibody; IgG: immunoglobulin G; C4: complement 4; F/SLS: focal/sclerosing lymphocytic sialadenitis; SCS: sclerosing chronic sialadenitis; UWS: unstimulated whole saliva

Table 2

Multivariate models assessing the association of selected phenotypic features of Sjögren's syndrome with salivary and lacrimal gland function outcome measures

A. "Unstimulated whole saliva flow <0.1 ml/min vs ≥0.1 ml/min"

Phenotypic feature	Unadjusted OR	P value	Adjusted OR (95% CI)	P value
Age ≥60 years	2.04 (1.60–2.62)	<0.0001	2.12 (1.64–2.77)	<0.0001
Female gender	2.14 (1.39–3.30)	0.0005	1.92 (1.23–3.02)	0.0043
Anti-SSA and/or -SSB	0.96 (0.74–1.26)	0.7909	1.35 (0.99–1.82)	0.0513
Focus score≥2	2.59 (2.07–3.25)	<0.0001	2.50 (1.98–3.15)	<0.0001
ACA	13.42 (5.54–44.18)	<0.0001	12.24 (4.91–41.02)	<0.0001

B. " Schirmer's <5 mm/5 min vs ≥5 mm/5 min"

Phenotypic feature	Unadjusted OR	P value	Adjusted OR (95% CI)	P value
Age ≥60 years	1.40 (1.11–1.77)	0.0041	1.46 (1.14–1.86)	0.0022
Female gender	1.02 (0.66–1.58)	0.9229	1.18 (0.76–1.84)	0.4694
Anti-SSA and/or -SSB	1.28 (0.98–1.66)	0.0663	1.55 (1.17–2.07)	0.0026
Focus score ≥2	2.02 (1.62–2.52)	<0.0001	1.97 (1.58–2.46)	<0.0001
ACA	2.21 (1.37–3.66)	0.0009	2.52 (1.50–4.36)	0.0004

Abbreviations: ACA: anticentromere antibody