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Sjögren's syndrome at the crossroad of polyautoimmunity

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ABSTRACT

The coexistence of autoimmune diseases (i.e., polyautoimmunity) in Sjögren's syndrome (SS) was investigated in a cross-sectional study involving 410 patients. Logistic regression analysis and the Rogers and Tanimoto index were used to evaluate risk factors and clustering, respectively. There were 134 (32.6%) patients with polyautoimmunity. The most frequent and closer coexistent diseases were autoimmune thyroid disease (21.5%), rheumatoid arthritis (8.3%), systemic lupus erythematosus (7.6%), and inflammatory bowel disease (0.7%) which together constituted a cluster group. There were 35 (8.5%) patients with multiple autoimmune syndrome. Besides disease duration, a history of habitual smoking and spontaneous abortion were found to be risk factors for the developing of polyautoimmunity. This study discloses a high prevalence of polyautoimmunity in SS, its associated risk factors and the grouping pattern of such a condition. These results may serve to define plausible approaches to study the common mechanisms of autoimmune diseases.

1. Introduction

Autoimmune diseases (ADs) are complex diseases resulting of the interaction between both genetics and environmental factors over time. They begin with the loss of immunological tolerance to self-antigens and later manifests as a heterogeneous group of disorders resulting in a spectrum of syndromes that can target specific organs or cause systemic compromise [1]. The etiology of ADs remains poorly understood but common features among them and a plausible common background for autoimmunity are emerging and being recognized [2]. It is well known that a patient that develops an AD has an increased risk of developing another one [1–3]. Polyautoimmunity (PA) and multiple autoimmune syndrome (MAS) are terms used to describe the presence of more than one AD in the same patient. PA refers to ADs co-occurring within patients while MAS is a term used when a patient develops 3 or more well-defined ADs [1].

Sjögren's syndrome (SS) is a chronic AD characterized by sicca symptoms due to the effect of lymphocyte infiltration of the exocrine glands and autoantibody production. SS has been reported to be associated with other ADs such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), autoimmune thyroid disease (AITD), systemic sclerosis (SSc) and, less frequently, multiple sclerosis (MS) and antiphospholipid syndrome (APS) [3]. Pierre Youinou and colleagues were one of the first to bring to our attention the coexistence of autoimmune disorders in patients with SS [61]. Herein, we report the prevalence of PA in a large cohort of patients with SS, its associated factors and the grouping pattern of ADs.

2. Patients and methods

2.1. Study population

This was a cross-sectional study in which 410 patients were included at the Center for Autoimmune Diseases Research (CREA), at the University of Rosario in Bogota and Medellin, Colombia, as previously described [4,5]. Patients with more than one AD fulfilled criteria for each additional disease [6]. For SS, patients met the American-European Consensus Group criteria which always included a positive minor salivary gland biopsy (MSGB) [7]. Patients fulfilled the American College of Rheumatology (ACR) criteria for the diagnosis of SLE, SSc and RA and McDonald criteria for MS [8–11]. The information on patient demographics and cumulative

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clinical and laboratory data was obtained by physical examination, interview or chart review. Twenty six ADs were searched in the SS cohort based on international validated criteria including autoimmune adrenal insufficiency (AAI: Addison's disease); alopecia areata (AA); autoimmune hepatitis (AIH), AITD; APS; biliary inflammatory disease (BID; i.e., primary sclerosing cholangitis and primary biliary cirrhosis); celiac disease (CD); demyelinating autoimmune diseases (DAD; i.e., transverse myelitis (TM) and MS); dermatomyositis/polymyositis (DM/PM); inflammatory bowel disease (IBD; i.e., ulcerative colitis and Crohn's disease); myasthenia gravis (MG); pernicious anemia (PeA); pemphigus (PF); psoriasis (Pso); RA; relapsing polychondritis (RePo); sarcoidosis (Sar); SSc; SLE; type 1 diabetes mellitus (T1D), vasculitis (Vas); and vitiligo (VIT) [5]. Data were collected in an electronic and secure database. Only data from patients with a confirmed diagnosis for each presented AD were included in the analysis. Local institutional review board and the ethics committee approved the study.

2.2. Statistical analysis

Descriptive results are shown in averages ± standard deviation or median and interquartile ranges (IQRs) and in percentages. First, bivariate analyses were done in search of the association between PA and clinical variables. These variables were analyzed using X^2 tests or Fisher's exact tests when the factors were dichotomous. Kolmogorov–Smirnov normality test was done for quantitative continuous variables and the *T*-test or Mann–Whitney *U* test for means differences were used accordingly. Next, for each clinical variable that was significantly associated with PA in bivariate analyses, a multivariate logistic regression model that included PA as the dependent variable was created. Additionally, adjustment for duration of the disease was made. *P* values of 0.05 were considered significant. Odds ratios (OR) that measured the effect size of clinical variables on PA were computed together with their 95% confidence interval (CI). The adequacy of logistic models was assessed using the Hosmer–Lemeshow goodness-of-fit test. All reported logistic models fit well. These analyses were done by using the Statistical Package for the Social Sciences (SPSS, v.20, Chicago, IL).

