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Phenotypic characterization of juvenile idiopathic arthritis in African American children

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Abstract

Objectives—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 CARRA Registry, and replicated the findings in a JIA cohort from a large center in South Eastern USA.

Methods—Children with JIA enrolled in the multi-center CARRA Registry and from Emory University comprised the study and replication cohorts. Phenotypic data on Non-Hispanic AA children were compared with NHW children with JIA using Chi-square, Fisher's exact and Wilcoxon rank sum tests.

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 RF-positive polyarthritis in both CARRA (13.4% vs. 4.7%, $p=5.3\times 10^{-7}$) and Emory (26.8% vs. 6.1%, $p=1.1\times 10^{-5}$) cohorts. AA children had positive tests for RF and CCP more frequently, but oligoarticular or early onset 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 years; $p=1.4\times 10^{-8}$).

Conclusions—Compared to NHW children, AA children with JIA are more likely to have RF/CCP positive polyarthritis, and 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 African American children.

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Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic arthritis with a prevalence of 16 to 150 per 100,000 children under age 16.(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 US, 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 South Eastern USA.

Methods

This study utilized data from two independent JIA cohorts. The CARRA Registry had subjects with JIA enrolled from 55 pediatric rheumatology centers in the USA 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.

Data for the CARRA Registry were collected as previously described.(7, 10) For both cohorts, demographic and disease-related data were collected at 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 International League of Associations for Rheumatology (ILAR) classification criteria, laboratory tests, and medication usage. Laboratory tests evaluated included: ANA, anti-CCP, HLA-B27, and 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.

Since 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, being multi-racial, or 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 confirmed to the NIH 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. Since the clinical joint assessment is insensitive compared to imaging modalities, and furthermore since the duration of follow up 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 follow-up analyses we considered nominal significance ($p < 0.05$). Fisher's exact tests were used to compare categorical variables. Since the ages of onset and enrollment were not normally distributed (Wilkes Shapiro test for normality $p < 1 \times 10^{-6}$), we used the Wilcoxon rank sums to compare median ages between AA and NHW subjects. All analyses were performed in the R programming language (<http://www.r-project.org>).

Institutional Review Board 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 everyone reported having access to care, 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 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%, Bonferronicorrected p value, $p_{\text{corr}} = 0.0003$) and RF-positive polyarticular JIA (13.4% vs 4.7%, $p_{\text{corr}} = 5.3 \times 10^{-7}$), compared to NHW children. By contrast, AA children had a significantly lower frequency of oligoarticular JIA compared to NHW children (26.1% vs. 37.2%, $p_{\text{corr}} = 0.002$). Persistent oligoarticular JIA demonstrated a trend towards significance. In addition, AA children also had a significantly lower frequency of psoriatic JIA (2.1% vs. 6.4%, $p_{\text{corr}} = 0.02$). The frequencies of RF-negative polyarticular JIA was not significantly different in AA children compared to NHW subjects after correction for multiple-testing.

Of the four 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. 43.4%, $p < 1.1 \times 10^{-5}$). Similar to the CARRA Registry, oligoarticular JIA occurred less frequently in AA children compared to 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 to 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 to NHW subjects, but these differences were not statistically significant. However, the point estimates of the OR were similar in magnitude, and the 95% confidence intervals overlapped between the CARRA Registry and Emory Cohorts, suggesting that our replication sample is under-powered.

In the CARRA Registry, we found that positive IgM-RF test, positive anti-CCP test, and steroid use were significantly more frequent among AA cases of JIA compared to NHW subjects (Table 2). These features were confirmed in the Emory replication cohort as well. The frequency of AA children who had greater than 5 joints involved was significantly more than NHW children in the Emory cohort, but not the CARRA Registry cohort. The prevalence of uveitis was not significantly different between AA and NHW subjects with JIA in both 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 to 5.2 years in NHW subjects ($p_{\text{corr}} = 1.3 \times 10^{-11}$). This was confirmed in the Emory cohort (9.1 years for AA vs. 6.1 years for NHW, $p = 0.009$). Similarly, AA subjects with JIA were significantly older at enrollment in both cohorts (9.6 vs. 6.5 years in the CARRA Registry, $p_{\text{corr}} = 4.3 \times 10^{-11}$; 9.8 vs. 6.6 years in the Emory cohort, $p = 0.011$). Since 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 to NHW children (8.5 vs. 5.0 years in the CARRA Registry $p_{\text{corr}} = 2.5 \times 10^{-8}$). Although the median onset age among AA children with JIA, excluding RF-positive JIA was higher compared to NHW subjects in the Emory cohort, this difference did not reach statistical significance (8.4 years vs 5.3 years, $p = 0.08$). Similarly, AA children with JIA excluding RF-positive polyarticular JIA were older at enrollment in the CARRA registry compared to NHW children (9.3 vs. 6.2 years $p_{\text{corr}} = 1.4 \times 10^{-8}$). Again, the median enrollment age of AA children with JIA, excluding RF-positive JIA, was higher compared to NHW in the Emory cohort, but this difference was not statistically significant (9.2 years vs 6.0 years, $p = 0.08$).

