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An Early View of the International Sjögren's Syndrome Registry

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Introduction

Of the major autoimmune connective tissue diseases, Sjögren's syndrome (SS) is perhaps the least well understood. Both primary and secondary forms of SS occur, but their phenotypes are not well defined. At least 10 sets of diagnostic/classification criteria for SS have been applied since 1965 (1–11), but none to date have been universally adopted or accepted by the American College of Rheumatology. These criteria have often identified patients with similar clinical features, but not necessarily with a common disease process. There is little longitudinal data on SS. The absence of recognized classification criteria contributes to delays in diagnosis for individual patients and hampers SS research due to small sample sizes and heterogeneously diagnosed patient populations.

To address these issues, the ongoing Sjögren's International Collaborative Clinical Alliance (SICCA) was funded under a US National Institutes of Health (NIH) contract beginning in 2003. The goals of the SICCA project are: design and implement an international SS registry for collecting and storing clinical data and biospecimens, develop standardized classification/diagnostic criteria for SS that are universally applicable, and provide these resources for future studies of SS funded by the NIH or comparable agencies.

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Subjects and Methods

SICCA is an ongoing longitudinal multisite observational study that is developing and studying a large and growing cohort of uniformly evaluated individuals from ethnically diverse populations to achieve the goals previously mentioned. SICCA participants must be at least 21 years old and have at least 1 of the following: symptoms of dry eyes or dry mouth; a previous suspicion or diagnosis of SS; elevated serum antinuclear antibodies (ANA), positive rheumatoid factor (RF), anti-SSA, or anti-SSB; bilateral parotid enlargement in a clinical setting of SS; a recent increase in dental caries; or have diagnoses of rheumatoid arthritis or systemic lupus erythematosus and possibly have secondary SS. Individuals are enrolled using broad criteria to create a cohort reflecting a wide range of symptoms or signs, from possible early SS to well-established disease. However, to avoid circular reasoning in developing a new definition of SS, no diagnostic labels are used at study entry even for participants previously diagnosed with primary SS.

SICCA recruits participants using announcements in patient support group publications and public media, and from patients referred by intramural and extramural practices or clinics with populations meeting these enrollment criteria. Enrollment began in the fall of 2004 at 6 international SICCA Research Groups that recruit, enroll, and examine participants, and collect and ship biospecimens to the central repository in San Francisco. These groups are located at the University of Buenos Aires and German Hospitals, Buenos Aires, Argentina; the Peking Union Medical College Hospital, Beijing, China; the Copenhagen University Hospital, Glostrup, Denmark; Kanazawa Medical University, Ishakawa, Japan; the King's College London, London, UK; and the University of California at San Francisco. Members of the SICCA Research Groups are listed in Appendix A.

All SICCA groups use the same protocol-directed methods to provide uniform evaluations and record data from ocular, oral, and rheumatologic examinations and biospecimen collections. The latter include serum, DNA, whole and parotid saliva, tears, conjunctival cells, frozen and paraffin-embed-

ded labial salivary gland (LSG) biopsy specimens, peripheral blood mononuclear cells, and plasma from all participants and DNA from blood-related controls. SICCA participants who have any objective measures of salivary hypofunction, ocular dryness, any focal lymphocytic infiltration in their LSG biopsy specimen, or positive anti-SSA or anti-SSB (95.3% of the cohort so far) at their baseline examination, are being recalled 2 years later to repeat all examinations and specimen collections. Participants with no positive objective tests are not recalled. This group may serve as controls in future analyses. SICCA clinical questionnaires, data collection forms, and protocols for clinical examination and specimen collection are available for review from the SICCA Web site (URL: http://sicca.ucsf.edu).

Early lessons from the SICCA project

Preliminary cohort-wide analyses of SICCA data have already provided new information about SS. Data from 1,208 baseline evaluations and 134 recall evaluations were available for these analyses. The demographic and SS-related phenotypic characteristics of the SICCA cohort at this stage are summarized in Table 1. Interestingly, positive responses to the questions, "Does your mouth feel dry?" or "Do your eyes feel dry?" were not statistically associated with the presence of focal lymphocytic sialadenitis (focus score >1), serum anti-SSA, anti-SSB, or ocular staining ≥3 (indicating keratoconjunctivitis sicca [KCS]). Responses to more specific questions such as, "Do you need to sip liquids to swallow dry foods?" or "Does your mouth feel dry when eating a meal?" (13) were associated with the presence of LSG biopsy focus scores >1 ($P = 0.001$ and $P = 0.007$, respectively), but had weaker or no associations with serum anti-SSA or anti-SSB ($P = 0.03$ and $P = 0.08$ respectively). Analysis of future followup examination data should reveal whether these symptomatic individuals develop signs of primary SS over time.

