Phenotypic Characterization of Juvenile Idiopathic Arthritis in African American Children

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ABSTRACT. ***Objective.*** Juvenile idiopathic arthritis (JIA) affects children of all races. Prior studies suggest that phenotypic features of JIA in African American (AA) children differ from those of non-Hispanic white (NHW) children. We evaluated the phenotypic differences at presentation between AA and NHW children enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, and replicated the findings in a JIA cohort from a large center in the southeastern United States.

Methods. Children with JIA enrolled in the multicenter CARRA Registry and from Emory University formed the study and replication cohorts. Phenotypic data on non-Hispanic AA children were compared with NHW children with JIA using the chi-square test, Fisher's exact test, and the Wilcoxon signed-rank test.

Results. In all, 4177 NHW and 292 AA JIA cases from the CARRA Registry and 212 NHW and 71 AA cases from Emory were analyzed. AA subjects more often had rheumatoid factor (RF)-positive polyarthritis in both the CARRA (13.4% vs 4.7%, $p = 5.3 \times 10^{-7}$) and the Emory (26.8% vs 6.1%, $p = 1.1 \times 10^{-5}$) cohorts. AA children had positive tests for RF and cyclic citrullinated peptide antibodies (CCP) more frequently, but oligoarticular or early onset antinuclear antibody (ANA)-positive JIA less frequently in both cohorts. AA children were older at onset in both cohorts and this difference persisted after excluding RF-positive polyarthritis in the CARRA Registry (median age 8.5 vs 5.0 yrs, $p = 1.4 \times 10^{-8}$).

Conclusion. Compared with NHW children, AA children with JIA are more likely to have RF/CCP-positive polyarthritis, are older at disease onset, and less likely to have oligoarticular or ANA-positive, early-onset JIA, suggesting that the JIA phenotype is different in AA children. (J Rheumatol First Release February 15 2016; doi:10.3899/jrheum.150891)

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Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic arthritis with a prevalence of 16 to 150 per 100,000 children under 16 years of age[1]. Although JIA affects girls and boys of all races, epidemiologic studies indicate phenotypic differences between different racial categories. JIA affects girls twice as commonly as boys in the United States, whereas boys are more frequently affected in India and Turkey[2,3]. Similarly, different racial groups demonstrate differences in the distribution of JIA categories[4]. Studies from North America, which included small numbers of children of African ancestry, have suggested phenotypic differences in JIA between children of African and European ancestry[5,6]. A large study from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry concluded that race and ethnicity were variably associated with joint damage, pain, and functional ability[7].

While the etiology of JIA is multifactorial, there is evidence for a genetic predisposition to JIA[8]. Genome-wide studies in individuals of European ancestry have identified

17 JIA-associated variants[9]. Other than investigations of *HLA* variants in small cohorts, there have been no genetic studies of JIA in African American (AA) children. Characterization of phenotypic differences, if any, between genetically heterogeneous populations is a prerequisite to genetic studies. To improve the understanding of the epidemiology of JIA, we sought to evaluate phenotypic differences at presentation between AA and non-Hispanic white (NHW) children in the CARRA Registry and replicate the findings in a JIA cohort from a large urban, academic medical center in the southeastern United States.

MATERIALS AND METHODS

Our study used data from 2 independent JIA cohorts. The CARRA Registry had subjects with JIA enrolled from 55 pediatric rheumatology centers in the United States from May 2010 to July 2012. At the time of our study, the CARRA Registry included 5188 cases with JIA. Of those, 83 subjects had been enrolled at our center and were removed from the CARRA analyses. The independent replication cohort (Emory Cohort) consisted of children with JIA who were enrolled in the South Eastern Registry of Childhood Arthritis from the Pediatric Rheumatology Clinics at Emory University, Atlanta, Georgia, USA.

Data for the CARRA Registry were collected as previously described[7,10]. For both cohorts, demographic and disease-related data were collected at the time of enrollment. Disease characteristics compared between AA and NHW children included age at disease onset (self-reported by patients/parents at the time when symptoms first developed), age at enrollment, JIA category by the International League of Associations for Rheumatology classification criteria, laboratory tests, and medication usage. Laboratory tests evaluated included antinuclear antibodies (ANA), anticyclic citrullinated peptide antibodies (anti-CCP), HLA-B27, and rheumatoid factor (RF). Results were recorded as positive, negative, or unknown. Positive and negative values were in comparison to reference values as defined by the laboratory where the tests were done.

