Joint Bone Spine 86 (2019) 620–626

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Original article

Geoepidemiology of Sjögren's syndrome in Latin America

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suppl. Informations

ARTICLE INFO

Article history:
Accepted 6 February 2019
Available online 16 February 2019

Keywords:
Sjögren's syndrome
Colombia
Latin America
Autoimmune diseases
Ancestry
Ethnicity

ABSTRACT

Objective: To evaluate the geoepidemiology of Sjögren's syndrome (SS) in Latin America.
Methods: This was a three phase study in which original data from a Colombian cohort of patients with SS is presented, followed by a systematic review of Colombian and Latin American studies. Lastly, the geoepidemiology of SS in Latin America was assessed by comparing the clinical characteristics of the region with those of the rest of the world by means of a meta-analysis approach.
Results: Data from 2970 patients from Latin America and 18019 patients from Europe, North America and Asia were analyzed. Colombian patients have a lower age at disease onset than those from other Latin American countries and a higher rate of positivity of antinuclear antibodies and rheumatoid factor. A significant difference in the proportion of female patients in Latin America compared with Europe and North America was observed. The spectrum of disease in Latin American was similar to North American patients, while strong differences were noticed between Latin American and European and Asian patients. Noteworthy, a paucity of reports including African and African-descendent patients was observed.
Conclusions: The clinical spectrum of SS differs between countries and continents. Genetic differences relying upon ancestry could explain these findings. However, environmental factors have proven to be important determinants in the development of autoimmune diseases (i.e., autoimmune ecology). Thus, ancestry and the autoimmune ecology should be considered in studies aimed to evaluate the geoepidemiology of SS and other autoimmune diseases.

1. Introduction

Sjögrenś syndrome (SS) is a chronic autoimmune disease (AD) characterized by a lymphocytic infiltration and inflammation of exocrine glands, mainly the lachrymal and salivary glands [1], with a high production of autoantibodies [2] and inflammatory mediators, resulting in glandular dysfunction. The clinical presentation of SS varies from glandular manifestations to systemic extra-glandular disease. It is more frequent among middle-aged women typically in the fifth to sixth decades of life. The prevalence of SS varies around the world [3]. A French study estimated a prevalence of 1.02 cases per 10,000 adults [95% confidence interval (95% CI) 0.85–1.22] [4] while a recent meta-analysis estimated a global prevalence of 60.82 cases per 100,000 inhabitants, and showed a higher pooled prevalence rate from the European studies compared to those from Asia [3].

Several factors may influence the epidemiology and clinical characteristics of a disease in a given location or population. Among these, genetic and environmental factors are the most important [5]. Several genetic studies have identified susceptibility HLA and non-HLA genes which have been incriminated in the pathogenesis of SS [6]. Patients with different ethnic origins appear to have different HLA susceptibility alleles [7]. Nevertheless, a meta-analysis showed that HLA-DQA1*05:01, DQB1*02:01 and DRB1*03:01 alleles described in Caucasians are also associated with SS in other populations [7]. Moreover, a recent genome-wide association study found polymorphisms at *KLRG1* gene to be associated with SS in Asians while no association was found in Europeans, *TNFAIP3* was found to be significantly associated in both populations [8]. These data suggest that genetic background expresses dissimilar configurations across populations and that heritability (i.e., the proportion of phenotypic variation in a population that is attributable to genetic variation among individuals) may account for these differences. However, whereas these differences are relevant from the clinical point of view in SS remains to be elucidated. A previous study evaluated the influence of geolocation and ethnicity on the expression of SS, and found significant differences in sicca symptoms and laboratory profile in intra-continent analysis in Europe, Asia and America as well as differences depending upon "ethnicity" [9]. Concerning environmental factors, previous viral infections have been associated as possible risk factors implicated in the development of SS [revised in [10]].

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https://doi.org/10.1016/j.jbspin.2019.02.004

Race, ethnicity and ancestry, all refer to the origin of a person or population, however they have different implications and considerations. The term race was initially created by biologists as a label that characterized a specific category when they were studying the species. This term was used between mid-nineteenth century to mid twentieth century resulting in crimes against humanity. It is now rarely used by the scientific community while ethnicity refers to cultural aspects of populations that may or may not share a common genetic origin [11]. Recently, a greater use of ethnicity is being encouraged as it conceives cultural differences that aid in the understanding of the processes of health and disease among populations [11]. Ancestry refers to the common origin that characterizes a specific population [12]. Several definitions of ancestry have been employed depending on the frame of reference used. Continental ancestry originates on the assumption of four main populations giving rise to the existing populations and is tightly correlated with race which has led to the interchangeability of terms. Besides, the comparison of an individual with contemporary populations living in a given location allows to determine the biogeographic ancestry of its presumed ancestors [12]. Last, estimating genetic ancestry requires an understanding of the distribution of variations among populations through history [12].

