

Sjögren Syndrome in Systemic Lupus Erythematosus: A Subset Characterized by a Systemic Inflammatory State

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ABSTRACT. Objective. An often-neglected subset of patients with systemic lupus erythematosus (SLE) is those with secondary Sjögren syndrome (SLE-sSS). Further, primary SS overlaps and can be difficult to delineate from SLE. To shed light on the SLE-sSS subset, we investigated a large and well-characterized SLE cohort, comparing patients with SLE-sSS and SLE patients without SS (SLE-nonsSS) and controls.

Methods. We included 504 consecutive patients with SLE, fulfilling the 1982 revised American College of Rheumatology criteria, and 319 controls from the general population, matched for age and sex to the first 319 patients. SLE-sSS was defined according to the American-European Consensus Criteria (AECC). A thorough clinical examination, including subjective and objective quantifications of sicca symptoms, was performed in all participants. Autoantibodies and 20 selected cytokines were measured by luminex and multiplex analysis, respectively.

Results. SLE-sSS, as defined by AECC, occurred in 23% of the patients with SLE. In comparison to SLE-nonsSS, the SLE-sSS group was older and more frequently female. Leukopenia and peripheral neuropathy were more frequent and nephritis less frequent. Circulating levels of 6/20 investigated proinflammatory cytokines [tumor necrosis factor- α , interleukin (IL) 6, monocyte chemoattractant protein 4, macrophage inflammatory protein 1 β , IL-12/IL-23p40, and interferon γ -induced protein 10], total IgG, anti-SSA/Ro52, anti-SSA/Ro60, anti-SSB/La antibodies, and rheumatoid factor (IgM and IgA) were higher in the SLE-sSS group ($p < 0.05$ for all comparisons).

Conclusion. The frequency of SLE-sSS increased with age and affected roughly one-quarter of all patients with SLE. Despite less internal organ involvement, a systemic inflammatory state with high levels of proinflammatory cytokines is present in the SLE-sSS subgroup. This is a novel observation that may affect future understanding and treatment of the SLE-sSS subset. (First Release April 15 2020; J Rheumatol 2020;47:865–75; doi:10.3899/jrheum.190250)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS SJÖGREN SYNDROME SICCA SYMPTOMS
SJÖGREN SYNDROME ANTIGEN A SJÖGREN SYNDROME ANTIGEN B CYTOKINES

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Systemic lupus erythematosus (SLE) is a chronic autoimmune systemic disease characterized by enhanced auto-antibody production and formation of immune complexes. SLE is also a very heterogeneous condition involving many organ systems, and disease activity varies from persistently mild to life-threatening¹. A state of systemic inflammation, often associated with complement consumption, enhanced activity in the type I interferon system, as well as high levels of proinflammatory cytokines [e.g., tumor necrosis factor- α (TNF- α), interleukin 6 (IL-6), IL-8, and interferon γ -induced protein (IP)-10], is common in SLE^{2,3,4,5}. While the general prognosis of SLE has improved, mortality rates remain more than 2-fold higher than in the general population, and cardiovascular diseases constitute a growing share of mortality causes^{6,7,8}.

It has become increasingly clear that different subsets of the SLE population exist. Already in 1959, Heaton suggested that Sjögren syndrome (SS) is a chronic and relatively benign form of SLE⁹. More recently, several studies have identified autoantibody clusters/immune phenotypes, which vary in clinical symptoms, biomarkers, and prognosis^{10,11,12,13,14}. An SLE phenotype characterized by antibodies to SSA and SSB antigens (also referred to as Ro/La) consistently appeared in these studies, but this supposedly milder SLE subset has so far achieved limited scientific attention.

The diagnosis of SS is a clinical entity, based on dryness of eyes and mouth due to destructive inflammation in the exocrine glands, especially tear and salivary glands. SS can exist in isolation, as primary SS (pSS), or with other rheumatic diseases, referred to as secondary SS (sSS). A major difference according to the 2002 Revised American-European Consensus Criteria (AECC) is the classification where the serologic item (SSA/SSB antibodies) is included for pSS, but not for sSS¹⁵. In SLE these autoantibodies are common, usually stable over time, and they appear early, even several years before disease onset^{16,17}.

The clinical SLE-sSS phenotype has been described as a mild version of SLE with dominance of skin and joint manifestations and with less severe internal organ involvement, and in particular, less nephritis^{9,18,19}. Differences and similarities between pSS and SLE with SS (SLE-sSS) have been studied²⁰, but to what extent the inflammatory pattern differs between SLE-sSS and SLE patients without SS (SLE-nonsSS) is not known, and this information may be important regarding treatment perspectives.

In our present study, subjective and objective symptoms of sSS, defined according to AECC¹⁵, from a large and well-characterized cohort of consecutive SLE patients and matched controls are presented. To our knowledge, no previous study has investigated patients with SLE and matched population controls for both subjective and objective symptoms of SS and associated SSA/SSB autoantibodies. The primary outcomes were occurrence, and clinical and immunological characteristics of the SLE-sSS

subgroup. As secondary outcomes, we performed stratified analyses based on anti-SSA/SSB profiles.

MATERIALS AND METHODS

Patients and controls. Patients with SLE managed at the Department of Rheumatology, Karolinska University Hospital and Danderyd's Hospital (Stockholm) who fulfilled 4 or more items of the American College of Rheumatology (ACR) 1982 revised classification criteria for SLE²¹ were invited to participate during the inclusion period of February 2004 to December 2014.

Population controls were individually matched for sex, age, and region of residence to the first 319 patients with SLE. The remaining 185 patients with SLE did not have matched controls. Matching was performed through use of the national registration number, which includes date of birth and is coded for sex. The only exclusion criteria were a diagnosis of SLE or SS.

Clinical and routine laboratory characterization. A structured protocol, similar for patients and controls, was used. Medical charts were reviewed. A rheumatologist performed a clinical examination and evaluated general health and features of SLE, including all items according to the ACR 1982 classification criteria²¹. SLE disease activity was determined with both Systemic Lupus Activity Measure (SLAM)²² and the SLE Disease Activity Index 2000 (SLEDAI-2K)²³. Permanent organ damage was evaluated with Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI)²⁴.

