

Anti-centromere antibody positive Sjogren's syndrome is associated with worse sicca symptoms than primary Sjogren's syndrome alone

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Abstract:

Objectives:

To determine whether positive ACA serology affects the severity of sicca symptoms in pSS patients.

Methods:

Evaluation to detect subjective and objective sicca symptoms included questionnaires, physical examination, and pathology. pSS was classified according the 2002 AECG criteria. All patients were evaluated for presence of anti-Ro, anti-La, and ACA serology. pSS patients were categorized into ACA+ SS and ACA- SS. The two groups were compared for measures of severity of oral and ocular sicca.

Results:

The pSS group had 446 patients, of whom 26 were ACA+ SS. Subjective ocular sicca measured 7.0 ± 2.4 (out of 10) in ACA+ SS and 6.4 ± 2.6 in ACA- SS ($p = 0.197$). Objective ocular sicca measured $3.2\text{mm} \pm 1.8\text{mm}/5$ mins in ACA+ SS and $4.2\text{mm} \pm 4.4\text{mm}/5$ mins in ACA- SS ($p = 0.038$).

Subjective oral sicca measured 8.5 ± 1.4 in ACA+ SS and 6.7 ± 2.4 in ACA- SS ($p < 0.001$). Objective oral sicca measured $0.1\text{mL} \pm 0.2\text{mL}/15$ mins in ACA+ SS and $0.4 \text{ mL} \pm 1.0\text{mL}/15$ mins in ACA- SS ($p < 0.001$).

Only 35% of ACA+ SS patients were anti-Ro or anti-La positive compared with 77% of the ACA- SS patients ($p < 0.001$). There was no significant difference in MSG fibrosis or focus scores between ACA+ SS and ACA- SS patients.

Conclusions:

ACA+ SS is associated with more severe objective ocular sicca and more severe subjective and objective oral sicca compared to ACA- SS. The majority of ACA+ SS patients meet AECG criteria for pSS despite negative serology for anti-Ro/La antibodies.

Introduction:

The purpose of our study was to determine whether the presence of anti-centromere antibodies (ACA) affects the severity of sicca signs and symptoms in patients diagnosed with primary Sjogren's syndrome (pSS).

Sjogren's syndrome (SS) is a chronic autoimmune disease that mainly affects the exocrine glands¹. Sicca symptoms of xerophthalmia (ocular dryness) and xerostomia (oral dryness) are the most prevalent symptoms in SS¹. In overlapping autoimmune disorders, there can be a clinical difference in severity to at least one of the diseases².

The American European classification criteria (AECG) for SS defined secondary Sjogren's syndrome as the presence of signs and symptoms of dry eyes or dry mouth in another well-defined major connective tissue disease³. In 2012, the American College of Rheumatology proposed new classification criteria for SS that challenged the distinction between primary and secondary Sjogren's syndrome⁴. With respect to SS, the terms "primary" and "secondary" have been controversial because overlap in connective tissue disease is common. It can often be unclear which disease occurred first, or if one was secondary to the other⁵⁻⁷. This is as true of Sjogren's as it is with any other connective tissue disease. The presence of anti-centromere antibody has been reported in 1.4-10.85%^{7,8,16,27} of patients with pSS. Many of these patients have overlap features of limited scleroderma.

Methods:

Patients who were found at pre-screening to have objective signs of dry eyes or dry mouth, positive anti-Ro or anti-La antibodies, or a history of parotitis were referred to the Multidisciplinary Sjogren's Clinic at University Health Network for further evaluation. All patients were evaluated according to a standardized protocol between 1992 and 2014. Evaluation included patients' global assessment of xerophthalmia and xerostomia on standardized 10cm Visual Analogue Scale (VAS).

Demographic features were collected for each patient in the study population. Data were collected on subjective and objective xerophthalmia and xerostomia in patients diagnosed with SS.

Xerophthalmia was objectively measured using the Schirmer's-1-test (S1T)⁹ and a van Bijsterveld scale for ocular staining using Rose-Bengal or Lissamine Green^{10,11}.

Unstimulated whole salivary flow (USSF)¹⁴ was measured twenty four hours off all anticholinergic or sympathomimetic medication. All patients evaluated had a minor salivary gland (MSG) biopsy and the results were assessed by the same pathologist according to protocol for presence of focal lymphocytic sialadenitis and a focus score was assigned. Degree of fibrosis was also graded. A score of 0 meant no fibrosis. A score of 3 meant confluent fibrosis. Extractable nuclear antigens (ENA) and ACA were assayed using the BioPlex Multiplex 2200 test kit which relies on indirect immunofluorescence.