Latin America and the Caribbean (LAC) is a rapidly growing region with almost 630 million inhabitants composed of Mexico, Central and South America, and the islands of the Caribbean [13]. As we have previously recalled "the Americas were first inhabited by people crossing the Bering Land Bridge from northeast Asia into Alaska well over 10,000 years ago. Native Americans descend from at least three streams of Asian gene flow. Europeans arrived after 1492 following Christopher Columbus's voyages. African people were captured and taken to America by the transatlantic slave trade from the 16th to the 19th centuries. Hence, the population of LAC comprises a variety of ancestries, ethnic groups, and races, making the region one of the most diverse in the world. The specific composition varies from country to country: many have a predominance of European-Native American, or Mestizo, population; in others, Native Americans are a majority; some are dominated by inhabitants of European ancestry; some countries' populations are primarily Mulatto. To a less extent, Black, Asian, and Zambo (mixed Black and Native American) are also identified regularly" [13]. Noteworthy, ethnic self-identification is culturally and biologically complex and in admixed populations is not correlated with self-reported ancestry which should be no longer evaluated by questionnaire but rather by the use of ancestry informative markers at the molecular level [14].

As expected, due to ancestry, important differences among Latin American countries and within countries exist. Ruiz-Linares et al. [15] and Homburger et al. [16] found variations in ancestry between Brazil, Chile, Colombia, Mexico and Peru depending on the geographical area of each country, however all three ancestries (i.e., Africans, Europeans and Native Americans) were present in all the countries with a high proportion of Native Americans. The Native American component of Mexicans shows a higher relation with Native Mesoamericans while that of Chileans and Peruvians is more related with Andean natives, and Colombians with Chibchan-Paezan groups [17]. Rojas et al. [14] highlighted differences in the frequencies of European, Amerindian and African haplogroups among the regions of Colombia, with a higher African ancestry in the coastal regions and the southwest regions. The pattern of ancestry in Latin America also differs by the X or Y chromosomes being the X chromosome linked with a higher Amerindian ancestry and the Y chromosome with a higher European ancestry [17,18] favored by the higher migration of men into the Americas, especially Iberian men who reached South America [19]. Besides, the exposure of Native Americans to novel environmental challenges during the colonization period hypothesizes in the possibility that selection could have occurred leading to regional differences and specific characteristics that have been observed in the HLA region [17]. Deng et al. [20] evaluated this possibility and found an excess of African ancestry in Latin American populations in genes with a potential role in the susceptibility or resistance to infections (HLA region, *IGH* and *MASP2*) supporting the theory of selection driven by infectious diseases.

Several studies have used the racial/ethnic classification of the different populations to establish comparisons and associations with specific characteristics and disease risk. The NCBI (PubMed) defines five continental population groups depending on the location of their ancestral origins in each of the continents [21]: African, American Native, Asian, European, and Oceanic ancestry groups. Besides, nine ethnic groups are defined [22]: African Americans, Amish, Arabs, Asian Americans, Hispanic Americans, Mexican Americans, Inuits, Jews and Roma. Hispanic Americans are considered those who live in the United States and their origin is from Mexico, Puerto Rico, Cuba, Central or South America or any other Spanish culture or origin [22]. The term "Latino" is classified under the MeSH term "Hispanic American". However, as previously mentioned, there are strong ancestry differences among "Latinos" and "Hispanic Americans" Fig. 1.

Given the differences and similarities in the genetic factors associated with SS among populations and the different characteristics observed between them, we aimed to evaluate the geoepidemiology of SS in Latin America by comparing the clinical and sociodemographic characteristics of Colombian patients with those from Latin America and from other continental populations.

2. Methods

This was a three phase study in which original data from a Colombian cohort of patients with SS is presented, followed by a systematic review of Colombian and Latin American studies. Lastly, the geoepidemiology of SS in Latin America was assessed by comparing the clinical characteristics of the region with those of the rest of the world [23].

2.1. Cohort

A total of 293 consecutive patients with stablished SS were included. Subjects have been followed at the Center for Autoimmune Diseases Research (CREA) in Bogota, Colombia. All subjects fulfilled the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2016 classification criteria for SS [24]. The patientśdata were obtained by interview, standardized forms, physical examination and medical records review and collected in an electronic and secure database, as previously reported in detail [10].

2.2. Review of the literature

A systematic review of Colombian and Latin American studies (based on sample size, reported clinical characteristics and availability of data for comparisons) describing the sociodemographic and clinical characteristics of SS patients was done. In addition, for comparisons, a descriptive review of the most relevant studies from Europe, Asia, North America and Africa was also done. Articles were found through database search in Pubmed, Embase, LILACS and Scielo including the terms "Sjögren's syndrome" and "Latin America", "South America" and each of the Latin American countries included individually in the search. Additionally, the terms "Europe", "Asia", "North America" and

Table 1
General characteristics of SS patients.