The Rogers and Tanimoto index [12,13], a method of distances for binary data, was used to measure PA (i.e., association of ADs). The distances reflect the closeness of two individuals in a metric space as does the Euclidian distance. This is the best distance measure for symmetric data based on the rank results and interpretability because of acceptable distribution of the data, with a wide range and a small variance. Contingency tables of size 2×2 were generated including pair of variables for comparison among all. The next mathematical formula was implemented:

$$S(x_i, x_j) = \frac{a+d}{a+2b+2c+d}$$

Finally, the results generated were incorporated in a matrix of 12×12 and therefore the cluster analysis was performed. The cluster analysis developed was a hierarchical method to identify natural clustering within the data set. This method clusters the individuals with similarities by the existent distances between them. Software R-project version 2.14.2 was applied for the analysis. The function *hclust* was implemented. This function performs a hierarchical cluster analysis using a set of dissimilarities for the *n* objects being clustered. Initially, each object is assigned to its own cluster and then the algorithm proceeds iteratively, at each stage joining the two most similar clusters, continuing until there is just a single cluster. At each stage distances between clusters are completed based on the maximum distance or their minimally similarity between its components. For these distances, a dendrogram was constructed.

3. Results

There were 410 patients included in this study of whom 276 (66.8%) presented with SS alone and 134 (32.6%) had PA. There were 35 (8.5%) patients who had two or more ADs in addition to SS (i.e., MAS). Most of the subjects were women (96.2%). Out of a total of 26 ADs evaluated there were 12 diseases coexisting with SS, of which the most frequent were AITD, RA, SLE and APS (Table 1).

Several variables were seen to be associated with SS and PA in the bivariate analysis. These included a longer duration of SS ($p = 0.003$), arthritis ($p = 0.006$), antinuclear antibody (ANA) positivity ($p = 0.018$), positive smoking status ($p = 0.002$), spontaneous abortions ($p = 0.001$), and depression ($p = 0.002$). As expected, patients with SS and PA had an increased use of disease-modifying antirheumatic drugs (DMARDs) ($p = 0.024$) (Table 2).

In the multivariable analysis, besides duration of disease ($p = 0.04$), positive smoking status and a history of spontaneous abortions remained significantly associated with PA (Table 3).

The most prevalent MAS cases were SS-AITD-SLE ($n = 8$), followed by SS-AITD-RA ($n = 6$), SS- SLE-APS ($n = 6$) and SS-RA-SLE ($n = 6$) representing different phenotypes of the disease. A categorization of our patients who developed MAS is shown in Table 4.

A total of 134 individuals with SS and PA were included for the cluster analysis. A graphic visualization of the results from the hierarchical clustering was done by means of a dendrogram (Fig. 1), showing a tree graph in which each node represents a stage from the clustering process from the bottom (i.e., 0.0) to the top (i.e., 1.0). There were eight clusters of which six were composed by an independent variable and being the most dissimilar as compared with those that were grouped in a lower level (Fig. 1).

4. Discussion

Herein we report a high prevalence of PA (32.6%) in patients with SS. Our analyses showed duration of disease, ever smoking and past history of spontaneous abortions to be risk factors for developing PA in SS. Otherwise, neither specific clinical or immunological characteristics of SS (i.e., sicca symptoms, autoantibodies, etc.) nor sociodemographic variables were associated with PA.

Our results are similar to previous results [14,15]. Of the 114 patients with SS described by Lazarus and Isenberg [15] PA was observed in 33.3% while 7.9% had MAS. Gonzalez et al. [14] investigated 285 Argentinian patients with SS and found PA in 31.5% of them with similar coexistent ADs found in our study. However, they

Table 1
Polyautoimmunity in patients with SS.

AD	n[a]	Prevalence (%)
AITD	88/410	21.5
RA	33/400	8.3
SLE	27/354	7.6
APS	9/346	2.6
SSc	5/348	1.4
VAS	3/277	1.1
IBD	2/276	0.7
MS	1/348	0.3
VIT	1/276	0.4
AIH	1/276	0.4
PSO	1/276	0.4
PeA	1/276	0.4

AD: autoimmune disease; SS: Sjögren's syndrome; AITD: autoimmune thyroid disease; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; SSc: systemic sclerosis; VAS: vasculitis; IBD: inflammatory bowel disease; MS: multiple sclerosis; VIT: vitiligo; AIH: autoimmune hepatitis; PSO: psoriasis; PeA: pernicious anemia.

[a] The denominator represents the patients in whom the AD was investigated and recorded.

Table 2
Demographic and clinical characteristics of 410 patients with SS.

Characteristic	SS alone $N = 276$	SS − polyautoimmunity $N = 134$			p
Disease duration	4 (6)[a]	7.86 (7)[a]			0.003
Age at diagnosis	46.7 ± 14.8[b]	47.9 ± 14.2[b]			0.95
Age at onset	45.4 ± 13.8[b]	43.3 ± 13.3[b]			0.197
Characteristics	SS alone (%)	SS − polyautoimmunity (%)	OR	95%CI	p
Arthritis	91/190 (47.9)	70/109 (64.2)	1.95	1.2–3.16	0.006
Urticaria	21/209 (10)	25/117 (21.4)	2.43	1.29–4.57	0.005
Use of DMARD	19/100 (19)	24/70 (34.3)	2.22	1.10–4.49	0.024
Antimalarial treatment	58/100 (58)	26/70 (37.1)	0.43	0.23–0.80	0.007
ANA positivity	112/135 (83)	87/93 (93.5)	2.98	1.16–7.63	0.018
Positive smoking status[c]	27/98 (27.6)	35/68 (51.5)	2.79	1.46–5.34	0.002
Hair dying	2/94 (2.1)	8/66 (12.1)	6.34	1.30–30.93	0.017
Dyslipidemia	7/98 (7.1)	11/62 (17.7)	2.80	1.02–7.68	0.039
Gastritis	5/94 (5.3)	9/62 (14.5)	3.02	0.96–9.49	0.049
Depression	10/94 (10.6)	19/64 (29.7)	3.55	1.52–8.27	0.002
Anemia	2/93 (2.2)	9/62 (14.5)	7.73	1.61–37.11	0.007
Osteoporosis	2/93 (2.2)	10/63 (15.9)	8.58	1.81–40.67	0.004
Spontaneous abortions[c]	2/94 (2.1)	11/63 (17.5)[d]	9.73	2.08–45.59	0.001

