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Ethnicity and disease severity in ankylosing spondylitis a cross-sectional analysis of three ethnic groups

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Abstract

The purpose of this study is to compare disease severity in ankylosing spondylitis (AS) in three ethnic groups. We assessed 925 AS patients (57 Blacks, 805 Whites, 63 Latinos) enrolled in the longitudinal Prospective Study of Outcomes in AS (PSOAS) for functional impairment, disease activity, and radiographic severity. Comparisons of clinical characteristics and HLA-B27 frequency for each group were performed, in two multivariable regression models, we compared the baseline Bath Ankylosing Spondylitis Radiographic Index (BASRI) and modified Stokes Ankylosing Spondylitis Spine Score (mSASSS) by ethnicity, adjusting for covariates. Blacks had greater functional impairment (Bath Ankylosing Spondylitis Functional Index) (median 62.5 vs. 27.8 in Whites and 38.1 in Latinos; $p < 0.0001$); higher disease activity (Bath Ankylosing Spondylitis Disease Activity Index), (median 5.9 vs. 3.5 in Whites and 4.5 in Latinos; $p < 0.0001$), erythrocyte sedimentation rate (median 27.0 in Blacks vs. 10.0 in Whites and 17.0; $p < 0.0001$), and C-reactive protein levels (median 1.2 vs. 0.4 mg/dL in Whites and 0.9 in Latinos; $p < 0.0001$). Baseline BASRI and mSASSS were higher in Blacks (mean 9.5 and median 38.2, respectively) compared to Whites (7.3 and 6.4) and Latinos (7.3 and 8.1), ($p = 0.004, 0.007$), respectively, more significant as disease duration increased. HLA-B27 occurred in 62.5% of Blacks, 85.3% of Whites, and 86.7% of Latinos ($p < 0.0001$). On multivariable analysis, higher BASRI and mSASSS were associated with Black ethnicity, after adjusting for disease duration and gender as well as TNF inhibitor (TNFi) usage, smoking status, or education level. Blacks with AS have more severe disease compared to either Whites or Latinos.

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Compliance with ethical standards

Disclosures None.

Keywords

Ankylosing spondylitis; Blacks; Disease severity; HLA-B27; Latinos

Background

Axial spondyloarthritis (AxSpA) and ankylosing spondylitis (AS) are known to have a lower prevalence in Blacks and Africans than in other ethnic groups [1–4]. AS is three times more common and AxSpA nearly twice as common in American Whites than in American Blacks [1, 4]. In part, this has been attributed to the lower frequency of HLA-B27 in Blacks both in the US and in most but not all African ethnic groups [3, 5, 6] and, in Latinos, in the US [6], although the only study to examine the frequency of AxSpA in Mexican-Americans residing in the US showed similar frequency as Whites (1.5%) [4]. However, an early study of Black AS patients from the US and another from Burkina Faso showed the frequency of HLA-B27 in AS to range between 50 and 60% [5, 7], and other studies in Africa found even lower frequencies [2] compared to up to 90% of White patients [8]. Furthermore, in Whites, HLA-B27 positivity was associated with earlier age at disease onset, higher rates of anterior uveitis, a shorter delay to diagnosis from first symptoms, and an increased familial incidence of AS in Black and white patients [9]. There are no previous studies comparing objective, validated measures of disease severity of Black patients relative to White patients with AS. Likewise, the issue of AS severity in Latinos has not been examined comparatively except in one study that only examined national registries from Latin American and Europe [10].

In this study, we used objective clinical and radiographic measurements and validated outcome tools to analyze disease activity and severity in Blacks, Whites, and Latinos enrolled in a longitudinal outcome study and investigated the association of HLA-B27 with AS in these groups.