All participants were evaluated for the individual items of SS according to the AECC¹⁵. Subjective ocular and oral symptoms were recorded as defined by the validated questionnaire. Objective measurements were Schirmer's test and whole unstimulated salivary flow (WUSF) over 15 min²⁵. For controls, these objective measurements were only performed if subjective symptoms were present. Data on fulfillment of each item were collected. The amount of tears and saliva were recorded. If a salivary gland biopsy had been performed earlier, results were retrieved from the patient's records. Patients who had not had a salivary gland biopsy, when this was needed to determine whether they fulfilled the sSS criteria, were regarded as not having sSS. The attending rheumatologist assessed these patients as not having sSS, and hence that a salivary gland biopsy was not necessary.

Laboratory measurements. Fasting blood samples were drawn at inclusion. Laboratory tests were performed at the Swedish Board for Accreditation and Conformity Assessment (SWEDAC; www.swedac.se)—accredited Clinical Chemistry and Immunology Laboratories at the Karolinska University Hospital. Routine laboratory tests and analyses of complement factors and immunoglobulins were performed on fresh samples according to clinical routine.

Antinuclear antibodies were analyzed by indirect immunofluorescence on HEp-2 cells (Immunoconcepts). Antibodies to specific nuclear antigens (dsDNA, SSA/Ro52, SSA/Ro60, SSB/La, Sm, RNP) and phospholipid-related antigens [cardiolipin IgG, IgM, and β_2 -glycoprotein I (β_2 -GPI), IgG, IgM] were analyzed by multiplexed bead technology (Luminex) using BioPlex 2200 system (Bio-Rad) according to the specifications of the manufacturer. Patients who were simultaneously positive for SSA/Ro52, SSA/Ro60, and SSB/La are referred to as triple SSA/SSB-positive. The cutoff for anticardiolipin and anti- β_2 -GPI fulfills the 99th percentile of the general population in Stockholm, as described²⁶. Lupus anticoagulant (LAC) was determined using a modified Russell's viper venom method (Biopool) using Bioclot LAC.

IgA, IgG, and IgM rheumatoid factor (RF) were measured with a Phadia2500 instrument at Phadia ThermoFisher Uppsala. Cutoffs for RF isotypes were determined as > 95% specificity compared with 100 blood donors for IgA and IgM RF and for 285 population controls for IgG RF.

Mesoscale Discovery (MSD) multiplex analysis of cytokines EDTA-plasma samples were analyzed on the MSD V-PLEX Human Cytokine 30-plex kit (K15054D; MSD) according to the manufacturer's instructions, as previously reported⁴. In short, the plasma samples were thawed at room temperature and diluted twice for proinflammatory and

cytokine analyses, and 4 times for chemokine analysis in sample diluents. The diluted samples were incubated on the MSD plates for 2 h at room temperature with shaking. Plates were washed and incubated an additional 2 h with detection antibodies. After washing, 2× Read buffer T was added and the plates were analyzed in a Sector Imager 6000. Calibrator and plasma samples were analyzed in duplicates. Using the MSD Workbench software, the responses of the calibrator concentrations were plotted as log signal unit on the vertical (y) axis versus log concentration on the horizontal (x) axis. A weighted 4-parameter logistic fit equation was used for curve fitting and back calculation of plasma sample concentrations.

Statistical analysis. Patient and control characteristics are presented as mean ± SD, median (interquartile range), or percentages, depending on data type and distribution.

Groups were compared with the Student t test, Wilcoxon rank-sum test, or chi-square tests as appropriate. We used nonparametric tests when log transformation of continuous variables did not give a nearly normal distribution. Adjustment for age was performed by multiple logistic regression.

Calculations were performed using JMP software (SAS Institute). A 2-sided p value < 0.05 was considered statistically significant.

The local Ethics Committee at Karolinska Institutet approved the study (Dnr 03-556, Dnr 2017/1570-32). All study subjects gave written informed consent to participate in the study.

RESULTS

The 504 patients and 319 matched controls were well matched for age, but the female percentage was slightly lower among the patients (86.3% vs 92.2%; $p = 0.01$). The patients with SLE were 33.9 ± 15.5 years at diagnosis, and their disease duration was 12.1 ± 12.3 years. Basic characteristics are presented in Table 1.

Patients with SLE-sSS versus SLE-nonsSS. SLE-sSS was present in 23.2% of the patients with SLE. Patients with SLE-sSS were older at inclusion (54.6 ± 13.6 vs 43.4 ± 14.7 yrs; $p < 0.0001$) and at SLE onset (40.4 ± 15.6 vs 31.9 ± 14.9 yrs; $p < 0.0001$). The percentage of patients with SLE-sSS increased with age, as demonstrated in Figure 1. The frequency of females was higher in the SLE-sSS group compared to SLE-nonsSS (95.7% vs 83.4%; $p = 0.0007$; Table 1).

We performed additional calculations to illustrate potential bias regarding the 132 patients with SLE who were regarded as SLE-nonsSS by their attending rheumatologist, but could have been reclassified after a biopsy. Results are presented in Supplementary Table 1 (available with the online version of this article).

Autoantibodies. Sjögren-associated autoantibodies SSA/Ro52, SSA/Ro60, and SSB/La were more common in patients with SLE-sSS versus SLE-nonsSS (47.9% vs 21.8%, $p < 0.0001$; 59% vs 35.9%, $p < 0.0001$; 37.6% vs 18%, $p < 0.0001$, respectively), but 39.3% of the SLE-sSS patients were negative for all 3 antibodies. The frequency of SSA/Ro52 and SSA/Ro60 was highest among young patients aged 21–30 (Figure 2). Further, RF of the IgM (38.6% vs 19.9%; $p = 0.0005$) and the IgA (45.9% vs 28.0%; $p = 0.004$) isotypes were more frequent in SLE-sSS as compared to SLE-nonsSS. Anti-dsDNA autoantibodies were nonsignificantly less prevalent in SLE-sSS than among SLE-nonsSS patients (31.3% vs 41%; $p = 0.06$; Table 1).

SLE manifestations, disease activity, and damage. In the SLE-sSS group, leukopenia and peripheral neuropathy were more common than in the SLE-nonsSS (57.3% vs 45.2%, $p = 0.02$; and 15.4% vs 7.5%, $p = 0.01$, respectively), while nephritis was less frequent (31.9% vs 42.6%; $p = 0.03$).

Organ damage (SDI score > 1), was more frequent in the SLE-sSS group (73% vs 59.9%; $p = 0.01$), but this difference did not remain after age adjustment. High disease activity, as measured by SLAM (score > 6) was more common in the SLE-sSS group (67.2% vs 57.1%; $p = 0.05$), whereas SLEDAI scores were similar in both groups (Table 1).