SD: standard deviation; SS: Sjögren's syndrome; ANA: antinuclear antibodies; OR: odds ratio; CI: confidence interval; DMARD: Disease-modifying antirheumatic drug.
[a] Median (Interquartile range).
[b] Mean ± standard deviation.
[c] Positive smoking status and spontaneous abortions were assessed by a self-reported, validated questionnaire and were defined as having smoked at least one pack year in lifetime and having at least one spontaneous abortion in lifetime, respectively.
[d] Out of 11 SS-PA patients only one had antiphospholipid syndrome.

observed a high prevalence of CD among their SS patients. Although CD shares similar physiopathologic mechanisms with SS and has been associated with other ADs such as T1D, it is a rare disease in Colombians [16,17]. We did not observe CD among our SS patients. Differences between the study of Gonzalez et al. and ours may be attributed to differences in heritability and environmental factors (i.e., foods high in gluten) between populations.

4.1. Smoking and SS

Smoking per se is considered a risk factor for both the development of ADs such as RA, SLE and AITD, and positivity of autoantibodies [18–20]. Pathophysiological mechanisms have been described including influence on lymphocytic and plasma cell functions, apoptosis and effects on cytokines and hormonal imbalances. In RA, tobacco exposure can drive development of cyclic citrullinated protein antibody (anti-CCP) and bring about a higher disease severity as manifested by joint erosions and extra-articular involvement [19,21]. Just as in SLE, habitual smoking is associated with double stranded DNA autoantibody (anti-dsDNA) positivity. An association between smoking, anti-dsDNA, development of lupus nephritis and SLE activity has been reported [18]. In AITD, smoking is associated with a higher risk of Graves' disease and Hashimoto's thyroiditis and is related to more severe eye disease [20]. Finally, a controversial effect of habitual smoking on the spectrum of the disease has been reported in SS. Manthorpe et al. [22] showed that SS patients who smoked had anti-Ro and anti-La antibodies less frequently and a lower MSGB focus score than those who did not smoke. They explain that smoking may lower the focus score in the MSGB by reducing the lymphocyte infiltration in salivary glands thus reducing the production of anti-Ro and anti-La antibodies. Karabulut et al. [23] showed an association between SS, ANA titers, and habitual smoking. In the present cohort, ANA positivity was a considered a risk factor for developing PA.

Table 3
Risk factors associated with polyautoimmunity in SS (multivariate analysis[a]).

Characteristics	SS alone %	Polyautoimmunity %	AOR	95% CI	p
Positive smoking status[b]	27.6	51.5	2.86	1.18–6.94	0.02
Abortions[b]	2.1	17.5	10.87	1.47–80.08	0.02
ANA positivity	83	93.5	8.55	1–73.05	0.05

SS: Sjögren's syndrome; ANA: antinuclear antibodies; AOR: adjusted odds ratio; CI: confidence interval.
[a] Adjusted for variables significantly associated with PA in the bivariate analysis.
[b] Positive smoking status and abortions were assessed by a self-reported, validated questionnaire and were defined as having smoked at least one pack year in lifetime and having at least one spontaneous abortion in lifetime, respectively.

Table 4
Categorization of multiple autoimmune syndrome in 35 patients in the present cohort of SS patients.

#	SS	AITD	RA	SLE	APS	SSc	VAS	IBD	VIT	AIH	PSO	PeA
1	a	a		a								
2	a	a		a								
3	a	a		a								
4	a	a		a								
5	a	a	a	a								
6	a	a		a								
7	a	a		a								
8	a	a		a								
9	b	b	b									
10	b	b	b									
11	b	b	b									
12	b	b	b									
13	b	b	b									
14	b	b	b									
15	c			c	c							
16	c			c	c							
17	c			c	c							
18	c			c	c							
19	c			c	c							
20	c			c	c							
21	d		d	d			d					
22	d		d	d			d					d
23	d		d	d								
24	d		d	d		d		d				
25	d		d	d								
26	d		d	d								
27	e	e							e			
28	e					e		e				
29	e	e					e					
30	e	e			e							
31	e				e		e					
32	e		e								e	
33	e					e				e		
34	e	e							e			
35	e			e		e						

SS: Sjögren's syndrome; AITD: autoimmune thyroid disease; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; SSc: systemic sclerosis; AIH: autoimmune hepatitis; PSO: psoriasis; VAS: vasculitis; IBD: inflammatory bowel disease; VIT: vitiligo; PeA: pernicious anemia.
[a] SS-AITD-SLE phenotype (One patient also had associated RA).
[b] SS-AITD-RA phenotype.
[c] SS-SLE-APS phenotype.
[d] SS-SLE-RA (One patient also had associated SSc and IBD, other had associated VAS, and other had associated VAS and PeA).
[e] Other multiple autoimmune syndrome phenotypes.