Because our primary aim was to compare the phenotypic features between AA and NHW subjects, we excluded subjects who identified themselves as belonging to a race other than AA or NHW, were multiracial, or who listed their ethnicity as Hispanic. The basis for race and ethnicity designations were self-reports by subject's parents based on demographic data collection questionnaires that conformed to the US National Institutes of Health guidelines on race and ethnicity. Accordingly, subjects' parents were first asked about ethnicity (Hispanic or Latino and/or not Hispanic or Latino) and then race (white, Asian, black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, unknown, or do not wish to provide).

Statistical analysis. To compare phenotypic characteristics between AA and NHW cohorts, we first tested for differences in the CARRA Registry cohort and then attempted to replicate the significant findings in the Emory cohort. Because the clinical joint assessment is insensitive compared with imaging modalities, and because the duration of followup is variable, some of the children thought to have persistent oligoarticular JIA could develop extended disease. Hence we combined persistent and extended oligoarticular JIA subcategories into a single category of oligoarticular JIA. We applied a Bonferroni correction for multiple testing to the CARRA Registry analyses based on the effective number of independent tests (n = 17) and inferred using the number of principal components required to explain > 95% of overall phenotypic variation. For followup analyses, we considered nominal significance ($p < 0.05$). Fisher's exact tests were used to compare categorical variables. Because the ages of onset and enrollment were not normally distributed (Wilkes Shapiro test for normality $p < 1 \times 10^{-6}$), we used the Wilcoxon signed-rank test to compare median ages between AA and NHW subjects. All analyses were performed in the R programming language (www.r-project.org). Institutional Review Board (IRB) approval was given for this study by Emory University. CARRA sites also had local IRB approval to provide data to the CARRA Registry.

RESULTS

In all, 4469 eligible children with JIA from the CARRA Registry (4177 NHW and 292 AA) and 283 children from the Emory cohort (212 NHW children and 71 AA) were analyzed. Almost every one reported having access to healthcare, either from a commercial or government-sponsored plan (98.9% NHW children vs 98.3% AA children in the CARRA database, and 100% of NHW and AA children in the Emory database). Table 1 shows the distribution of JIA categories by race. In the CARRA Registry cohort, AA children with JIA were significantly more likely to have systemic JIA (14.8% vs 7.0%, Bonferroni-corrected p value, $p_{corr} = 0.0003$) and RF-positive polyarticular JIA (13.4% vs 4.7%, $p_{corr} = 5.3 \times 10^{-7}$) compared with NHW children. In contrast, AA children had a significantly lower frequency of oligoarticular JIA compared with NHW children (26.1% vs 37.2%, $p_{corr} = 0.002$). Persistent oligoarticular JIA demonstrated a trend toward significance. In addition, AA children also had a significantly lower frequency of psoriatic JIA (2.1% vs 6.4%, $p_{corr} = 0.02$). The frequencies of RF-negative polyarticular JIA were not significantly different in AA children compared with NHW subjects after correction for multiple testing.

Of the 4 statistically significant associations observed in the CARRA Registry cohort, the RF-positive polyarticular JIA and oligoarticular JIA results were replicated in the Emory cohort. Similar to the CARRA Registry cohort, we observed a higher frequency of RF-positive JIA in our AA subjects compared to NHW subjects (26.8% vs 6.1%, $p < 1.1 \times 10^{-5}$). Similar to the CARRA Registry, oligoarticular JIA occurred less frequently in AA children compared with NHW in the Emory cohort (26.8% vs 43.4%, $p = 0.014$). In particular, the Emory cohort showed that the frequency of persistent oligoarticular JIA was significantly lower in AA compared with NHW children (11.3% vs 32.1%, $p = 5.7 \times 10^{-4}$). Similar to the CARRA Registry cohort, we observed a higher frequency of systemic JIA and a lower frequency of psoriatic JIA in our AA subjects compared with NHW subjects, but these differences were not statistically significant. However, the point estimates of the OR were similar in magnitude, and the 95% CI overlapped between the CARRA Registry and Emory cohorts, suggesting that our replication sample was underpowered.

In the CARRA Registry, we found that positive immunoglobulin M-RF test, positive anti-CCP test, and steroid use were significantly more frequent among AA cases of JIA compared with NHW subjects (Table 2). These features were confirmed in the Emory replication cohort as well. The frequency of AA children who had > 5 joints involved was significantly higher than among the NHW children in the Emory cohort, but not the CARRA Registry cohort. The

Table 1. Age at onset and enrollment, and distribution of JIA categories between AA and NHW subjects in the CARRA Registry and Emory cohort. There were 291 AA subjects and 4148 NHW subjects with JIA in the CARRA Registry. There were 71 AA subjects and 212 NHW subjects with JIA in the Emory cohort. Values are n (%) unless otherwise specified.

