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Systemic phenotype related to primary Sjögren's syndrome in 279 patients carrying isolated anti-La/SSB antibodies

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Key words: primary Sjögren's syndrome, isolated La/SSB auto-antibodies, anti-Ro/SSA antibodies, systemic disease, ESSDAI, big data

Competing interests: page S93.

ABSTRACT

Objective. To evaluate the systemic phenotype associated with the presence of isolated anti-La/SSB antibodies in a large international registry of patients with primary Sjögren's syndrome (pSS) fulfilling the 2002 classification criteria.

Methods. The Big Data Sjögren Project Consortium is an international, multicentre registry created in 2014. Baseline clinical information from leading centres on clinical research in SS of the 5 continents was collected. Combination patterns of anti-Ro/SSA-La/SSB antibodies at the time of diagnosis defined the following four immunological phenotypes: double positive (combined Ro/SSA and La/SSB,) isolated anti-Ro/SSA, isolated anti-La/SSB, and immunonegative.

Results. The cohort included 12,084 patients (11,293 females, mean 52.4 years) with recorded ESSDAI scores available. Among them, 279 (2.3%) had isolated anti-La/SSB antibodies. The mean total ESSDAI score at diagnosis of patients with pSS carrying isolated anti-La/SSB was 6.0, and 80.4% of patients had systemic activity (global ESSDAI score ≥ 1) at diagnosis. The domains with the highest frequency of active patients were the biological (42.8%), glandular (36.8%) and articular (31.2%) domains. Patients with isolated anti-La/SSB showed a higher frequency of active patients in all ESSDAI domains but two (articular and peripheral nerve) in comparison with immune-negative patients,

and even a higher absolute frequency in six clinical ESSDAI domains in comparison with patients with isolated anti-Ro/SSA. In addition, patients with isolated anti-La/SSB showed a higher frequency of active patients in two ESSDAI domains (pulmonary and glandular) with respect to the most active immunological subset (double-positive antibodies). Meanwhile, systemic activity detected in patients with isolated anti-La/SSB was overwhelmingly low. Even in ESSDAI domains where patients with isolated anti-La/SSB had the highest frequencies of systemic activity (lymphadenopathy and muscular), the percentage of patients with moderate or high activity was lower in comparison with the combined Ro/SSA and La/SSB group.

Conclusion. Patients carrying isolated La/SSB antibodies represent a very small subset of patients with a systemic SS phenotype characterised by a significant frequency of active patients in most clinical ESSDAI domains but with a relative low frequency of the highest severe organ-specific involvements. Primary SS still remains the best clinical diagnosis for this subset of patients.

Introduction

Primary Sjögren syndrome (pSS) is a systemic autoimmune disease that mainly affects middle-aged women (1). Aetiopathogenically, the disease targets the exocrine glands that are infiltrated by lymphocytes (focal sialadenitis) (2). More than 95% of patients present with

oral and/or ocular dryness (3), although they may also develop a wide variety of systemic manifestations (4). pSS is not a rare disease, affecting around 1 out of 400 people (5).

Patients with pSS may have a wide variety of circulating autoantibodies directed to nuclear and cytoplasmic antigens and related to B-cell hyperactivation, a key immunopathogenic marker of the disease (6, 7). Immunological markers play a central role not only in the diagnosis of the disease, but also in predicting their outcomes (8). Anti-Ro/SSA antibodies are the most specific SS-related autoimmune marker, and cryoglobulins and hypocomplementaemia, the main prognostic markers (9). Among other autoantibodies frequently detected in primary SS, rheumatoid factor (RF) and anti-La/SSB antibodies are not included in the 2016 ACR/EULAR set of classification criteria (10), although both are detected in nearly half the patients and have been traditionally considered as key immunological markers of the disease (11, 12). The La/SSB protein is involved in RNA metabolism pathways, including binding and protecting poly(U) termini of nascent RNA polymerase III transcripts from exonuclease digestion, processing 5' and 3' ends of pre-tRNA precursors, acting as an RNA chaperone (13). Autoantibodies reacting with this protein are found in the sera of patients with pSS, overwhelmingly linked to the presence of concomitant anti-Ro/SSA antibodies. The presence of anti-Ro/SSA and/or anti-La/SSB was a mandatory criterion for the fulfilment of the 2002 AECG and 2012 ACR criteria for SS in the absence of focal sialadenitis (1). However, Baer *et al.* (14) supported that the La/SSB-positive/Ro/SSA-negative antibody profile should be interpreted cautiously in a patient with suspected SS. Derived from the results reported by these authors from the SICCA cohort, La/SSB autoantibodies were eliminated from the 2016 ACR/EULAR classification criteria for SS (10). Studies in patients with isolated La/SSB autoantibodies are very few (14, 15), with no information about their systemic phenotype classified according to the EULAR

Sjögren's Syndrome Disease Activity Index (ESSDAI) classification (16).

The objective of this study was to analyse the systemic ESSDAI phenotype associated with the presence of isolated anti-La/SSB antibodies in patients with pSS fulfilling the 2002 classification criteria from a large international registry.

Methods

Patients

The Big Data Sjögren Project Consortium is an international, multicentre registry established in 2014 to take a "high-definition" picture of the main features of pSS following a worldwide data-sharing cooperative merging of pre-existing clinical SS databases from leading centres on clinical research in SS of the 5 continents (17). The centres share a harmonised data infrastructure and conduct cooperative online efforts in order to refine already collected data in each centre. Inclusion criteria were the fulfilment of the 2002 classification criteria (18). Exclusion criteria for considering SS as a primary disease were chronic HCV/HIV infections, previous lymphoproliferative processes, and associated systemic autoimmune diseases. Diagnostic tests for SS (ocular tests, oral tests and salivary gland biopsy) were carried out according to the recommendations of the European Community Study Group (19). The study was approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, registry HCB/2015/0869).