Cytokines and other biomarkers. Higher levels of total IgG characterized the SLE-sSS group ($p = 0.009$). Cytokines were measured in 432 SLE patients and 315 controls. Of 30 investigated cytokines, 20 were reliably detectable and evaluated; of these, 19/20 were higher in SLE than in controls, as previously reported⁴. When comparing the SLE-sSS to the SLE-nonsSS group, 6/20 cytokines (TNF- α , IL-6, MCP-4, MIP-1 β , IL12/IL-23p40, and IP-10) were upregulated in SLE-sSS (Table 1).

Exclusion of the 132 patients, who could have been reclassified after biopsy, yielded similar results except for IL12/IL-23p40 and IP-10, which no longer differed significantly.

SSA/Ro52. SLE-sSS ($p < 0.0001$), leukopenia ($p = 0.04$), and lymphopenia ($p = 0.05$) were more common among patients with SLE who were positive for SSA/Ro52, whereas malar rash ($p = 0.04$) and seizures ($p = 0.02$) were less frequent than in patients negative for SSA/Ro52 (Table 2).

SSA/Ro60. SSA/Ro60-positive patients were more often affected by sSS ($p < 0.0001$), leukopenia ($p = 0.0006$), and photosensitivity ($p = 0.02$), and less affected by discoid lesions ($p = 0.02$), nephritis ($p = 0.05$), vasculitis ($p = 0.03$), and peripheral neuropathy ($p = 0.02$; Table 2).

SSB/La. In the SSB/La-positive patient group, sSS ($p < 0.0001$), arthritis ($p = 0.002$), leukopenia ($p = 0.0003$), and lymphopenia ($p = 0.05$) were more common, but nephritis ($p = 0.0005$) was less common (Table 2).

Sicca symptoms. In all investigated groups (SLE-sSS, SLE-nonsSS, and controls), subjective symptoms of ocular and/or oral sicca symptoms were less frequent than objective measurements of reduced tear and saliva production. While subjective symptoms clearly differed between SLE-nonsSS and controls in all age spans, objectively measured tear production was similar in the age spans > 40 years, and differences were small also for WUSF after the age of 50 years (Figure 3 and Figure 4).

Ocular sicca symptoms. In the SSA/Ro52-, SSA/Ro60-, and SSB/La-positive groups, 41.4%, 39.3%, and 44.2%, respectively, presented with subjective ocular sicca symptoms. Figures were similar for the triple SSA/SSB-positive patients (44.9%; Supplementary Figure 1A, available with the online version of this article).

Table 1. Basic characteristics of patients with SLE, controls, and SLE-sSS versus SLE-nonsSS.