For our purposes we counted each of the CREST manifestations (calcinosis, Raynaud's phenomenon (RP), esophageal dysmotility, sclerodactyly and telangiectasia) as a "feature" of limited scleroderma. All patients were evaluated for CREST manifestations by history and physical examinations. X-rays of the hands were performed in all patients. The protocols of this study adhered to the Declaration of Helsinki.

pSS was classified according the AECG Criteria³. Patients that met the pSS classification for Primary Sjogren's Syndrome were further categorized into ACA+ SS and ACA- SS. Groups were compared to determine differences in the prevalence of sicca symptoms, severity of sicca symptoms, and serological markers including IgG quantification and anti-Ro and anti-La antibodies.

A 2-tailed student t-test with heterogenous variance was used to evaluate statistical significance when comparing differences between groups. A p-value < 0.05 was considered statistically significant. All statistical analyses were conducted using SAS 9.3.

Ethics approval was received from the University Health Network Research Ethics Board at the University of Toronto for this study with submission number 19-5454.0. Patients' written consent was waived as patient data is anonymized and no personal details can be identified.

Results:

Of 609 patients evaluated at the Multidisciplinary Sjogren's Clinic, 446 met the AECG classification criteria for pSS. Within the pSS group (n = 446), there were 26 patients with positive ACA serology. These 26 patients (5.8% of pSS group) were designated as ACA+ SS. There were 420 patients without ACA (94.2% of pSS group) and these were designated as ACA- SS.

The demographic characteristics of the two patient groups (ACA+ SS, ACA- SS) are summarized in Table 1. The flow diagram for patient enrolment is summarized by Figure 1.

An additional 8 patients with ACA positivity were assessed in the Multidisciplinary Sjogren's Clinic because of complaints of dry eyes or mouth. These patients did not satisfy the AECG Classification Criteria for pSS. There was no statistically significant difference in the prevalence or severity of sicca symptoms among ACA+ patients regardless of whether criteria for pSS were met.

Among the 446 patients with pSS, on a VAS, the mean severity of ocular sicca symptoms was $7.0 \pm 2.4/10$ in ACA+ SS patients and $6.4 \pm 2.6/10$ in ACA- SS patients ($p = 0.197$). The mean S1T in ACA+ SS patients was $3.2\text{mm} \pm 1.8\text{mm}/5$ mins and in ACA- SS pts was $4.2\text{mm} \pm 4.4\text{mm}/5$ mins ($p = 0.038$). However, there was no difference in the mean van Bijsterveld score between ACA+ SS ($5.7 \pm 2.2/9$) and ACA- SS ($5.6 \pm 2.3/9$) ($p = 0.232$).

On a VAS, the mean score for severity of oral sicca symptoms was $8.5 \pm 1.4/10$ in ACA+ SS patients and $6.7 \pm 2.4/10$ in ACA- SS patients ($p < 0.001$). The mean value for USSF was $0.1\text{mL} \pm 0.2\text{mL}/15\text{min}$ for ACA+ SS and $0.4\text{mL} \pm 1.0\text{mL}/15$ mins for ACA- SS. While this difference is statistically significant ($p < 0.001$), there is an overlap in standard deviation between the two groups. Similarly, a greater number of ACA+SS patients had a focus score >1 (92%) compared with ACA-SS patients (84%). This difference was also highly significant ($p < 0.001$) (Table 1). However, there was no statistically significant difference in the mean focus score between the ACA+ SS (focus score 5.5) and ACA- SS (focus score 4.0) groups. There was no significant difference in either the mean fibrosis score or the duration of xerophthalmia or xerostomia between the ACA+ SS and ACA- SS groups.

The CREST features in ACA+ SS patients were not very severe or prevalent. Among ACA+ SS patients, 58% had two or fewer stigmata of CREST syndrome with RP and sclerodactyly being the predominant findings. Clinically, as expected, RP was more prevalent among ACA+ SS patients (88%) than ACA- SS patients (28%). This difference was highly significant ($p < 0.001$). There were no statistically significant differences between the two groups regarding extraglandular features such as dental problems (decayed, missing, or filled teeth), parotitis, parotid gland swelling, lymphoma, vasculitis, or hypothyroidism.

Serological differences:

Elevated IgG was seen in 24% of the ACA+ SS patients and 57% of the ACA- SS patients ($p < 0.001$). There was a significant difference in the level of IgG between the ACA+SS (12.4g/L) and ACA-SS (19.4g/L) groups ($p < 0.001$). Only 35% of the ACA+ SS patients had positive serology for anti-Ro or anti-La

antibodies compared with 77% of the ACA- SS patients ($p < 0.001$). Nonetheless these ACA positive patients met the AECG Classification Criteria for pSS, mainly based on an abnormal MSG biopsy.

