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ORIGINAL RESEARCH

Impact of patient ancestry on heterogeneity of Sjögren's disease

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ABSTRACT

Objectives We aimed to compare disease characteristics between primary Sjögren's syndrome (pSS) patients of African ancestry (AA) and Caucasian ancestry.

Methods We conducted a retrospective, case–control study in a French national and European referral centre for pSS. All patients with pSS of AA were matched with two Caucasians patients having similar follow-up duration. We explored clinical and biological parameters associated with a cumulative EULAR Sjögren's Syndrome Disease Activity Index (cumESSDAI ≥5) (consisting of individual clinESSDAI domain maximum throughout follow-up).

Results We identified 74 patients of AA matched with 148 Caucasian. Median age at pSS diagnosis was younger in AA patients (43 years (IQR 33–51) vs 56 years (44.8–59.2), p<0.001). AA patients presented higher median titre of gammaglobulins (18.5 g/L (IQR 15–22.8) vs 13.4 g/L (9.9–16.9), p<0.001), more frequently positive for anti-SSA (88% vs 72%, p=0.007) and anti-RNP (11% vs 2.7%, p=0.023) antibodies. During the follow-up (median: 6 years (IQR 2–11)), AA patients presented more systemic complications: arthritis, myositis, interstitial lung disease, lymphadenopathy, central nervous system involvement. Median cumESSDAI score was higher in AA patients (7.5 (IQR 3.2–16.0) vs 4.0 (IQR 2.0–9.0), p=0.002). Interestingly, in multivariate analyses, factors associated with disease activity were sub-Saharan AA (OR 2.65 (95% CI 1.06 to 6.94)), rheumatoid factor (OR 2.50 (95% CI 1.28 to 4.96)) and anti-RNP positivity (OR 11.1 (95% CI 1.88 to 212)).

Conclusion Patients of AA display higher disease activity with a hallmark of higher B-cell activation. Studies to investigate biological drivers behind such differences are needed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In systemic lupus erythematous (SLE), patients of African ancestry present higher disease activity, morbidity and higher mortality in case of end-stage renal disease than other patients.

⇒ Primary Sjögren's syndrome shares, in some aspects, a common pathogenic framework with SLE, however, we found no longitudinal study that comprehensively compared symptoms, disease activity over time or treatments in patients of African ancestry to other ethnicity.

WHAT THIS STUDY ADDS

⇒ Our study is the first to reveal that African ancestry, particularly sub-Saharan African ancestry, is an independent driver of a higher disease activity with distinct domain involved and autoantibody profile.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Physicians should be particularly aware of the over-representation of infrequent organ activity such as muscular, pulmonary and central nervous system involvement in patients of African ancestry.

INTRODUCTION

Autoimmune diseases are complex by nature. In some people with specific genetic background, environmental triggers encountering genetic dysregulation might lead to overstimulation of the immune system. This interaction between genetics and environment might promote loss of tolerance leading to the development of autoimmunity. In some diseases, it has been shown that ethnicity can influence disease phenotype. This is notably the case in systemic lupus erythematous (SLE), in which disease burden is higher in patients from African ancestry (AA) than in Caucasian patients, with more end-stage renal disease and higher mortality.[1] In addition, ethnicity might also influence the treatment response in lupus nephritis (LN).[2] Socioeconomics factors could in part explain these differences, as the interaction between ethnicity and poverty has been associated with disease activity,[3] along with genetic polymorphisms.[4–6]

Although primary Sjögren's syndrome (pSS) and SLE vary by their clinical presentation, they share common pathogenic background, including interferon (IFN) signature[7] and B cell activation. Increase in B-cell activating factor (BAFF) is at the crossroad between these diseases. Its overexpression is well described in both diseases and may favour development of autoreactive lymphocytes.[8]

Table 1 Demographic, clinical and biological characteristics of pSS patients according to ancestry