Variable	Current series $n = 293$	Colombia[a] $n = 950$	Other countries in Latin America $n = 2020$	Global Latin America $n = 2970$	Asia $n = 2280$	Europe $n = 13542$	North America $n = 2197$
Gender, female	278 (94.88)	932/950 (98.10)	1947/2020 (96.38)	2879/2970 (96.93)	2194/2280 (96.22)	12624/13542 (93.22)	2135/2312 (92.34)
Age at disease onset	44.18 (42.69, 45.67)	44.8 (39.48, 50.11)	51.80 (47.42, 56.18)	48.98 (46.46, 51.49)	41.7 (36.26, 47.13)	54.40 (52.32, 56.47)	-
Smoking (ever)	96/257 (37.35)	158/323 (48.91)	–	192/423 (45.39)	6/315 (1.90)	137/611 (22.42)	–
Polyautoimmunity	132 (45.05)	266/703 (37.83)	197/439 (44.87)	463/1142 (40.54)	–	101/445 (22.69)	–
RA	52 (17.74)	85/693 (12.26)	–	85/693 (12.26)	–	1/445 (0.22)	–
SLE	50 (17.06)	77/647 (11.90)	27/354 (7.62)	77/647 (11.90)	–	6/445 (1.34)	–
AITD	46 (15.69)	159/785 (20.25)	28/169 (16.56)	187/954 (19.60)	46/401 (11.47)	106/675 (15.70)	–
SSc	13 (4.43)	18/641 (2.80)	–	18/641 (2.80)	–	1/445 (0.22)	–
APS	3 (1.02)	11/639 (1.72)	–	12/639 (1.87)	–	–	–
PBC	1 (0.34)	1/293 (0.34)	–	1/293 (0.34)	–	–	–
MS	2 (0.68)	3/641 (0.46)	–	3/641 (0.46)	–	–	–
SVV	1 (0.34)	4/570 (0.70)	–	4/570 (0.70)	–	–	–
AIH	1 (0.34)	2/569 (0.35)	–	2/569 (0.35)	–	–	–
Xerophthalmia	274 (93.51)	274/293 (93.51)	680/756 (89.94)	954/1049 (90.94)	995/1423 (69.92)	11523/12260 (93.98)	1502/1527 (98.36)
Xerostomy	279/280 (99.64)	279/280 (99.64)	585/656 (89.17)	930/1036 (89.76)	1145/1423 (80.46)	11585/12365 (93.69)	1513/1527 (99.08)
Xeromycteria	117/283 (41.34)	117/283 (41.34)	29/74 (39.18)	146/357 (40.89)	–	–	–
Xerotrachea	47/279 (16.84)	47/279 (16.84)	6/74 (8.10)	53/353 (15.01)	–	–	–
Cutaneous involvement	14/82 (17.07)	15/82 (18.29)	7/78 (8.97)	21/160 (13.12)	161/1450 (11.10)	–	161/1450 (11.10)
Urticaria	45/282 (15.95)	96/690 (10)	15/552 (2.71)	111/1242 (8.93)	–	–	–
Raynaud's phenomenon	75/282 (26.59)	105/428 (42.33)	92/678 (13.56)	197/1106 (8.77)	–	992/4494 (22.07)	35/304 (11.51)
Cutaneous vasculitis	17/282 (6.02)	30/364 (8.24)	48/490 (9.79)	78/854 (9.13)	–	254/2325 (10.92)	11/304 (3.61)
Cutaneous ulcers	9/282 (3.19)	9/282 (3.19)	11/695 (1.58)	20/977 (2.04)	–	–	–
Purpura	–	12/177 (6.77)	50/695 (7.19)	55/777 (7.07)	–	117/1780 (6.57)	–
Photosensibility	87/282 (30.85)	87/282 (30.85)	–	87/282 (30.85)	–	–	13/304 (4.27)
Dysphagia	56/279 (20.07)	56/279 (20.07)	5/74 (6.75)	61/353 (17.28)	–	–	–
Gastritis	99/278 (35.61)	113/434 (26.03)	10/74 (13.51)	123/508 (24.21)	–	–	–
Hepatitis	11/279 (3.94)	11/279 (3.94)	–	11/279 (3.94)	51/315 (16.19)	–	–
Splenomegaly	6/283 (2.12)	6/283 (2.12)	–	6/283 (2.12)	–	17/723 (2.35)	–
Renal tubular acidosis	1/278 (0.35)	1/278 (0.35)	11/174 (6.32)	12/452 (2.65)	60/315 (19.04)	1/1115 (0.089)	–
Glomerulonephritis	5/278 (1.79)	5/278 (1.79)	5/316 (1.58)	10/594 (1.68)	–	1/1115 (0.089)	–
Arthralgia/Arthritis	225/283 (79.50)	296/429 (68.69)	48/78 (61.53)	344/507 (67.85)	184/483 (38.09)	904/2085 (43.35)	–
Arthralgia	219/283 (77.38)	259/365 (70.95)	133/185 (71.89)	392/550 (78.40)	–	1333/2619 (50.89)	–