Characteristics	SLE	Controls	p	SLE-sSS	SLE-nonsSS	p
N (%)	504 (100)	319 (100)		117 (23.2)	387 (76.7)	
Basic characteristics, mean \pm SD or n (%)						
Age, yrs	46.0 \pm 15.2	47.4 \pm 14.6	0.20	54.6 \pm 13.6	43.4 \pm 14.7	< 0.0001
Age at SLE onset, yrs	33.9 \pm 15.5	ND	ND	40.4 \pm 15.6	31.9 \pm 14.9	< 0.0001
Disease duration, yrs	12.1 \pm 12.3	ND	ND	14.2 \pm 12.8	11.5 \pm 12.1	0.16
No. SLE criteria*	5.7 \pm 1.4	ND	ND	5.7 \pm 1.5	5.7 \pm 1.4	0.40
Sex, female	435 (86.3)	294 (92.2)	0.01	112 (95.7)	323 (83.4)	0.0007
Smoking, current	96 (19.0)	47 (14.6)	0.22	20 (17.1)	76 (19.6)	0.58
Smoking, ever	258 (51.2)	151 (46.9)	0.22	62 (53)	196 (50.6)	0.65
Primary SS	108 (21.6)	ND	ND	25 (21.9)	83 (21.6)	0.99
Autoantibody positivity, n (%)						
Anti-dsDNA	190/491 (38.7)	5/317 (1.6)	< 0.0001	36/115 (31.3)	154/376 (41)	0.06
Anti-SSA-Ro52	140/501 (27.9)	3/317 (0.9)	< 0.0001	56/117 (47.9)	84/384 (21.8)	< 0.0001
Anti-SSA-Ro60	206/499 (41.3)	5/317 (1.6)	< 0.0001	69/117 (59)	137/382 (35.9)	< 0.0001
Anti-SSB-La	113/501 (22.6)	10/317 (3.1)	< 0.0001	44/117 (37.6)	69/384 (18)	< 0.0001
Anti-Sm	94/501 (18.8)	1/317 (0.3)	< 0.0001	19/117 (16.2)	75/384 (19.5)	0.42
Anti-SmRNP	130/497 (26.2)	0/317 (0)	< 0.0001	29/116 (25)	101/381 (26.5)	0.74
Anti-RNP 68	51/500 (10.2)	0/317 (0)	< 0.0001	11/117 (9.4)	40/383 (10.4)	0.74
Anti-RNP A	129/496 (26.0)	10/317 (3.1)	< 0.0001	30 (25.6)	99/379 (26.1)	0.91
aCL IgG	108/423 (25.5)	2/318 (0.6)	< 0.0001	24/97 (24.7)	84/326 (25.8)	0.83
aCL IgM	26/432 (6.0)	1 (0.3)	< 0.0001	8/96 (8.3)	18/336 (5.4)	0.32
Anti- β_2 GPI IgG	110/417 (26.4)	2 (0.6)	< 0.0001	24/95 (25.3)	86/322 (26.7)	0.77
Anti- β_2 GPI IgM	33/434 (7.6)	1 (0.3)	< 0.0001	8/96 (8.3)	25/338 (7.4)	0.82
RF IgG	52/339 (15.3)	10/261 (3.8)	< 0.0001	17/80 (21.2)	35/259 (13.5)	0.09
RF IgM	88/364 (24.2)	14/283 (4.9)	< 0.0001	32/83 (38.6)	56/281 (19.9)	0.0005
RF IgA	109/341 (32.0)	12/282 (12.4)	< 0.0001	34/74 (45.9)	75/267 (28.0)	0.004
Other laboratory analyses, mean \pm SD or n (%)						
IgA, g/l	2.90 \pm 1.46	2.30 \pm 1.06	< 0.0001	3.19 \pm 1.80	2.82 \pm 1.32	0.38
IgG, g/l	13.63 \pm 5.54	10.89 \pm 2.14	< 0.0001	14.85 \pm 5.99	13.25 \pm 5.35	0.009
IgM, g/l	1.24 \pm 1.26	1.26 \pm 0.69	0.0002	1.23 \pm 1.09	1.24 \pm 1.31	0.89
C3, g/l	0.88 \pm 0.26	1.06 \pm 0.21	< 0.0001	0.90 \pm 0.26	0.87 \pm 0.26	0.33
C4, g/l	0.15 \pm 0.08	0.21 \pm 0.06	< 0.0001	0.16 \pm 0.08	0.15 \pm 0.07	0.16
Lupus anticoagulant	104 (20.7)	ND	< 0.0001	20 (17.1)	84 (21.8)	0.27
Cytokines, median (IQR) [#]						
TNF- α , pg/ml	4.5 (3.1–6.2)	2.3 (2.0–2.8)	< 0.0001	4.9 (3.6–7.1)	4.4 (3.0–6.0)	0.008
IL-6, pg/ml	1.2 (0.7–2.2)	0.5 (0.4–0.7)	< 0.0001	1.5 (0.8–3.0)	1.1 (0.6–2.0)	0.009
MCP-4, pg/ml	78 (53.6–123.8)	55.8 (40.8–81.1)	< 0.0001	94.9 (66.9–131.3)	74.7 (52.4–120.0)	0.019
MIP-1 β , pg/ml	72.7 (50.8–108.1)	43.7 (33.4–56.4)	< 0.0001	81.1 (54.8–123.6)	68.9 (50.3–105.1)	0.020
IL-12/23p40, pg/ml	180.6 (122.9–286.3)	131.0 (99.5–179.3)	< 0.0001	211.3 (141.4–363.8)	177.1 (119.6–274.5)	0.031
IP-10, pg/ml	744.4 (457.5–1497.4)	352.13 (258.9–478.9)	< 0.0001	808.0 (536.4–1911.7)	726.4 (440.8–1471.0)	0.036
SLE manifestations (ever), n (%) [*]						
Malar rash	246 (48.8)	0 (0)	< 0.0001	55 (47.0)	191 (49.4)	0.65
Discoid lesions	88 (17.5)	0 (0)	< 0.0001	17 (14.5)	71 (18.3)	0.34
Photosensitivity	318 (63.1)	57 (17.8)	< 0.0001	82 (70)	236 (61)	0.07
Oral ulcers	168/502 (33.5)	11 (3.4)	< 0.0001	41 (35)	127/385 (33)	0.67
Arthritis	406/503 (80.7)	13 (4.0)	< 0.0001	93 (79.5)	313/386 (81.1)	0.70
Pleuritis	185/503 (36.8)	2 (1)	< 0.0001	50 (42.7)	135/386 (35)	0.12
Pericarditis	88/503 (17.5)	0 (0)	< 0.0001	24 (20.5)	64/386 (16.6)	0.32
Nephritis	202/503 (40.2)	1 (0.3)	< 0.0001	37/116 (31.9)	165 (42.6)	0.03
Psychosis	10 (2)	2 (1)	0.11	1 (1)	9 (2.3)	0.46
Seizures	49 (9.7)	5 (1.6)	< 0.0001	11 (9.4)	38 (9.8)	0.89
Leukopenia	242 (48)	3 (1)	< 0.0001	67 (57.3)	175 (45.2)	0.02
Lymphopenia	273 (54.2)	2 (1)	< 0.0001	68 (58.1)	205 (53)	0.32
Thrombocytopenia	100 (19.8)	2 (1)	< 0.0001	24 (20.5)	76 (19.6)	0.83
Raynaud phenomenon	195 (38.7)	10 (3.1)	< 0.0001	51 (43.6)	144 (37.2)	0.21
Vasculitis	57/498 (11.4)	0 (0)	< 0.0001	9/116 (7.8)	48/382 (12.6)	0.15
Interstitial lung disease	24 (4.8)	0 (0)	< 0.0001	7 (6.0)	17 (4.4)	0.47
Peripheral neuropathy	47/501 (9.4)	6 (1.9)	< 0.0001	18 (15.4)	29/384 (7.5)	0.01
Disease activity and damage indices						
SLICC/ACR DI > 1	314/499 (62.9)	ND	ND	84/115 (73.0)	230/384 (59.9)	0.01
SLAM > 6	298/501 (59.5)	ND	ND	78/116 (67.2)	220/385 (57.1)	0.05
SLEDAI > 2	356/500 (71.2)	ND	ND	82/116 (70.7)	274/384 (71.4)	0.88

When measurements are missing, nos. are given as ratios (no. positive/total no. tested or available). Primary SS: fulfills criteria for primary Sjögren syndrome with the exception that patients are diagnosed with SLE. [#] Cytokines were determined in 432 patients with SLE and 315 controls. ^{*} SLE criteria were determined according to ACR 1982 classification criteria. Values in bold face are statistically significant. SLE: systemic lupus erythematosus; SLE-sSS: SLE patients with secondary Sjögren syndrome; SLE-nonsSS: SLE patients without secondary Sjögren syndrome; aCL: anticardiolipin; Ig: immunoglobulin; β_2 -GPI: β_2 -glycoprotein I; C: complement factor; RF: rheumatoid factor; IQR: interquartile range; TNF: tumor necrosis factor; IL: interleukin; MCP: monocyte chemoattractant protein; MIP: macrophage inflammatory protein; IP: interferon γ -induced protein; SLICC/ACR DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLAM: Systemic Lupus Activity Measure; SLEDAI: SLE Disease Activity Index, ND: not determined.