In the process of developing new classification criteria for SS, we use area-proportional Venn diagrams to visualize the interrelationship between various phenotypic characteristics of SS (14). Figure 1 illustrates the overlapping relationships of 3 objective SS signs in the cohort (72% exhibit positive ocular staining for KCS, 42% positive LSG biopsy specimen, 39% positive serum anti-SSA and/or anti-SSB, and 20% none of these). Interestingly, 3% of the participants had only an abnormal focus score, 2% had only a positive serology to anti-SSA or anti-SSB, whereas 28% had only an abnormal ocular staining score. The high proportion of participants with only abnormal ocular staining led us to compare this subgroup (termed KCS-only; n = 323) with those having KCS and at least 1 of the 2 other main phenotypic features of SS, specifically focal lymphocytic sialadenitis with a focus score >1 and/or anti-SSA or anti-SSB antibodies (termed SS-KCS; n = 510). KCS-only participants had significantly lower levels of serum autoantibodies (RF, ANA titer, IgG), better ocular physiologic tests (Schirmer's test, tear break-up time), more frequent use of anticholinergic drugs and/or cigarettes ($P < 0.0001$ for all), and were older ($P = 0.001$) compared with SS-KCS participants. This suggests that KCS-only cases may represent a distinct entity of seroneg-

Table 1. Demographic characteristics and Sjögren's syndrome (SS)–related phenotypic characteristics in 1,208 participants enrolled in the Sjögren's International Collaborative Clinical Alliance registry as of September 15, 2008*

Characteristics	Value†
Baseline enrollment sources	
Argentina	221 (18)
China	236 (20)
Denmark	231 (19)
Japan	184 (15)
UK (since May 2007)	55 (5)
US	281 (23)
Women	1,116 (93)
SS characteristics	
Dry mouth	1,093 (91)
Dry eyes	1,025 (85)
Both dry mouth and dry eyes	960 (80)
Positive anti-SSA/Ro	456 (39)
Positive anti-SSB/La	289 (25)
Positive anti-SSA and anti-SSB	285 (26)
Positive rheumatoid factor	468 (40)
Positive antinuclear antibody titer ≥1:40	787 (67)
Positive hepatitis C antibody (repeatedly positive)	15 (1)
Hypergammaglobulinemia (IgG >1,445 mg/dl)	484 (41)
Unanesthetized Schirmer's test ≤5 mm in 5 minutes	388 (33)
Tear break-up time <10 seconds	991 (83)
Ocular staining score ≥3 (max of left and right)‡	869 (72)
Unstimulated whole salivary flow <0.5 ml/5 minutes	666 (55)
Labial salivary gland biopsy specimen results	
Nonspecific/sclerosing chronic sialadenitis	409 (34)
Granulomatous inflammation/within normal limits	11 (1)
Inadequate specimen	26 (2)
Focal lymphocytic sialadenitis (n = 740)§	762 (63)
Score >1	500 (68)
Score 1	27 (4)
Score <1	213 (29)
Continuous variables	
Age, median (range) years	54 (21–90)
Unstimulated whole salivary flow rate, median (25th–75th percentile) ml/5 minutes	0.42 (0.13–0.93)
Stimulated parotid flow, median (25th–75th percentile) ml/minute	0.12 (0.03–0.26)

* Values are the number (percentage) unless indicated otherwise.
† Denominators vary due to missing observations (<3%) for some variables.
‡ Assessed by fluorescein staining of the cornea and lissamine green staining of the interpalpebral conjunctivae. A score ≥3 represents the presence of keratoconjunctivitis sicca.
§ Based on criteria from ref. 12.

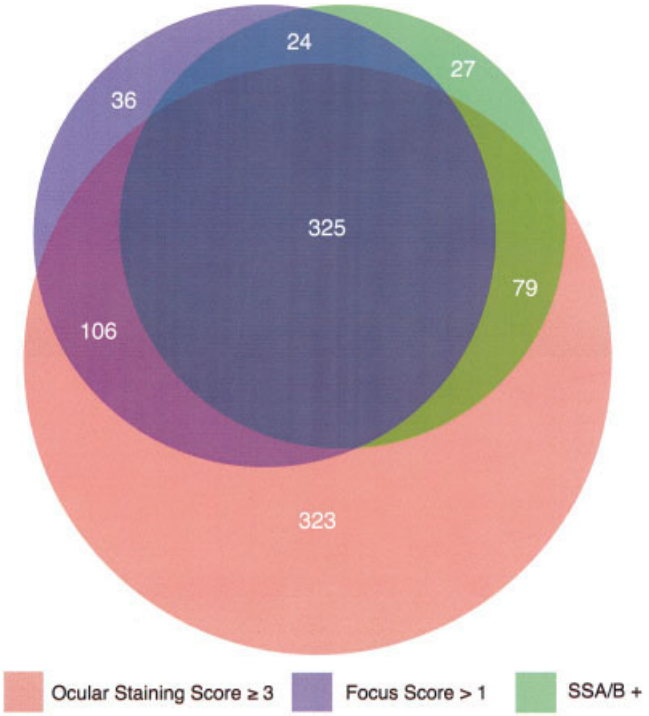

Figure 1. An area-proportional Venn diagram of the Sjögren's International Collaborative Clinical Alliance (SICCA) cohort (n = 1,156) illustrates the partially overlapping relationships of 3 objective signs of Sjögren's syndrome: positive serum anti-SSA or SSB, labial salivary gland (LSG) biopsy specimens with focal lymphocytic sialadenitis and a focus score >1, and an ocular surface stain score ≥3.