Arthritis	121/283 (42.75)	297/664 (44.72)	359/1074 (33.42)	956/1738 (55.0)	86/483 (17.80)	301/2319 (12.97)	79/304 (25.98)
Myalgia	108/283 (38.16)	108/283 (38.16)	–	108/283 (38.16)	–	169/639 (26.44)	–
Parotid gland swelling	40/283 (14.13)	40/283 (14.13)	178/549 (32.42)	218/832 (26.20)	98/483 (20.28)	1559/4701 (33.16)	–
Persistent parotid swelling	4/282 (1.41)	4/282 (1.41)	–	4/282 (1.41)	–	57/255 (22.35)	–
Lymphadenopathy	33/283 (11.66)	33/283 (11.66)	5/100 (5)	38/383 (9.92)	–	187/1739 (10.75)	–
Lymphoma	–	–	5/321 (1.55)	5/321 (1.55)	–	75/2191 (3.42)	–
Neoplasia	12/113 (10.61)	12/113 (10.61)	5/65 (9.23)	17/178 (9.55)	–	–	–
Neurological compromise	25/278 (8.99)	34/360 (6.66)	78/662 (11.78)	112/1022 (10.95)	–	107/780 (13.71)	34/303 (11.22)
PNS compromise	22/278 (7.91)	22/278 (7.91)	63/679 (9.27)	85/957 (8.88)	–	270/3502 (7.70)	–
CNS compromise	3/278 (1.07)	3/278 (1.07)	17/252 (6.74)	20/530 (3.77)	–	25/1410 (1.77)	–
Depression	51/272 (18.75)	80/430 (18.60)	8/65 (12.30)	88/495 (17.77)	–	–	–
Anemia	47/274 (17.15)	58/429 (13.51)	40/295 (13.55)	98/724 (35.76)	–	258/1574 (16.39)	–
Dyslipidemia	80/274 (29.19)	98/434 (22.58)	31/165 (18.78)	129/599 (21.53)	–	145/437 (33.18)	–
Osteoporosis	44/272 (16.17)	56/428 (12.61)	8/65 (12.30)	64/493 (12.98)	–	–	–
Objective oral tests	111/177 (94.87)	111/177 (94.87)	205/243 (84.36)	316/420 (75.23)	890/1066 (83.48)	3535/4427 (79.85)	581/825 (70.42)
Positive salivary flow	84/160 (52.50)	84/160 (52.50)	473/554 (85.37)	557/714 (78.01)	972/1276 (76.17)	2380/3998 (59.52)	886/1394 (63.55)
Positive sialography	34/59 (57.62)	34/59 (57.62)	1/1 (100)	35/60 (58.33)	341/467 (73.01)	1065/1238 (86.02)	–
Objective ocular tests	150/174 (86.20)	150/174 (86.20)	199/243 (81.89)	349/417 (83.69)	1162/1293 (89.86)	8829/10579 (83.45)	717/841 (85.25)
Positive Schirmerś test	150/174 (86.20)	150/174 (86.20)	440/572 (76.92)	590/746 (79.08)	1347/1601 (84.13)	3908/4763 (82.04)	750/1402 (53.49)
Positive MSG biopsy	160/293 (54.60)	160/293 (54.60)	636/730 (87.12)	796/1023 (77.81)	843/1044 (80.74)	6275/9125 (68.76)	844/1322 (63.84)
Positive ANAs	239/245 (97.55)	493/537 (91.80)	510/790 (64.55)	1003/1327 (75.58)	1485/1666 (89.13)	10283/12598 (81.62)	950/1235 (76.92)
Positive Ro/SSA	195/248 (78.62)	379/495 (76.56)	671/1050 (63.90)	1050/1545 (67.96)	1418/1697 (83.55)	8107/12622 (64.22)	1056/1882 (56.11)
Positive La/SSB	115/229 (50.21)	205/476 (43.06)	432/1085 (39.81)	637/1561 (40.80)	827/1686 (49.05)	4898/12573 (38.95)	710/1882 (37.72)
Rheumatoid factor	129/181 (71.27)	129/181 (71.27)	315/801 (39.32)	446/982 (45.41)	584/984 (59.34)	5487/11559 (47.46)	546/1154 (47.31)
Low C3	–	–	66/726 (23.91)	66/726 (23.91)	167/813 (20.54)	1191/9086 (13.10)	32/728 (4.39)
Low C4	–	–	102/726 (14.04)	102/726 (14.04)	77/814 (9.45)	1219/9053 (13.46)	634/5188 (12.22)
Cryoglobulinemia	–	–	63/803 (7.84)	63/803 (7.84)	2/218 (0.91)	832/8569 (9.70)	3/42 (7.14)
Hypergammaglobulinemia	–	–	81/373 (21.71)	81/373 (21.71)	–	909/1881 (48.32)	69/137 (50.36)
Hypocomplementemia	–	–	26/299 (8.69)	26/299 (8.69)	–	116/537 (21.60)	5/138 (3.62)