Materials and methods

Patients

Patients were participants in the Prospective Study of Outcomes in AS (PSOAS), an observational study of predictors of AS severity that included 961 patients at the time of this analysis of whom 925 were used for this analysis, the others being from other ethnic groups or of mixed ethnicity. Patients were recruited from the investigators' clinics, patient support groups (such as the Spondylitis Association of America), and community rheumatologists. Patients were at least 18 years old and met the modified New York Criteria for AS [11]. Patients were included from five study sites: Cedars-Sinai Medical Center in Los Angeles, California, the University of Texas Health Science Center at Houston (UTH), the NIH Clinical Center, the University of California at San Francisco (UCSF), and the Princess Alexandra Hospital in Brisbane, Australia (PAH). The research carried out was in compliance with the Helsinki Declaration, and each institution had the study approved by their respective institutional review boards (IRB), and each participating subject reviewed and signed an informed consent form.

Clinical information was obtained by reviewing medical records, by administering questionnaires, and by examining each patient at the baseline visit. Gender, age, educational status, ethnicity (self-reported), date of axial symptom onset, date of enrollment (when consent to participate was signed), disability status, and history of uveitis, psoriasis, inflammatory bowel disease, or heart disease were recorded. Medication use and family history of spondyloarthritis (SpA) were also queried. Instruments filled out by the patients included self-reported pain on a visual analogue scale, disease activity as measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [12] as well as by C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and functional capacity as measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) [13]. Radiographic severity was measured by the Bath Ankylosing Spondylitis Radiographic Index (BASRI) [14] and the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) [15].

Genetic analyses

Blood samples were obtained, and genomic DNAwas extracted by standard methods. HLA-B locus typing was performed using single-stranded conformational polymorphism with commercially available kits (One Lambda, Canoga Park, CA, USA). The frequencies of HLA-B27 were compared with those in a nationally representative sample of the general US population [6].

Statistical analyses

Univariable comparisons of clinical characteristics for Black, White, and Latino (persons of Mexican, Cuban, Puerto Rican, or South American ancestry) patients were performed using the chi-square test or ANOVA test and its non-parametric counterpart (Kruskal-Wallis Test) when necessary. In both univariable and multivariable models, we compared the BASRI and mSASSS total for Blacks ($n = 57$), Latinos ($n = 63$), and White patients ($N = 805$) by constructing regression models using generalized estimating equation (GEE) to account for intra-family correlation (839 patients from 818 families). Poisson model for BASRI and zero-inflated negative binomial model for mSASSS were constructed after over dispersion, and zero-inflation were examined to determine which model better fit the data; i.e., whether a negative binomial or zero-inflated model needs to supersede a Poisson model. Possible confounders were assessed by identifying variables that were significantly associated with ethnicity and BASRI or mSASSS, and effect modifiers were also evaluated while developing a final multivariable model. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) at a statistical significance level of 0.05.

Results

Comparison of disease features between three ethnic groups with AS

Eight hundred five White, 57 Black, and 63 Latino patients from the PSOAS study were examined for comparison. There was a lower proportion of men among Blacks compared to Whites and Latinos, but this difference was only marginally significant ($p = 0.05$; Table 1). There were no significant differences in age at disease onset, though Latinos had a lower age at study enrollment. Whites were more likely to have completed college and less likely to be receiving disability. HLA-B27 occurred least frequently in Blacks (62.5%) compared to

Whites (85.3%) and Latinos (86.7%). This compared with 1.1% in US Blacks, 7.5% in Whites, and 4.6% in Latinos in the 2009 National Health and Nutrition Examination Survey, respectively, ($p < 0.0001$).

Comparing the three ethnic groups, Blacks had greater disease activity either by subjective measures (as measured by the BASDAI (median [IQR] = 5.9 [4.3, 7.7]/10 cm) compared to Whites (3.5 [1.7, 5.5]/10 cm) or Latinos (4.5/10 cm [$p < 0.0001$]) or by objective measures, either the ESR (median [IQR] = 27 [9.5, 40.0] mm/h compared to 10 [5.0, 20.0] mm/h in whites or 17 [7.0, 29.0] mm/h in Latinos, $p < 0.001$) or CRP (median [IQR] = 1.2 [0.4, 2.3] mg/dL in Blacks compared to 0.4 [0.2, 0.9] mg/dL in Whites and 0.9 [0.4, 1.6] mg/ dL in Latinos, $p < 0.0001$).

