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ORIGINAL ARTICLE

Primary Sjögren's Syndrome as a Systemic Disease: A Study of Participants Enrolled in an International Sjögren's Syndrome Registry

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Objective. **To study the prevalence of extraglandular manifestations in primary Sjögren's syndrome (SS) among participants enrolled in the Sjögren's International Collaborative Clinical Alliance (SICCA) Registry.**

Methods. **A total of 1,927 participants in the SICCA registry were studied, including 886 participants who met the 2002 American–European Consensus Group (AECG) criteria for primary SS, 830 "intermediate" cases who had some objective findings of primary SS but did not meet AECG criteria, and 211 control individuals. We studied the prevalence of immunologic and hematologic laboratory abnormalities, specific rheumatologic examination findings, and physician-confirmed thyroid, liver, and kidney disease, as well as lymphoma among SICCA participants.**

Results. **Laboratory abnormalities, including hematologic abnormalities, hypergammaglobulinemia, and hypocomplementemia, frequently occurred among primary SS cases and were more common among the intermediate cases than among control participants. Cutaneous vasculitis and lymphadenopathy were also more common among primary SS cases. In contrast, the frequency of physician-confirmed diagnoses of thyroid, liver, and kidney disease and lymphoma was low and only primary biliary cirrhosis was associated with primary SS case status. Rheumatologic and neurologic symptoms were common among all SICCA participants, regardless of case status.**

Conclusion. **Data from the international SICCA registry support the systemic nature of primary SS, manifested primarily in terms of specific immunologic and hematologic abnormalities. The occurrence of other systemic disorders among this cohort is relatively uncommon. Previously reported associations may be more specific to select patient subgroups, such as those referred for evaluation of certain neurologic, rheumatologic, or other systemic manifestations.**

INTRODUCTION

Sjögren's syndrome (SS) is one of the most common autoimmune diseases, with an estimated prevalence of approximately 0.6% and a 20:1 female predilection (1,2). SS may occur in isolation and has been referred to as primary SS or in conjunction with another connective tissue disease, most commonly rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). This association is often termed secondary SS.

The cardinal features of SS, including keratoconjunctivitis sicca and salivary gland hypofunction, presumably result from progressive lymphocytic inflammation in affected exocrine glands. While the hallmark features of SS

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Significance & Innovations

- Although the hallmark features of primary Sjögren's syndrome (SS) include glandular manifestations, there is convincing evidence that primary SS is a systemic disease with various extraglandular manifestations (EGMs).
- We assess the prevalence of specific EGMs among more than 1,900 participants in the Sjögren's International Collaborative Clinical Alliance Registry.
- Our results support the systemic nature of primary SS, based primarily on the presence of several immunologic and hematologic abnormalities. We also find that the prevalence of specific organ manifestations in primary SS is relatively low, and these abnormalities may be more common among select patient subgroups.

are related to exocrine gland dysfunction, there is substantial evidence that primary SS is a systemic autoimmune process. Such evidence includes: 1) the frequent presence of autoantibodies (e.g., antinuclear antibodies [ANAs], SSA/Ro antibodies, and SSB/La antibodies), 2) the presence of SS in conjunction with other systemic connective tissue diseases, and 3) the reported association of SS with a number of extraglandular manifestations (EGMs).

There is extensive literature describing EGMs in SS. One of the earliest reported associations was the increased incidence of lymphoma in patients with SS (3–7). Several reports describe the occurrence of other EGMs, such as neurologic, pulmonary, and other organ-specific diseases. For example, renal tubular acidosis, thyroiditis, primary biliary cirrhosis, and autoimmune hepatitis are classically thought to be related to SS. However, the prevalence of these disorders among SS patients varies widely between cohorts, and the association of these EGMs with SS is less well defined.

In the current study, we describe the prevalence of EGMs among participants in the Sjögren's International Collaborative Clinical Alliance (SICCA) Registry (8) and we examine associations between EGMs and specific objective phenotypic features of SS. SICCA participants are recruited worldwide into a registry designed to support studies of etiologic factors and outcomes in SS. The registry also provides an opportunity to study EGM prevalence in individuals suspected to have SS, but who fail to meet the 2002 American–European Consensus Group (AECG) criteria for SS. The diversity of the collection in terms of ethnicity, recruitment source, and disease severity, in conjunction with the extensive data collected on each participant, provides a valuable resource for studying EGMs in SS.

