Editorial

Unraveling the Phenotypic Variability of Juvenile Idiopathic Arthritis across Races or Geographic Areas — Key to Understanding Etiology and Genetic Factors?

Juvenile idiopathic arthritis (JIA) comprises a heterogeneous group of illnesses, all displaying joint inflammation, but with distinct clinical phenotypes, disease courses, outcomes, and presumably, genetic background and pathophysiology[1]. It is the most common rheumatologic condition in children and a major cause of short- and longterm disability. The current International League of Associations for Rheumatology (ILAR) classification recognizes 7 disease categories, defined on the basis of the clinical and laboratory features present in the first 6 months of illness[2].

Although the etiology and pathogenesis of JIA are still poorly understood, it is hypothesized that a genetically susceptible individual could develop an uncontrolled and harmful immune response toward a self-antigen upon exposure to an environmental trigger[3]. However, although several inciting factors have been suspected, including infectious agents, vaccinations, traumatisms, and maternal smoking, proof is still elusive.

Instead, there is strong evidence for a genetic predisposition to JIA[4]. The importance of genetic determinants has been demonstrated by instances of familial aggregation of JIA and by the monozygotic twin concordance rate of 25%–40%. In addition, numerous associations between human leukocyte antigen (HLA) polymorphisms and JIA subtypes have been reported. Recent genome-wide studies in individuals of European ancestry have identified a number of new susceptibility loci also in non-HLA regions[4].

Over the past 3 decades, several epidemiologic surveys have documented a remarkable, yet unexplained, disparity in the prevalence of JIA subtypes among different geographic areas or racial/ethnic groups[5,6,7,8,9,10,11,12,13]. In Western countries, the most common category is oligoarthritis, but this form is rare in India, New Zealand, The Middle East, and South Africa, where polyarthritis predominates. Systemic arthritis accounts for an increased proportion of childhood arthritis in Asia, with reported frequency in Thailand and Japan as high as 50%. A greater incidence of enthesitis-related arthritis has been registered in India, Taiwan, and aboriginal populations of Mexico and Canada, reflecting, in part, the high frequency of HLA-B27 in these populations. African American (AA) and black South African patients have a higher rate of rheumatoid factor (RF)-positive polyarthritis, whereas juvenile psoriatic arthritis (PsA) is rare in Turkey, Egypt, and Thailand. There is evidence that European ancestry may be an important predisposing factor for antinuclear antibody (ANA)-positive JIA associated with uveitis[7,14]. Conversely, both ANA positivity and ocular involvement are rarely encountered in JIA patients living in the Middle East, East Asia, India, New Zealand, and Central America. An example of the worldwide discrepancy in the prevalence of JIA subtypes is presented in Table 1.

In this issue of *The Journal*, Fitzpatrick, *et al*[15] add to these data by comparing the phenotypic characteristics at disease presentation between AA and non-Hispanic white (NHW) children in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry cohort (n = 4469). The authors also evaluated whether the same findings were detectable in a smaller cohort from a large urban, academic medical center (Emory University) in the southeastern United States (n = 283). In the CARRA registry, they found that AA children were significantly more likely to have systemic arthritis and RF-positive polyarthritis compared to NHW children. By contrast, the AA sample had a significantly lower frequency of oligoarthritis and juvenile PsA compared to NHW children. Only 2 of the 4 statistically significant associations observed in the CARRA registry (those for RF-positive polyarthritis and oligoarthritis) were replicated in the Emory cohort. However, the trends were similar also for systemic arthritis and juvenile PsA, although the differences were not significant, probably owing to the insufficient size of the confirmation sample.

An intriguing finding of Fitzpatrick, *et al* is that AA

See JIA in African American children, *page 799*

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Table 1. Prevalence of JIA subsets and other selected features in various countries*.

Country[reference]	Italy[5] (n = 618)	Scandinavia[6] (n = 315)	Canada[7] (n = 1082)	Costa Rica[8] (n = 122)	Turkey[9] (n = 634)	Oman[10] (n = 107)	South Africa[11] (n = 78)	India[12] (n = 235)	Taiwan[13] (n = 195)
Years of patient enrollment	2007–2009	1997–1998	1984–2002	1993–1995	2008–2009	2004–2013	2010–2011	1994–2005	1995–2010
Mean/median age at onset, yrs	2.9	6.8	6.9	10.8	4.3	6.8	8	12	9.5
Female	79.1	62.5	65.6	61.5	55.8	71	50	41.7	45
Systemic arthritis	7.4	4	14.5	3.6	14.5	17.8	7.7	8	19
Oligoarthritis	58.7	46	38.6	70.9	41.3	31.8	26.8	21	23.1
RF-negative polyarthritis	22.3	21[a]	20.6	16.4[a]	20.3	39.2	26.9	17	11.8
RF-positive polyarthritis	1.5		3.1		3.2	7.5	14	12	4.6
Psoriatic arthritis	2.4	3	11.3	9.1[b]	2.1	0.9	1.3	1	1.5
Enthesitis-related arthritis	2.1	4	10.6		18.9	2.8	23	36	37.4
Undifferentiated arthritis	4	22	1.3	—	—	0	—	5	2.6
Uveitis	15.6[c]	8.6[d]	13.1	3.3	11.6	0	—	3.8	6.7
Positive ANA	58.3[c]	33.5[e]	55.7	6.3	30.1	21.5	4.5[f]	12.5[g]	8.7[m]
Positive HLA-B27	—	—	30.6[h]	26.3[i]	16.7	—	23.1	48.3[l]	32.3