	African, N=74*	Caucasian, N=148*	P value†
Follow-up duration	6.0 (2.0, 11.0)	6.0 (2.0, 11.0)	>0.9
Age at symptoms onset	40.0 (30.0, 48.0)	52.0 (37.8, 59.2)	**<0.001**
Age at Sjögren's diagnosis	43.0 (33.0, 51.0)	56.0 (44.8, 64.0)	**<0.001**
Sex, female	68/74 (92%)	139/148 (94%)	0.6
Fatigue	43/52 (83%)	72/138 (52%)	**<0.001**
Oral dryness	61/74 (82%)	133/148 (90%)	0.12
Eye dryness	53/74 (72%)	127/148 (86%)	**0.011**
Shiermer abnormal	29/46 (63%)	74/108 (69%)	0.5
Low salivary flux	12/41 (29%)	37/95 (39%)	0.3
Chisholm score 3–4	55/66 (83%)	96/123 (78%)	0.4
Raynaud syndrome	20/74 (27%)	34/148 (23%)	0.5
Salivary gland enlargement	31/74 (42%)	50/148 (34%)	0.2
Arthritis	20/74 (27%)	18/148 (12%)	**0.006**
Myositis	4/74 (5.4%)	1/148 (0.7%)	**0.043**
Pulmonary involvement	13/74 (18%)	16/148 (11%)	0.2
ILD	8/74 (11%)	5/148 (3.4%)	**0.035**
Lymphadenopathy	19/74 (26%)	15/148 (10%)	**0.002**
Splenomegaly	0/74 (0%)	2/148 (1.4%)	0.6
Subacute cutaneous lupus	0/74 (0%)	6/148 (4.1%)	0.2
Purpura	6/74 (8.1%)	15/148 (10%)	0.6
CNS involvement	4/74 (5.4%)	1/148 (0.7%)	**0.043**
Retrobulbar optic neuritis	1/4 (25%)	0/1 (0%)	–
Cerebral vasculitis	2/4 (0%)	0/1 (0%)	–
Acute demyelinating encephalomyelitis	1/4 (25%)	0/1 (0%)	–
Transverse myelitis	0/4 (0%)	1/1 (0%)	–
PNS involvment	2/74 (2.7%)	13/148 (8.8%)	0.15
Renal involvement	4/74 (5.4%)	6/148 (4.1%)	0.7
Lymphoma	6/74 (8.1%)	6/148 (4.1%)	0.2
Gammaglobulins titre (g/L)	18.5 (15.0, 22.8)	13.4 (9.9, 16.9)	**<0.001**
β2-microglobulin titre (mg/L)	2.3 (1.9, 2.7)	2.2 (1.8, 2.9)	>0.9
Rheumatoid factor	30/74 (41%)	79/148 (53%)	0.071
anti-SSA	65/74 (88%)	106/148 (72%)	**0.007**
anti-SSB	28/74 (38%)	58/148 (39%)	0.8
anti-DNA	1/74 (1.4%)	4/148 (2.7%)	0.7
anti-Sm	1/74 (1.4%)	0/148 (0%)	0.3
anti-RNP	8/74 (11%)	4/148 (2.7%)	**0.023**
Cryoglobulinaemia	15/74 (20%)	26/148 (18%)	0.6
Low C3	0/74 (0%)	6/148 (4.1%)	0.2
Low C4	14/74 (19%)	35/148 (24%)	0.4
ESSPRI	6.0 (4.5, 7.3)	5.7 (4.4, 6.6)	0.8
cumESSDAI	7.5 (3.2, 16.0)	4.0 (2.0, 9.0)	**0.002**
cumClinESSDAI	8.0 (2.0, 15.0)	4.5 (2.0, 9.0)	**0.011**
Steroids	23/74 (31%)	48/148 (32%)	0.8
Immunosuppressors	20/74 (27%)	31/148 (21%)	0.3
No of immunosuppressors			0.5

Continued

Table 1 Continued

	African, N=74*	Caucasian, N=148*	P value†
0	54/74 (73%)	117/148 (79%)	
1	14/74 (19%)	23/148 (16%)	
≥2	6/74 (8.1%)	8/148 (5.4%)	

bold indicates p-value: < or = to 0.05
*Median (IQR); n/N (%).
†Wilcoxon rank sum test; Pearson's $\chi 2$ test; Fisher's exact test.
CNS, central nervous system; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; ILD, interstitial lung disease; PNS, peripheral nervous system; pSS, primary Sjögren's syndrome.

Data focusing on ethnicity and its impact in pSS are scarce. A study found pSS to be twice as frequent in non-European individuals than in Europeans.[9] In another report, ethnicity influenced prevalence of sicca symptoms along with biological parameters such as anti-nuclear (ANA) and anti-SSA/Ro antibodies positivity.[10] None of these studies focused specifically on patients of AA.

