Advances in Rheumatology

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To be or not to B27 positive: implications for the phenotypes of axial spondyloarthritis outcomes. Data from a large multiracial cohort from the Brazilian Registry of Spondyloarthritis

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Abstract

Background There is a remarkable variability in the frequency of HLA-B27 positivity in patients with spondyloarthritis (SpA), which may be associated with different clinical presentations worldwide. However, there is a lack of data considering ethnicity and sex on the evaluation of the main clinical and prognostic outcomes in mixed-race populations. The aim of this study was to evaluate the frequency of HLA-B27 and its correlation with disease parameters in a large population of patients from the Brazilian Registry of Spondyloarthritis (RBE).

Methods The RBE is a multicenter, observational, prospective cohort that enrolled patients with SpA from 46 centers representing all five geographic regions of Brazil. The inclusion criteria were as follow: (1) diagnosis of axSpA by an expert rheumatologist; (2) age ≥18 years; (3) classification according to ASAS axial. The following data were collected via a standardized protocol: demographic data, disease parameters and treatment historical.

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Results A total of 1096 patients were included, with 73.4% HLA-B27 positivity and a mean age of 44.4 (±13.2) years. Positive HLA-B27 was significantly associated with male sex, earlier age at disease onset and diagnosis, uveitis, and family history of SpA. Conversely, negative HLA-B27 was associated with psoriasis, higher peripheral involvement and disease activity, worse quality of life and mobility.

Conclusions Our data showed that HLA-B27 positivity was associated with a classic axSpA pattern quite similar to that of Caucasian axSpA patients around the world. Furthermore, its absence was associated with peripheral manifestations and worse outcomes, suggesting a relevant phenotypic difference in a highly miscegenated population.

Keywords Axial spondyloarthritis, HLA-B27, Genetics, Register-study, ASDAS-CRP, Ankylosing spondylitis

Background

Since its association with ankylosing spondylitis (AS) was discovered 50 years ago [1, 2], HLA-B27 has been considered an important genetic marker and also plays a significant role in the 2009 classification criteria for axial spondyloarthritis (axSpA) [3]. Early epidemiological studies showed that HLA-B27 was more prevalent in white populations in Northern Europe, which also had a greater prevalence of axSpA [4]. In the same context, the heterogeneity in the prevalence and clinical presentation of SpA observed in different regions of the world seems to be associated with the prevalence of HLA-B27 in these populations [5].

Clinically, HLA-B27 is associated with axial involvement and acute anterior uveitis in patients with a younger age at onset and a positive family history of axSpA [6, 7]. The association with worse radiographic progression in axSpA patients is another important characteristic [8]. Recently, HLA-B27 has also been shown to be an important phenotypic marker in peripheral spondyloarthritis (SpA); in the ASAS PerSpA study, the presence of HLA-B27 was associated with male sex, earlier age at onset, and the presence of axial involvement, tarsitis, and uveitis even in patients with peripheral SpA [9]. Its potential association with a better response to treatment in axSpA patients was also demonstrated [10].

Progression to axSpA and mortality can also be associated with HLA-B27. A Dutch study showed that the progression to axSpA at the 5-year-follow-up in first degree relatives of patients with axSpA was greater only in the HLA-B27-positive group in a pre-SpA cohort [11]. The lifetime recurrence rate of axSpA appears to be greater in first-degree relatives of HLA-B27 patients, and interestingly, affected mothers can transfer the disease more frequently to their offspring than can their affected fathers [12]. A recent study evaluating the 35-year-follow-up of a British axSpA cohort revealed increased mortality associated with HLA-B27, especially in women, in patients with radiographic axSpA, but not in patients with non-radiographic axSpA [13]. Recent findings emphasize that analysis of axSpA patients may also need to consider the distinct profile of the disease in women [14–16].