Categories	CARRA Registry				Emory**			
	AA	NHW	OR (95% CI)	p*	AA	NHW	OR (95% CI)	p
Age at onset^	8.9	5.2		**1.27×10^{-11}**	9.1	6.1		**0.009**
Age at enrollment^	9.6	6.5		**4.26×10^{-11}**	9.8	6.6		**0.011**
Systemic JIA	43 (14.8)	292 (7.0)	2.29 (1.58–3.25)	**0.0003**	8 (11.3)	13 (6.1)	1.94 (0.66–5.23)	0.189
Polyarthritis RF–	72 (24.7)	1283 (30.9)	0.73 (0.55–0.97)	0.5031	15 (21.1)**	50 (23.6)**	0.87 (0.42–1.72)**	0.746**
Polyarthritis RF+	39 (13.4)	196 (4.7)	3.12 (2.10–4.53)	**5.3×10^{-7}**	19 (26.8)	13 (6.1)	5.55 (2.42–13.10)	**1.1×10^{-5}**
Oligoarticular JIA	76 (26.1)	1546 (37.2)	0.59 (0.45–0.78)	**0.0023**	19 (26.8)	92 (43.4)	0.48 (0.26–0.86)	**0.014**
Persistent	63 (21.7)	1218 (29.4)	0.66 (0.49–0.89)	0.0827	8 (11.3)**	68 (32.1)**	0.27 (0.11–0.61)**	**5.7×10^{-4}****
Extended	13 (4.5)	328 (7.9)	0.54 (0.28–0.96)	0.5162	11 (15.5)**	24 (11.3)**	1.43 (0.60–3.26)**	0.405**
Psoriatic	6 (2.1)	265 (6.4)	0.31 (0.11–0.69)	**0.0233**	1 (1.4)	10 (4.7)	0.29 (0.01–2.10)	0.301
ERA	36 (12.4)	419 (10.1)	1.26 (0.85–1.82)	1.0000	7 (9.9)**	29 (13.7)**	0.69 (0.24–1.72)**	0.537**
Undifferentiated	8 (2.8)	105 (2.5)	1.09 (0.45–2.25)	1.0000	2 (2.8)**	5 (2.4)**	1.2 (0.11–7.53)**	1.000**

Significant data are in bold face. * P values are reported after multiple-hypothesis correction. Multiple-testing correction was performed by applying a Bonferroni correction based on the effective number of independent tests (17) in our sample. ^ Age at onset and enrollment of all cases with JIA are reported in median years. ** Entries from the Emory study represent tests that were not part of the replication; we include these values strictly for informative purposes. JIA: juvenile idiopathic arthritis; AA: African American; NHW: non-Hispanic white; CARRA: Childhood Arthritis and Rheumatology Research Alliance; RF: rheumatoid factor; ERA: enthesitis-related arthritis.

Table 2. Distribution of phenotypic characteristics in AA and NHW children with JIA in the CARRA Registry and Emory cohort.