In this study, we described and compared demographic characteristics, biological parameters, disease activity, outcome and treatment in pSS patients of AA with

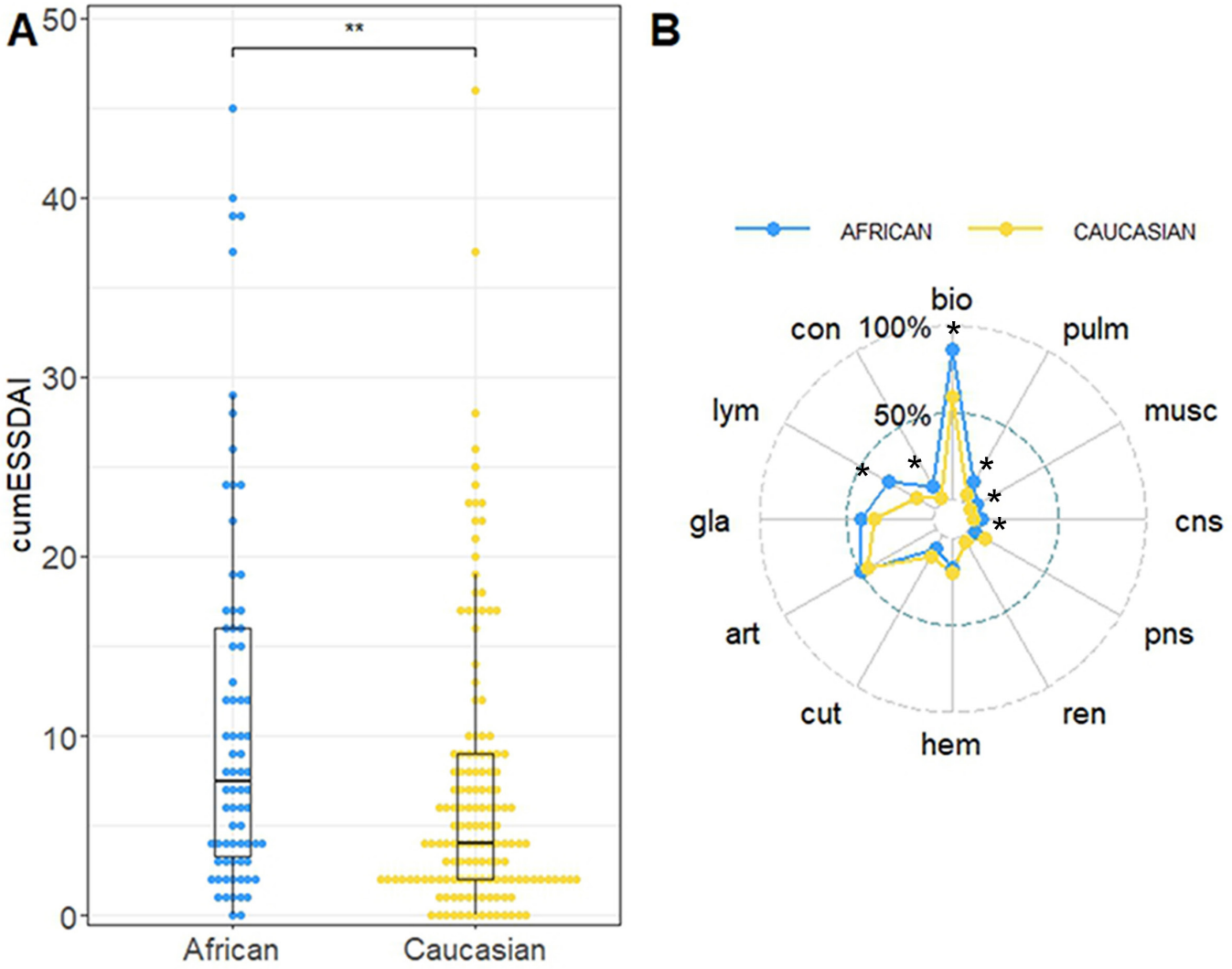

Figure 1 Cumulative ESSDAI score comparison and domain activity according to ancestry Cumulative ESSDAI score according to ancestry (A), percentage of patients presenting any ESSDAI domain level of activity, low, moderate or high, during follow-up (B). *p<0.05 with Fisher's exact test. art, articular; bio, biological; cns, central nervous system; con: constitutional; cut: cutaneous; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; gla, glandular; hem: haematological; lympm, lymphadenopathy; musc, musculararpns; pns, peripheral nervous system; pulm, pulmonary; ren, renal.