Definition of variables

Disease diagnosis was defined as the time when the attending physician confirmed fulfilment of the 2002 classification criteria (18). At this time, the main features of the disease were retrospectively collected and analysed. The following clinical variables were selected in order to be harmonised and further refined: age, gender, ethnicity, country of residence, fulfilment of the 2002 classification criteria items, anti-nuclear antibodies, rheumatoid factor, C3 and C4 levels, cryoglobulins, and organ-by-organ ESSDAI scores. By June 2020, the participant centres had included 12,862 valid patients from 25

countries; for this specific study, we excluded 778 patients due to a lack of recorded information on the clinical ESSDAI domains (598 patients) and/or immunological phenotype at diagnosis (196 patients). Systemic involvement at diagnosis was retrospectively classified and scored according to the ESSDAI (20), which evaluates 12 domains or organ systems, and clinESSDAI (21), which evaluates the same domains but excluding the last (biological domain). Each domain is divided into 3-4 levels according to the degree of activity and scored as 0 (no activity), 1 (low activity), 2 (moderate activity) or 3 (high activity). Disease activity states (DAS) were calculated as: no activity (global score = 0), low activity (global score 1-4), moderate activity (global score 5-13) and high activity (global score ≥ 14). Different combination patterns of anti-Ro/SSA/La/SSB antibodies allowed obtaining the following four immunological phenotypes: isolated anti-Ro/SSA, isolated anti-La/SSB, double positive (combined Ro/SSA and La/SSB) and immune-negative. A new variable "activity subsets" was created with the following categories: no activity (ESSDAI score = 0), no high activity in any ESSDAI domain and high activity in ≥ 1 ESSDAI domain.

Statistical analysis

Descriptive data are presented as mean and standard deviation (SD) for continuous variables and numbers and percentages (%) for categorical variables. The Chi-square test was used to study systemic activity at the time of diagnosis of pSS according to the immunological phenotypes. One-way analysis of variance test was used to compare the mean ESSDAI and clinESSDAI scores. Clustered bar charts and polar area charts were constructed to compare systemic activity according to the immunological phenotypes. To handle missing data due to non-evaluated features, "available case analysis" was assumed for the comparisons according to the immunological phenotypes. All significance tests were two-tailed and values of $p < 0.05$ were considered significant. p -values were not adjusted for multiple testing. All analyses were

conducted using the R v. 3.6.3. for Windows statistical software package (<https://www.R-project.org/>).

Results

The cohort included 12,084 patients (11,293 females, mean 52.4 years) with recorded ESSDAI scores available. The baseline characteristics of the 279 patients with pSS carrying isolated La/SSB autoantibodies are summarised in Table I. Two hundred and sixty-three (94.3%) were women with a mean age at diagnosis of pSS of 51.7 (standard deviation 14.9) years. The frequencies of fulfilment of the 2002 classification criteria items were 95.0% for dry eye, 92.8% for dry mouth, 85.9% for abnormal ocular tests, 69.9% for positive minor salivary gland biopsy and 80.2% for abnormal oral diagnostic tests. The frequency of other immunological markers at diagnosis was: positive ANA in 65.7% of patients, positive RF in 23.8%, low C3 levels in 11.1%, low C4 levels in 9.5% and positive serum cryoglobulins in 2.1% of patients.

The mean total ESSDAI score at diagnosis of patients with pSS carrying isolated anti-La/SSB was 6.0 (SD 7.0); 80.4% of patients had systemic activity (global ESSDAI score ≥ 1) at diagnosis (Table I). The domains with the highest frequency of active patients were the biological (42.8%), glandular (36.8%) and articular (31.2%) domains. The systemic activity at the time of diagnosis of pSS was widely associated with the immunological phenotypes (Table II and Fig. 1). Patients with isolated anti-La/SSB showed significantly increased frequency of activity in lymphadenopathy, glandular and muscular ESSDAI domains compared with the other immunological phenotypes ($p < 0.001$). Although there was no association between immunological phenotypes and articular, pulmonary, peripheral nervous system (PNS), central nervous system (CNS) ESSDAI domains ($p > 0.05$) (Table II), patients with isolated La/SSB antibodies showed a higher frequency of active patients in all ESSDAI domains but two (articular and peripheral nerve) in comparison with immune-negative patients, and even a higher absolute frequency in six

clinical ESSDAI domains in comparison with patients with isolated Ro/SSA (Fig. 1). In addition, patients with isolated La/SSB antibodies showed a higher frequency of active patients in two ESSDAI domains (pulmonary and particularly in the glandular domain) with respect to the most active immunological subset (double-positive antibodies). The distribution of the degree of activity (no activity, low, moderate and high) for each domain according to different immunological phenotypes is summarised in Table III. Between the three phenotypes (combined Ro/SSA and La/SSB, isolated anti-La/SSB and isolated anti-Ro/SSA), moderate and high activity are globally more frequent in patients with combined Ro/SSA and La/SSB (Table III and Fig. 2). Patients with isolated La/SSB autoantibodies had a lower frequency of patients with moderate/high activity in the lymphadenopathy, cutaneous, pulmonary, muscular and CNS ESSDAI involvements, even in comparison with immune-negative patients, while in contrast, they showed a higher rate of patients with moderate/high activity in the articular domain in comparison with the other immunological phenotypes, except for isolated La/SSB. Meanwhile, isolated anti-La/SSB was mainly associated with low activity. Even in ESSDAI domains where patients with isolated anti-La/SSB had the highest frequencies of systemic activity (lymphadenopathy and muscular), the percentage of patients with moderate or high activity was higher in combined Ro/SSA and La/SSB group than isolated anti-La/SSB (3.3% in combined Ro/SSA and La/SSB vs. 2.2% in isolated anti-La/SSB for lymphadenopathy domain; 1.1% in combined Ro/SSA and La/SSB vs. 0% in isolated anti-La/SSB for muscular domain) (Table III and Fig. 2).