4.2. Spontaneous abortion in SS and APS

In the present cohort 11 patients with SS and PA presented at least one spontaneous abortion of which only one had diagnosis of

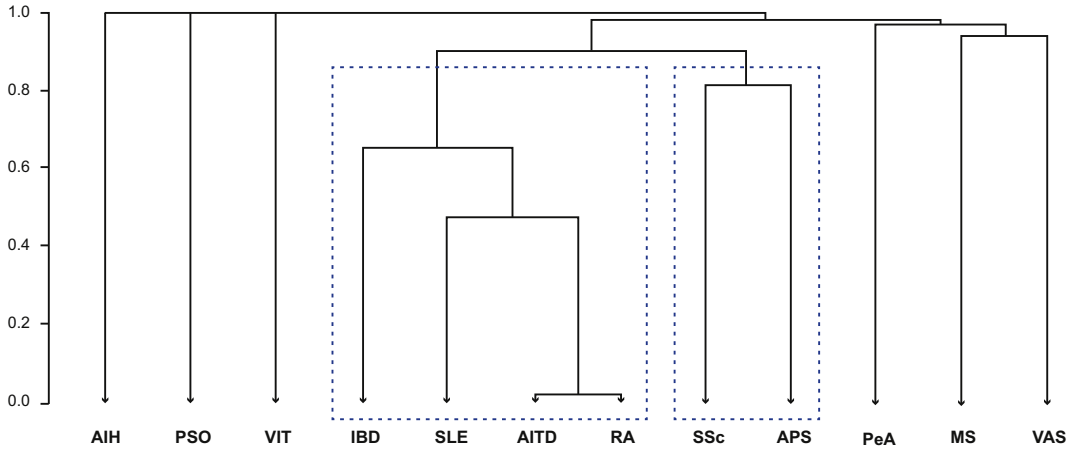

Fig. 1. *Polyautoimmunity dendrogram in Sjögren's syndrome*. Dotted line boxes show two clusters groups. The other six ADs form each one an independent group. Distances between association coefficients are shown from 0.0 to 1.0. The lower the distance the strongest the association with SS. AIH: autoimmune hepatitis; PSO: psoriasis; VIT: vitiligo; BD: inflammatory bowel disease; SLE: systemic lupus erythematosus; AITD: autoimmune thyroid disease; RA: rheumatoid arthritis; SSc: systemic sclerosis; APS: antiphospholipid syndrome; PeA: pernicious anemia; MS: multiple sclerosis; VAS: vasculitis.

APS. Other five presented associated RA and four presented SLE. The pregnancy outcomes in SS have been related to a worst prognosis when it is associated to other ADs specially SLE [24]. Other study showed that women with SS had an increased risk of fetal loss, which was not associated with elevated levels of anti-cardiolipin antibodies (ACA) or anti-Ro or anti-La. Finally they concluded that risk of fetal loss in primary SS is similar to that in women with SLE [25].

Although it is not a very common association, antiphospholipid antibodies (aPL) can be found in SS patients. Ramos-Casals et al. [26] reported that aPL were present in 13% of the patients in their study. ACA were found in 19 patients and lupus anticoagulant (LA) in 19. The majority of SS patients who had aPL had extraglandular involvement (69%) and after a followup, 4% fulfilled the classification criteria for APS [26]. In the present cohort of SS patients nine patients (2.6%) fulfilled the classification criteria for APS.

4.3. SS and AITD

The most common AD found in the present cohort associated with SS was AITD. The association between these two diseases and their relationship with other ADs are considered the most prevalent [15,27]. Patients with AITD have a ten times greater chance of developing SS, and SS patients have a nine times higher chance of developing AITD [27]. There is a phylogenetic relationship between the thyroid gland and salivary gland both of which derive from the gastrointestinal tract. They also have similar functions since both are able to concentrate iodine. Their functionality is not the only similarity. Hashimoto thyroiditis, considered the most prevalent of AITDs, shares the same lymphocytic infiltrate as SS [28]. The relationship between SS-AITD has been reported to have a prevalence of 15%–32% [29,30]. Clinical differences between patients with associated AITD have been described extensively. Lazarus et al. [15] reported that a diagnosis of AITD occurred prior to the diagnosis of SS in most of the patients in his study. Patients with SS-AITD can be characterized by a greater compromise of salivary glands [31], increased risk of developing thyroid mucosa-associated tissue (MALT) lymphoma, and increased risk of parotid lymphoma [27]. Also immunological associations have been described such as higher prevalence of antiparietal cell autoantibodies, thyroglobulin antibodies (TgAb), autoantibodies to thyroid peroxidase (TPOAb) [29]. HLA-DR3 (DRB1:03:01) was associated with SS and hypothyroidism which suggests that both of them have a possible genetic predisposition [27]. Scofield et al. [32] reported MAS associated with AITD in 30% of SS-SLE patients. In the study of Youinou's group [62] thyroid disease was more frequent in SS patients than in controls (30% versus 4%; $p = 0.004$), as were anti-TPOAb and TgAb (11% versus 3%; $P < 0.02$, and 3% versus 1%, not significant). Noteworthy, most of the patients with thyroid-related autoantibodies at entry developed AITD thereafter [62].