Table 2 Demographic, clinical and biological characteristics of pSS patients according to ancestry in sub-group populations

	Caucasian vs sub-Saharan			Caucasian vs Afro-Caribbean	
	Caucasian, N=148*	Sub-Saharan, N=43*	P value†	Afro-Caribbean, N=31*	P value†
Follow-up duration	6.0 (2.0, 11.0)	5.0 (2.5, 11.0)	>0.9	6.0 (2.0, 11.5)	0.9
Age at symptoms onset	52.0 (37.8, 59.2)	35.5 (25.5, 44.0)	**<0.001**	44.5 (36.5, 51.0)	**0.047**
Age at Sjögren's diagnosis	56.0 (44.8, 64.0)	40.0 (31.0, 48.0)	**<0.001**	47.0 (36.5, 53.5)	**<0.001**
Sex, Female	139/148 (94%)	39/43 (91%)	0.5	29/31 (94%)	>0.9
Fatigue	72/138 (52%)	26/31 (84%)	**0.001**	17/21 (81%)	**0.013**
Oral dryness	133/148 (90%)	33/43 (77%)	**0.025**	28/31 (90%)	>0.9
Eye dryness	127/148 (86%)	31/43 (72%)	**0.036**	22/31 (71%)	**0.044**
Shiermer abnormal	74/108 (69%)	16/28 (57%)	0.3	13/18 (72%)	0.8
Low salivary flux	37/95 (39%)	7/27 (26%)	0.2	5/14 (36%)	0.8
Chisholm score 3–4	96/123 (78%)	34/40 (85%)		21/26 (81%)	0.8
Lymphoma	6/148 (4.1%)	3/43 (7.0%)	0.4	3/31 (9.7%)	0.2
Gammaglobulins titre (g/L)	13.4 (9.9, 16.9)	19.6 (14.7, 24.2)	**<0.001**	17.6 (15.0, 21.0)	**<0.001**
β2-microglobulintitre (mg/L)	2.2 (1.8, 2.9)	2.3 (2.0, 2.7)	>0.9	2.2 (1.9, 2.7)	0.8
Rheumatoid Factor	79/148 (53%)	17/43 (40%)	0.11	13/31 (42%)	0.2
anti-SSA	106/148 (72%)	38/43 (88%)	**0.025**	27/31 (87%)	0.073
anti-SSB	58/148 (39%)	20/43 (47%)	0.4	8/31 (26%)	0.2
anti-DNA	4/148 (2.7%)	0/43 (0%)	0.6	1/31 (3.2%)	>0.9
anti-SM	0/148 (0%)	1/43 (2.3%)	0.2	0/31 (0%)	
anti-RNP	4/148 (2.7%)	7/43 (16%)	**0.003**	1/31 (3.2%)	>0.9
Cryoglobulinaemia	26/148 (18%)	8/43 (19%)	0.9	7/31 (23%)	0.5
Low C3	6/148 (4.1%)	0/43 (0%)	0.3	0/31 (0%)	0.6
Low C4	35/148 (24%)	9/43 (21%)	0.7	5/31 (16%)	0.4
cumClinESSDAI	4.5 (2.0, 9.0)	9.0 (4.0, 18.0)	**0.002**	6.0 (2.0, 12.0)	0.5
Steroid prescription	48/148 (32%)	19/43 (44%)	0.2	4/31 (13%)	**0.029**
Immunosuppressors	31/148 (21%)	16/43 (37%)	**0.029**	4/31 (13%)	0.3

*n/N (%); median (IQR).
†Pearson's $\chi 2$ test; Wilcoxon rank sum test; Fisher's exact test.
CNS, central nervous system; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; PNS, peripheral nervous system; pSS, primary Sjögren's syndrome.

matched Caucasian controls from two departments of a French national and European referral centre for SS.

METHODS

Study design and setting

We have conducted a retrospective case–control study. Eligible patients were screened in two departments belonging to a French national and European referral centre for SS either through out patients' records for suspicion and follow-up of SS, or inpatients with an International Classification of Diseases, 10th Revision code for SS.