Discussion

Autoantibodies are the only laboratory criterion included in the three last international classification criteria for pSS proposed since 1993 (10, 18, 19), although the number has been reduced progressively. The 1993 European included 4 antibodies (ANA, RF, Ro/SSA and/or La/SSB), the 2002 Criteria

2 (anti-Ro/SSA and anti-La/SSB) and the 2016 ACR/EULAR, only one (Ro/SSA) (10, 18, 19). Despite the progressive restrictive inclusion of autoantibodies, sensitivity/specificity figures obtained by each set of criteria were quite similar. After the exclusion of the La/SSB autoantibodies from the 2016 criteria, sensitivity and specificity were 96%/95%, respectively, while for the 2002 criteria, the figures were 96%/94%.

Human La/SSB protein is an essential factor in the biology of both coding and non-coding RNAs, and is one of the principal autoantigens implicated in the etiopathogenesis of SS (13) considering the frequency of anti-La/SSB antibodies, their association with the main SS-related features and their prognostic significance (22). Anti-La/SSB antibodies are detected in 45% of patients, and their concomitant presence with anti-Ro/SSA antibodies has been associated with a higher frequency of abnormal diagnostic tests and higher mean ESSDAI scores in comparison with immune-negative patients (23). Anti-La/SSB antibodies have a high diagnostic specificity for SS (24) and Theander *et al.* (25) reported that the predictive value for developing the disease was highest in asymptomatic carriers of anti-La/SSB antibodies (OR = 34) than in those carrying anti-Ro60 antibodies (OR = 30). The etiopathogenic central role of the La/SSB autoantigen in SS, confirmed by several studies published in the last 20 years, clearly supports the inclusion of La/SSB autoantibodies into the typical immunological spectrum of the disease (26-30).

A recent interest in characterising SS patients carrying isolated La/SSB autoantibodies has emerged after the exclusion of this subset of patients from the recently proposed European/American classification criteria (10). This exclusion was based on the manuscript published by Baer *et al.* (14) in the SICCA cohort reporting that patients with isolated La/SSB antibodies had lower ocular staining and salivary focus scores in comparison with the seronegative group, although they also had a higher frequency of dry mouth, higher median Schirmer test and a higher frequency

Table I. Baseline characteristics of 279 patients with primary Sjögren's syndrome carrying isolated La/SSB autoantibodies.

Variable	Patients (%)
Gender (female)	263 (94.3%)
Age at diagnosis	51.7 ± 14.9
Dry eye	265 (95%)
Dry mouth	259 (92.8%)
Abnormal ocular tests	214/249 (85.9%)
Schirmer's test	193/249 (77.5%)
Rose bengal score/other ocular dye score	121/159 (76.1%)
Positive minor salivary gland biopsy	128/183 (69.9%)
Abnormal oral diagnostic tests	195/243 (80.2%)
Unstimulated whole salivary flow	164/207 (79.2%)
Parotid sialography	102/121 (84.3%)
Salivary scintigraphy	87/97 (89.7%)
Antinuclear antibodies positive	178/271 (65.7%)
Rheumatoid factor positive	61/256 (23.8%)
C3 low	28/252 (11.1%)
C4 low	24/252 (9.5%)
Positive cryoglobulins	3/141 (2.1%)
Ethnicity	
White	212/274 (77.4%)
Asian	29/274 (10.6%)
Hispanic	17/274 (6.2%)
Black/African-American	2/274 (0.7%)
Others	14/274 (5.1%)
Geolocation	
Europe	151/250 (60.4%)
America	68/250 (27.2%)
Asia	28/250 (11.2%)
Africa	3/250 (1.2%)
Australia	0/250 (0%)
ESSDAI (n=271)	6.0 ± 7.0
ClinESSDAI (n=272)	6.3 ± 7.8
Disease activity states	
Low (ESSDAI score 1-4)	145/271 (53.5%)
Moderate (ESSDAI score 5-13)	97/271 (35.8%)
High (ESSDAI score ≥14)	29/271 (10.7%)
Activity subsets	
No activity (ESSDAI = 0)	53/271 (19.6%)
No high activity in any domain	201/271 (74.2%)
High activity in at least 1 domain	17/271 (6.3%)
ESSDAI domains [†]	
Constitutional	27/272 (9.9%)
Lymphadenopathy	29/272 (10.7%)
Glandular	100/272 (36.8%)
Articular	85/272 (31.2%)
Cutaneous	14/272 (5.1%)
Pulmonary	37/272 (13.6%)
Renal	12/272 (4.4%)
Muscular	21/272 (7.7%)
Peripheral nervous system	12/272 (4.4%)
Central nervous system	6/272 (2.2%)
Haematological	46/272 (16.9%)
Biological	116/271 (42.8%)

[†]Any score ≥1 in each domain.

of abnormal unstimulated whole saliva flow results. Comparisons were made among patients with a suspected SS (either primary or associated), and among the 3514 SICCA participants enrolled, only 45% fulfilled the 2002/2012 criteria. In contrast, another study carried

out in pSS patients compared the clinical manifestations of 29 anti-Ro/SSA-negative, anti-La/SSB-positive subjects to the manifestations found in other immunological subgroups and found no significant differences for the objective findings of lacrimal or salivary gland

dysfunctions, although those carrying isolated La/SSB autoantibodies had a lower mean age at diagnosis and some systemic features were numerically less frequent, especially joint disease and persistent cough, in comparison with those carrying Ro/SSA autoantibodies (15).