Data are shown as positive data over total number of patients with available information, and percentage. Age at disease onset is expressed as mean (95% confidence intervals). Details and references to the included studies are described in the supplementary material.
RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; AITD: autoimmune thyroid disease; SSc: systemic sclerosis; APS: antiphospholipid syndrome; PBC: primary biliary cholangitis; MS: multiple sclerosis; SVV: small vessel vasculitis; AIH: autoimmune hepatitis; PNS: peripheral nervous system; CNS: central nervous system; MSG: minor salivary gland; ANAs: antinuclear antibodies.
[a] Includes data from current series.

"Africa" were also included. We searched for studies reporting on sociodemographic, clinical and laboratory characteristics of patients with SS. Two authors (PRJ and JMA) independently reviewed the references and selected those with pertinent information. Data regarding gender, age, age at onset, polyautoimmunity, sicca symptoms (i.e., xerophthalmia, xerostomia, xeromycteria and xerotrachea), extraglandular manifestations (i.e., pulmonary, renal, cutaneous, hematological, neurological, gastrointestinal and lymphoproliferative) and autoantibodies, including antinuclear antibodies (ANAs), anti-Ro/SSA, anti-La/SSB, and rheumatoid factor (RF) were extracted from each study. Data from Colombia, Latin America and non-Latin America were summarized separately.

2.3. Statistical analyses

A univariate analysis was done. Categorical variables were analyzed by frequencies. Results are reported in percentages, and mean and 95% confidence intervals (95% CI). The comparisons between Colombia and Latin America, and between Latin America and Asia, Europe and North America were done by means of meta regression fixed effect model, using Metafor R package (http://www.jstatsoft.org/v36/i03/). For quantitative variables, the effect size used was the raw mean, and to compare among regions the mean difference was estimated using the fixed effects meta regression model. For qualitative variables, effect size used was the

logit-transformed proportion, and to compare among regions the logarithm of the odds ratio was estimated using the fixed effects meta regression model. For mean difference and odds ratio, 95% CI are provided. Statistical analyses were done by using the statistical program R v.3.4.4.

2.4. Ethics statement

This study was classified as minimal-risk research in compliance with Act 008430/1993 of the Ministry of Health of the Republic of Colombia. All patients voluntarily agreed to participate in the study and gave written informed consent. The institutional review board of the Universidad del Rosario approved the study design.

2.5. Role of the funding source

This work was supported by Universidad del Rosario (ABN011), Bogota, Colombia.

3. Results

In our cohort of 293 patients with SS, the majority (94.8%) were female with a median age of 53 years (IQR 35 - 53) and median disease duration of 7 years (IQR 2–12). The sociodemographic and clinical characteristics of SS patients in Colombia, Latin America, Asia, Europe and North America are described in Table 1, characteristics and references to the included studies are shown in supplementary material [Appendix A, tables S1-S2; See the supplementary material associated with this article online].

We included 18 articles reporting data on 16 Latin American studies, and the current series, with a total population of 2970 patients diagnosed with SS from Colombia ($n = 950$), Brazil ($n = 239$), Chile ($n = 78$), Mexico ($n = 470$), Argentina ($n = 980$), and one including patients from South America (n = 253). A total of 21 articles reporting representative data of 18019 patients with SS were included in the studies from Asia ($n = 2280$), Europe ($n = 13542$) and North America ($n = 2197$). The classification criteria used were the European criteria 1993 [25], AECG 2002 [26], ACR 2012 [27], and ACR/EULAR 2016 [24]. A summary of the main characteristics of the included studies in Latin America and Non-Latin America is shown in Appendix A (table S1 and table S2, respectively).

There was just one study from Africa [28] in which 57 patients were included. The majority (90%) were female with a mean disease duration of 5.38 (SD 4.11) years. Anti-Ro/SSA and anti-La/SSB was reported positive in 77.19% and 80.7% of patients. The most common manifestation was joint involvement (87.7%) followed by Raynaudś phenomenon, pulmonary involvement and CNS compromise. The authors reported a high prevalence of fatigue in Moroccan patients which chowed no association with the immunological status.

The effect of the continental population group on the main clinical characteristics is shown in Table 2.

4. Discussion

Our results showed that the clinical expression of SS differs depending on the continental population group (Fig. 1) [3,4,29,30,31,32,33,34,36].

Colombian patients appear to have a higher rate of urticaria and dysphagia, than do patients from other countries of Latin America. The significantly higher frequency of positive ANAs and RF, and the tendency for a higher frequency of anti-Ro/SSA among Colombians suggest a more marked autoimmune response. However, it could also reflect differences in the diagnostic approach and evaluation of patients. Although Colombian patients showed a higher frequency of xerostomy they had a lower percentage of positive salivary flow which could be in part due to differential reporting of variables among studies as not all included the totality of variables analyzed.

A female predominance is characteristic of SS, however we observed a significant difference in the rate of female patients in Latin America compared with Europe and North America indicating a more marked female-to-male ratio in Latin America.

Latin American patients had a higher prevalence of AITD compared with Asians. The prevalence of non-autoimmune hypothyroidism is higher in iodine-deficient regions (i.e., South East Asia, South America and Central Africa) while AITD, specifically Gravesd́isease, is more frequently encountered in iodine-replete populations [37]. Besides iodine, several environmental factors and susceptibility genes have been associated with the development of AITD and could explain the differences observed between populations [10]. In addition, given that ADs are influenced by genetic and environmental factors, differences in prevalence are expected between geographic regions and populations because genetic and environmental factors vary depending of populations and geography (e.g., latitudinal gradient).