Participants

Cases were defined as pSS patients of AA. All cases fulfilled ACR/EULAR 2016 criteria for pSS and did not meet diagnostic criteria for other connective tissue diseases such as rheumatoid arthritis, SLE, scleroderma or mixed connective tissue disease. Patients who presented an associated connective tissue disease at pSS diagnosis or during follow-up were excluded. Ancestry based on parents' origin was either self-declared if patients attended a standardised visit for suspicion of SS, or otherwise reported by physicians. Patients were not included if ancestry could not be ascertained. Each patient of AA has been paired with two randomly selected Caucasian controls from the same centre. In order to properly compare disease activity over time, we also matched cases and controls based on follow-up duration, thus limiting selection bias.

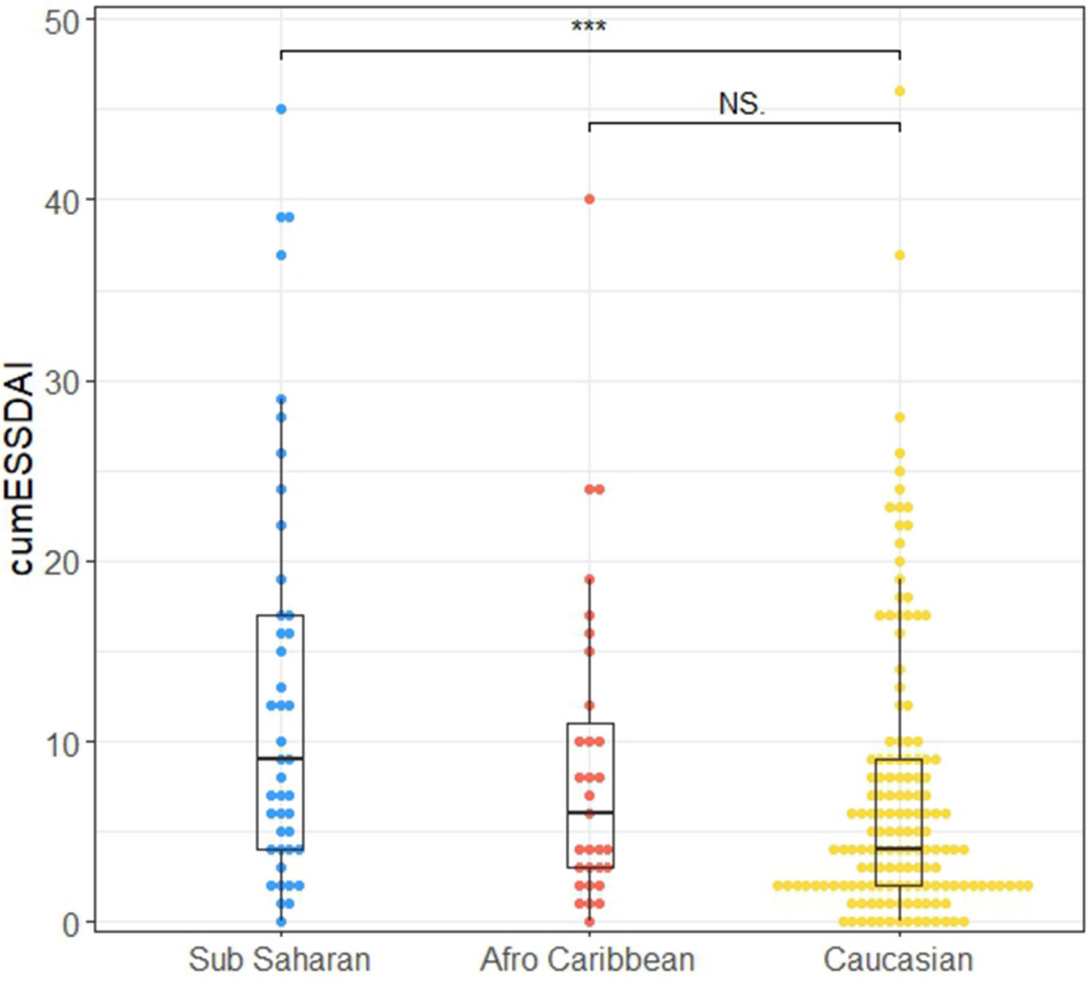

Figure 2 Cumulative ESSDAI score according to ancestry in subgroup populations Cumulative ESSDAI score according to subgroups of ancestry. ***p<0.001 with Fisher's exact test. ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index.