The immunological profile defined by the presence of circulating Ro/SSA and/or La/SSB autoantibodies has a key role in driving the systemic phenotype of pSS (22). Therefore, biopsy-proven patients with pSS without circulating anti-Ro/SSA/La/SSB antibodies have a specific phenotypic profile characterised by an older age, a higher frequency of sicca symptoms, a lower frequency of abnormal diagnostic tests and a milder immunological profile (23), and also had a lower risk of lymphoma and a lower level of B-cell expansion (31). In contrast, the presence of anti-Ro/SSA-La/SSB antibodies is clearly associated with a more active systemic phenotype, especially when patients carried both autoantibodies (double Ro/SSA-La/SSB positivity). Quartuccio *et al.* compared Ro/SSA-La/SSB(+) and Ro/SSA-La/SSB(-) patients and found a younger age at diagnosis and a higher frequency of glandular swelling, purpura, leukopenia, lymphoma, low C3, low C4, hypergammaglobulinaemia, rheumatoid factor and serum cryoglobulins in Ro/SSA-La/SSB(+) patients (31). We also reported that anti-Ro/SSA and anti-La/SSB antibodies are associated with global systemic activity, especially anti-Ro/SSA, whose positivity at diagnosis also correlated with a higher activity score in the articular, cutaneous and renal domains (3), and other studies have reported similar findings (24, 32, 33). In contrast, patients carrying only one autoantibody (isolated Ro/SSA, or isolated La/SSB) may have an intermediate systemic phenotype (22).

Our results found that patients carrying isolated La/SSB autoantibodies had a systemic ESSDAI phenotype clearly different from that reported in immune-negative pSS patients. Several ESSDAI parameters, including general scores (ESSDAI, clinESSDAI, moderate/high DAS) and organ-specific clinical domains, pointed out a significantly

Table II. Systemic activity at the time of diagnosis of pSS according to the immunological phenotype.

	Immunological phenotypes					p
	n	Double positive (Ro/SSA and La/SSB) (n=5401)	Isolated anti-La/SSB (n=279)	Isolated anti-Ro/SSA (n=4050)	Immunonegative (n=2936)	
ESSDAI	11,674	7.0 ± 8.4	6.0 ± 7.0	5.5 ± 6.5	4.4 ± 5.7	<0.001
ClinESSDAI	11,918	7.0 ± 9.2	6.3 ± 7.8	5.7 ± 7.2	4.9 ± 6.3	<0.001
Disease activity states	11,674					<0.001
Low (ESSDAI score 1-4)		2546 (51.1)	145 (53.5)	2263 (59.5)	1744 (66.7)	
Moderate (ESSDAI score 5-13)		1707 (34.2)	97 (35.8)	1127 (29.6)	651 (24.9)	
High (ESSDAI score ≥ 14)		731 (14.7)	29 (10.7)	416 (10.9)	218 (8.3)	
Activity subsets	11,717					<0.001
No activity (ESSDAI = 0)		627 (12.5)	53 (19.6)	770 (20.2)	766 (29.2)	
No high activity in any domain		3968 (79.3)	201 (74.2)	2777 (72.7)	1687 (64.2)	
High activity in at least 1 domain		406 (8.1)	17 (6.3)	272 (7.1)	173 (6.6)	
ESSDAI domains[†]						
Constitutional	12,084	575 (11.2)	27 (9.9)	353 (9.0)	205 (7.4)	<0.001
Lymphadenopathy	12,084	519 (10.1)	29 (10.7)	283 (7.2)	190 (6.9)	<0.001
Glandular	12,084	1158 (22.6)	100 (36.8)	725 (18.5)	459 (16.6)	<0.001
Articular	12,084	1886 (36.7)	85 (31.2)	1459 (37.3)	1024 (37.0)	0.253
Cutaneous	12,084	641 (12.5)	14 (5.1)	317 (8.1)	136 (4.9)	<0.001
Pulmonary	12,084	555 (10.8)	37 (13.6)	392 (10.0)	271 (9.8)	0.132
Renal	12,084	315 (6.1)	12 (4.4)	139 (3.6)	46 (1.7)	<0.001
Muscular	12,084	129 (2.5)	21 (7.7)	80 (2.0)	31 (1.1)	<0.001
Peripheral nervous system	12,084	304 (5.9)	12 (4.4)	217 (5.5)	158 (5.7)	0.692
Central nervous system	12,084	94 (1.8)	6 (2.2)	64 (1.6)	59 (2.1)	0.495
Haematological	11,918	1427 (28.2)	46 (16.9)	797 (20.6)	343 (12.7)	<0.001
Biological	11,750	3234 (64.3)	116 (42.8)	1769 (46.3)	726 (27.6)	<0.001

[†]Any score ≥1 in each domain.

Table III. Level of activity in each ESSDAI domain at diagnosis stratified by immunological phenotypes.