PATIENTS AND METHODS

At the time of this study, 2,090 participants were enrolled in the SICCA registry. Complete details related to this registry have been described previously (8). In brief, inclusion in the SICCA registry requires at least 1 of the following: symptoms of dry eyes or dry mouth; prior suspicion/diagnosis of SS; positive serum anti-SSA, anti-SSB, rheumatoid factor (RF), or ANA; increase in dental caries; bilateral parotid gland enlargement; or a possible diagnosis of secondary SS. These broad inclusion criteria have resulted in a cohort of individuals with a wide range of symptoms and signs related to SS. Participants in the current study were enrolled at 9 SICCA sites within 7 countries, including Argentina (University of Buenos Aires and German Hospital, Buenos Aires), China (Peking Union Medical College Hospital, Beijing), Denmark (Rigshospitalet, Copenhagen), Japan (Kanazawa Medical University, Ishikawa), the UK (King's College London, London), India (Aravind Eye Hospital, Madurai), and the US (University of California, San Francisco, University of Pennsylvania, Philadelphia, and Johns Hopkins University, Baltimore, Maryland) (collaborators for the SICCA sites are shown in Appendix A). Because the presence of another connective tissue disease may confound findings related to EGMs, we excluded from this analysis participants with a diagnosis of SLE, RA, scleroderma (systemic sclerosis), or other connective tissue diseases (n = 132). We also excluded participants with incomplete key data required to determine their primary SS case status at the time of this study (n = 31), thereby leaving 1,927 participants included in the current study.

Every participant in the SICCA cohort undergoes a systematic and extensive assessment of symptoms and signs related to SS. Uniform protocol-driven data collection methods are used at each SICCA site for the completion of questionnaires, recording of findings from detailed rheumatologic, ocular, and oral examinations, and the acquisition of biospecimens. Complete details of SICCA enrollment forms, protocols and methods for physical examinations, and biospecimen collection may be found at http://sicca.ucsf.edu/.

Assessment of ocular and oral involvement. Ocular and oral symptoms are assessed during an interview and include 18 questions related specifically to oral symptoms and 10 questions related to ocular symptoms. Salivary gland dysfunction is assessed by measurement of unstimulated whole salivary (UWS) flow rate and by stimulated parotid flow rate. UWS <0.1 ml in 1 minute is considered to be a positive test for salivary hypofunction as established by Navazesh and colleagues (9). Each participant also undergoes a minor salivary gland biopsy, and the tissue is independently examined by 2 histopathologists calibrated in this assessment. In the first step, a histopathologic diagnosis is assigned to each specimen under 1 of 6 different categories: focal lymphocytic sialadenitis (FLS; with or without evidence of sclerosis), within normal limits, nonspecific chronic inflammation, sclerosing chronic sialadenitis, granulomatous inflammation, and (mucosa-associated lymphoid tissue) lymphoma (10). Only those specimens with the diagnosis of FLS are then assessed to determine the focus score, a semiquantitative measure of FLS noted in minor labial salivary gland biopsy specimens. Diagnoses of FLS with focus scores ≥ 1 focus per 4 mm^2 represent the salivary component of SS (11) and are strongly associated with the ocular and serologic components of SS and reflect SS autoimmunity (10).

Lacrimal dysfunction is assessed by performing the Schirmer test (<5 mm of wetting in 5 minutes is considered to be a positive test) (12) and calculating an ocular staining score (OSS). The OSS, which replaces the rose bengal score, is a new method of evaluating conjunctival and corneal damage due to keratoconjunctivitis sicca (13). The technique involves fluorescein staining of the cornea and lissamine green staining of the interpalpebral conjunctiva to calculate an OSS. The OSS may have a value ranging from 0 (no corneal or conjunctival staining detected) to 12 for each eye. OSS scores ≥3 are considered abnormal and represent keratoconjunctivitis sicca.