Variables and data sources

Based on computerised and paper medical files, we retrospectively collected sex, age at beginning of symptoms and age at diagnosis of pSS. We gathered Sjögren's-related symptoms such as sicca, parotid gland enlargement and extraglandular manifestations of pSS including occurrence of lymphoma at any time before or after diagnosis. Biological and immunological features included anti-nuclear antibodies (ANA), anti-SSA/Ro, anti- SSB/La, anti-DNA, anti-Sm and anti-RNP, gammaglobulins and β2-microglobulinaemia titres, complement levels and presence of cryoglobulinaemia. We gathered histological data of accessory salivary glands biopsies. We assessed EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) at each consult with available information and retained each category's maximum ESSDAI score during the follow-up. We then calculated a cumulative ESSDAI (cumESSDAI) score per patient as the sum of each category's maximum score during the follow-up. Using the same method, we calculated a cumulative ClinESSDAI (cumClinESSDAI) score, a variant which excludes the biological domain.[11] We additionally calculated a median EULAR Sjögren's Syndrome Patient Reported Index score per patient when possible. Lastly, we gathered any pSS-related treatments prescribed at diagnosis and onward.

Statistical analysis

Our main analysis consisted of comparing patients of AA and Caucasians. We subsequently explored demographic, clinical and biological characteristics in patients of AA (sub-Saharan African and Afro-Caribbean) and of Caucasian ancestry. Lastly, we explored clinical and biological parameters associated with a cumulative clinESSDAI ≥5. We used as outcome clinESSDAI rather than ESSDAI in order to explore gammaglobulin titres, cryoglobulin and low complement level.

Data are presented as mean±(SD) or medians (IQR) as appropriate for continuous variables and number (%) for qualitative variables. Wilcoxon rank test and one-way analysis of variance tests were used to compare continuous variables. χ^2 or Fisher's exact test was used to compare categorical features. In order to investigate clinical and biological parameters associated with an

elevated clinESSDAI, After exploring variables associated with a cumClinESSDAI ≥5 in an univariate binomial logistic regression, we integrated in a multivariate logistic regression model all variables with p<0,15. Statistical analysis were performed on R V.4.2.1.

Patients and public involvement

No patients or public were involved in the design, reporting or dissemination of our study.

RESULTS

Differences between pSS patients of African and Caucasian ancestry

Of the 1269 pSS patients fulfilling ACR/EULAR 2016 diagnostic criteria, we identified 74 patients of AA to whom we matched 148 Caucasian patients based on follow-up duration and centre. A detailed flow chart is presented in online supplemental figure S1. Median follow-up duration was of 6.0 years (IQR 2.0–11.0) in both groups. Median age at pSS diagnosis was younger in AA patients than in Caucasians (43 years (IQR 33.0–51.0) vs 56.0 years (44.8–59.2), p<0.001), with similar proportion of female across groups (92% vs 94%, respectively, p=0.6). Median delay between first symptoms and diagnosis was not statistically difference between patients of AA and Caucasians (2.0 years (IQR 0.0–4.0) vs 2.0 years (IQR 1–7), respectively, p=0.06) (online supplemental figure S2). During the follow-up, patients of AA presented more frequently with arthritis (27% vs 12%, p=0.006), myositis (5.4% vs 0.7%, p=0.043), interstitial lung disease (ILD) (11% vs 3.4%, p=0.035), lymphadenopathy (26% vs 10%, p=0.002), pSS related central nervous system affliction (5.4% vs 0.7%, p=0.43). Caucasians tended to present more frequently with axonal neuropathy (1.4% vs 8.1%, p=0.065). Results are presented in table 1.

Regarding immunologic workup, AA patients presented higher median titres of gammaglobulins (18.5 g/L (IQR 15–22.8) vs 13.4 g/L (9.9–16.9), p<0.001) and were more frequently positive for anti-SSA (88% vs 72%, p=0.007) and anti-RNP (11% vs 2.7%, p=0.023). Of note, we initially detected four AA patients with anti-Sm/nRNP but after careful checking using immunodot, three of these four patients had anti Sm/nRNP that are less specific of SLE[12] and only one had isolated anti Sm. None of these four patients had specific features of SLE. Caucasians tended to present more frequently with positive rheumatoid factor (41% vs 53%, p 0.07). One and four patients in the AA and Caucasian group, respectively, presented with measurable anti-DNA antibodies positivity on one or more occasion during the follow-up (median follow-up of 15 years (IQR 9–15)). None of these patients presented SLE clinical manifestations such as acute cutaneous lupus or LN.