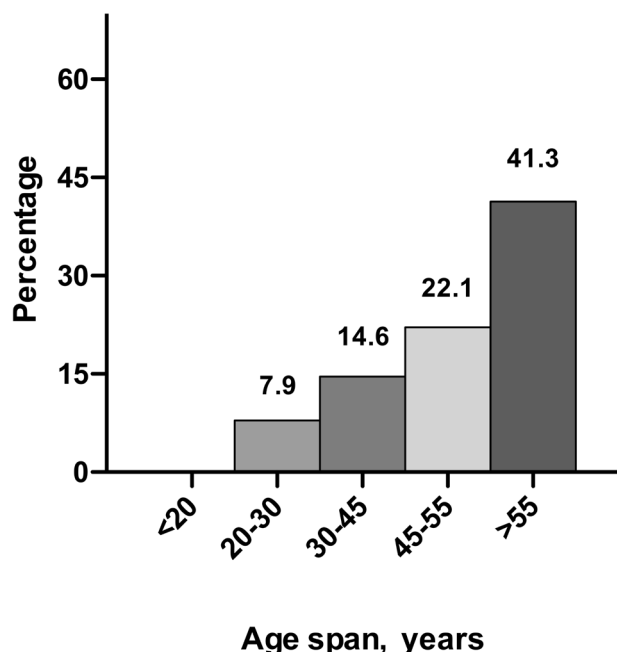


Figure 1. Age-stratified frequencies (%) of SLE-sSS. SLE: systemic lupus erythematosus; SLE-sSS: SLE patients with secondary Sjögren syndrome.

Oral sicca symptoms. In the SSA/Ro52–, SSA/Ro60–, and SSB/La-positive groups, 49.2%, 52.7%, and 50.9%, respectively, presented with subjective oral sicca symptoms. Figures were similar for the triple SSA/SSB-positive patients (53.9%; Supplementary Figure 1B, available with the online version of this article).

Sicca symptoms in triple SSA/SSB-negative SLE patients and controls. Among patients who were negative for all 3 SSA/SSB antibodies, 36.9% reported subjective oral sicca symptoms, 24.6% reported ocular sicca symptoms and 16.8% were diagnosed with sSS. In the control group, 7.5% reported oral and 7.1% ocular symptoms (Supplementary Figures 1A–B, available with the online version of this article).

DISCUSSION

According to the revised AECC¹⁵, SLE-sSS occurred in 23% of patients in this large and well-defined cohort of consecutive SLE patients. It is a novel observation that, despite less internal organ involvement, higher levels of proinflammatory cytokines were present in the SLE-sSS group than in the SLE-nonsSS. We also confirm that older age, female sex, and SSA/SSB antibodies, not included in the AECC definition of sSS, were positively associated with SLE-sSS. However, notably a large minority (39%) of SLE-sSS patients were negative for all 3 SSA/SSB antibodies.

To our knowledge, this is the first study to investigate whether systemic inflammation, as measured by cytokine levels, differs between SLE-sSS and SLE-nonsSS. Although SLE-sSS is often considered a less severe form of SLE, the

levels of several proinflammatory cytokines — TNF- α , IL-6, MCP-4, MIP-1 β , IL-12/IL23p40, and IP-10 — were higher in SLE-sSS than in SLE-nonsSS patients. As previously reported, the investigated cytokines were also upregulated in SLE versus controls, and they were positively associated with SLE disease activity⁴. TNF- and IL-6 have also been reported as high in pSS²⁷. Interestingly, an IP-10 antagonist ameliorated the progression of autoimmune sialoadenitis in MRL/lpr mice²⁸. Further, hypergammaglobulinemia, a well-known feature of SS²⁹, was in our study consequently more common among SLE-sSS patients, although the levels of IgG were usually below 20 mg/ml. We previously reported that low total IgM levels were associated with an SSA/SSB-positive profile in SLE²⁹, but using the AECC, IgM levels were similar in SLE-sSS and SLE-nonsSS subgroups.

The occurrence of SLE-sSS in our study (23%) is higher than that reported by most previous studies (6–14%)^{18,20,30,31,32}. An important reason for this discrepancy is likely attributable to our meticulous investigation procedures. In contrast to most studies, we measured tear and saliva production in all patients with SLE, regardless of whether subjective symptoms were present. It was a general finding that objectively reduced production of tear and saliva is more common than subjectively reported sicca symptoms. The high frequency of SLE-sSS is likely also affected by ethnicity. Our study population is mostly of European white origin and Baer, *et al* previously reported that in whites, as compared to other American ethnicities, frequencies of SLE-sSS were higher at 18% versus 14%¹⁸.

The frequencies of SLE-sSS increased with age. Patients with SLE-sSS were on average 9 years older than SLE-nonsSS, both at disease onset and at inclusion. Similar age differences were also reported previously^{18,20,30,33,34}. The difference in age at SLE onset did however not remain after controlling for present age. Comparable findings were reported by Baer, *et al*, who investigated a large multiethnic SLE cohort¹⁸ and by Manoussakis, *et al*³⁰. In line with these observations, Nossent and Swaak showed a rising percentage of SLE-sSS during a 4-year followup of patients with SLE¹⁹. To further clarify whether sicca symptoms correlated with age, we stratified SLE-sSS, SLE-nonsSS, and controls by age. The results demonstrated that the prevalence of both subjective and objective sicca symptoms increase with age also in the SLE-nonsSS group and in controls. Thus, in some of the older patients with SLE-sSS, the AECC criteria may diagnose patients with sSS who have more age-related than immunological aberrations. Taken together, the present and previous studies demonstrate that sSS is an age-related complication among patients with SLE^{18,19}.

The presence of SSA/SSB autoantibodies and their positive association to sicca symptoms is well recognized. Earlier studies reported that these antibodies occur together^{12,16}. We observed that the prevalence of oral and ocular dryness was