4.4. SS and RA

The coexistence of SS and RA has been reported in 4%–30% of the different studies [33,34]. The impact of SS on the course of RA has not been studied extensively but some authors have correlated it with a higher severity of dry eye symptoms although the relation between RA activity and dryness severity is unclear [35]. Kauppi et al. [36] also showed a higher incidence of hematological malignancies (especially non-Hodgkin's lymphoma) in patients with SS-RA. Arthritis is a common extraglandular manifestation in SS and, in most of the studies, rheumatoid factor (RF) positivity is shown in about 50% of patients. In one study, this positivity was associated with a decreased parotid salivary flow and, in another, it was associated with a higher lymphocytic infiltrate in MSGB [28,37,38]. Anti-CCP is found in patients with radiographic erosive RA but can be also found in SS, especially in those patients who have articular involvement. It is considered more sensitive and specific than the RF for the diagnosis of RA [39]. Iwamoto et al. [40] showed how a group of patients with SS with articular manifestation and patients with associated RA had a similar anti-CCP positivity. Anti-CCP can be present years before the first signs of RA so anti-CCP positivity in SS could be a predictor of RA development in the future.

4.5. SS and SLE

Previous reports showed SS can be associated with SLE in 19%–33% of the cases [33]. Baer et al. [41] pointed out that diagnosis of SLE preceded that of SS more frequently than SS preceded that of SLE. The same scenario has happened in other studies where SS is developed after a diagnosis of SLE [15,33]. This shows the importance of studying PA in patients that have already been diagnosed with any AD. Other authors showed a more insidious disease course but with a benign prognosis suggesting a possible protective effect of the SS-SLE phenotype on the development of a fully expressed

SLE. Ramos-Casals et al. [42] implied SS-SLE patients had a phenotype characterized by milder SLE systemic compromise but predominantly SS symptoms. Some of the associations included in literature are a higher incidence of photosensitivity, oral ulcers, Raynaud's phenomenon, renal tubular acidosis and interstitial lung disease in patients with SS-SLE while nephrotic syndrome, CNS involvement and facial rash are less commonly found compared with SLE only patients. In laboratory findings, these patients show higher ESR and C4 and also higher RF, anti-Ro and anti-La positivity rates [43,44]. Serological findings of both anti-Ro and anti-La antibodies in patients with only SLE can be considered a marker for a phenotype of patients who are older at disease onset, sicca complex, less renal disease, and HLA-DR3 association [41].

Manoussakis et al. [45] showed SS-SLE patients were older and had an increased frequency of the DRB1*03:01 allele compared with healthy controls. Anti-dsDNA is not usually found in patients with SS but recent studies suggest that high levels of anti-dsDNA in SS patients may develop associated SLE [26]. We have observed in SS-SLE patients a lack of influence of SS on the severity of SLE (i.e., lupus nephritis) [46].

4.6. SS and SSc

Sicca symptoms may be observed in SSc due to the fibrotic compromise of exocrine glands; however, following classification criteria, the coexistence of SS and SSc is infrequent. On the other hand, PA in SSc is a frequent condition [3], indicating that diagnosis of SSc preceded that of SS much more frequently than SS preceded that of SSc. Salliot et al. [47] reported a higher incidence of peripheral neuropathy and arthritis and, in general, a milder disease course in SS-SSc patients. Furthermore, Avouac et al. [48] related the combination to a milder disease course for SSc which, in the presence of SS, was associated with the limited cutaneous subtype and a lower prevalence of pulmonary lesions. In a recent study Koumakis et al. [49] showed that besides the coexistence of SS and SSc, SS was also frequent in first degree relatives of patients with SSc. Raynaud's Phenomenon (RP) is one of the main characteristics of SSc [15]. Garcia-Carrasco et al. [50] showed that the prevalence of RP in SS patients was 13%. This subphenotype was associated with a higher frequency of extraglandular features (cutaneous and articular involvement) and positive immunological markers (ANAS and anti-Ro) but when compared to SSc alone patients, it was related to a milder disease course [50].

4.7. SS and MS

Some of the extraglandular manifestations of SS are peripheral nervous system and central nervous system (CNS) alterations and they have been described with different prevalences [51]. Although SS-MS is not a very common association, some studies report a prevalence of 1%–3% [52]. Nevertheless, Seze et al. [53] reported a prevalence of 16.6% in a group of MS patients and proposed that SS should be screened for in patients with primary progressive MS. Annunziata et al. [54] evaluated the frequency of SS symptoms in MS patients. About 9.5% of them suffered SS symptoms. Sicca symptoms were related to higher expanded disability status scale scores, low frequency of gadolinium-enhanced MRI-positive lesions, and cerebral disturbances.

4.8. SS and MAS

MAS consists of the presence of three or more ADs in the same patient. Up to five ADs have been reported as existing simultaneously [1,55–57]. The probability of this happening goes beyond statistical chance and epidemiologic inferences which suggests that there are common pathophysiological mechanisms giving origin to all ADs present [57,58]. The prevalence of MAS has been described to be 4%–8% among patients with ADs in different studies [15,32,59]. Our group previously reported in a systematic literature review including 142 cases of MAS in which 79 cases involved SS (55.6% of the total cases) [3]. The present cohort showed a high prevalence of 4 specific phenotypes with MAS (SS-AITD-SLE, SS-AITD-RA, SS-SLE-APS, and SS-RA-SLE). This indicates common mechanisms among ADs [57].