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

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 JIA patients from Michigan.(6) Notably, this study only included cases with oligoarticular and polyarticular JIA. AA subjects had a significantly increased onset age compared to NHW children (11.8 years vs. 8.9). About 20% of AA subjects were RF-positive compared to < 4% of NHW children. Saurenmann et al. investigated a multiethnic cohort of 758 children from Toronto.(5) Despite this cohort's larger size, only 31 children were classified as Black (out of 159 Non-European subjects), compared to 599 White children. RF-positive polyarthritis was more frequent among Black children, compared to White children in the same study (From table 3; 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 to White children. Systemic JIA and RF-positive polyarthritis was more frequent among AA children compared to 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 their comparisons 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 to non-Hispanic subjects.(10) Race was not addressed in this 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 to 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. In order 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 South Eastern USA with a substantial AA population.

Our replication cohort had over twice the number of AA subjects compared to the earlier studies by Schwartz and Saurenmann.(5, 6)

We confirm previously reported findings that AA children with JIA are older at onset compared to NHW children with JIA. We have shown 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 to NHW children. We believe that our observations provide a framework for additional investigations to characterize JIA in racially diverse patient populations. Furthermore, 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.

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Table 1

Age at onset and enrollment and distribution of JIA categories between AA and NHW subjects in the CARRA Registry and Emory cohort.

Category	CARRA Registry				Emory**			
	African American N (%)	Non-Hispanic White N (%)	OR (95% CI)	P-value*	African American N (%)	Non-Hispanic White N (%)	OR (95% CI)	P-value
Age at onset [^]	8.9	5.2		1.27E-11	9.1	6.1		0.009
Age at Enrollment [^]	9.6	6.5		4.26E-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	<i>15 (21.1)</i>	<i>50 (23.6)</i>	<i>0.87 (0.42, 1.72)</i>	<i>0.746</i>
Polyarthritis RF +	39 (13.4)	196 (4.7)	3.12 (2.10, 4.53)	5.3E-07	19 (26.8)	13 (6.1)	5.55 (2.42, 13.10)	1.1E-05
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	<i>8 (11.3)</i>	<i>68 (32.1)</i>	<i>0.27 (0.11, 0.61)</i>	<i>5.7E-04</i>
Extended	13 (4.5)	328 (7.9)	0.54 (0.28, 0.96)	0.5162	<i>11 (15.5)</i>	<i>24 (11.3)</i>	<i>1.43 (0.60, 3.26)</i>	<i>0.405</i>
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)	<i>0.69 (0.24, 1.72)</i>	<i>0.537</i>
Undifferentiated	8 (2.8)	105 (2.5)	1.09 (0.45, 2.25)	1.0000	2 (2.8)	5 (2.4)	<i>1.2 (0.11, 7.53)</i>	<i>1.000</i>

* 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.

** Italicized entries from the Emory study represent tests that were not part of the replication; we include these values strictly for informative purposes.

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.

Table 2

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

Feature	CARRA				Emory**				
	African American		Non-Hispanic White		African American		Non-Hispanic White		P-value
	Total Sample Size	Number (%) with this trait	Total Sample Size	Number (%) with this trait	Total Sample Size	Number (%) with this trait	Total Sample Size	Number (%) with this trait	
Female	292	192 (65.8)	4177	3017 (72.2)	71	50 (70.4)	212	148 (69.8)	1.03 (0.55, 1.96)
RF Positive	102	24 (23.5)	1413	114 (8.1)	69	19 (27.5)	208	18 (8.7)	3.99 (1.83, 8.73)
CCP Positive	134	30 (22.4)	1579	122 (7.7)	59	20 (33.9)	181	19 (10.5)	4.34 (1.99, 9.53)
ANA Positive	249	103 (41.4)	3695	1842 (48.9)	69	21 (30.4)	208	69 (33.2)	0.88 (0.46, 1.64)
HLA-B27 Positive	167	22 (13.2)	2254	343 (15.2)	52	4 (7.7)	149	26 (17.4)	0.40 (0.10, 1.23)
Uveitis	278	17 (6.1)	3996	468 (11.7)	71	9 (12.7)	212	29 (13.7)	0.92 (0.36, 2.13)
>5 Joints ever involved	287	161 (56.1)	4134	2247 (54.4)	71	47 (66.2)	212	88 (41.5)	2.75 (1.52, 5.07)
Steroids (ever used)	196	127 (64.8)	2691	1446 (53.7)	71	48 (67.6)	212	93 (43.9)	2.66 (1.47, 4.94)
DMARD	288	205 (71.2)	4162	3064 (73.6)	71	60 (84.5)	212	162 (76.4)	1.68 (0.80, 3.82)
Biologics	290	153 (52.8)	4161	1818 (43.7)	71	32 (45.1)	212	80 (37.7)	1.35 (0.76, 2.41)

* 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.

** Italized entries from the Emory study represent tests that were not part of the replication; we include these values strictly for informative purposes.

RF: Rheumatoid factor; CCP: Cyclic citrullinated peptide; ANA: Anti-nuclear antibody, HLA-B27: Human leukocyte antigen B27; DMARD: Disease modifying anti rheumatic drug;