When functional capacity, as measured by the BASFI, was compared, Blacks similarly were impaired more statistically significantly (median [IQR] = 62.5 [35.7, 79.4]/ 100 mm) compared to Whites 27.8 [12.6, 52.3]/100 mm or Hispanics median [IQR] = 38.1 [15.5, 60.0]/100 mm, $p < 0.0001$.

Blacks also had greater baseline radiographic severity as measured by the mSASSS (which takes into account only lumbar and cervical spinal severity)—median [IQR] = 38.2 [46.0, 55.2] compared to 6.4 [0, 32.6] for whites and 8.1 [0, 35.9] for Latinos ($p = 0.007$). A similar finding was observed when measured by the BASRI, which also takes into account the hip and sacroiliac joint involvement—mean (SD) = 9.5(4.2) in Blacks compared to 7.3 (4.1) in Whites and Latinos ($p = 0.004$).

No significant differences were seen between the three groups in NSAID or TNFi usage, despite a trend to less TNFi usage in Blacks. Of note was a similar frequency of acute anterior uveitis in Blacks versus Whites, despite the lower frequency of HLA-B27, as well as psoriasis (8.6 vs. 11.0%, $p = 0.95$) (Table 1) and IBD (12.2 vs. 6.7%, $p = 0.2$), respectively.

Factors associated with radiographic severity based on Poisson and zero-inflated negative binomial regression models

Findings from the univariable Poisson regression models using GEE method indicate that Blacks had greater radiographic severity than Whites ($p = 0.001$) or Latinos ($p = 0.02$) as seen by higher BASRI scores. These differences persisted in multivariable models, that adjusted for disease duration, gender, TNFi usage, education, smoking, diabetes, or disability status compared with Whites ($p < 0.0001$) and with Latinos ($p = 0.01$). Independent associations were also seen with BASRI score severity with disease duration, gender, diabetes, current smoking, and occupational disability but not with TNFi use or educational status (Table 2).

Using GEE zero-inflated negative binomial regression models, Blacks also had greater radiographic severity as seen by higher mSASSS scores than Whites ($p = 0.02$) in the univariable model although the difference lost significance when compared with Latinos. In the multivariable model, this significant difference between Blacks and Whites persisted ($p = 0.002$) and Latinos had higher mSASSS than Whites ($p = 0.001$), when adjusted for

disease duration, gender, TNFi usage, education, smoking, diabetes, or disability status. Independent associations were also seen with mSASSS score severity with disease duration, gender, diabetes, occupational disability but not with TNFi use, current smoking, or educational status (Table 2).

Discussion

This study shows clear differences in disease activity, functional impairment, and radiographic severity comparing Blacks, Whites, and Latinos with AS. It is noteworthy that Latinos ranked intermediate in these parameter between Whites and Blacks. It is possible that the observed differences are secondary to inequalities in socioeconomic factors though we attempted to adjust for some of these factors by inclusion of educational status in the multivariable models. Furthermore, differences in disease severity between these groups might be secondary to a higher index of suspicion for diagnosing AS in Whites, leading to detection of milder cases in Whites (detection bias). Our data also indicate that AA patients tended, albeit not significantly so, to undergo less treatment with biologic agents, despite having more severe disease. This finding underscores the importance of health policy measures that address ethnic disparities in treatment of AS.