ESSDAI Domains [weight factor]	Double positive (Ro/SSA and La/SSB)			Isolated anti-La/SSB			Isolated anti-Ro/SSA			Immunonegative		
	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
Constitutional [3]	473 (9.2)	102 (2)	*	23 (8.5)	4 (1.5)	*	309 (7.9)	44 (1.1)	*	188 (6.8)	17 (0.6)	*
Lymphadenopathy [4]	349 (6.8)	108 (2.1)	62 (1.2)	23 (8.5)	5 (1.8)	1 (0.4)	188 (4.8)	55 (1.4)	40 (1)	134 (4.8)	31 (1.1)	25 (0.9)
Glandular [2]	846 (16.5)	312 (6.1)	*	83 (30.5)	17 (6.2)	*	569 (14.6)	156 (4)	*	380 (13.7)	79 (2.9)	*
Articular [2]	1382 (26.9)	407 (7.9)	97 (1.9)	58 (21.3)	17 (6.2)	10 (3.7)	1037 (26.5)	339 (8.7)	83 (2.1)	757 (27.3)	207 (7.5)	60 (2.2)
Cutaneous [3]	152 (3)	429 (8.4)	60 (1.2)	6 (2.2)	6 (2.2)	2 (0.7)	109 (2.8)	183 (4.7)	25 (0.6)	48 (1.7)	75 (2.7)	13 (0.5)
Pulmonary [5]	337 (6.6)	177 (3.4)	41 (0.8)	31 (11.4)	5 (1.8)	1 (0.4)	258 (6.6)	97 (2.5)	37 (0.9)	180 (6.5)	73 (2.6)	18 (0.7)
Renal [5]	177 (3.4)	87 (1.7)	51 (1)	8 (2.9)	4 (1.5)	0 (0)	96 (2.5)	31 (0.8)	12 (0.3)	26 (0.9)	10 (0.4)	10 (0.4)
Muscular [6]	75 (1.5)	35 (0.7)	19 (0.4)	21 (7.7)	0 (0)	0 (0)	55 (1.4)	20 (0.5)	5 (0.1)	24 (0.9)	4 (0.1)	3 (0.1)
Peripheral nervous system [5]	164 (3.2)	110 (2.1)	30 (0.6)	8 (2.9)	3 (1.1)	1 (0.4)	117 (3)	76 (1.9)	24 (0.6)	109 (3.9)	33 (1.2)	16 (0.6)
Central nervous system [5]	**	58 (1.1)	36 (0.7)	**	6 (2.2)	0 (0)	**	39 (1)	25 (0.6)	**	7 (1.3)	22 (0.8)
Haematological [2]	1145 (22.6)	218 (4.3)	64 (1.3)	35 (12.9)	6 (2.2)	5 (1.8)	623 (16.1)	135 (3.5)	39 (1)	283 (10.5)	47 (1.7)	13 (0.5)
Biological [1]	1781 (35.4)	1453 (28.9)	*	91 (33.6)	25 (9.2)	*	1211 (31.7)	558 (14.6)	*	564 (21.5)	162 (6.2)	*

*Corresponding domain does not include "high" activity level.** Corresponding domain does not include "low" activity level.

higher systemic activity in the subset of patients with isolated La/SSB autoantibodies, not only in comparison with immune-negative subset, but also in comparison with patients carrying isolated Ro/SSA autoantibodies for most of the clinical ESSDAI domains, suggesting a systemic disease pattern closer to that reported in the double-positive immunological subset of patients. However, some findings showed

specific systemic characteristics not previously reported, especially when a more detailed analysis of the distribution of patients with low, moderate and high activity was carried out in clinical ESSDAI domains among the four immunological subsets of patients. Thus, patients with isolated anti-La/SSB antibodies had a higher frequency of active patients (global ESSDAI score ≥1) in most clinical ESSDAI domains in

comparison with the immune-negative and isolated Ro/SSA subsets, but the frequency of active patients with moderate or high activity was significantly lower. In contrast, patients with isolated La/SSB showed the lowest frequency of active patients in the articular domain compared with the other immune phenotypes, but among the active patients, the frequency of those classified as moderate and high activity was