Patients with SS are known to be at an increased risk of developing lymphoma, especially non-Hodgkin lymphoma, as a consequence of the B-cell hyperactivity that characterizes the disease [38]. A meta-analysis described a risk ratio of 13.76 (95% CI 8.53–18.99) for the development of lymphoma in SS patients compared to healthy individuals [39]. Factors such as monoclonality, cryoglobulinemia, low C4 levels, recurrent or persistent parotid gland enlargement, cutaneous vasculitis and purpura have been observed to be associated with the development of lymphoma [38]. A lower rate of persistent and recurrent parotid gland swelling, hypergammglobulinemia and hypocomplementemia in Latin American patients compared with those from Europe was noticed, which may explain the lower prevalence of lymphoma in Latin American patients. Although a tendency for a lower frequency of lymphoma in Latin American patients compared with Europeans was observed, comparisons did not yield statistical significance.

The positivity rate of ANAs in the Latin American patients was lower compared with Asians. It has been shown that anti-Ro/SSA positive patients have a higher frequency of altered Schirmerś test, positive minor salivary gland (MSG) biopsy, low C4 and both ANAs and RF positivity [40]. These results are supported by the study of Bunya et al. [41] who described an increased odds of positive serology with a positive Schirmerś test. Besides, Brito-Zeron et al. [9] described an increased prevalence of positive ANA, RF anti-Ro/SSA, anti-La/SSB and low C4 as well as a decreased frequency of positive MSG biopsy in patients from North America compared with those from South America. We could not validate these results (Table 2).

The discovery of ethnogenetic risk factors, disease gradients, clusters of autoimmunity and specific characteristics associated with a specific location or population highlights the importance of geoepidemiology and a possible link with ancestry [23]. Studies on geolocation and ancestry in SS are scarce; however, a possible effect of both in the development and course of the disease is plausible, as it has been described in other ADs. In a recent review by Shapira et al. [23], the authors stressed the role of genetic factors influencing the development of ADs (e.g., RA and SLE) as the risk differs between ethnic groups that reside in the same country. The aforementioned meta-analysis of the epidemiology of SS [3] reported an overall incidence rate (IR) of 6.92 (95% CI 4.98–8.86) per 100,000 person-years at risk and an overall prevalence rate (PR) of 60.82 (95% CI 43.69–77.94) cases per 100,000 habitants. Differences were observed regarding location as the IRs reported for Asia, Europe and USA were 6.57, 3.9 to 5.3, and 3.9, respectively [3]. Besides, Brito-Zerón et al. [9] have discussed a potential north-south gradient in ADs and described intra-continental differences in the clinical characteristics of patients with SS suggesting immune and/or genetic

Table 2
Comparisons of clinical and sociodemographic characteristics[a].