*Data are percentages, unless otherwise indicated. [a] RF-negative and RF-positive polyarthritis combined; [b] includes children with probable juvenile ankylosing spondylitis, juvenile psoriatic arthritis, and arthropathies associated with inflammatory bowel disease; [c] data from reference[14]; [d] in the first 6 months of illness; [e] tested in 197 patients; [f] tested in 67 patients; [g] tested in 184 patients; [h] tested in 206 patients; [i] tested in 110 patients; [l] tested in 143 patients; [m] patients with ANA titer ≥ 1:160. JIA: juvenile idiopathic arthritis; RF: rheumatoid factor; ANA: antinuclear antibody.

children were significantly older at onset, even after the exclusion of the subgroup with RF-positive polyarthritis, which is known to present at a later age. This finding is in keeping with previous observations that the effect of age on disease presentation may be independent of ILAR category[14]. That the prevalence of uveitis was comparable between the AA and NHW cohorts was unexpected, given the greater frequency in NHW children in both cohorts of children with the early-onset ANA-positive subset, which is characterized by the highest risk of uveitis. This finding contrasts with the results of a previous CARRA study, which found that JIA-associated uveitis was less common in non-Hispanic AA children than in NHW children[16].

The results obtained by Fitzpatrick, *et al*, together with previous literature reports, underscore the existence of true differences in the disease phenotypes of JIA across different races or ethnic groups, which may reflect diversity in genetic determinants, and perhaps environmental triggers. Thus, epidemiologic studies can provide important clues to understanding of disease predisposition and etiologies. As Fitzpatrick, *et al* point out, the precise characterization of the phenotypic differences between genetically heterogeneous populations is a prerequisite to properly designing genetic studies and to generate hypotheses regarding environmental factors that may influence the disease.

That said, it is important to emphasize the potential caveats of epidemiologic studies performed to date. It has been argued that the differences observed between geographic areas may reflect underrepresentation of milder forms of JIA, particularly oligoarthritis, because of referral bias, which could be attributed to restrictions in access to healthcare facilities. An indirect confirmation of this phenomenon was provided by an analysis of a multiethnic cohort in a large Western tertiary care hospital, which in contrast with some studies from India, did not find any difference in the percentage of patients with persistent oligoarthritis between patients of Indian subcontinent descent and either the total JIA cohort or the patients of European ancestry[7]. This limitation does not apply to the study by Fitzpatrick, *et al,* as nearly all their patients had access to health insurance. Other sources of bias in published studies may result from disparities in the case ascertainment method (e.g., accurate systematic visits versus survey questionnaires sent to health practitioners) or in the type of study (e.g., clinic-based vs population-based).

A further shortcoming is that the possible confounding influence on the phenotype of the convergence of race and ethnicity has seldom been taken into account. As discussed by Fitzpatrick, *et al*, although race and ethnicity are often used interchangeably, they entail different concepts: race may reflect biologic differences, whereas ethnicity reflects unique cultures. Thus, the dissection of race from ethnicity may enhance the suitability of patient samples to genetic studies. It should be recognized, however, that many countries are racially or ethnically more homogeneous than the USA, which may make it difficult to discern the relative influence of these elements.

The classification criteria used to define the individual JIA subsets may also hamper the clinical meaning of existing studies. Several criticisms have been raised to the current classification scheme for JIA, particularly regarding the use of the number of affected joints or the presence of psoriasis as criteria to define homogeneous groups[17]. Observations indicate that patients with early-onset (diagnosis before 6 years of age), ANA-positive, RF-negative JIA constitute a homogeneous disease entity, irrespective of the ILAR classification[14,17]. Further, there is solid evidence that substantial clinical heterogeneity exists within the ensemble of children

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with juvenile PsA, which has led to claims that this condition should not be treated as a single disease entity, as is done in the ILAR classification, or that it should even be removed as an independent category[18]. Growing clinical and immunopathologic data suggest that systemic arthritis is heterogeneous as well, and that it should be regarded as a syndrome, rather than as a single disease, encompassing a heterogeneous group of disorders sharing autoinflammatory pathways[19]. These issues should be considered so that appropriate patient subgroups are included in future genetic analyses.

Unfortunately, Fitzpatrick, *et al* did not attempt to stratify their patients according to the emerging concepts in JIA classification. Further, although their patient sample is quite sizeable, their data were obtained only in North America and thus may not be generalizable.

Broader insights into the worldwide variability of JIA phenotypes will come out of the multinational study of the EPidemiology, treatment and Outcome of Childhood Arthritis (EPOCA Study)[20]. This project, which is coordinated by the Pediatric Rheumatology International Trials Organization (PRINTO) and which has so far collected around 9000 patients from 42 countries on 5 continents, is primarily aimed at gaining information on the frequency and characteristics of JIA subtypes in different geographic and racial settings, the therapeutic approaches adopted by pediatric rheumatologists practicing in diverse countries, and the current health status of children with JIA throughout the world.

The work of Fitzpatrick, *et al* is an important step forward in the understanding of the influence of race on JIA subtype susceptibility and phenotype. Overall epidemiologic data corroborate the evidence for a role of genetics in influencing disease risk and characteristics, and lend support to the hypothesis that different forms of chronic arthritis in childhood arise through distinct etiopathologic pathways. Future epidemiologic, genetic, and pathophysiologic studies should take into account the compelling evidence that disease heterogeneity is not adequately identified by the current classification scheme.

ACKNOWLEDGMENT

The authors thank Professor Alberto Martini for his critical reading of the manuscript.

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J Rheumatol 2016;43:683-5; doi:10.3899/jrheum.160173

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