The subject of disease severity of AS in patients of African descent has received little attention. Chalmers et al. [2] reported a series of eight AS patients seen over 4 years at a large South African teaching hospital, noting that only one was HLA-B27 positive and that "the patients reported in this study appeared to have disease of unusual severity," although admitting that selection bias may have influenced this. Ouédraogo et al [7] observed 13 cases of AS in 2 years of rheumatologic practice among 1439 patients (0.9%) from Burkina Faso, finding a 55% frequency of HLA-B27. Results of BASDAI, BASFI, and the presence of syndesmophytes and hip involvement in a cross-sectional analysis were also reported in this small cohort. Overall, the author noted "the disease seems more severe among patients seen in Burkina Faso."

The lower frequency of HLA-B27 observed in Blacks is compatible with early studies in this regard [5]. However, the only difference between the HLA-B27 negative and positive Blacks was earlier age at disease onset in the HLA-B27 positives (30.8 ± 12.1 years in the HLA-B27 negatives compared with 23.6 ± 7.3 years), as has been observed in Whites [9].

There are few comparative studies that have address severity of AS in Latin Americans. Benegas et al. [10] examined patients from National Registries, including 2356 patients from Europe and 1083 from Latin America. A lower prevalence of HLA-B27 was found in the Latino group (71%) compared to Europeans (83%). There was also a greater frequency of peripheral arthritis and enthesitis in Latinos compared to Europeans with AS (57 vs. 42%) and enthesitis (54 and 38%). Also seen in this study was slightly greater functional impairment (BASFI score 4.8 in Latin-American AS patients versus 4.3 in Europeans) and worse AS-related Quality of Life (ASQoL) (7 in Latin-Americans vs. 6 in Europeans). However, the authors did not regard these differences as being clinically relevant [10]. This also appears regarding the data from BASFI (4.3 vs. 4.8) and the ASQoL (6 vs. 7) [10]. Anti-TNF usage was similar in the two groups (14 vs. 15%, respectively) although NSAID

and DMARD use were more frequent in Latin-Americans. In the present study, Latino patients had greater radiographic severity (by mSASSS) than that in Whites, but less than that in Blacks. While the explanation for this is unclear, socioeconomic reasons affecting access to care are likely at work.

We cannot rule out the possibility that more severely affected Blacks and Latinos are likely to be diagnosed with AS or to volunteer for study participation. Given the greater proportion of Black women with AS, one might postulate that genetic differences might be contributing to more severe disease in these patients.

In conclusion, our study suggests that Black and, albeit less so, Latino patients have more severe disease than White patients with AS, as well as a lower frequency of HLA-B27. The reasons for this, whether genetic or socioeconomic, could not be determined from this study and require further study.

Acknowledgments

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Table 1

Clinical characteristics of AS patients by ethnicity

Variable	Blacks (*n* = 57)	Whites (*n* = 805)	Latinos (*n* = 63)	*p* value[*]
Male (%)[a]	63.2	74.2	82.5	0.05
Age at symptom onset, mean years (SD)[b]	26.8 (10.2)	24.0 (9.1)	23.8 (9.2)	0.08
Age at enrollment, mean years (SD)[b]	44.7 (11.6)	45.9 (14.4)	38.9 (10.7)	<0.001
Disease duration, mean years (SD)[b]	18.5 (10.1)	21.9 (14.3)	15.0 (10.8)	<0.0001
Education, college degree (%)[a]	59.5	84.5	61.9	<0.0001
Disabled (%)[a]	30.0	8.0	22.2	<0.0001
Working for pay (%)[a]	37.5	50.7	42.9	0.15
Retired (%)[a]	10.0	10.6	3.2	0.17
Student (%)[a]	5.0	4.7	3.2	0.85
Uveitis (%)[a]	26.0	25.4	19.1	0.53
Cardiovascular disease (%)[a]	40.0	32.8	27.0	0.34
Diabetes	10.0	5.6	3.2	0.35
HLA-B27 positivity (%)[a]	62.5	85.3	86.7	<0.0001
Baseline BASDAI (0–10), median (IQR)[c]	5.9 (4.3, 7.7)	3.5 (1.7, 5.5)	4.5 (2.9, 6.5)	<0.0001
Baseline BASFI (0–100), median (IQR)[c]	62.5 (35.7, 79.4)	27.8 (12.6, 52.3)	38.1 (15.5, 60.0)	<0.0001
Baseline BASRI (1.5–16), mean (SD)[c]	10.3 (5.8, 13.0)	7.0 (3.5, 11.0)	7.5 (4.0, 11.0)	0.004
Baseline mSASSS (0–64), median (IQR)[c]	38.2 (46.0, 55.2)	6.4 (0.0, 32.6)	8.1 (0.0, 35.9)	0.007
Baseline CRP (mg/dL), median (IQR)[c]	1.2 (0.4, 2.3)	0.4 (0.2, 0.9)	0.9 (0.4, 1.6)	<0.0001
Baseline ESR (mm/h), median (IQR)[c]	27.0 (9.5, 40.0)	10.0 (5.0, 20.0)	17.0 (7.0, 29.0)	<0.001
Baseline NSAIDS use (%)[a]	67.7	69.2	73.7	0.76
Baseline TNFi use (%)[a]	26.0	42.0	36.8	0.16