5. Conclusions

This study confirms the high prevalence of PA in SS and discloses its associated risk factors as well as the grouping pattern of such a complication. According to our results PA does not seem to significantly influence the outcome of SS. In addition, PA explains in part the commonalities found among ADs including genetic and environmental factors. Most of the studies in SS could be confounded by variables such as small cohort sizes, variation in allele frequencies due to ancestry [60] and also by PA. This would lead to poorly reproducible results. Therefore, the assessment and clustering of PA in SS and others ADs will help to define plausible approaches to study the common mechanisms of these diseases (i.e., autoimmune tautology) [57].

6. Appreciation to Pierre Youinou

The CREA is very pleased and honored to contribute to the special issue in recognition of the enormous and outstanding work of Professor Pierre Youinou. We are very proud of his friendship and support. Pierre has recently retired from Brest University and is a figure that is well known in rheumatology and immunology and particularly his work on B cells. This is part of the Journal of Autoimmunity's special series to present review articles on timely subjects in recognition of distinguished figures in autoimmunology [63–71].

Conflict of interest statement

The authors report no conflicts of interest.

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References

[1] Anaya JM, Corena R, Castiblanco J, Rojas-Villarraga A, Shoenfeld Y. The kaleidoscope of autoimmunity: multiple autoimmune syndromes and familial autoimmunity. Expert Rev Clin Immunol 2007;3:623–35.
[2] Rojas-Villarraga A, Toro C-E, Espinosa G, Rodríguez-Velosa Y, Duarte-Rey C, Mantilla RD, et al. Factors influencing polyautoimmunity in systemic lupus erythematosus. Autoimmun Rev 2010;9:229–32.
[3] Rojas-Villarraga A, Amaya-Amaya J, Rodriguez-Rodriguez A, Mantilla RD, Anaya J-M. Introducing polyautoimmunity: secondary autoimmune diseases no longer exist. Autoimmune Dis 2012;2012:254319.
[4] Anaya JM, Correa PA, Mantilla RD, Arcos-Burgos M. HLA-DQB1, and HLA-DRB1 polymorphism in Colombian patients with primary Sjögren's syndrome. Semin Arthritis Rheum 2002;31:396–405.
[5] Amador-Patarroyo MJ, Mantilla RD, Giraldo-Villamil JM, Rodriguez-Rodriguez A, Rojas-Villarraga A, Anaya JM. Comparison of clinical and