Classification of primary SS cases. The 2002 AECG criteria for primary SS (14) were applied to the cohort. The AECG criteria were defined for SICCA participants using the specified oral/salivary, ocular, and systemic components, substituting the SICCA OSS for rose bengal staining, and a definition of participant-reported ocular and oral symptoms based on questions most closely matching the corresponding questions used in the AECG criteria. The 886 participants (of 1,927) who met these criteria were classified as primary SS cases. The remaining 1,041 participants who did not meet AECG criteria for primary SS were classified into 2 groups on the basis of the presence (versus absence) of objective SS-related findings. More specifically, participants who met at least 1 of the following 4 objective criteria (n = 830) were classified as intermediate cases: 1) anti-SSA/SSB antibodies, 2) FLS with focus score ≥1, 3) OSS ≥3, and 4) UWS <0.1 ml/minute. Participants who met none of these objective criteria (n = 211) were classified as controls.

Assessment of EGMs. *Laboratory data.* Blood is collected from each SICCA participant at the time of enrollment for characterization of autoantibodies and quantification of immunoglobulin and complement levels. The ANA titer is determined by an immunofluorescence staining method. RF, C3, C4, and immunoglobulin (IgA, IgG, and IgM) levels are determined by immunoturbidimetric assays. Anti-SSA (Ro) and anti-SSB (La) are determined using a fully automated Luminex-based precoated multibead assay (Bioplex 2200 ANA screen). With the exception of the complete blood count, all laboratory tests for SICCA enrollees are performed by the same licensed laboratory (Quest Diagnostics).

Rheumatologic signs and symptoms. As part of the medical history, participants are asked a series of standardized questions related to rheumatologic symptoms. Rheumatologic questions assess symptoms of morning stiffness lasting more than 1 hour, as well as symptoms of joint pain and swelling. Each participant also undergoes a thorough rheumatologic examination to assess the following: 1) joint tenderness, synovitis, or deformities in the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and wrist and elbow joints, 2) cervical, axillary, or inguinal lymphadenopathy, and 3) evidence of Raynaud's phenomenon or cutaneous vasculitis.

Organ-specific diseases. As part of the medical history questionnaire that each participant completes upon entry, participants are asked about thyroid, liver, or kidney disease, and lymphoma. If a participant reports 1 or more of these conditions, details are sought from his/her treating physician. More specifically, information is requested from physicians about the following 8 disorders: Graves' disease, Hashimoto thyroiditis, interstitial nephritis, primary biliary cirrhosis, autoimmune hepatitis, renal tubular acidosis, glomerulonephritis, and lymphoma. Treating physicians are also asked to provide information about any other systemic disorders present.

Statistical analysis. Descriptive statistics were used to define the prevalence of EGMs among SICCA participants. Fisher's exact test was used to assess the association between presence of specific EGMs and primary SS status (primary SS versus intermediate cases versus controls). Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to describe the magnitude of the observed associations between case status and specific EGMs. All statistical analyses were performed using STATA 11 software (StataCorp LP).

RESULTS

Demographic characteristics of the 886 primary SS cases, 830 intermediate cases, and 211 controls are summarized in Table 1. In the primary SS group, as expected, most participants were women (95%), with a mean age at SICCA enrollment of 52 years. The ethnic distribution of the study sample reflects the geographic locations of the 9 international recruitment sites. There were fewer women and more current smokers in the intermediate case and control groups.

In Table 2 we summarize SS-related characteristics among participants, according to case status. The frequency of dry eye and dry mouth symptoms was high in each of the 3 groups, but the duration of dry eye and dry mouth symptoms was higher among primary SS cases. As

Table 1. Demographic characteristics of 1,927 SICCA participants*

	Primary SS (n = 886)	Intermediate (n = 830)	Control (n = 211)
Age, mean (range) years	52 (21–89)	55 (21–90)	52 (22–87)
Women, no. (%)	838 (95)	747 (90)	181 (86)
Ethnicity, no. (%)			
African	19 (2)	15 (2)	1 (0.5)
Asian/Pacific Islander	367 (41)	212 (26)	37 (18)
White	354 (40)	453 (55)	135 (64)
Hispanic	91 (10)	89 (11)	23 (11)
American Indian	10 (1)	9 (1)	4 (2)
Other	45 (5)	52 (6)	11 (5)
Smoking, no. (%)			
Current	30 (3)	115 (14)	32 (15)
Prior	239 (27)	262 (32)	60 (29)

* Primary Sjögren's syndrome (SS) cases are defined as participants in the Sjögren's International Collaborative Clinical Alliance (SICCA) cohort who meet 2002 American–European Consensus Group (AECG) criteria for primary SS. Intermediate cases are defined as participants who do not meet 2002 AECG criteria but who have at least 1 positive objective SS-related finding (see below for details). Controls are defined as participants who have normal or negative results for all 4 SS-related objective findings (negative anti-SSA and anti-SSB, focus score <1, ocular staining score <3, and unstimulated whole salivary flow >0.1 ml/1 minute).