Latin America, especially Brazil, is traditionally a region of remarkable racial miscegenation. In addition to the original indigenous population, the White from Europe, Blacks brought from Africa, and later Asian populations comprise a large multiracial nation in Brazil. This racial diversity is associated with the heterogeneity of the clinical presentation of SpA in the Brazilian population [17], a finding quite similar to that demonstrated in North American individuals [18, 19]. Recently, a national Brazilian study analyzing more than 5 million healthy bone marrow donors showed a prevalence of 4.35% of HLA-B27 positivity in the Brazilian population, ranging from 4.85% in Whites to 2.92% in nonmiscegenate Blacks [20].

Therefore, the present study evaluated the frequency of HLA-B27 and its clinical-epidemiological associations in a large population of patients with axSpA from the Brazilian Registry of Spondyloarthritis (*Registro Brasileiro de Espondiloartrites*—RBE).

Methods

Design

The RBE is a multicenter, observational, prospective cohort that enrolled patients with SpA from 46 centers representing all five main geographic regions of Brazil from 2018 to 2023. To participate in this study, patients needed to meet the following inclusion criteria [1]: had a diagnosis of axSpA by an expert rheumatologist [2]; were aged older than 18 years; and [3] were classified according to the ASAS axial criteria [3].

Data, which included demographic data (age, sex, skin color, work situation), positivity of HLA-B27 and disease parameters (axial and/or peripheral involvement, extra-musculoskeletal manifestations—EMM, comorbidities and treatment), were collected in a standardized protocol on the REDCap platform.

Disease outcomes

For patients with axSpA, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [21] and Ankylosing Spondylitis Disease Activity Score (ASDAS) [22] using erythrocyte sedimentation rate (ESR) and C-reactive

protein (CRP) were used to measure disease activity. Other indices, such as Bath Ankylosing Spondylitis Functional Index (BASFI) [23], Bath Ankylosing Spondylitis Metrology Index (BASMI) [24], Ankylosing Spondylitis Quality of Life (ASQoL) [25], and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [26] were also measured.

Ethics

The study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Ethical Committee (Comissão de Ética para Análise de Projetos de Pesquisa—CAPPesq) of Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Brazil (ID CAAE: 49299415.7.1001.0068). Written informed consent was obtained from all participants.

Statistical analysis

To characterize the participants' profile, absolute and relative frequencies, means and standard deviations (SDs) were calculated. Comparisons of means between two groups were performed using Student's t test for independent samples. To verify the normality of the data, Kolmogorov-Smirnov test was applied. In the case of normality violation, Mann-Whitney non-parametric test was used. The chi-square test (or Fischer's exact test for small samples) were used to evaluate associations among categorical variables.

A logistic regression model in which HLA-B27 positivity was used as the dependent variable and appropriate adjustments were performed considering all independent variables that had a statistical significance of up to 10% in the univariate analysis. The P value was considered significant if it was less than 5%. Multiple linear regression models were also constructed for the main outcomes in patients with axSpA (ASDAS-CRP, BASDAI, BASFI, BASMI, and ASQoL). Statistical analyzes were performed using the IBM SPSS Statistics for Windows (Version 27.0. Armonk, NY: IBM Corp and GraphPad Software, Boston, Massachusetts USA, version 10) and RStudio 2023.06.1+524 "Mountain Hydrangea" for Windows.

Results

Among the 1392 patients with SpA registered in the RBE, 1096 had axSpA, with 73.4% of HLA-B27 positivity. It was notably associated with male sex ($p=0.004$), younger age at onset of symptoms ($p<0.0001$) and at diagnosis ($p<0.0001$), family history of SpA ($p=0.03$), uveitis manifestation ($p=0.0001$), and lower prevalence of psoriasis ($p<0.0001$). Furthermore, the axSpA patients who were HLA-B27 negative had greater disease activity, as measured by the BASDAI ($p=0.02$) and ASDAS ($p=0.004$); worse quality of life, as assessed by the ASQoL ($p=0.03$), more impaired mobility, as assessed by the BASMI ($p=0.045$) and more frequent peripheral involvement, as assessed by the painful joint count ($p=0.007$). See Table 1.