Discussion:

The presence of overlapping autoimmune diseases is not uncommon in patients who are being evaluated for SS. There's no doubt that the presence of two overlapping autoimmune diseases influences one another. Scleroderma (SSc), as defined by clinical features such as sclerodactyly, overlapping with primary Sjogren's syndrome (SSc-SS) was characterised by milder SSc with a lower severity and prevalence of sclerodactyly, lung fibrosis, and systemic involvement⁷. In a French cohort, Salliot and her colleagues found that among the SSc-SS group ($n = 20$), there was a greater frequency of RP, objective xerophthalmia, peripheral neuropathy, arthritis, and additional autoimmune disorders, especially primary biliary cholangitis (PBC), compared to the SS group⁷. Similar to the ACA+ SS group in our study, they found that their SSc-SS patients had a statistically significant lower prevalence of specific autoantibodies including RF, anti-Ro, anti-La compared to SS patients⁷. In their cohort, SSc-SS overlap also displayed a classic SS phenotype with recurrent salivary gland enlargement, purpura, fatigue, arthralgia, and leukocytopenia^{7,8}.

ACA is positive mostly in patients with SSc with CREST features¹⁷ and has been detected in 50-96% of CREST syndrome patients¹⁶. The prevalence of ACA in SS has been reported to be 1.4-10.85%^{7,8,16,27}. In our cohort positive ACA was seen in 5.8% of our pSS patients. We have demonstrated that among pSS patients who are also ACA+, there is more severe dryness of the eyes as measured by the S1T, subjective xerostomia on VAS, and objective loss in saliva production (USSF). More ACA+ SS patients had a focus score >1 than in ACA- pSS patients.

Previous studies have shown that ACA+ SS patients have a lower prevalence of anti-Ro or anti-La antibodies¹⁸⁻²⁰ compared with ACA- SS^{21,22}. Among SSc-SS patients, there is a 21-33% prevalence of positive anti-Ro antibodies^{2,18,20}. Other groups have found that approximately 60% of their SSc patients with sicca symptoms were positive for anti-Ro antibodies^{2,19}. Our results show a similar prevalence of anti-Ro or anti-La antibodies in 35% of ACA+ SS patients.

The lower prevalence of anti-Ro and anti-La antibodies in the ACA+ SS group indicates that many of these patients depended upon the finding of a positive MSG biopsy to meet the AECG classification criteria. These are overlap cases and many would have been missed if classification as pSS depended upon the finding of anti-Ro/La antibodies (i.e.: it is necessary to do the MSG biopsy to diagnose many ACA+ patients as Sjogren's syndrome).

Avouac et al. notes that in biopsy samples from 50 (55%) of 91 patients with Systemic Sclerosis and sicca complaints, they observed fibrotic lesions (considered mild in 13, moderate in 17, and severe in 20), and samples from 18 of the 91 patients (20%) had a focus score ≥ 1 ². Even though there is more fibrotic minor salivary gland involvement in patients with systemic sclerosis with sicca², ACA+ SS patients are dry because of true inflammation in the salivary glands. Our results did not show a significant difference in MSG fibrosis between ACA+ SS and ACA- SS patients. We found a significantly higher proportion of ACA+ SS patients with focus score ≥ 1 (92% vs. 84%). However, there did not appear to be a difference between the focus scores of the ACA+ SS and ACA- SS patients.

This raises major questions about the essential difference between Progressive Systemic Sclerosis and ACA+ Limited Scleroderma, where the overlap with SS is more frequent than would be expected, and the MSG biopsy pathology is more like SS than like systemic sclerosis.

Sicca syndrome is common in systemic sclerosis (60%) and is associated with salivary fibrosis⁷, more severe disease, and a higher mortality rate². Abnormalities of collagen gene transcription may be

responsible for tissue and vascular fibrosis, causing glandular fibrosis in systemic sclerosis^{2,28}. The pathology in the ACA+ SS patients does not seem to follow this morphology.

A limitation of comparing the ACA+ SS and ACA- SS patients in our study is that there are relatively few ACA+ SS patients. Thus, each ACA+ SS patient represents a greater fraction of the overall ACA+ SS group. However, our results show there is a highly significant difference in severity of sicca symptoms and objective severity between the two groups.