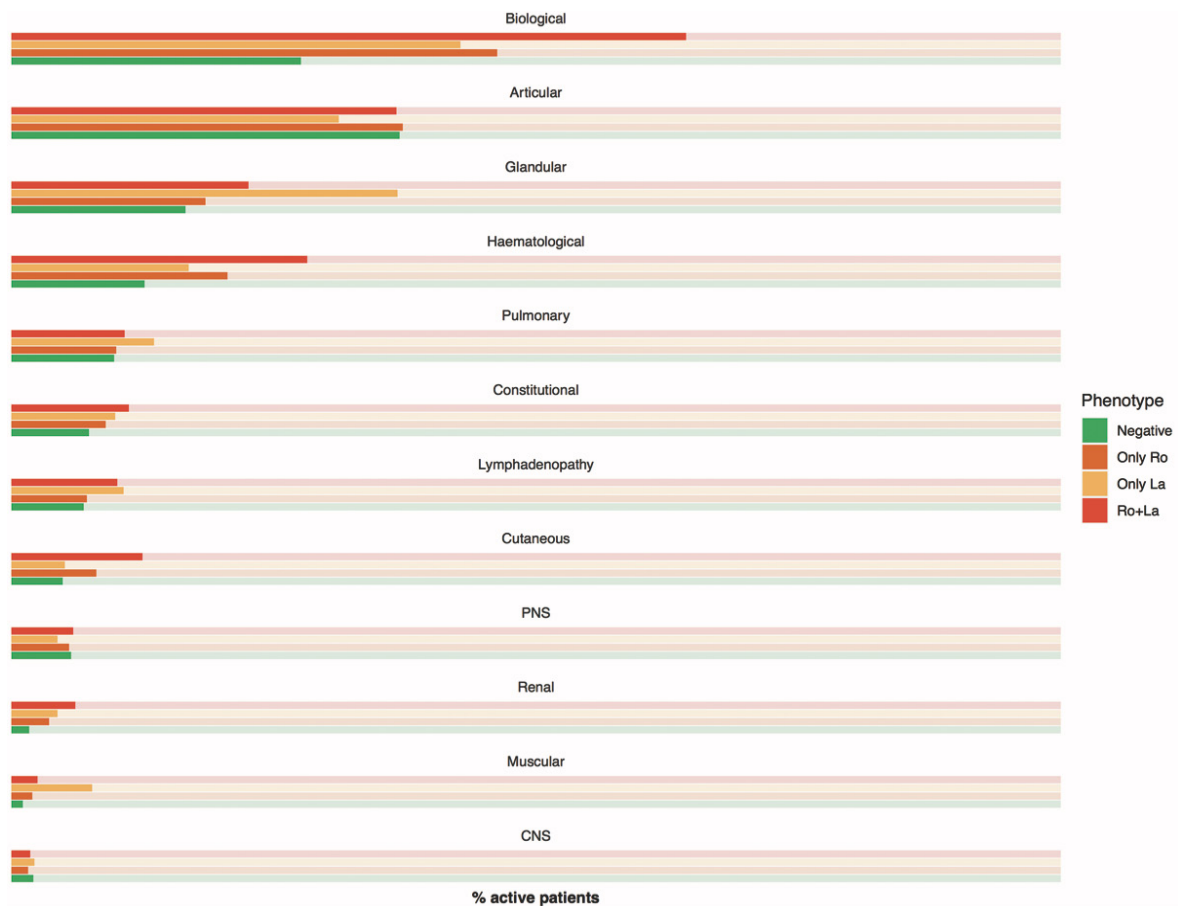


Fig. 1. Frequency of active patients (ESSDAI ≥ 1) in the ESSDAI domains according to the Ro/SSA and La/SSB immunological profile.

the highest among all immunological subtypes, except for isolated La/SSB. Considering the lower mean age at SS diagnosis of patients carrying isolated La/SSB antibodies (15, 23) suggesting that these patients may develop the disease early (4), the systemic phenotype we found is very specific and clearly different from that reported in the other immunological subtypes. There are no studies prospectively following patients with isolated La/SSB antibodies, and it would be interesting to analyse how these patients may develop a more complicated disease during follow-up. Although previous studies have suggested that patients with isolated La/SSB antibodies should be excluded when searching for a more aetiopathogenic – homogeneous population to study (*i.e.* clinical trials) (14, 15), our results and other findings previously reported are not supporting this. Firstly, as previously mentioned, is the key role of anti-La/SSB antibodies as the earliest immunological marker related

to the development of pSS in asymptomatic patients (25). Secondly, is the lack of significant differences in the results of the main diagnostic tests for ocular and oral involvement stated by the studies carried out in pSS patients (14, 15, 23). Thirdly, is that the systemic phenotype related to isolated La/SSB antibodies is much closer to that reported for patients with combined Ro/SSA-La/SSB antibodies than for the systemic phenotype reported in immune-negative patients, conferring circulating Ro/SSA-La/SSB autoantibodies a central role for driving the systemic disease expression (higher in those carrying both antibodies, moderate in those carrying a single antibody, mild in those with negative antibodies) (22). When the search for a homogeneous SS patient population was claimed by some studies as the key reason for excluding patients carrying isolated anti-La/SSB antibodies, the same reasoning could be applied for excluding patients without circulating Ro/SSA

antibodies. SS patients who are anti-Ro/SSA positive anti-La/SSB negative and classified as SS by a positive biopsy, constitute a subset of patients that is so far distinct from immune-positive patients in terms of systemic disease and prognosis.

The results of this study should be interpreted with caution, and some limitations should be pointed out. Studies including very large number of cases may detect some differences which, although statistically significant, may not be relevant clinically, and further studies are necessary to confirm their clinical relevance in smaller, but more homogeneous populations. The predominant presence of European patients could also limit the generalisation of the results in other ethnic subpopulations less frequently reported. Other sources of heterogeneity may include the variable amount of missing data for some variables and the immunological assays used by the different centres. Despite the limitations, the number of