Overall disease activity, assessed by cumESSDAI, was higher in AA patients with a median cumESSDAI score of 7.5 (IQR 3.2–16.0) vs 4.0 (IQR 2.0–9.0) in Caucasians (p=0.002) (figure 1A). This difference remained when comparing cumClinESSDAI (table 1). Patients of AA presented more frequently with activity in the constitutional, pulmonary, lymphadenopathy, muscular, central nervous system and biological domains (figure 1B). Frequency of prescription of steroids, hydroxychloroquine and immunosuppressors was not different between both groups (table 1).

Does origin of AA influence pSS manifestations?

Among the AA population, we distinguished 43 patients of sub-Saharan AA and 31 of Afro-Caribbean ancestry. As shown in table 2, most statistical differences between AA patients and Caucasians are limited to the sub-Saharan AA population, except for age at pSS diagnosis, ocular dryness and serum gammaglobulins level which followed similar trends in Afro-Caribbean and sub-Saharan African patients. Of note, median cumESSDAI score was not different between Afro-Caribbean and Caucasians (6.0 (IQR 2.0–12.0) vs 4.5 (IQR 2.0–9.0), respectively, p=0.5) contrarily to sub-Saharan AA patients (9.0 (IQR 4.0–17.0) vs 4.5 (IQR 2.0–9.0), p≤0.001) (figure 2). In the sub-Saharan African group, immunosuppressors were more frequently prescribed than in the Caucasian group (37% vs 21%, p=0.029).

AA as an independent driver of disease activity

We observed that AA patients had more biomarkers of B cells activation and a higher cumulative disease activity. These two parameters have been shown to be associated in pSS.[13] We; therefore, investigated whether ancestry remained associated with disease activity independently of biological markers. In table 3, we present results of univariate and multivariate analysis of features associated with a clinCumESSDAI ≥5. In the univariate analysis, we found that disease activity was associated with sub-Saharan AA (OR 2.58 (95% CI 1.26 to 5.59)), with higher follow-up duration (OR 2.58 (95% CI 1.26 to 5.59)), rheumatoid factor (OR 2.45 (95% CI 1.43 to 4.25)), anti-RNP (OR 9.81 (95% CI 1.86 to 181)) and cryoglobulin positivity (OR 2.64 (95% CI 1.28 to 5.80)). We also found an inverse correlation with age at pSS diagnosis (OR 0.978 (95% CI 0.960 to 0.996)). In multivariate analysis, sub-Saharan AA was independently associated with higher disease activity (OR 2.65 (95% CI 1.06 to 6.94)), as well as rheumatoid factor (OR 2.50 (95% CI 1.28 to 4.96)) and anti-RNP positivity (OR 11.1 (95% CI 1.88 to 212)).

DISCUSSION

This study is the first to compare demographic, clinical and biological characteristics of pSS patients of AA with Caucasians. We observed that patients of AA were younger at diagnosis, presented higher rates of arthritis, myositis, ILD, lymphadenopathy and CNS involvement. They had higher anti-RNP positivity and higher titres of gammaglobulins. Disease activity was higher in patients of AA compared with Caucasians as reflected by the cumESSDAI score.

Table 3 Univariate and multivariate analysis of parameters associated with a clinCumESSDAI ≥5

	Univariate analysis			Multivariate analysis*		
Characteristic	OR	95% CI	P value	OR	95% CI	P value
Origin						
Caucasian	—	—		—	—	
Afro-Caribbean	1.21	0.56 to 2.68	0.62	1.53	0.61 to 3.94	0.4
Sub-Saharan	2.58	1.26 to 5.59	**0.012**	2.65	1.06 to 6.94	**0.040**
Follow-up duration	1.06	1.02 to 1.11	**0.009**	1.04	0.99 to 1.10	0.11
Age at Sjögren's diagnosis	0.978	0.960 to 0.996	**0.021**	0.98	0.96 to 1.01	0.2
Sex						
Female	—	—		—	—	
Male	0.70	0.24 to 2.02	0.51	—	—	
Oral dryness	1.75	0.79 to 3.96	0.17	—	—	
Eye dryness	1.14	0.58 to 2.23	0.71	—	—	
Shiermer abnormal	0.98	0.50 to 1.92	0.95	—	—	
Low salivary flux	1.01	0.50 to 2.04	0.98	—	—	
Chisholm score						
0–2	—	—		—	—	
3–4	1.04	0.50 to 2.13	0.91	—	—	
Gammaglobulins titre (g/L)	1.04	0.99 to 1.08	0.11	0.98	0.92 to 1.04	0.4
Rheumatoid factor	2.45	1.43 to 4.25	**0.001**	2.50	1.28 to 4.96	**0.008**
anti-SSA	1.51	0.81 to 2.84	0.20	—	—	
anti-SSB	1.44	0.84 to 2.51	0.19	—	—	
anti-RNP	9.81	1.86 to 181	**0.030**	11.1	1.88 to 212	**0.028**
Cryoglobulin	2.64	1.28 to 5.80	**0.011**	1.82	0.81 to 4.28	0.2
Low C4	1.55	0.81 to 3.03	0.19	—	—	