Table 2. SS-related characteristics of 1,927 SICCA participants*

	Primary SS (n = 886)	Intermediate (n = 830)	Control (n = 211)
Symptoms			
Dry mouth	827 (93)	729 (88)	187 (89)
Dry eyes	773 (87)	688 (83)	176 (83)
Duration of dry mouth symptoms, no. years (range)	6.6 (0–66.5)	5.9 (0–60)	4.5 (0–54)
Duration of dry eye symptoms, no. years (range)	7.2 (0.1–66.5)	6.7 (0.1–60.4)	5.3 (0–47.6)
Serologic results			
Anti-SSA (Ro)	676 (76)	49 (6)	0
Anti-SSB (La)	435 (49)	26 (3)	0
Rheumatoid factor	528 (60)	121 (15)	19 (9)
Antinuclear antibody titer (≥1:320)	567 (64)	131 (16)	18 (9)
SS-related objective findings			
Ocular staining score ≥3	809 (91)	615 (74)	0
Schirmer test ≤5 mm/5 minutes (mean)	385 (43)	194 (23)	23 (11)
Unstimulated salivary flow rate <0.1 ml/1 minute	626 (71)	432 (52)	0
Focus score ≥1†	722 (81)	56 (7)	0

* Values are the number (percentage) unless indicated otherwise. See Table 1 for definitions of primary SS case, intermediate, and control groups. SS = Sjögren's syndrome; SICCA = Sjögren's International Collaborative Clinical Alliance Registry.
† Focal lymphocytic sialadenitis based on labial salivary gland biopsy with focus score ≥1 (10).

expected based on our case definitions, the frequency of autoantibodies or abnormalities of objective ocular or oral test results was much higher in the primary SS group and lowest in the control group. In the intermediate group, an abnormal OSS was the most common finding (74%), followed by decreased UWS flow rate (52%).

Table 3 reports the frequency of each histopathologic category among the 3 groups of participants. Among the 1,160 (60%) participants with either of the diagnoses of FLS, 777 (67%) had a focus score ≥1. In 25 cases we were unable to calculate the focus score due to inadequate size of the glandular tissue biopsy sample.

Table 4 summarizes the frequency of EGMs assessed in this study, according to case status. Laboratory abnormalities occurred frequently among primary SS cases and were more common among the intermediate cases than the controls. Most of the differences in laboratory abnormalities were highly statistically significant and easily surpassed even a very conservative Bonferroni correction for multiple comparisons. Among the 64% of primary SS cases with an ANA titer ≥1:320, the most common pattern was speckled (59%), followed by SSA (21%) and centromere patterns (10%). Among the 60% of primary SS cases with a positive RF test, the mean titer was 109 IU/ml.

Joint symptoms occurred commonly among all SICCA participants, regardless of case status, with approximately one-third of SICCA participants reporting joint stiffness lasting more than 1 hour and 60% reporting joint pain and/or swelling (data not shown). Among individuals with synovitis documented on rheumatologic examination, the most common sites were the wrists (30%), PIP (28%), MCP (22%), and elbow joints (20%). Cutaneous vasculitis ($P < 10^{-5}$) and lymphadenopathy ($P = 0.022$) were more commonly observed among primary SS cases, although the association with lymphadenopathy should be interpreted with caution given the number of examination findings compared (Table 4).

Prevalence of extraglandular disorders. The prevalence of physician-confirmed diagnoses of 8 specific extraglandular disorders assessed is summarized in Table 4. Among all SICCA participants at the time of study entry, 450 participants reported a diagnosis of thyroid, liver, or kidney disease, and/or lymphoma. Of these, we were able to obtain either confirmation or rejection of the reported diagnosis from the treating physicians for 365 (81%) participants. Although the overall frequency of these disorders was low, we observed significant differences in the frequency of primary biliary cirrhosis among the 3 case groups ($P = 0.033$). However, given the number of EGMs assessed, this association should be interpreted with caution.