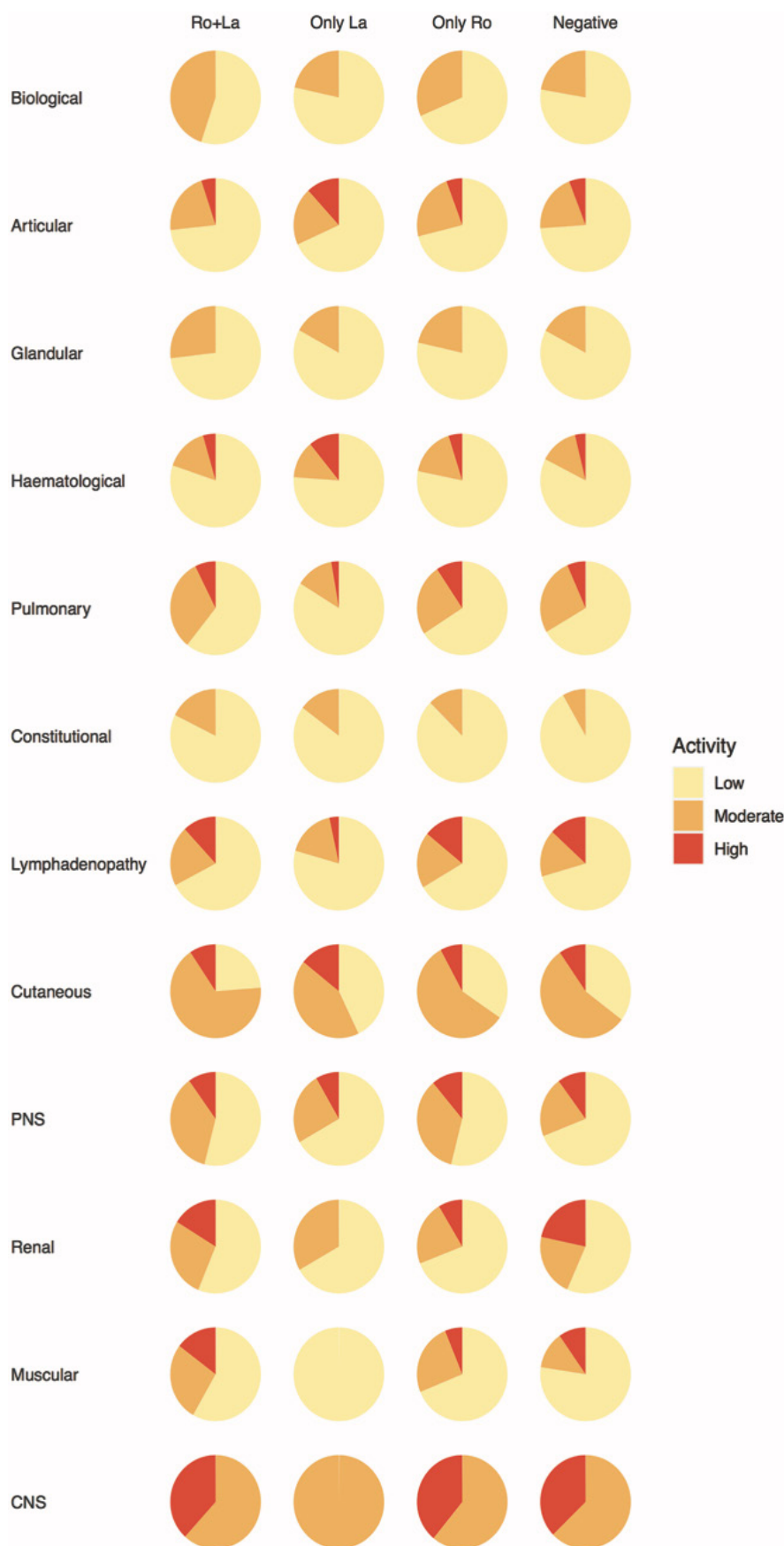


Fig. 2. Frequency of active patients presenting with low, moderate and high activity in the ESSDAI domains according to the Ro/SSA and La/SSB immunological profile.

patients with isolated La/SSB antibodies we analysed (n=279) is 5-times higher than that reported in the study by Baer *et al.* and 10-times higher than that reported in the study by Danda *et al.*, conferring a more solid interpretation of the results.

In summary, patients carrying isolated anti-La/SSB antibodies represent a very small subset of patients (2%) with an active systemic SS phenotype much closer to that found in patients carrying anti-Ro/SSA antibodies than that reported for immune-negative Ro/SSA-La/SSB patients. Our findings identified a very specific systemic phenotype characterised by a significant frequency of active patients in most organ-specific clinical ESSDAI domains but with a relative low frequency of the highest severe involvements. Considering our results in the largest series of patients carrying isolated La/SSB antibodies reported until now, pSS still remains the best clinical diagnosis for this subset of patients.

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Competing interests

T. Mandl works as medical advisor for Novartis;

M. Rischmueller is an investigator on clinical trials in Sjögren’s syndrome for BMS and Novartis;

S.E. Carsons has received research funds from Novartis and Glaxo Smith Kline;

J. Morel has received less than 8000 Euro from BMS and GSK.

The other authors have declared no competing interests.