serological findings between two populations with Sjögren's Syndrome (SS) in Colombia. J Clin Rheumatol 2012;18(Suppl.):S21.
[6] Anaya JM, Tobon GJ, Vega P, Castiblanco J. Autoimmune disease aggregation in families with primary Sjögren's syndrome. J Rheumatol 2006;33:2227–34.
[7] Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, 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; 61:554–9.
[8] Arnett FC, Edworthy SM, Bloch D, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
[9] Mcdonald WI, Compston A, Edan G, Goodkin D, Hartung H-peter, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121–7.
[10] Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
[11] Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980; 23:581–90.
[12] Rodriguez M, Alvarez S, Bravo E. Coeficientes de Asociacion. Mexico: Plaza y Valdes Editores; 2001.
[13] Rogers DJ, Tanimoto TT. A computer program for classifying plants. Science 1960;132:1115–8.
[14] Gonzalez P, Seisdedos R, Techera L, Salvatori F, Fonseca ML, Pucci P, et al. Sindrome de Sjögren y enfermedades autoinmunes adicionales: Perfil clinico, inmunologico e histologico. Experiencia con 285 pacientes. Grupo GESSAR. J Clin Rheumatol 2012;18(Suppl.):S21.
[15] Lazarus MN, Isenberg DA. Development of additional autoimmune diseases in a population of patients with primary Sjögren's syndrome. Ann Rheum Dis 2005;64:1062–4.
[16] Anaya J-M, Castiblanco J, Tobón GJ, García J, Abad V, Cuervo H, et al. Familial clustering of autoimmune diseases in patients with type 1 diabetes mellitus. J Autoimmun 2006;26:208–14.
[17] Wilches Luna A, Gomez Lopez de Mesa C. Enfermedad celíaca en niños. Rev Col Gastroenterol 2010;25:204–13.
[18] Freemer MM, King Jr TE, Criswell LA. Association of smoking with dsDNA autoantibody production in systemic lupus erythematosus. Scand J Immunol 2006;65:581–4.
[19] Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2010;69:70–81.
[20] Tomer Y, Huber A. The etiology of autoimmune thyroid disease: a story of genes and environment. J Autoimmun 2009;32:231–9.
[21] Rojas-Villarraga A, Diaz FJ, Calvo-Páramo E, Salazar JC, Iglesias-Gamarra A, Mantilla RD, et al. Familial disease, the HLA-DRB1 shared epitope and anti-CCP antibodies influence time at appearance of substantial joint damage in rheumatoid arthritis. J Autoimmun 2009;32:64–9.
[22] Manthorpe R, Benoni C, Jacobsson L, Kirtava Z, Larsson Å, Liedholm R, et al. Lower frequency of focal lip sialadenitis (focus score) in smoking patients. Can tobacco diminish the salivary gland involvement as judged by histological examination and anti-SSA/Ro and anti-SSB/La antibodies in Sjögreńs syndrome? Ann Rheum Dis 2000;59:54–60.
[23] Karabulut G, Kitapcioglu G, Inal V, Kalfa M, Yargucu F, Keser G, et al. Cigarette smoking in primary Sjögren's syndrome: positive association only with ANA positivity. Mod Rheumatol 2011;21:602–7.
[24] Takaya M, Ichikawa Y, Shimizu H, Uchiyama M, Moriuchi J, Arimori S. Sjögren's syndrome and pregnancy. Tokai J Exp Clin Med 1991;16:83–8.
[25] Julkunen H, Kaaja R, Kurki P, Palosuo T, Friman C. Fetal outcome in women with primary Sjögren's syndrome. A retrospective case-control study. Clin Exp Rheumatol 1995;13:65–71.
[26] Ramos-Casals M, Nardi N, Brito-Zerón P, Aguiló S, Gil V, Delgado G, et al. Atypical autoantibodies in patients with primary Sjögren syndrome: clinical characteristics and follow-up of 82 cases. Semin Arthritis Rheum 2006;35: 312–21.
[27] Jara LJ, Navarro C, Brito-Zerón MDP, García-Carrasco M, Escárcega RO, Ramos-Casals M. Thyroid disease in Sjögren's syndrome. Clin Rheumatol 2007;26: 1601–6.
[28] Anaya JM, Ramos-Casals M, García-Carrasco M. Síndrome de Sjögren. 1st ed. Medellín, Colombia: Corporación para Investigaciones Biológicas; 2001.
[29] Ramos-Casals M, García-Carrasco M, Cervera R, Gaya J, Halperin I, Ubieto I, et al. Thyroid disease in primary Sjögren syndrome. Study in a series of 160 patients. Medicine 2000;79:103–8.
[30] Lin DF, Yan S, Zhao Y, Zhang W, Li MT, Zeng XF, et al. Clinical and prognostic characteristics of 573 cases of primary Sjögren's syndrome. Chin Med J 2010; 123:3252–7.
[31] Warfvinge G, Larsson A, Henricsson V, Ericsson UB, Hansen B, Manthorpe R. Salivary gland involvement in autoimmune thyroiditis, with special reference to the degree of association with Sjögren's syndrome. Oral Surg Oral Med Oral Pathol 1992;74:288–93.
[32] Scofield RH, Bruner GR, Harley JB, Namjou B. Autoimmune thyroid disease is associated with a diagnosis of secondary Sjögren's syndrome in familial systemic lupus. Ann Rheum Dis 2007;66:410–3.
[33] McDonagh JE, Isenberg DA. Development of additional autoimmune diseases in a population of patients with systemic lupus erythematosus. Ann Rheum Dis 2000;59:230–2.
[34] Andonopoulos AP, Drosos AA, Skopouli FN, Acritidis NCMH. Secondary Sjogren's syndrome in rheumatoid arthritis. J Rheumatol 1987;14:1098–103.
[35] Fujita M, Igarashi T, Kurai T, Sakane M, Yoshino S, Takahashi H. Correlation between dry eye and rheumatoid arthritis activity. Am J Ophthalmol 2005; 140:808–13.
[36] Kauppi M, Pukkala E. Elevated incidence of hematologic malignancies in patients with Sjögren's syndrome compared with patients with rheumatoid arthritis (Finland). Cancer Causes Control 1997;8:201–4.
[37] Atkinson JC, Travis WD, Slocum L, Ebbs WLFP. Serum anti-SS-B/La and IgA rheumatoid factor are markers of salivary gland disease activity in primary Sjögren's syndrome. Arthritis Rheum 1992;35:1368–72.
[38] Ramos-Casals M, Cervera R, Font J, García-Carrasco M, Espinosa G, Reino S, et al. Young onset of Primary Sjögren's syndrome: clinical and immunological characteristics. Lupus 1998;7:202–6.
[39] Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med 2007;146:797–809.
[40] Iwamoto N, Kawakami A, Tamai M, Fujikawa K, Arima K, Aramaki T, et al. Determination of the subset of Sjogren's syndrome with articular manifestations by anticyclic citrullinated peptide antibodies. J Rheumatol 2009;36: 113–5.
[41] Baer AN, Maynard JW, Shaikh F, Magder LS, Petri M. Secondary Sjogren's syndrome in systemic lupus erythematosus defines a distinct disease subset. J Rheumatol 2010;37:1143–9.
[42] Ramos-Casals M, Brito-Zerón P, Font J. The overlap of Sjögren's syndrome with other systemic autoimmune diseases. Semin Arthritis Rheum 2007;36: 246–55.
[43] Xu D, Tian X, Zhang W, Zhang X, Liu B, Zhang F. Sjogren's syndrome-onset lupus patients have distinctive clinical manifestations and benign prognosis: a case-control study. Lupus 2010;19:197–200.
[44] Theander E, Jacobsson LTH. Relationship of Sjögren's syndrome to other connective tissue and autoimmune disorders. Rheum Dis Clin North Am 2008; 34:935–47.
[45] Manoussakis MN, Georgopoulou C, Zintzaras E, Spyropoulou M, Stavropoulou A, Skopouli FN, et al. Sjögren's syndrome associated with systemic lupus erythematosus. Arthritis Rheum 2004;50:882–91.
[46] Rojas-Villarraga A, Toro CE, Espinosa G, Pineda-Tamayo R, Varela DC, Amézquita-Gómez L, et al. Does Sjögren syndrome or autoimmune thyroid disease influence lupus nephritis? Lupus 2010;19:S-150.
[47] Salliot C, Mouthon L, Ardizzone M, Sibilia J, Guillevin L, Gottenberg J-E, et al. Sjogren's syndrome is associated with and not secondary to systemic sclerosis. Rheumatology (Oxford) 2007;46:321–6.
[48] Avouac J, Sordet C, Depinay C, Ardizonne M, Sibilia J, Kahan A, et al. Systemic sclerosis-associated Sjögren's syndrome and relationship to the limited cutaneous subtype: results of a prospective study of sicca syndrome in 133 consecutive patients. Arthritis Rheum 2006;54:2243–9.
[49] Koumakis E, Dieudé P, Avouac J, Kahan A, Allanore Y. Familial autoimmunity in systemic sclerosis - results of a French-based case-control family study. J Rheumatol 2012;39:532–8.
[50] García-carrasco M, Sisó A, Ramos-casals M, Rosas J, Red GD, Gil V, et al. Raynaud's phenomenon in primary Sjögren's syndrome. Prevalence and clinical characteristics in a series of 320 patients. J Rheumatol 2002;29: 726–30.
[51] Anaya J-M, Villa LA, Restrepo L, Molina JF, Mantilla RD, Vargas S. Central nervous system compromise in primary Sjögren's syndrome. J Clin Rheumatol 2002;8:189–96.
[52] Miró J, Peña-Sagredo JL, Berciano J, Insúa S, Leno C, Velarde R. Prevalence of primary Sjögren's syndrome in patients with multiple sclerosis. Ann Neurol 1990;27:582–4.
[53] Seze JD, Devos D, Castelnovo G, Labauge P, Dubucquoi S. The prevalence of Sjögren syndrome in patients with primary progressive multiple sclerosis. Neurology 2001;57(8):1359–63.
[54] Annunziata P, De Santi L, Di Rezze S, Millefiorini E, Capello E, Mancardi G, et al. Clinical features of Sjogren's syndrome in patients with multiple sclerosis. Acta Neurol Scand 2011;124:109–14.
[55] Humbert P, Dupond J. Multiple autoimmune syndromes. Ann Med Interne 1988;139:159–68.
[56] Turkcapar N, Olmez U, Ozer D, Duzgun N, Duman M. A case of overlap syndrome with rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and secondary Sjögren's syndrome. Rheumatol Int 2006;26:841–5.
[57] Anaya JM. Common mechanisms of autoimmune diseases (the autoimmune tautology). Autoimmun Rev 2012 Feb 12 [Epub ahead of print].
[58] Anaya JM, Castiblanco J, Rojas-Villarraga A, Pineda-Tamayo R, Levy RA, Gómez-Puerta J, et al. The multiple autoimmune syndromes. Clin Rev Allergy Immunol, in press.
[59] Chambers SA, Charman SC, Rahman A, Isenberg DA. Development of additional autoimmune diseases in a multiethnic cohort of patients with systemic lupus erythematosus with reference to damage and mortality. Ann Rheum Dis 2007;66:1173–7.
[60] Ice JA, Li H, Adrianto I, Lin PC, Kelly JA, Montgomery CG, et al. Genetics of Sjögren's syndrome in the genome-wide association era. J Autoimmun 2012:28 [Epub ahead of print].