According to the multivariate analysis, the final logistic regression model (with HLA-B27 as the dependent variable) showed a significant association between positivity for HLA-B27 and male sex (OR=1.49; 95%CI=1.01–2.35, $p=0.02$), earlier age at disease onset ($p=0.01$), the presence of uveitis (OR=1.62; 95%CI=1.05–2.79, $p=0.02$) and the absence of psoriasis (OR=0.25; 95%CI=0.11–0.58, $p=0.001$). Furthermore, in patients with axSpA, the absence of HLA-B27 was associated with increased disease activity, as measured by the ASDAS-CRP ($p=0.026$). OR should be used solely to understand the effect size of the relationship between categorical variables. In this passage, there is no OR because ASDAS was not treated as categorical but rather as numerical, which went unnoticed during the review process.

To better understand the aforementioned association observed between HLA-B27 and lower ASDAS-CRP in axSpA patients, we explored several linear regression models with axSpA outcome measures (ASDAS-CRP, BASDAI, BASFI, BASMI, and ASQoL) as the dependent variables. The optimal fit model demonstrated an association between higher ASDAS-CRP scores and absence of HLA-B27 ($p=0.014$), along with male sex ($p=0.006$), older age ($p=0.002$), shorter duration of symptoms ($p=<0.001$), increased painful joint count ($p=0.007$), and more frequent use of current NSAIDs ($p=0.001$). Among the other axSpA outcome measures, only BASDAI showed an association with the absence of HLA-B27 ($p=0.046$). Table 2 shows the final multivariate linear regression models for all the main outcomes in patients with axSpA.

Discussion

At this time when new biomarkers were first discovered in axSpA patients half a century after the discovery of the association between HLA-B27 and AS [27], it is important to understand the entire spectrum of disease associated with both the presence and absence of HLA-B27 in different populations worldwide. With the expansion of the concept of axSpA, HLA-B27 research has become even more valuable for assisting in both the diagnosis and prognosis of this disease [3, 28]. This study in a significantly heterogeneous sample of the Brazilian population showed that while the presence of HLA-B27 was associated with the classic phenotype observed in patients from more homogeneous populations in Europe and North America, the absence of HLA-B27 seems to be associated with the peripheral manifestations of axSpA

Table 1 Demographic and clinical features of axial SpA patients included in the RBE

Characteristic	Total population (n = 1096)	HLA-B27 positive (n = 805)	HLA-B27 negative (n = 291)	p Value
Male gender (n, %)	803 (73.3)	609 (75.7)	194 (66.7)	**0.004**
Disease duration (years, SD)	18.3 (12.0)	18.6 (12.5)	17.4 (10.8)	0.485
Mean age at symptoms onset (years, SD)	28.4 (12.0)	27.0 (11.6)	32.2 (12.2)	**< 0.001**
Mean age at diagnosis (years, SD)	34.2 (12.4)	32.7 (11.7)	38.1 (12.5)	**< 0.001**
Mean delay in diagnosis (years, SD)	9.1 (9.3)	9.1 (9.7)	9.3 (8.4)	0.284
Race (self-reported skin color)				0.121
White (n, %)	537 (50.9)	412 (53.0)	125 (44.8)	
Black (n, %)	76 (7.2)	52 (6.7)	24 (8.6)	
Brown (*Pardos*) (n, %)	387 (36.6)	271 (34.9)	116 (41.6)	
Yellow (Asian Brazilians) (n, %)	38 (3.6)	30 (3.9)	8 (2.9)	
Indigenous (n, %)	18 (1.7)	12 (1.5)	6 (2.2)	
BMI (mean, SD)	26.5 (4.8)	26.4 (4.6)	26.8 (5.2)	0.493
Family history of SpA (n, %)	109 (22.1)	86 (24.7)	23 (15.8)	**0.032**
EMMs				**< 0.001**
Any (n, %)	231 (34.8)	170 (35.4)	61 (33.3)	
Psoriasis (n, %)	39 (5.9)	15 (3.1)	24 (13.1)	
IBD (n, %)	30 (4.5)	14 (2.9)	16 (8.7)	
Uveitis (n, %)	176 (26.5)	147 (30.6)	29 (15.8)	
Painful enthesis count (mean, SD)	5.0 (4.7)	5.0 (4.8)	5.1 (4.5)	0.554
Painful joint count (mean, SD)	6.9 (10.5)	5.7 (8.7)	9.8 (13.5)	**0.007**
Swollen joint count (mean, SD)	3.6 (4.2)	3.3 (4.0)	4.3 (4.5)	0.24
BASDAI (mean, SD)	4.1 (2.5)	4.0 (2.5)	4.3 (2.4)	**0.019**
ASDAS-CRP (mean, SD)	3.4 (1.7)	3.3 (1.7)	3.7 (1.8)	**0.004**
ASQoL (mean, SD)	7.5 (5.6)	7.3 (5.7)	8.1 (5.4)	**0.034**
BASMI (mean, SD)	3.9 (2.1)	3.8 (2.1)	4.2 (2.1)	**0.045**
BASFI (mean, SD)	4.6 (2.9)	4.5 (2.9)	4.8 (2.8)	0.059