ative KCS that is significantly less severe than SS-KCS. Additional recall data will allow us to explore if KCS-only subjects progress into SS-KCS or whether KCS-only is a disease entity distinct from SS.

Currently, 78% of baseline participants screened for followup completed the followup examinations (21% of whom declined a second biopsy), ~10% are being scheduled or waiting for followup examination, and 12% refused further participation. In preliminary analyses of LSG biopsy specimens (n = 108) after 2 years of followup, we found marked disease progression in 2 participants. One participant progressed from focal lymphocytic sialadenitis with a focus score of 4 foci/4 mm^2 at baseline to confluent follicular lymphocytic proliferation 2 years later. In the other participant, the baseline biopsy specimen demonstrated focal lymphocytic sialadenitis with a focus score of 9 foci/4 mm^2 and in 2 years the participant had progressed to marginal zone/mucosa-associated lymphoid tissue lymphoma with diffuse and homogenous B cell (CD20 positive) proliferation. The number of recall specimens will continue to increase for the duration of the registry, therefore providing valuable additional data related to this important issue.

There were no significant changes in the serologic and physiologic tests (e.g., salivary flow rates, Schirmer's test, and tear break-up time) during the 2-year period between baseline and followup examinations (n = 134 patients). Overall, there was no measurable progression or regression in this group, but this is preliminary data based on small numbers and only a 2-year followup time. However, there appears to be a subgroup of participants on a faster track of progression detectable through progression of their LSG biopsy specimen.

The data from recall examinations will inform the characterization of the natural history of SS through analysis of progression of individual symptoms and signs, assessing the onset of extra glandular diseases, and supporting validation of preliminary classification criteria developed from baseline examination data. Our ultimate goal is to provide reliable data and analysis from which to describe the phenotype of primary SS, new classification criteria for identifying the disease, and uniformly well-documented biospecimens for future research on SS.

AUTHOR CONTRIBUTIONS

Dr. Daniels 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 design. Daniels, Criswell, C. Shiboski, S. Shiboski, Schiødt, Greenspan.

Acquisition of data. Daniels, S. Shiboski, Lanfranchi, Dong, Schiødt, Umehara, Sugai, Challacombe, Greenspan.

Analysis and interpretation of data. Daniels, Criswell, C. Shiboski, S. Shiboski, Umehara, Sugai, Greenspan.

Manuscript preparation. Daniels, Criswell, C. Shiboski, S. Shiboski, Lanfranchi, Umehara, Sugai, Greenspan.

Statistical analysis. Daniels, C. Shiboski, S. Shiboski.

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APPENDIX A: PROFESSIONAL COLLABORATORS FOR THE SJÖGREN'S INTERNATIONAL COLLABORATIVE CLINICAL ALLIANCE

In addition to the authors, professional collaborators for the SICCA project and locations are the University of California, San Francisco: K. Sack, J. Whitcher, A. Wu, D. Greenspan, D. Cox, R. Jordan, Y. DeSouza, M. Rasmussen, N. McNamara, D. Lee, D. Drury, L. Scott; University of Buenos Aires and German Hospitals, Buenos Aires, Argentina: A. Heidenreich, C. Vollenweider, I. Adler, A. Smith, M. Gandolfo, P. M. Bisio, A. Keszler, A. Chirife, S. Daverio, V. Kambo; Peking Union Medical College Hospital, Beijing, China: Y. Zhao, M. Li, W. Zheng, J. Su, Q. Shi, Y. Wang, S. Tong, S. Zhang, J. Zhao, D. Du, J. Xiao, H. Wang, Q. Wu, C. Zhang, W. Meng; Copenhagen University Hospital, Glostrup, Denmark: P. Helin, S. Johansen, S. Jensen, P. Ibsen, T. Schnefeldt, A. Vang; Kanazawa Medical University, Ishikawa, Japan: K. Kitagawa, Y. Masaki, M. Tanaka, N. Ogawa, K. Shimoyama, T. Sawaki, K. Hagiwara, T. Nojima, N. Kurose, M. Hondo, M. Takahashi, T. Kawanami, K. Fujimoto; King's College London, London, UK: P. Shirlaw, B. Jacobs, B. Kirkham, G. Larkin, P. Morgan, E. Odell.

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