Associations between EGMs and objective SS-related manifestations. To determine whether certain EGMs among the primary SS cases were associated with specific SS-related objective criteria, we compared the prevalence of EGMs among the 886 primary SS cases defined on the basis of presence (versus absence) of the 4 SS-related objective findings that are included in the AECG criteria (SSA and/or SSB antibodies, focus score ≥1, OSS ≥3, and UWS flow rate <0.1 ml/minute). The results of these analyses are shown in Table 5.

Overall, the pattern of association results suggests that a decreased UWS flow rate is less strongly associated with the presence of EGMs than the other 3 objective criteria assessed. The similarity in association results across these 3 objective findings is not unexpected given the strong associations among these objective findings, as reported previously (8). Among all participants in the SICCA cohort, the OR describing the association of an OSS ≥3 with the presence of SSA and/or SSB antibodies is 4.3 (95% CI 3.3–5.6, $P = 9.1 \times 10^{-33}$). Similarly, the OR describing the association between the presence of FLS (i.e., focus score ≥1) and the presence of these antibodies is 10.0 (95% CI

Table 3. Histopathologic patterns in minor salivary gland biopsy tissue among 1,927 SICCA participants*

Histopathologic pattern	Primary SS (n = 858)	Intermediate (n = 828)	Controls (n = 211)	Total
Focal and focal/sclerosing lymphocytic sialadenitis				
Focus score ≥1	721 (84)	56 (7)	0 (0)	777 (40)
Focus score <1	62 (7)	232 (28)	64 (30)	358 (19)
Within normal limits	3 (<1)	20 (2)	6 (3)	29 (2)
Nonspecific chronic inflammation/sclerosing chronic sialadenitis	71 (8)	520 (63)	141 (67)	732 (38)
Mucosa-associated lymphoid tissue	1 (<1)	0	0	1 (<1)

* Values are the number (column percentages). At the time of this report, there were 25 focal lymphocytic sialadenitis cases with insufficient glandular tissue to determine a focus score. There were 3 cases with granulomatous inflammation and 2 cases with missing biopsy sample tissue. SICCA = Sjögren's International Collaborative Clinical Alliance Registry; SS = Sjögren's syndrome.

8.1–12.4, $P = 1.6 \times 10^{-116}$). In contrast, associations between these objective criteria and symptoms of dry eyes or mouth are much weaker and not statistically significant, with the exception of an association of dry eye symptoms with an OSS ≥3.

Association between EGMs and focus score. To determine whether specific EGMs were associated with high focus score values, we classified each SICCA participant with FLS according to the value of the focus score (≥1 to 3 for low, ≥3 to 6 for moderate, and ≥6 for high) and examined associations with EGMs. We found that higher focus score values were associated with RF positivity, ANA titers ≥1:320, hypergammaglobulinemia (IgG), hypocomplementemia (low C4), and anemia.

Analysis of EGMs and symptom duration among primary SS cases. To evaluate the relationship between duration of dry eye or mouth symptoms and EGMs, we compared the frequency of EGMs between primary SS cases with self-reported symptom duration (either dry eye or dry mouth symptoms) >10 years (n = 224) versus those re-

Table 4. Extraglandular manifestations among 1,927 SICCA participants*

Characteristic	Primary SS (n = 886)	Intermediate (n = 830)	Control (n = 211)	*P*†
Laboratory tests				
RF positivity	528 (60)	121 (15)	19 (9)	1.4×10^{-03}
ANA titer ≥1:320	567 (64)	131 (16)	18 (9)	1.5×10^{-117}
IgG >1,760 mg/dl	347 (39)	38 (5)	3 (1.4)	3.7×10^{-89}
IgA >463 mg/dl	77 (9)	18 (2)	4 (2)	3.4×10^{-10}
IgM >368 mg/dl	28 (3)	20 (2)	3 (1)	0.359
C3 <90 mg/dl	139 (16)	118 (14)	34 (16)	0.632
C4 <16 mg/dl	163 (18)	80 (10)	21 (10)	2.6×10^{-7}
WBCs <4,000/mm^3	197 (22)	53 (6)	8 (4)	6.1×10^{-26}
Anemia‡	178 (20)	78 (9)	15 (7)	8.3×10^{-12}
Platelet count <140,000/μl	48 (5)	23 (3)	3 (1)	0.003
Physical examination findings				
Joint synovitis on examination	74 (8)	80 (10)	15 (7)	0.453
Raynaud's phenomenon	127 (14)	91 (11)	23 (11)	0.089
Cutaneous vasculitis	34 (4)	5 (1)	3 (1)	9.3×10^{-6}
Lymphadenopathy	66 (8)	37 (5)	9 (4)	0.022
Confirmed diagnoses				
Graves' disease	21 (2.4)	10 (1.0)	1 (0.5)	0.075
Hashimoto thyroiditis	47 (5.3)	46 (6.0)	7 (3.0)	0.451
Interstitial nephritis	2 (0.2)	1 (0.1)	0	1.0
Primary biliary cirrhosis	17 (1.9)	5 (1.0)	1 (0.5)	0.033
Autoimmune hepatitis	9 (1.0)	5 (1.0)	0	0.312
Renal tubular acidosis	4 (0.5)	1 (0.1)	0	0.521
Glomerulonephritis	3 (0.3)	4 (0.5)	1 (0.5)	0.782
Lymphoma	5 (0.6)	3 (0.4)	0	0.679