Variable	Colombia (n = 950) vs. Rest of Latin America (n = 2020)	Latin America (n = 2970) vs. Asia (n = 2280)	Latin America (n = 2970) vs. Europe (n = 13542)	Latin America (n = 2970) vs. North America (n = 2197)
Gender, female	1.26 (0.63, 2.49)	0.93 (0.64, 1.34)	**1.85 (1.39, 2.45)**	**2.05 (1.45, 2.89)**
Age at disease onset	**7.01 (0.12, 13.89)**	**-7.28 (-13.27, -1.29)**	**5.42 (2.16, 8.68)**	–
Smoking (ever)	1.88 (0.25, 14.17)	**40.97 (12.61, 133.07)**	**3.11 (1.51, 6.42)**	–
Polyautoimmunity	0.63 (0.23, 1.74)	–	2.70 (0.80, 9.15)	–
RA	–	–	**62.58 (7.05, 555.29)**	–
SLE	–	–	**9.75 (2.90, 32.74)**	–
AITD	1.35 (0.68, 2.68)	**1.95 (1.13, 3.37)**	1.35 (0.90, 2.02)	–
SSc	–	–	**13.07 (1.42, 120.40)**	–
PBC	–	–	**0.07 (0.009, 0.56)**	–
AIH	–	–	**0.19 (0.04, 0.84)**	
Xerophthalmia	0.90 (0.04, 19.57)	**3.80 (1.10, 13.16)**	0.75 (0.22, 2.58)	0.33 (0.09, 1.18)
Xerostomy	**33.47 (1.22, 917.43)**	2.10 (0.53, 8.34)	0.71 (0.18, 2.78)	**0.16 (0.04, 0.69)**
Xeromycteria	1.09 (0.65, 1.85)	–	–	–
Xerotrachea	2.30 (0.94, 5.60)	–	–	–
Pulmonary involvement	–	**0.16 (0.05, 0.58)**	0.64 (0.21, 1.99)	–
Cutaneous involvement	2.09 (0.66, 6.65)	–	1.08 (0.53, 2.22)	–
Urticaria	**5.89 (3.37, 10.28)**	–	-	–
Raynaudś phenomenon	2.01 (0.73, 5.54)	–	0.76 (0.40, 1.45)	1.45 (0.34, 6.12)
Cutaneous vasculitis	1.03 (0.35, 3.03)	–	0.89 (0.50, 1.60)	2.95 (0.94, 9.31)
Cutaneous ulcers	2.04 (0.84, 4.98)	–	–	–
Purpura	0.87 (0.29, 2.59)	–	1.06 (0.65, 1.75)	–
Photosensibility	–	–	–	**9.99 (5.42, 18.39)**
Dysphagia	**3.47 (1.33, 9.00)**	–	–	–
Gastritis	1.58 (0.26, 9.49)	–	–	–
Hepatitis	–	**0.21 (0.11, 0.42)**	–	–
Splenomegaly	–	–	0.90 (0.35, 2.31)	–
Renal tubular acidosis	0.05 (0.0007, 3.99)	**0.22 (0.12, 0.42)**	**58.16 (7.52, 449.85)**	–
Glomerulonephritis	0.94 (0.27, 3.29)	-	2.15 (0.27, 16.98)	–
Arthralgia/Arthritis	0.89 (0.14, 5.83)	2.43 (0.62, 9.45)	1.71 (0.76, 3.83)	–
Arthralgia	0.51 (0.07, 3.62)	–	3.27 (0.81, 13.19)	–
Arthritis	0.55 (0.13, 2.45)	4.04 (0.45, 36.49)	**5.68 (1.41, 22.99)**	2.49 (0.27, 22.57)
Myalgia	–	–	1.43 (0.36, 5.75)	–
Parotid gland swelling	0.42 (0.035, 5.08)	1.33 (0.11, 15.36)	0.58 (0.17, 1.99)	–
Persistent parotid swelling	–	–	**0.05 (0.02, 0.14)**	–
Lymphadenopathy	2.51 (0.42, 15.10)	–	1.13 (0.36, 3.54)	–
Lymphoma	–	–	0.55 (0.19, 1.60)	–
Neoplasia	1.43 (0.48, 4.25)	–	–	–
Neurological compromise	0.75 (0.47, 1.22)	–	0.78 (0.58, 1.06)	1.03 (0.68, 1.58)
PNS compromise	0.91(0.21, 4.02)	–	1.25 (0.59, 2.69)	–
CNS compromise	0.15 (0.02, 1.41)	–	**3.10 (1.22, 7.89)**	–
Depression	1.63 (0.75, 3.55)	–	–	–
Anemia	0.68 (0.21, 2.23)	–	0.81 (0.22, 2.95)	–
Dyslipidemia	1.10 (0.49, 2.50)	–	0.48 (0.21, 1.08)	–
Osteoporosis	1.00 (0.36, 2.79)	–	–	–
Objective oral tests	0.31 (0.03, 3.61)	1.12 (0.28, 4.52)	1.38 (0.34, 5.55)	1.92 (0.48, 7.74)
Positive salivary flow	**0.17 (0.05, 0.59)**	1.03 (0.37, 2.91)	2.64 (0.94, 7.40)	1.20 (0.43, 3.40)
Positive sialography	0.56 (0.02, 16.44)	0.63 (0.36, 1.10)	**0.28 (0.16, 0.48)**	–
Objective ocular tests	1.38 (0.1, 19.64)	0.69 (0.16, 2.89)	0.77 (0.18, 3.18)	0.80 (0.19, 3.35)
Positive Schirmerś test	1.90 (0.28, 12.97)	0.77 (0.32, 1.82)	0.73 (0.31, 1.72)	1.76 (0.74, 4.21)
Positive MSG biopsy[b]	0.13(0.01, 1.41)	0.54 (0.13, 2.32)	2.35 (0.56, 9.89)	0.45 (0.10, 1.91)
Positive ANA	**6.97 (2.77, 17.55)**	**0.44 (0.24, 0.82)**	0.70 (0.38, 1.28)	0.80 (0.43, 1.49)
Positive Ro/SSA	2.06 (0.61, 6.94)	0.74 (0.36, 1.53)	1.60 (0.79, 3.23)	1.54 (0.75, 3.13)
Positive La/SSB	0.98 (0.44, 2.19)	1.00 (0.62, 1.63)	1.34 (0.84, 2.13)	1.16 (0.72, 1.88)
Rheumatoid factor	**3.54 (1.69, 7.42)**	0.88 (0.59, 1.32)	0.95 (0.65, 1.39)	1.15 (0.77, 1.72)
Low C3	–	0.44 (0.14, 1.36)	0.64 (0.21,2.00)	2.56 (0.79, 8.26)
Low C4	–	1.12 (0.45, 2.78)	0.70 (0.29, 1.67)	0.97 (0.39, 2.41)
Cryoglobulinemia	–	4.78 (0.94, 24.33)	0.50 (0.22, 1.16)	0.58 (0.14, 2.44)
Hypergammaglobulinemia	–	–	**0.31 (0.18, 0.56)**	**0.29 (0.13, 0.66)**
Hypocomplementemia	–	–	**0.34 (0.22, 0.54)**	2.55 (0.96, 6.78)

Significant results (P < 0.05) are presented in bold. Age at disease onset is reported as the mean difference and 95% CI.
See Table 1 for abbreviations.

[a] Data show odds ratios (OR) and 95% confidence intervals (95% CI).

[b] Analysis took into consideration the percentage of positive results of the total number of MSG biopsies done in each study.

differences as the driving cause. Although ancestry has been suggested to influence the development of SS [42], no large studies on this topic exist.