Conclusion:

Our findings indicate that the presence of ACA is associated with more severe xerostomia symptoms in patients diagnosed with pSS. ACA+ SS is associated with objective measures of more profound xerostomia and xerophthalmia compared to ACA- SS. Furthermore, there is a higher prevalence of RP and a lower prevalence of anti-Ro and anti-La serology in ACA+ SS patients. Aside from a difference in RP prevalence, there were no statistically significant differences in extraglandular manifestations between the two groups.

Lastly, the majority of ACA+ SS patients meet the AECG criteria for pSS despite having negative serology for anti-Ro or anti-La antibodies. This may suggest that anti-Ro or anti-La serology may be less useful when trying to diagnose pSS in the presence of ACA+ patients. In view of an evolving potential therapeutic armamentarium for SS, and the finding of inflammatory rather than fibrotic pathology in ACA+SS, this study also highlights the importance of doing a MSG biopsy in ACA+ patients with objective evidence of decreased salivary flow, decreased Schirmer's test or abnormal Van Bijsterveld staining. We take note of the essential difference in pathology of the MSG biopsy in ACA+ patients with sicca complaints compared to Progressive Systemic Sclerosis patients with similar sicca symptoms.

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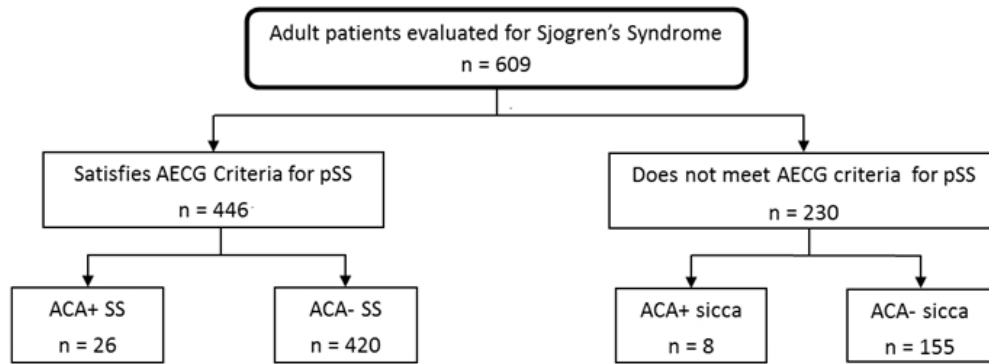


Figure 1: Flowchart for patient enrollment.

121x45mm (144 x 144 DPI)

Table 1: Comparison between ACA+ SS and ACA- SS.

	ACA+ SS (n = 26)	ACA- SS (n = 420)	p-value
Demographics			
Age, mean \pm STD (years)	55.7 \pm 10.5	53.2 \pm 13.4	NS
Sex			
Male	0	39	NS
Female	26	381	NS
Clinical Differences			
Prevalence of Raynaud's phenomenon (%)	88	28	p < 0.001
Serological Markers			
Prevalence of positive Ro/La antibodies (%)	35	77	p < 0.001
Prevalence of elevated serum IgG (%)	24	57	p < 0.001
Average levels of serum IgG (gm/L)	12.4	19.4	p < 0.001
Xerophthalmia			
Prevalence of xerophthalmia (%)	96	96	NS
Severity of xerophthalmia (on VAS, max 10)	7 \pm 2.4	6.4 \pm 2.6	NS
Average Rose Bengal score	5.7 \pm 2.2	5.6 \pm 2.3	NS
Schirmer's-1 test (mm/5 mins)	3.2 \pm 1.8	4.2 \pm 4.4	p < 0.05
Duration (range, years)	5.4 (0 – 20)	7.5 (0 – 50)	NS
Xerostomia			
Prevalence of xerostomia (%)	100	98	NS
Severity of xerostomia (on VAS, max 10)	8.5 \pm 1.4	6.7 \pm 2.4	p < 0.001
USSF (mL/15 mins)	0.1 \pm 0.2	0.4 \pm 1.0	p < 0.001
Duration (range, years)	5.8 (0 – 22)	6.8 (0 – 45)	NS
Salivary gland biopsy			
Focus Score \geq 1 (%)	92	84	p < 0.001
Average focus score	5.5 \pm 4.3	4.0 \pm 3.3	NS
Average fibrosis score (out of 3)	1.0 \pm 0.82	1.1 \pm 0.68	NS

Normal serum IgG levels are 7-16 g/L in healthy patients. VAS = visual analogue score. Rose-Bengal test evaluates ocular surface epithelial damage (out of 9). Schirmer's-1 test measures lacrimal gland production. USSF (unstimulated salivary flow; normal USSF \geq 1.5mm/15 min). Salivary gland biopsy positive result: \geq 1 focus per 4mm². NS: not significant.