* Values are the number (percentage) unless indicated otherwise. Primary Sjögren's syndrome (SS) cases are defined as participants in the Sjögren's International Collaborative Clinical Alliance (SICCA) Registry cohort who meet 2002 American–European Consensus Group (AECG) criteria for primary SS. Intermediate cases are defined as participants who do not meet 2002 AECG criteria but who have at least 1 positive objective SS-related finding (see below for details). Controls are defined as participants who have normal or negative results for all 4 SS-related objective findings (negative anti-SSA and anti-SSB, focus score <1, ocular staining score <3, and unstimulated whole salivary flow >0.1 ml/1 minute). RF = rheumatoid factor; ANA = antinuclear antibody; WBCs = white blood cells.
† By Fisher's exact test.
‡ Anemia is defined as hemoglobin <12 gm/dl in female participants and <13 gm/dl in male participants.

Table 5. Association of EGMs with SS-related objective criteria in 886 primary SS cases*

	SSA/SSB positive	FS ≥1	OSS ≥3	UWS <0.1 ml/1 minute
No. (%)	693 (78)	720 (81)	809 (91)	626 (71)
Laboratory tests				
RF positivity	5.6 (3.9–8.1)	3.1 (2.1–4.6)	3.6 (2.1–6.2)	1.6 (1.2–2.2)
ANA titer ≥1:320	2.3 (1.6–3.2)	2.7 (1.8–4.0)	3.2 (1.9–5.4)	1.6 (1.2–2.2)
IgG >1,760 mg/dl	5.8 (3.7–9.6)	3.8 (2.3–6.4)	3.4 (1.8–6.8)	ns
IgA >463 mg/dl	2.0 (1.0–4.4)	2.8 (1.1–9.1)	ns	ns
IgM >368 mg/dl	0.3 (0.1–0.6)	ns	ns	3.5 (1.1–18.4)
C3 <90 mg/dl	2.2 (1.3–4.0)	ns	2.3 (1.0–6.6)	ns
C4 <16 mg/dl	1.9 (1.2–3.2)	ns	2.8 (1.2–8.0)	ns
WBCs <4,000/mm^3	4.6 (2.6–8.8)	ns	ns	ns
Anemia†	2.6 (1.5–4.4)	ns	2.7 (1.2–7.0)	ns
Platelets <140,000/μl	ns	4.6 (1.2–39.7)	ns	ns
Physical examination findings				
Joint synovitis	0.5 (0.3–0.9)	ns	ns	ns
Raynaud's phenomenon	0.5 (0.3–0.8)	2.1 (1.1–4.5)	ns	ns
Cutaneous vasculitis	ns	ns	ns	ns
Lymphadenopathy	ns	ns	ns	ns

* Values are the odds ratio (95% confidence interval) unless indicated otherwise and are shown if $P < 0.05$. EGMs = extraglandular manifestations; SS = Sjögren's syndrome; FS = focus score; OSS = ocular staining score; UWS = unstimulated whole salivary flow rate; RF = rheumatoid factor; ANA = antinuclear antibody; ns = not significant; WBCs = white blood cells.
† Anemia is defined as hemoglobin <12 gm/dl in female participants and <13 gm/dl in male participants.

porting symptoms for <10 years (n = 492). Patients with symptom duration >10 years were more likely to have a positive ANA with a titer ≥1:320 (71% versus 61%; $P = 0.008$) and joint stiffness for >1 hour in the morning (35% versus 28%; $P = 0.041$), even after controlling for age. However, we did not observe significant differences in other immunologic or hematologic laboratory values, physical examination findings, or other rheumatic complaints based on symptom duration. Among the SS-related objective findings, participants with symptom duration >10 years were more likely to have a decreased UWS compared to those with symptom duration <10 years (82% versus 68%; $P < 0.005$). The other 3 objective SS-related criteria, SSA/SSB positivity, lymphocytic sialadenitis (focus score ≥1), and OSS ≥3, were not associated with symptom duration >10 years.