The results are expressed as the mean (SD) and n (%); *BMI* body mass index, *EMM* extra-articular manifestation, *IBD* inflammatory bowel disease, *BASDAI* bath ankylosing spondylitis disease activity index, *ASDAS–CRP* axial spondyloarthritis disease activity score-C reactive protein, *ASQoL* ankylosing spondylitis quality of life, *BASMI* bath ankylosing spondylitis metrology index, *BASFI* bath ankylosing spondylitis functional index, *SD* standard deviation

p-values in bold represent statistically significant findings

and worse outcome measures, a striking characteristic of miscegenated Latin-American populations.

Positivity for HLA-B27 was observed in 73.4% of the patients with axSpA. This finding is quite similar to that observed in a recent compilation of Brazilian studies with a grouped frequency of approximately 75% but with some variability between different geographic regions related to colonization, migration, culture and origins [20]. This relevant heterogeneity was also noted by another study comparing SpA patients from the Latin American Registry of SpA (RESPONDIA) with those from two European registries (the Spanish REGISPONSER and the Belgian GIANT) with a significantly lower prevalence of HLA-B27 in Latin-Americans (71% vs. 83%, respectively) [29]. A subsequent study analyzing 4067 patients from REGISPONSER and RESPONDIA showed that HLA-B27 negative patients had more peripheral involvement as the initial manifestation of SpA [30]. A recent publication evaluating 5557 patients with axSpA, members of an international patient network, revealed that Latin America was the continent with the lowest proportion of positive HLA-B27 (65%), ranging on other continents from 71% in Europe to 78% in Asia [31]. Corroborating this fact, an Argentinian study found a lower proportion of HLA-B27 (43%) in patients with axSpA [32].

Although HLA-B27 has been significantly associated with White ancestry, especially of Caucasian origin, the findings regarding HLA-B27 in the Brazilian population of African descent with axSpA are especially interesting. In the present study, 463 (42.2% of the total axSpA patients) are of African descent, most of whom are brown, with only 7.2% being nonmiscegenated Blacks. Even so, HLA-B27 positivity was 70% in brown patients and 68.4% in Black patients. A previous study evaluating the prevalence of HLA-B27 in three ethnic groups in the United States showed that the frequency of HLA-B27 positivity was significantly lower in Blacks (62.5%) than in Whites (85.3%) [33]. On the other hand, as the prevalence of HLA-B27 is very low (<1%) in Black populations in sub-Saharan Africa, rare descriptions of the frequency of HLA-B27 in these populations have been reported, predominantly with a very small number of patients [34].