IQR interquartile range, *Q1* first quartile, *Q3* third quartile

[*] Overall *p* values for three ethnic groups

[a] Chi-square test

[b] ANOVA test

[c] Kruskal-Wallis test

Table 2

Factors associated with BASRI and mSASSS based on univariable and multivariable regression models

Variable	BASRI[a]		mSASSS[b]	
	Rate ratio (95% confidence interval)	p value	Rate ratio (95% confidence interval)	p value
Univariable model				
Ethnicity				
Blacks vs. Whites	1.34 (1.13, 1.6)	0.001	1.8 (1.1, 2.9)	0.02
Black vs. Latinos[*]	1.31 (1.05, 1.64)	0.02	1.5 (0.8, 2.8)	0.19
Latinos[*] vs. Whites	1.02 (0.88, 1.2)	0.77	1.2 (0.8, 1.7)	0.44
Multivariable model				
Ethnicity				
Comparing scores in:				
Blacks vs Whites	1.4 (1.2, 1.6)	<0.0001	2.1 (1.3, 3.2)	0.002
Black vs Latinos[*]	1.3 (1.1, 1.5)	0.01	1.1 (0.6, 1.9)	0.71
Latinos[*] vs Whites	0.6 (−0.6, 1.7)	0.25	1.9 (1.3, 2.7)	0.001
Comparing disease duration				
9–20 years vs 9 years	1.5 (1.3, 1.7)	<0.0001	2.4 (1.8, 3.1)	<0.0001
20–30 years vs 9 years	1.8 (1.7, 2.0)	<0.0001	3.5 (2.7, 4.7)	<0.0001
> 30 years vs 9 years	2.1 (1.9, 2.3)	<0.0001	4.7 (3.5, 6.2)	<0.0001
Male vs Female	1.4 (1.3, 1.5)	<0.0001	2.5 (2.0, 3.1)	<0.0001
TNFi use vs no use	1.1 (0.99, 1.1)	0.09	1.1 (0.9, 1.3)	0.57
Diabetes vs no Diabetes	1.2 (1.1, 1.3)	<0.001	1.6 (1.1, 2.3)	0.01
Current smoker vs non smoker	1.1 (1.01, 1.2)	0.03	1.1 (0.9, 1.5)	0.38
Education (for one-level increase)	1.00 (0.98, 1.01)	0.75	1.01 (0.98, 1.04)	0.61
Disabled vs not Disabled	1.2 (1.03, 12.3)	0.01	1.7 (1.2, 2.4)	0.003

[*] Of Mexican, Cuban, Puerto Rican, or South American ancestry

[a] Based on Poisson regression model using GEE

[b] Based on zero-inflated negative binomial regression model using GEE