Analysis of EGMs and age among primary SS cases. To assess the relationship between the presence of EGMs and age, we compared the frequency of EGMs between primary SS cases who were age >65 years (n = 149) and those who were age ≤65 years (n = 734) at study entry. We found that primary SS patients who were age >65 years were less likely to be RF positive (52% versus 61%; $P = 0.05$), less likely to have hypergammaglobulinemia (31% versus 41%; $P = 0.020$), and less likely to have leukopenia, defined as white blood cell count <3,800/mm^2 (11% versus 18%; $P = 0.035$). These patients were also less likely to have anti-SSA or anti-SSB autoantibodies (68% versus 80%; $P = 0.001$), but they were more likely to have a decreased UWS flow rate (87% versus 67%; $P < 0.005$). We did not find significant differences in other laboratory abnormalities, physical examination findings, joint symptoms, or other SS-related characteristics according to age.

Neurologic symptoms. Participants in SICCA do not undergo objective neurologic testing. However, each participant is asked a series of questions related to neurologic symptoms during the medical interview. Forty-four percent of primary SS cases reported neurologic motor symptoms and 53% of primary SS cases reported neurologic sensory symptoms. In the control group, 60% of participants reported neurologic motor symptoms and 75% reported neurologic sensory symptoms, suggesting that these symptoms do not help distinguish primary SS cases from control individuals.

DISCUSSION

SS is a systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands and a range of extraglandular features. In this study, we analyzed data collected systematically from 1,927 participants enrolled in the international SICCA registry. The depth and breadth of data collected on both primary SS and non–primary SS participants allowed us to study many EGMs reportedly associated with SS based on application of the AECG criteria, as well as by specific objective features of SS.

Our results document a strong association between primary SS and certain immunologic findings such as hypergammaglobulinemia, low C4 levels, and certain autoantibodies. We also find that hematologic abnormalities (leukopenia, anemia, and thrombocytopenia) are common and significantly associated with primary SS case status, as was the physical examination finding of cutaneous vasculitis. These findings highlight clinically important EGMs in primary SS. However, our results also suggest that the prevalence of EGMs such as thyroid, liver, and kidney disease may be lower than reported previously. Further, although rheumatologic symptoms may be com-

mon among primary SS patients, these symptoms were not significantly more frequent among individuals with primary SS, at least when compared to non–primary SS individuals who underwent the same extensive process of phenotypic characterization but did not meet AECG or other objective criteria for primary SS.

This study provides an opportunity to examine EGMs in the context of salivary gland histopathology. In those patients with a diagnosis of FLS, we examined the relationship between the degree of salivary gland inflammation, measured by the focus score, and the presence of EGMs. Individuals with higher focus scores were more likely to have anemia and certain immunologic abnormalities. Additional details of relationships between salivary gland histopathology and phenotypic characteristics of SS among this cohort were recently reported (10).

Prior reports of EGMs in SS have consisted primarily of descriptions of case cohorts comprised exclusively of primary SS patients. For example, Ramos-Casals et al (15) described the presence of certain EGMs among a cohort of 1,010 Spanish patients with SS. Ramos-Casals et al employed laboratory studies and detailed objective tests to document the frequency of immunologic, lung, peripheral nerve, and renal abnormalities. Similarly, Skopouli et al (16) characterized specific lung, peripheral nerve, renal, and liver abnormalities in a sample of 261 Greek patients with primary SS seen between 1981 and 1995 and studied at 6-month intervals. These studies lacked comparative or control data, and therefore were limited in their ability to quantify associations of specific abnormalities with SS.