[61] Youinou P, Le Goff P, Blain F, Le Menn G. Association of systemic scleroderma, hepatopathy and Gougerot-Sjögren syndrome. 2 cases: coincidence of pathogenic relationship. Nouv Presse Med 1976;25(5):1983–5.
[62] D'Arbonneau F, Ansart S, Le Berre R, Dueymes M, Youinou P, Pennec YL. Thyroid dysfunction in primary Sjögren's syndrome: a long-term followup study. Arthritis Rheum 2003;49:804–9.
[63] Mackay IR, Leskovsek NV, Rose NR. The odd couple: a fresh look at autoimmunity and immunodeficiency. J Autoimmun 2010;35:199–205.
[64] Manoussakis MN, Kapsogeorgou EF. The role of intrinsic epithelial activation in the pathogenesis of Sjogren's syndrome. J Autoimmun 2010;35:219–24.
[65] Mavragani CP, Crow MK. Activation of the type I interferon pathway in primary Sjogren's syndrome. J Autoimmun 2010;35:219–24.
[66] Roguedas A-M, Pers J-O, Lemasson G, Devauchelle V, Tobon GJ, Saraux A, et al. Memory B-cell aggregates in skin biopsy are diagnostic for primary Sjogren's syndrome. J Autoimmun 2010;35:241–7.
[67] Vlachoyiannopoulos PG, Routsias JG. A novel mechanism of thrombosis in antiphospholipid antibody syndrome. J Autoimmun 2010;35:248–55.
[68] Gershwin ME, Shoenfeld Y. Chella David: a lifetime contribution in translational immunology. J Autoimmun 2011;37:59–62.
[69] Rose NR. The genetics of autoimmune thyroiditis: the first decade. J Autoimmun 2011;37:88–94.
[70] Behrens M, Smart M, Luckey D, Luthra H, Taneja V. To B or not to B: role of B cells in pathogenesis of arthritis in HLA transgenic mice. J Autoimmun 2011;37:95–103.
[71] Youinou P, Haralampos M. Moutsopoulos: a lifetime in autoimmunity. J Autoimmun 2010;35:171–5.