References

- BRITO-ZERÓN P, BALDINI C, BOOTSMA H *et al.*: Sjögren syndrome. *Nat Rev Dis Prim* 2016; 2: 16047.
- MARIETTE X, CRISWELL LA: Primary Sjögren's syndrome. *N Engl J Med* 2018; 378: 931-9.
- RAMOS-CASALS M, BRITO-ZERÓN P, SOLANS R *et al.*: Systemic involvement in primary Sjögren's syndrome evaluated by the EULAR-SS disease activity index: Analysis of 921 Spanish patients (GEAS-SS registry). *Rheumatology* 2014; 53: 321-31.
- BRITO-ZERÓN P, THEANDER E, BALDINI C *et al.*: Early diagnosis of primary Sjögren's syndrome: EULAR-SS task force clinical recommendations. *Expert Rev Clin Immunol* 2016; 12: 137-56.
- SISÓ-ALMIRALL A, KOSTOV B, MARTÍNEZ-CARBONELL E *et al.*: The prevalence of 78 autoimmune diseases in Catalonia (MASCAT-PADRIS Big Data Project). *Autoimmun Rev* 2020; 19: 102448.
- KROESE FGM, ABDULAHAD WH, HAACKE E *et al.*: B-cell hyperactivity in primary Sjögren's syndrome. *Expert Rev Clin Immunol* 2014; 10: 483-99.
- VITALI C, BOMBARDIERI S: Sjögren's syndrome, mixed cryoglobulinaemia and the monoclonal gammopathies. *Clin Exp Rheumatol* 1996; 14 (Suppl. 14): S59-63.
- BRITO-ZERÓN P, RAMOS-CASALS M, BOVE A *et al.*: Predicting adverse outcomes in primary Sjögren's syndrome: identification of prognostic factors. *Rheumatology* 2007; 46: 1359-62.
- RAMOS-CASALS M, BRITO-ZERÓN P, SISÓ-ALMIRALL A *et al.*: Primary Sjögren syndrome. *BMJ* 2012; 344.
- SHIBOSKI CH, SHIBOSKI SC, SEROR R *et al.*: 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome. *Ann Rheum Dis* 2017; 76: 9-16.
- RAMOS-CASALS M, BRITO-ZERÓN P, PEREZ-DE-LIS M *et al.*: Sjögren syndrome or Sjögren disease? The histological and immunological bias caused by the 2002 criteria. *Clin Rev Allergy Immunol* 2010; 38: 178-85.
- NOCTURNE G, VIRONE A, NG W-F *et al.*: Rheumatoid factor and disease activity are independent predictors of lymphoma in primary Sjögren's Syndrome. *Arthritis Rheumatol* 2016; 68: 977-85.
- BRITO-ZERÓN P, GHEITASI H, RETAMOZO S *et al.*: How hepatitis C virus modifies the immunological profile of Sjögren syndrome: analysis of 783 patients. *Arthritis Res Ther* 2015; 17: 250.
- BAER AN, MCADAMS DEMARCO M, SHIBOSKI SC *et al.*: The SSB-positive/SSA-negative antibody profile is not associated with key phenotypic features of Sjögren's syndrome. *Ann Rheum Dis* 2015; 74: 1557-61.
- DANDA D, SHARMA R, TRUONG D *et al.*: Anti-La/SSB positive, anti-Ro/SSA negative subset of primary Sjögren's syndrome: anti-La/SSB is a reality but is the disease? *Clin Exp Rheumatol* 2017; 35: 438-44.
- SEROR R, GOTTENBERG JE, DEVAUCHELLEN-PENSEC V *et al.*: European league against Rheumatism Sjögren's syndrome disease activity index and European League Against Rheumatism Sjögren's syndrome patient-reported index: A complete picture of primary Sjögren's syndrome patients. *Arthritis Care Res* 2013; 65: 1358-64.
- BRITO-ZERÓN P, ACAR-DENIZLI N, ZEHER M *et al.*: Influence of geolocation and ethnicity on the phenotypic expression of primary Sjögren's syndrome at diagnosis in 8310 patients: a cross-sectional study from the Big Data Sjögren Project Consortium. *Ann Rheum Dis* 2017; 76: 1042-50.
- VITALI C, BOMBARDIERI S, JONSSON R *et al.*: Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-8.
- VITALI C, BOMBARDIERI S, MOUTSOPOULOS HM *et al.*: Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993; 36: 340-7.
- SEROR R, THEANDER E, BRUN JG *et al.*: Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). *Ann Rheum Dis* 2015; 74: 859-66.
- SEROR R, MEINERS P, BARON G *et al.*: Development of the ClinESSDAI: A clinical score without biological domain. A tool for biological studies. *Ann Rheum Dis* 2016; 75: 1945-50.
- BRITO-ZERÓN P, RETAMOZO S, RAMOS-CASALS M: Phenotyping Sjögren's syndrome: towards a personalised management of the disease. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S198-209.
- BRITO-ZERÓN P, ACAR-DENIZLI N, NG W-F *et al.*: How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren Big Data Project). *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S102-12.
- VENABLES PJ, SHATTLES W, PEASE CT *et al.*: Anti-La/SSB (SS-B): a diagnostic criterion for Sjögren's syndrome? *Clin Exp Rheumatol* 1989; 7: 181-4.
- THEANDER E, JONSSON R, SJÖSTRÖM B *et al.*: Prediction of Sjögren's Syndrome Years Before Diagnosis and Identification of Patients With Early Onset and Severe Disease Course by Autoantibody Profiling. *Arthritis Rheumatol* 2015; 67: 2427-36.
- TZIOUFAS AG, HANTOUMI I, POLIHONIS M *et al.*: Autoantibodies to La/SSB/SSB in patients with primary Sjögren's syndrome (pSS) are associated with upregulation of La/SSB/SSB mRNA in minor salivary gland biopsies (MSGs). *J Autoimmun* 1999; 13: 429-34.
- GOURZI VC, KAPSOGEORGOU EK, KYRIAKIDIS NC *et al.*: Study of microRNAs (miRNAs) that are predicted to target the autoantigens Ro/SSA/SSA and La/SSB/SSB in primary Sjögren's Syndrome. *Clin Exp Immunol* 2015; 182: 14-22.
- YACIUK JC, PAN Y, SCHWARZ K *et al.*: Defective selection of thymic regulatory T cells accompanies autoimmunity and pulmonary infiltrates in Tcr α -deficient mice double transgenic for human La/SSB/Sjögren's syndrome-B and human La/SSB-specific TCR. *J Immunol* 2015; 194: 1514-22.
- PAN Z-J, HORTON CG, LAWRENCE C *et al.*: Plasmacytoid dendritic cells and type I interferon promote peripheral expansion of forkhead box protein 3(+) regulatory T cells specific for the ubiquitous RNA-binding nuclear antigen La/SSB/Sjögren's syndrome (SS)-B. *Clin Exp Immunol* 2016; 186: 18-29.
- MAHONY R, BROADBENT L, MAIER-MOORE JS *et al.*: The RNA binding protein La/SSB/SS-B promotes RIG-I-mediated type I and type III IFN responses following Sendai viral infection. *Sci Rep* 2017; 7: 14537.
- QUARTUCCIO L, BALDINI C, BARTOLONI E *et al.*: Anti-SSA/SSB-negative Sjögren's syndrome shows a lower prevalence of lymphoproliferative manifestations, and a lower risk of lymphoma evolution. *Autoimmun Rev* 2015; 14: 1019-22.
- TER BORG EJ, KELDER JC: Lower prevalence of extra-glandular manifestations and anti-SSB antibodies in patients with primary Sjögren's syndrome and widespread pain: evidence for a relatively benign subset. *Clin Exp Rheumatol* 2014; 32: 349-53. <http://europepmc.org/abstract/med/24529195>
- LOCHT H, PELCK R, MANTHORPE R: Clinical manifestations correlated to the prevalence of autoantibodies in a large (n=321) cohort of patients with primary Sjögren's syndrome: a comparison of patients initially diagnosed according to the Copenhagen classification criteria with the America. *Autoimmun Rev* 2005; 4: 276-1.