*Mutlivariate analysis adjusted on ancestry, follow-up duration, age at Sjögren's diagnosis, gammaglobulins titre, rheumatoid factor, cryoglobulin and anti-RNP positivity.
ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index.

Brito-Zerón *et al* showed, consistent with our results, that African-American pSS patients had younger disease onset compared with white pSS patients with higher titres of anti-SSA antibodies.[10] Anti-SSA positivity in pSS has been shown to be associated with younger age at diagnosis, higher prevalence of lymphoma, of purpura and of salivary gland enlargement.[14] Regarding biological characteristics, anti-SSA positivity has been shown to be associated with higher rates of hypergammaglobulins, with rheumatoid factor positivity and low complement levels.[14] Although patients of AA were younger than Caucasians with higher rates of hypergammaglobulinaemia, the phenotypic differences we observed between the two populations does not appear to be solely related to anti-SSA positivity since lymphomas, purpura and glandular domains were equally frequent.

Interestingly, higher disease activity in AA patients was restricted to patients from sub-Saharian AA and not found in patients of Afro-Caribbean ancestry. Although some common genetic background is shared between Afro-Caribbean and continental African populations,[15] these two groups differ with notably Amerindian admixture in the populations of Afro-Caribbean origin.[16] In addition, it has been shown in SLE that environmental factors could play a role in populations with close ancestry.[17] Studying such differences might uncover candidate genes for drivers of autoimmunity in patients of AA.

Although B-cell activation markers were more prevalent in AA patients, and particularly in sub-Saharan African patients, we showed that these patients still displayed higher disease activity after adjusting for these biomarkers. We solely accounted for routine biological workup and could not evaluate more specific cytokines such as sBAFF, whose expression can vary depending on geographical origin.[18] The level of BAFF expression may be associated with genetic polymorphism; recently, a BAFF variant associated with increased serum BAFF level has been shown to participate in the increased risk of SLE and multiple sclerosis in a Sardinian population; this variant was probably selected through evolution by augmenting resistance to malaria,[18] mechanism that could be also very pregnant in an AA population.

Moreover, we showed that anti-RNP positivity remained an independent predictor of disease activity and a possible distinct clinical phenotype of pSS patients with anti-RNP antibody as suggested in a previous study.[19]

One of our study's strengths is the effort made to depict patients' overall disease phenotype overtime rather than presenting a snapshot of disease activity in cross-sectional designs. Indeed, pSS evolves by flares intertwined with remission periods that can sometime last years. Therefore, when comparing disease burden with treatment prescription over time and long-term complications such as lymphoma occurrence, longitudinal studies are most adapted. Moreover, in order to limit selection bias, we ensured cases and controls had similar opportunity of presenting disease-related complications by matching on follow-up duration.

A limit to our study is its setting in tertiary centre without primary care data. One could argue that differences between groups could be explained by socioeconomic factors with unequal access to healthcare facilities in one group, which might underestimate prevalence of less severe cases while over-representing severe patients. However, France's healthcare access is free and universal without conditioning on employment, wealth nor immigration status, limiting such bias. Moreover, patients of AA are diagnosed at a younger age than Caucasian patients, are younger at symptoms onset and do not seem to suffer from diagnostic delay which might be at the origin of higher disease activity. We even observed a tendency towards greater delay in Caucasian patients, possibly because of lesser disease activity. We could not however adjust for income and education, and therefore, could not evaluate their impact on disease activity. Another limit of our study is its retrospective nature, which we justified by focusing mostly on standard information regarding pSS follow-up such as biological data, domain activity at each visit and treatments.

In conclusion, pSS patients of AA, notably of sub-Saharan AA, had a distinct disease expression compared with Caucasians pSS patients. More studies are needed to determine the drivers behind these phenotypic differences.

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