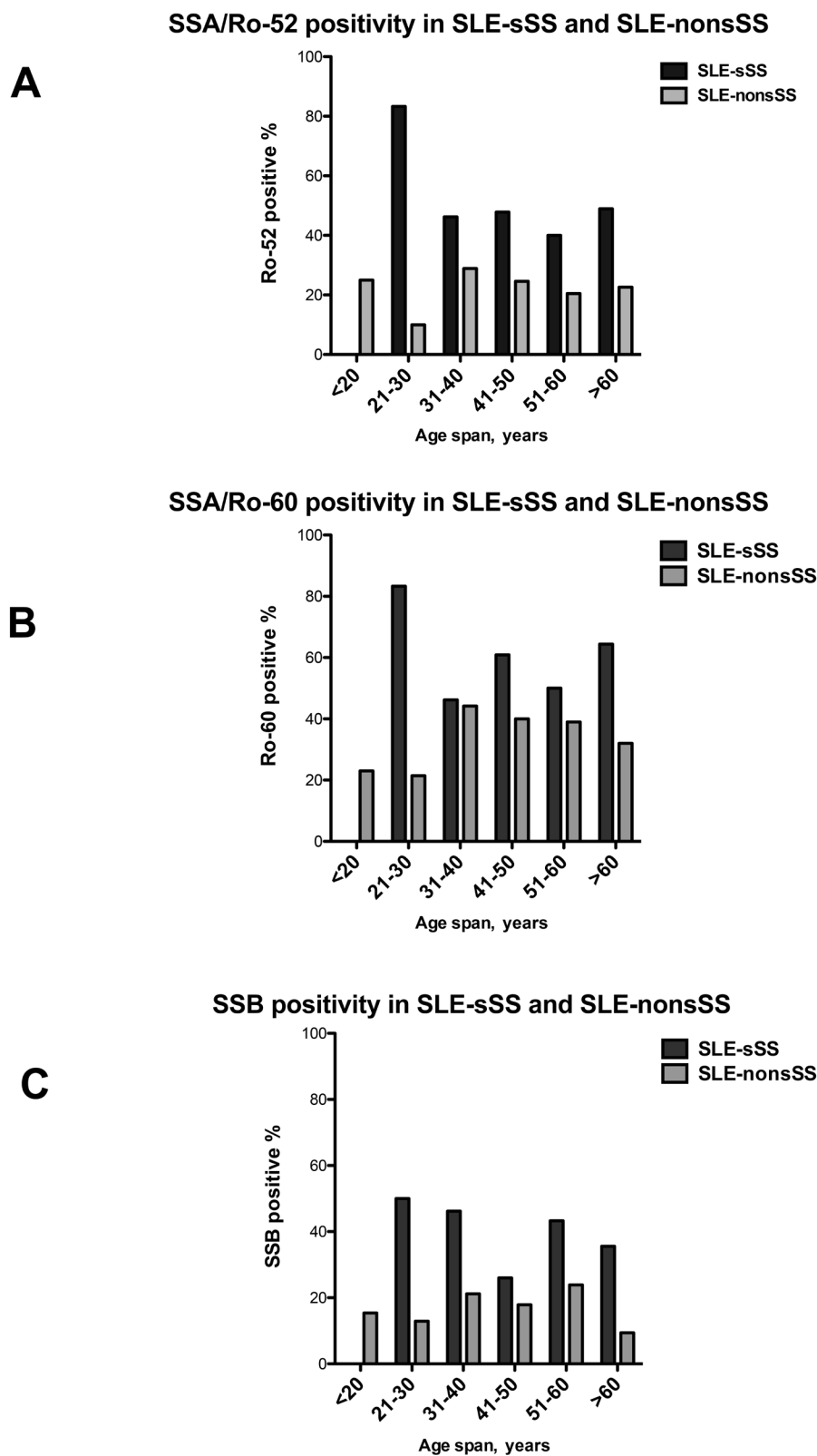


Figure 2. Occurrence of Sjögren-associated autoantibodies SSA/SSB in SLE-sSS and SLE-nonsSS patients, stratified for age. A. SSA-Ro52 positivity. B. SSA-Ro60 positivity. C. SSA-Ro52 positivity. SLE: systemic lupus erythematosus; SLE-sSS: SLE patients with secondary Sjögren syndrome; SLE-nonsSS: SLE patients without secondary Sjögren syndrome.

Table 2. Frequency of organ manifestations in all SLE patients versus in SSA/SSB-positive patients with SLE.

SLE Manifestations	Missing Data, n	SLE Cohort, N _{total} = 504 (100%)	anti-Ro52+ N _{Ro52+} = 140 (27.9%)	p	anti-Ro60+ N _{Ro60} = 206 (41.3%)	p	anti-La/SSB+ N _{La/SSB} = 113 (22.6%)	p
Secondary SS	0	117 (23.2)	56 (47.9)	< 0.0001	69/117 (59.0)	< 0.0001	44 (37.6)	< 0.0001
Malar rash	0	246 (48.8)	58 (41.4)	0.04	103 (50.0)	0.67	54 (47.8)	0.78
Discoid lesions	0	88 (17.5)	27 (19.3)	0.52	46 (22.3)	0.02	25 (22.1)	0.14
Photosensitivity	0	318 (63.1)	94 (67.1)	0.26	142/201 (68.9)	0.02	78/103 (69.0)	0.14
Oral ulcers	2	168 (33.5)	50 (35.7)	0.46	68/201 (33.0)	0.87	40/103 (35.4)	0.58
Arthritis	1	406 (80.7)	109 (77.9)	0.33	161/201 (78.2)	0.26	80/103 (70.8)	0.002
Pleuritis	1	185 (36.8)	53 (37.9)	0.75	73/201 (35.4)	0.61	48/103 (42.5)	0.14
Pericarditis	1	88 (17.5)	27 (19.3)	0.48	33/201 (16.0)	0.47	18/103 (15.9)	0.63
Nephritis	1	202 (40.2)	47/139 (33.8)	0.07	72/205 (35.1)	0.05	29/112 (25.9)	0.0005
Psychosis	0	10 (2)	2 (1.4)	0.57	5 (2.4)	0.57	1 (0.9)	0.33
Seizures	0	49 (9.7)	7 (5.0)	0.02	15 (7.3)	0.11	7 (6.2)	0.14
Leukopenia	0	242 (48.0)	77 (55.0)	0.04	117 (56.8)	0.0006	71 (62.8)	0.0003
Lymphopenia	0	273 (54.2)	85 (60.7)	0.05	121 (58.7)	0.06	70 (61.9)	0.05
Thrombocytopenia	0	100 (19.8)	25 (17.9)	0.46	42 (20.4)	0.79	23 (20.4)	0.90
RP	0	195 (38.7)	55 (39.3)	0.87	82 (39.8)	0.60	41 (36.3)	0.57
Vasculitis*	6	57 (11.4)	18/138 (13.0)	0.50	31/203 (15.3)	0.03	16/112 (14.3)	0.29
Interstitial lung disease	0	24 (4.8)	10 (7.1)	0.12	10 (4.9)	0.96	6 (5.3)	0.76
Peripheral neuropathy	3	47 (9.4)	15/139 (10.8)	0.45	26/204 (12.7)	0.02	13/112 (11.6)	0.32

Numbers are given as ratios (no. positive/total no. tested) when measurements are missing. Values are n (%) unless otherwise specified. Values in bold face are statistically significant. * All clinical vasculitis. SLE: systemic lupus erythematosus; SS: Sjögren syndrome; RP: Raynaud phenomenon; ILD: interstitial lung disease.

more pronounced in patients who are positive for all 3 antibodies (SSA/Ro52, SSA/Ro60, and SSB/La). Our study thus supports the presence of an autoantibody cluster related to the SLE-sSS subset^{10,11,29}. Although the presence of the SSA/SSB antibodies was associated with sicca symptoms, a considerable fraction of patients with SLE-sSS (39%) were negative for all 3 SSA/SSB antibodies. We also report higher frequencies of IgM and IgA RF in patients with SLE-sSS. Thus, the presence of sicca symptoms is not exclusively related to SSA/SSB antibodies, but also to increasing age, RF, and possibly to other unidentified factors.