Features	CARRA						Emory**					
	AA		NHW		OR (95% CI)	p*	AA		NHW		OR (95% CI)	p
	Total Sample Size, n	No. (%) with this Trait	Total Sample Size, n	No. (%) with this Trait			Total Sample Size, n	No. (%) with this Trait	Total Sample Size, n	No. (%) with this Trait		
Female	292	192 (65.8)	4177	3017 (72.2)	0.74 (0.57–0.96)	0.317	71	50 (70.4)**	212**	148 (69.8)**	1.03 (0.55–1.96)**	1.000**
RF+	102	24 (23.5)	1413	114 (8.1)	3.5 (2.04–5.85)	**$8.3E^{-5}$**	69	19 (27.5)	208	18 (8.7)	3.99 (1.83–8.73)	**$1.8E^{-4}$**
CCP+	134	30 (22.4)	1579	122 (7.7)	3.44 (2.12–5.46)	**$8.8E^{-6}$**	59	20 (33.9)	181	19 (10.5)	4.34 (1.99–9.53)	**$7.4E^{-5}$**
ANA+	249	103 (41.4)	3695	1842 (48.9)	0.71 (0.54–0.93)	0.179	69	21 (30.4)**	208**	69 (33.2)**	0.88 (0.46–1.64)**	0.767**
HLA-B27+	167	22 (13.2)	2254	343 (15.2)	0.85 (0.51–1.35)	1.00	52	4 (7.7)**	149**	26 (17.4)**	0.40 (0.10–1.23)**	0.114**
Uveitis	278	17 (6.1)	3996	468 (11.7)	0.49 (0.28–0.81)	0.054	71	9 (12.7)**	212**	29 (13.7)**	0.92 (0.36–2.13)**	1.000**
> 5 joints ever involved	287	161 (56.1)	4134	2247 (54.4)	1.14 (0.89–1.46)	1.000	71	47 (66.2)**	212**	88 (41.5)**	2.75 (1.52–5.07)**	**$3.49E^{-4}$****
Steroids, ever used	196	127 (64.8)	2691	1446 (53.7)	1.58 (1.16–2.18)	**0.049**	71	48 (67.6)	212	93 (43.9)	2.66 (1.47–4.94)	**$5.92E^{-4}$**
DMARD	288	205 (71.2)	4162	3064 (73.6)	0.89 (0.68–1.17)	1.000	71	60 (84.5)**	212**	162 (76.4)**	1.68 (0.80–3.82)**	0.183**
Biologics	290	153 (52.8)	4161	1818 (43.7)	1.44 (1.13–1.84)	0.056	71	32 (45.1)**	212**	80 (37.7)**	1.35 (0.76–2.41)**	0.326**

Significant data are in bold face. * P values are reported after multiple-hypothesis correction. Multiple-testing correction was performed by applying a Bonferroni correction based on the effective number of independent tests (17) in our sample. ** Entries from the Emory study represent tests that were not part of the replication; we include these values strictly for informative purposes. "E" = × 10. AA: African American; NHW: non-Hispanic white; JIA: juvenile idiopathic arthritis; CARRA: Childhood Arthritis and Rheumatology Research Alliance; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; ANA: antinuclear antibody; DMARD: disease-modifying antirheumatic drug.

prevalence of uveitis was not significantly different between AA and NHW subjects with JIA in both the CARRA and Emory cohorts.

When we analyzed the differences in ages, both cohorts revealed that AA children with JIA were significantly older at onset of disease and at the time of enrollment. In the CARRA Registry, the median onset age of AA JIA cases was 8.9 years compared with 5.2 years in NHW subjects ($p_{corr} = 1.3 \times 10^{-11}$). This was confirmed in the Emory cohort (9.1 yrs for AA vs 6.1 yrs for NHW, p = 0.009). Similarly, AA subjects with JIA were significantly older at enrollment in both cohorts (9.6 vs 6.5 yrs in the CARRA Registry, $p_{corr} = 4.3 \times 10^{-11}$; 9.8 vs 6.6 yrs in the Emory cohort, p = 0.011). Because the frequency of RF-positive polyarthritis (which is known to present at a later age) was increased in AA subjects, we repeated these analyses after excluding children with RF-positive polyarticular JIA. AA children with JIA excluding RF-positive JIA remained older at onset compared

with NHW children (8.5 vs 5.0 yrs in the CARRA Registry, $p_{corr} = 2.5 \times 10^{-8}$). Although the median onset age among AA children with JIA excluding RF-positive JIA was higher compared with NHW subjects in the Emory cohort, this difference did not reach statistical significance (8.4 yrs vs 5.3 yrs, p = 0.08). Similarly, AA children with JIA excluding RF-positive polyarticular JIA were older at enrollment in the CARRA registry compared with NHW children (9.3 vs 6.2 yrs, $p_{corr} = 1.4 \times 10^{-8}$). Again, the median enrollment age of AA children with JIA, excluding RF-positive JIA, was higher compared with NHW in the Emory cohort, but this difference was not statistically significant (9.2 yrs vs 6.0 yrs, p = 0.08).

It has been suggested that children with early onset and positive ANA constitute a homogeneous subphenotype of JIA, irrespective of the number of joints involved[5,11]. Hence, we determined the frequency of young (< 6 yrs) children with positive ANA. This phenotype was observed much more frequently in NHW children compared with AA children in both the CARRA Registry cohort (15.3% of AA vs 31.5% of NHW cases, $p_{corr} = 6.5 \times 10^{-7}$), as well as in the Emory replication cohort (9% of 67 AA vs 21.4% of 196 NHW cases, p = 0.03).