In conclusion, continental population groups significantly influence the clinical spectrum of SS. These differences could be attributed in part to the ancestral origin of the populations living in each continent which determines genetic characteristics of the individuals (Fig. 1). However, differential exposure to environmental factors, previous infections and cultural aspects vary between and within continental population groups, which could

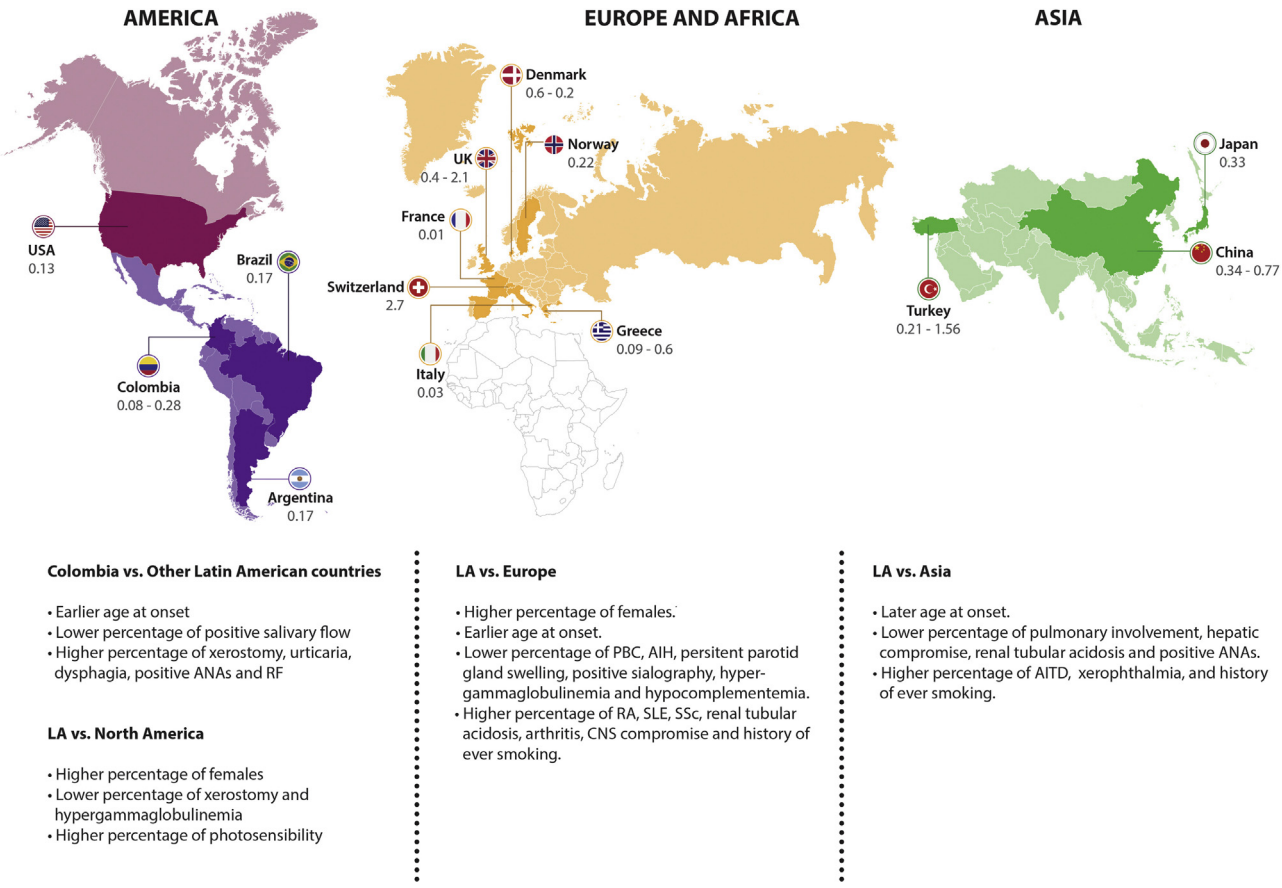

Fig. 1. Geoepidemiology of Sjögrenś syndrome. The figure shows the main prevalences in countries of North and South America, Europe and Asia as well as the main clinical characteristics of each population. Data are in percentages. Prevalence data from Argentina corresponds to the Qoomś population in Rosario, Argentina [3,4,29–35]. Studies on the prevalence of SS varies depending on diagnostic criteria used for its evaluation. As revised by Fernandez-Avila et al. [36], the lowest prevalence of SS was reported in France (0.01%, by using the American-European Consensus Group Criteria [4]) and the highest in Switzerland (2.7%, by using the Copenhagen criteria [36]). ANA: antinuclear antibodies; RF: rheumatoid factor; PBC: primary biliary cholangitis; AIH: autoimmune hepatitis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; CNS: central nervous system; AITD: autoimmune thyroid disease.

also influence the differences observed. The growing migratory phenomenon will allow to clarify the impact of environmental factors in the development of ADs as comparisons between populations with similar ancestry but living in different geographical areas could help in the identification of genetic and environmental factors acting as modifiers of the clinical profile and course of SS and other ADs.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

The authors are grateful to Manuel Rojas, Ruben D. Mantilla and colleagues from the Center for Autoimmune Disease Research (CREA), Bogota, for fruitful discussions and contributions. We also thank Natalia Bayona-Berdugo for her participation at the beginning of the study, and Alain J. Bautista for careful reading of the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2019.02.004.

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