Table 2 Multivariate linear regression models for the main outcomes in axial SpA patients

Dependent variable	Independent variables associated, according to the best-fitting model										
ASDAS-CRP	Male sex ***P*=0.006 B=0.13**	Older age ***P*=0.002 B=0.16**	Shorter duration of symptoms ***P*<0.0001 B=0.20**	Higher NSAID prescriptions ***P*=0.001 B=0.16**	HLA-B27 Absent ***P*=0.014 B=0.12**	Increased PJC ***P*=0.007 B=0.13**	–	–	–	–	–
BASDAI	–	–	–	–	HLA-B27 Absent ***P*=0.046 B=0.10**	Increased PJC ***P*<0.0001 B=0.07**	Longer diagnostic delay ***P*=0.0004 B=0.18**	Increased enthesis count ***P*<0.0001 B=0.29**	–	–	–
BASMI	–	–	Longer duration of symptoms ***P*<0.0001 B=0.35**	Higher NSAID prescriptions ***P*=0.01 B=0.12**	–	–	Longer diagnostic delay ***P*<0.0001 B=0.26**	–	BASDAI ***P*<0.0001 B=0.24**	–	–
BASFI	–	Older age ***P*=0.03 B=0.11**	Longer duration of symptoms ***P*=0.0001 B=0.19**	–	–	Increased PJC ***P*=0.001 B=0.14**	Longer diagnostic delay ***P*=0.02 B=0.11**	–	–	BASMI ***P*<0.0001 B=0.54**	–
ASQoL	–	–	–	–	–	–	–	–	BASDAI ***P*<0.0001 B=0.30**	–	BASFI ***P*<0.0001 B=0.29**

ASDAS-CRP axial spondyloarthritis disease activity score (C-reactive protein), *BASDAI* bath ankylosing spondylitis disease activity index, *ASQoL* ankylosing spondylitis quality of life, *BASMI* bath ankylosing spondylitis metrology index, *BASMI* bath ankylosing spondylitis metrology index, *NSAID* nonsteroidal anti-inflammatory drug, *PJC* painful joints count, *P* p value, *B* linear regression standardized coefficients

Bold formatting is intended solely to highlight the p-values and standardized B coefficients that were significant in each model (row)

More recently, a systematic review showed an unmet need regarding the paucity of population-data available to estimate it for the global SpA population [35].

From 1500 to 1889 (the year slavery was abolished in Brazil), more than nine million people were brought from Africa to the Americas. It is important to highlight that there is a correspondence between the geographic origin of different regions of Africa and certain destinations of the diaspora in the Americas, characterizing the differences in ancestry and miscegenation with relevant genetic diversity from the New World. Central-western regions of Africa, such as Nigeria, Senegal, Ghana, Gambia and Kenya, had a greater proportion of people taken to the Caribbean and North America, while Bantu people from southern and eastern Africa (Sub-Saharan) were more often taken to Brazil [36]. These ancestry details could explain the differences observed even in individuals of Black origin spread across the Americas. Thus, our study contributes to a better understanding of how HLA-B27 could impact axSpA outcomes in a miscegenated population.

Previous studies in Latin America have demonstrated that the clinical presentation of SpA may differ depending on the patient´s sex [37, 38]. Subsequent studies, after the publication of the SpA concept, have demonstrated that clinical investigation axSpA in women deserves to have a specific focus [14–16]. The present study confirmed that HLA-B27 was significantly less frequent in women. Additional and more comprehensive analyzes are needed the evaluation of female patients with axSpA.

A significantly earlier age at disease onset (5.2 years difference) was another important finding in this study, according to both univariate and multivariate analyses. These data confirm the findings of the PerSpA study, which revealed a significant 6-year difference in disease onset in HLA-B27 positive patients [39]. A post-hoc analysis of 2910 patients from the ASAS PerSpA study revealed that the HLA-B27 negative group of patients had a more delayed diagnosis, as well as a greater prevalence of peripheral arthritis and enthesitis, in addition to extra-articular manifestations [40].

The significant associations of negative HLA-B27 with worse outcome measures (BASDAI, ASDAS, ASQoL, and BASMI in univariate analysis; and only BASDAI and ASDAS in multivariate analysis) in patients with axSpA also deserve consideration. A recent review on the characterization of negative HLA-B27 revealed similar results, but disease activity was measured by ESR

and CRP [41] and not by the outcome measures recommended by the ASAS [42]. It is important to highlight the fact that although both the BASDAI and ASDAS were associated with a greater PJC, only BASDAI was associated with enthesitis (Table 2), probably because it has a specific question about entheses (question 4: "How would you describe the overall level of discomfort you have had in the past week from any areas tender to touch or pressure?") in its questionnaire.