Comparison of EGMs reported for different primary SS cohorts also reveals substantial variability. For example, Raynaud's phenomenon was described in 48% of the Greek cohort, 18% of the Spanish cohort, and 14% of the SICCA primary SS cases. Similarly, arthritis was detected in 23% of Greek, 15% of Spanish, and only 9% of SICCA primary SS cases. Possible reasons for these differences include variation in the specific populations studied, recruitment sources, and methods for assessing EGMs. Further, the definition of SS has been evolving over the past several decades, introducing another potentially important source of variation in prior studies of EGMs in primary SS. The various criteria employed in these and other studies encompass a wide range of symptoms, signs, and disease severity. Thus, it is difficult to assess the comparability of SS case groups without additional details of specific disease features. Indeed, this lack of specificity led us to examine the association between EGMs and more specific, objective disease features (Table 5).

The association of neurologic disorders with primary SS has attracted a lot of attention as a result of prior reports, such as those by Delalande et al (17) and Mori et al (18). Data from the SICCA registry indicate a very high frequency of neurologic motor and sensory symptoms in primary SS patients. However, we noted a similarly high frequency of neurologic symptoms among non–primary SS participants. A limitation of the SICCA collection is the lack of objective neurologic testing on participants. Thus, the prevalence of neurologic involvement in primary SS remains unclear.

Strengths of the current study include the large size and international nature of the SICCA cohort. Participants are recruited from a wide range of clinical and nonclinical sources, including rheumatologic, ophthalmologic, oral medicine, and various lay and patient organizations. The availability of a subset of participants with a high prevalence of nonspecific symptoms of dry eyes and dry mouth but absence of objective findings to support SS is a unique feature of the SICCA collection.

A limitation of the current study is the lack of a completely healthy (asymptomatic) control group of individuals. Although it would be of interest to study such a group, it is not feasible to assemble a sufficiently large, population-based control group characterized by the breadth of relevant variables, including the objective serologic, ocular, and oral measures obtained as part of this study. On the other hand, the diversity of the SICCA cohort should enhance the representativeness of the primary SS cases because it minimizes the selection bias that can result from enrolling patients only at certain sites or based on specific criteria, such as presence of neurologic or other systemic manifestations.

The large size and international nature of the SICCA registry strengthened our analysis, but also limited our ability to carefully characterize some of the EGMs. For example, we were not able to review details of some of the disorders, such as thyroid function tests or antibodies, or results of renal or liver biopsy. Instead, we had to rely on the confirmation of diagnoses by treating physicians. We also did not perform screening tests of serum or urine to identify new diagnoses of renal tubular acidosis or other disorders. For these reasons, we may have underestimated the prevalence of some systemic disorders. In particular, the prevalence of subclinical disease such as hypothyroidism may be underestimated because participants were not specifically screened for these conditions. However, the use of self-report diagnoses of thyroid and other disorders is common in large studies, such as the National Health and Nutrition Examination Study (19), and a strength of the current study was the systematic effort to confirm all reported diagnoses of thyroid and other conditions by treating physicians.

Although the duration of symptoms at the time of SICCA enrollment was substantial (6 to 7 years on average), the current analyses were limited to prevalent data at the time of enrollment. Some of these individuals may still develop one or more of these EGMs in the future. Previous studies suggest that at least some of these disorders, such as lymphoma, may not occur until many years of disease have elapsed (6,20). Although followup data on SICCA participants are currently limited, a subset of patients is being recalled after 2 years for a complete reevaluation. These followup data may improve our ability to capture incident cases of rare conditions such as lymphoma and primary biliary cirrhosis.

In conclusion, data from the international SICCA registry support the systemic nature of primary SS, manifest primarily in terms of specific autoantibody production and various immunologic and hematologic abnormalities. The concurrence of other systemic disorders among this cohort is relatively uncommon and previously reported associations may be more specific to select patient subgroups, such as those referred for evaluation of neurologic, rheumatologic, or other systemic manifestations. Longer-term

followup of patients in the SICCA registry and other primary SS populations will increase our understanding of rarer extraglandular features in primary SS.

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. Criswell 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. Malladi, Sack, Stephen C. Shiboski, Caroline H. Shiboski, Helin, Kirkham, Vollenweider, Greenspan, Daniels, Criswell.

Acquisition of data. Sack, Baer, Banushree, Dong, Helin, Kirkham, Li, Umehara, Vivino, Vollenweider, Zhang, Zhao, Greenspan, Daniels, Criswell.

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APPENDIX A: SJÖGREN'S INTERNATIONAL COLLABORATIVE CLINICAL ALLIANCE

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