Overall organ damage was more severe in the SLE-sSS group, but this difference did not remain after age adjustment. Regarding disease activity, we performed 2 validated indices: SLEDAI²³, a qualitative (presence vs absence) recording of symptoms and laboratory aberrations; and SLAM²², which grades symptom severity and includes subjective symptoms such as fatigue, headache, and arthralgia. SLEDAI measurements did not differ, whereas with SLAM, higher disease activity scores were observed in the SLE-sSS than in the SLE-nonsSS subgroup. This observation could possibly be explained by the inflammatory state, which may cause subjective and general symptoms such as muscle and joint pain, headache and fatigue, which are included in the SLAM but not in the SLEDAI index.

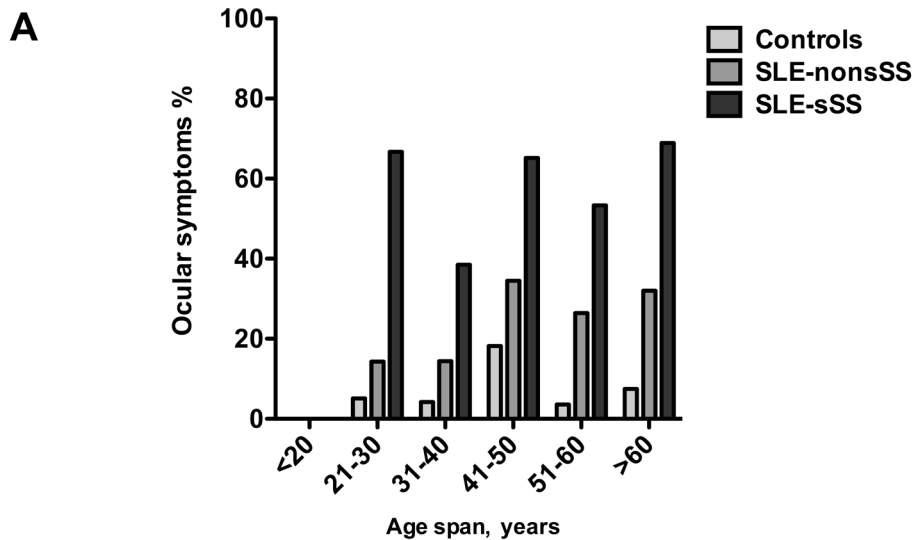
Consistent with earlier studies^{18,30,34}, the female predominance was more pronounced among SLE-sSS patients as compared to SLE-nonsSS (96% vs 84%). The very high percentage of female patients with SLE-sSS (96%) is similar to reports in pSS³⁰. The average age of disease onset

for SLE-sSS was older than for SLE-nonsSS (40.4 ± 15.6 vs 33.9 ± 14.9 yrs) but still considerably younger than the average age of onset for pSS, which is 55 years^{35,36}.

In clinical practice, it is often difficult to delineate pSS from SLE-sSS. Organ manifestations commonly reported in pSS are fever, lymphadenopathy, parotid gland enlargement, Raynaud phenomenon, interstitial lung disease, peripheral neuropathy, and vasculitis^{37,38,39}. All these clinical features, except parotid gland enlargement, were investigated in our present study, but only peripheral neuropathy differed and was more frequent in SLE-sSS than in SLE-nonsSS, demonstrating that the majority of these manifestations are shared between SLE and pSS. Of SLE manifestations, leukopenia was more common in the SLE-sSS group and there was also a positive trend for photosensitivity, both of which have been associated with the type I interferon signature. Nephritis was, in accordance with previous studies, less frequent in the SLE-sSS group, and anti-dsDNA positivity showed a similar trend^{18,20,30,34}. We conclude that patients with SLE-sSS and patients with pSS have many similarities and it is not surprising that among the patients with SLE-sSS, according to AECC, 21% also fulfilled the criteria for pSS, if we disregard the fact that they are diagnosed with SLE (a prerequisite for being evaluated for pSS).

The strengths of this study are the objective measurements of sicca symptoms in all patients with SLE, according to the AECC criteria and recommended practice in Sweden, in a well-characterized consecutively collected cohort of patients with SLE. However, if the investigating rheumatologist did not consider sSS to be present, we did not refer