Addressing the racial context, the North-South gradient observed in the healthy Brazilian population is also notable, where HLA-B27 becomes increasingly more frequent as we migrate from the North (with a predominantly miscegenated population) to the South (with a majority population of White European ancestry) [20]. Although the present study was not designed for this specific evaluation, we can infer that the association between not having HLA-B27 and higher ASDAS-CRP may be associated with greater peripheral involvement in patients with axSpA, regardless of functionality, mobility, or quality of life impairment. Thus, our data highlighted another unmet need in managing patients with combined axial and peripheral involvement.

Regarding EMMs, this study showed that while uveitis is significantly associated with the presence of HLA-B27, psoriasis is associated with its absence. The association of HLA-B27 with anterior uveitis is well known [43], and it has become increasingly common to manifest at the onset of axSpA [44]. The presence of psoriasis tends to be more frequent in HLA-B27-negative patients, even in early SpA cohorts [45], and it can be inferred that the presence of HLA-B27 reduces the chance of concomitant diagnosis of psoriasis [45, 46].

The main strength of this study is the possibility of using a representative population from the different geographic regions of the country, allowing us to evaluate the ethnic diversity of the Brazilian population, with half of the patients being non-white, similar to what is observed in the last geographic census of the Brazilian population [47]. The main weakness of our study, as frequently occurs in the evaluation of highly miscegenated populations, is the characterization of ethnicity; we chose to consider the skin color that patients attribute to themselves.

Conclusions

In a scenario where there are still unmet needs regarding the diagnosis and classification of axSpA [48], the study of different populations will help to better understand the distinct phenotypes of axSpA. As HLA-B27 can be associated with somewhat different phenotypes, according to its presence or absence, we can assume that HLA-B27 may be one of the factors associated with the heterogeneous presentation of axSpA in Brazil, a clearly miscegenated nation.

List of abbreviations

AS	Ankylosing spondylitis
ASAS	Assessment of spondyloarthritis international society
ASDAS	Axial spondyloarthritis disease activity score
ASQoL	Ankylosing spondylitis quality of life
axSpA	Axial spondyloarthritis
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
BASMI	Bath ankylosing spondylitis metrology index
BMI	Body mass index
bDMARD	Biological disease modifying anti-rheumatic drug
CRP	C-reactive protein
DMARDs	Disease modifying anti-rheumatic drug
EMM	Extramusculoskeletal manifestations
ESR	Erythrocyte sedimentation rate
MASES	Maastricht ankylosing spondylitis enthesitis score
IBD	Inflammatory bowel disease
NSAID	Nonsteroidal anti-inflammatory drug
RBE	Brazilian Registry of Spondyloarthritis
SD	Standard deviations
SpA	Spondyloarthritis

Acknowledgements

Not applicable.

Author contributions

All authors made a substantial contribution to discussion of the content and reviewed/edited the manuscript before submission. G.G.R., C.G.S., C.D.L.M., M.M.P. and P.D.S.P. wrote the manuscript.

Funding

This study was supported by grants provided by the Brazilian Society of Rheumatology.

Data availability

The authors confirm that the de-identified data supporting the findings of this study can be made available to others on approval of a written reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Ethical Committee (Comissão de Ética para Análise de Projetos de Pesquisa—CAPPesq) of Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Brazil (ID CAAE: 49299415.7.1001.0068). Written informed consent was obtained from all participants.

Consent for publication

The data presented here have not been published elsewhere and the article has not been submitted to any other journal. We give our consent for the publication of the current manuscript.

Competing interests

The authors declare no conflicts of interest.

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Received: 21 March 2024 / Accepted: 21 April 2024
Published online: 26 April 2024

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