DISCUSSION

Epidemiologic studies of JIA indicate that, while the predominant category of JIA in NHW children is oligoarticular JIA, RF-positive polyarthritis is more common among patients of African ancestry[6,12]. Schwartz, *et al* described a cohort of 35 AA and 137 NHW patients with JIA from Michigan[6]. Notably, the Schwartz study only included cases with oligoarticular and polyarticular JIA. AA subjects had a significantly increased onset age compared with NHW children (11.8 vs 8.9 yrs). About 20% of AA subjects were RF-positive compared with < 4% of NHW children. Saurenmann, *et al* investigated a multiethnic cohort of 758 children from Toronto[5]. Despite the cohort's larger size, only 31 children were classified as black (out of 159 non-European subjects) compared with 599 white children. RF-positive polyarthritis was more frequent among black children compared with white children in the same study (16.1% vs 2.2%, p < 0.001)[5].

The JIA cohort in the CARRA Registry has been investigated[7,10,13]. Race and ethnicity were found to be variably associated with joint damage, pain, and functional ability by Ringold, *et al*, who compared 234 AA and 78 Asian children with 4039 white children[7]. Onset age was higher among AA and Asian children compared with white children. Systemic JIA and RF-positive polyarthritis was more frequent among AA children compared with white children. The median pain score was higher among AA children. The authors also reported that patients of Hispanic ethnicity had a higher frequency of RF-positive polyarthritis. It should be noted that, in comparisons by Ringold, *et al* of racial differences between white, AA, and Asian children with JIA, patients with Hispanic ethnicity were not excluded, raising the possibility that ethnic differences might have influenced some of the results obtained. Similarly, in a study of the influence of Hispanic ethnicity on JIA from the CARRA Registry, Pelajo, *et al* found that subjects classified as Hispanic had a higher frequency of RF-positive polyarthritis compared with non-Hispanic subjects[10]. Race was not addressed in the study, raising the possibility that racial differences might have influenced some observed findings by including both white and black Hispanic subjects in the "Hispanic" category. Racial differences have also been described by Angeles-Han, *et al* in children with JIA-associated uveitis enrolled in the CARRA registry[13]. Non-Hispanic AA children with JIA had a decreased uveitis prevalence compared with NHW and were older at JIA diagnosis. We could not confirm this finding using a larger cohort after correction for multiple testing.

Our study differed from the earlier studies by addressing the potential effects on phenotype introduced by confluence of race and ethnicity[7,10]. Although both race and ethnicity share an ideology of common ancestry and are used interchangeably, race is generally believed to reflect biological differences, whereas ethnicity reflects unique cultures. Hispanic ethnicity includes people belonging to both white and black race. Our hypothesis is that the phenotypic features of JIA are different across racial and ethnic groups. To minimize confounding, we restricted our analyses to individuals who described themselves as being "non-Hispanic" in response to the question on ethnicity, then compared those who described being "white" or "African American" in response to the question on race. Our study also included a replication cohort to validate findings from the CARRA Registry from a large center in the southeastern United States with a substantial AA population. Our replication cohort had over twice the number of AA subjects compared with the earlier studies by Saurenmann, *et al* and Schwartz, *et al*[5,6].

We confirm previously reported findings that AA children with JIA are older at onset compared with NHW children with JIA. We have shown, to our knowledge, for the first time that the onset age of JIA is significantly higher among AA children with JIA, even after excluding RF-positive JIA. Almost every child in both cohorts in our study had access to health insurance, making it unlikely that access to care or lack thereof is an explanation for observed results. This suggests that there are true differences in the phenotype of JIA, perhaps reflecting differences in genetic background. In this regard, our findings are similar to the observation that onset age of inflammatory bowel disease is higher among AA children from a multicenter cohort of 1406 subjects[14]. Indian children with JIA demonstrate a latter onset age of 12 years[2]. By contrast, a cohort of 2102 children with JIA from Western Europe had a mean onset age of 5.4 years[15], similar to the NHW cohorts in our study.

The majority of children with rheumatic diseases are cared for by pediatric rheumatologists at academic medical centers,

and hence the results of our study are generalizable. We have shown that the phenotype of JIA is different in AA children compared with NHW children. We believe that our observations provide a framework for additional investigations to characterize JIA in racially diverse patient populations. Further, potential causes for the older onset age should be examined. Finally, a large cohort of AA children with JIA should be examined for similarities and differences in the genetic risk factors that have been reported in NHW children with JIA.

APPENDIX 1.

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