Ocular symptoms in Controls, SLE-nonsSS and SLE-sSS



Positive Schirmer's test in Controls, SLE-nonsSS and SLE-sSS

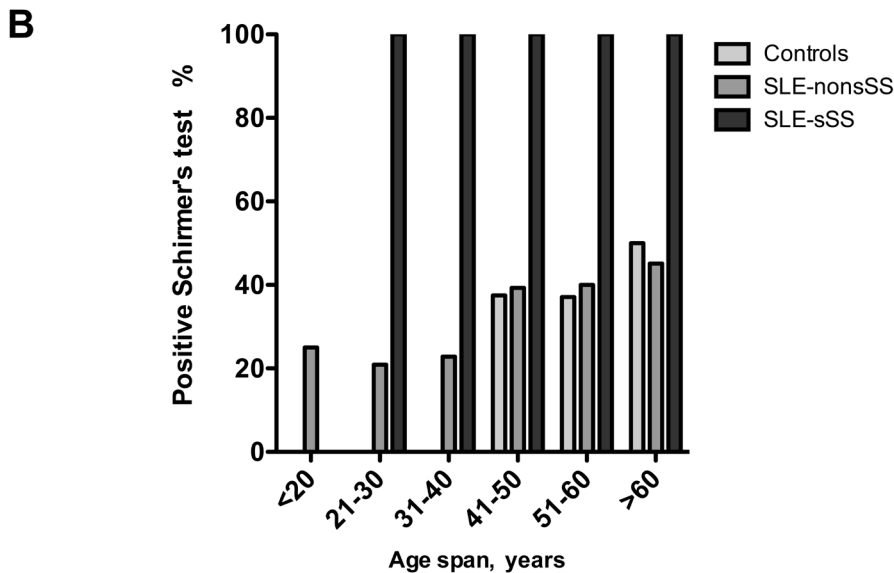
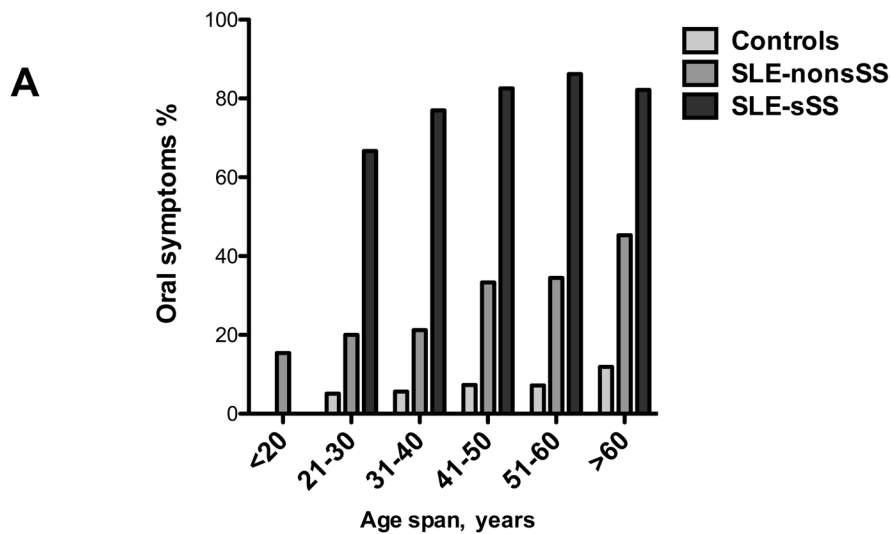


Figure 3. Subjective and objective ocular symptoms in patients with SLE-sSS and SLE-nonsSS, and in controls. A. Subjective ocular symptoms in controls, SLE-nonsSS, and SLE-sSS, as defined by a validated questionnaire according to item 1 in the American-European Consensus Criteria (AECC)¹⁵. B. Objective ocular symptoms in controls, SLE-nonsSS, and SLE-sSS, measured according to item 3 in AECC by Schirmer's test, where a positive value is given to an amount of < 5 mm of tears collected during 5 min from one or both eyes. SLE: systemic lupus erythematosus; SLE-sSS: SLE patients with secondary Sjögren syndrome; SLE-nonsSS: SLE patients without secondary Sjögren syndrome.

to an ophthalmologist for Rose Bengal staining or other ocular dye scores, to achieve full potential for all patients to fulfill item III (ocular signs) in the classification criteria. Similarly, salivary gland biopsies were only performed

when the investigating rheumatologist suspected that sSS could be present, despite not fulfilling items III and V (salivary gland involvement) according to WUSF. We are aware that previous studies have reported a lower sensitivity if

Oral symptoms in Controls, SLE-nonsSS and SLE-sSS



WUSF in controls, SLE-nonsSS & SLE-sSS

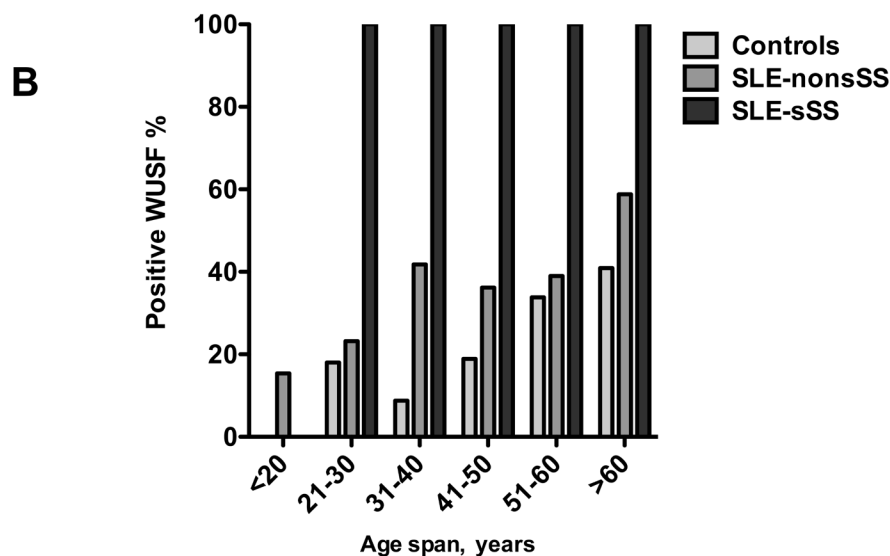


Figure 4. Subjective and objective oral symptoms in patients with SLE-sSS and SLE-nonsSS, and in controls. Subjective oral symptoms in controls, SLE-nonsSS, and SLE-sSS are as defined by a validated questionnaire according to item 2 in the American-European Consensus Criteria (AECC)¹⁵. Objective oral symptoms in controls, SLE-nonsSS, and SLE-sSS as measured according to item 5 in AECC¹⁵ by WUSF over 15 min, where a positive value is given to an amount of < 1.5 ml of saliva collected during 15 min. SLE: systemic lupus erythematosus; SLE-sSS: SLE patients with secondary Sjögren syndrome; SLE-nonsSS: SLE patients without secondary Sjögren syndrome; WUSF: whole unstimulated salivary flow.

only Schirmer's test and WUSF are used⁴⁰, and we have considered the risk for misclassification, but the rheumatologists assessed these patients clinically as SLE-nonsSS. To further illustrate this issue, we excluded the 132 patients in whom a biopsy could have made a difference, but this did

not essentially change the characteristic differences between SLE-sSS and SLE-nonsSS. Excluding these patients would also have changed the study's cross-sectional and consecutive design. Finally, we did not measure saliva and tear production in controls without sicca symptom. Because

positive objective measures were more common than subjective complaints, we may have underestimated the number of controls with impaired saliva/tear production.

Our investigations of the SLE-sSS subset demonstrate that it affects roughly one-quarter of patients with SLE, and the frequency increases with age. Autoantibodies SSA/SSB occur in the majority, but a large minority (39%) were SSA/SSB-negative. SLE-sSS shares many features with pSS such as a striking female predominance, older age at onset, and neuropathy. It is a novel observation, with possible therapeutic implications, that an inflammatory state occurs in SLE-sSS with higher levels of proinflammatory cytokines than in SLE-nonsSS.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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