Ethnic Differences in Risk for Pediatric Rheumatic Illness in a Culturally Diverse Population

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ABSTRACT. ***Objective.*** To analyze the differences of occurrence of pediatric rheumatic disease among various ethnic groups in a culturally diverse isolated geographic area.

Methods. A retrospective study of pediatric rheumatic diseases in a multiethnic area during a 6 year period.

Results. A group of 922 patients was categorized based on predominant ethnicity, and their risk of having acute rheumatic fever (ARF), juvenile rheumatoid arthritis (JRA), and systemic lupus erythematosus (SLE) was studied. Odds ratios (OR) were computed for each illness with Caucasians as the reference group. Results indicated that Polynesians were overrepresented among patients with ARF, having elevated OR that were significantly different from Caucasians (22.5–120.7, $p < 0.0001$). For SLE, the highest OR were obtained for Samoans, Filipinos, and Japanese. In contrast, for JRA, Filipinos and Japanese had OR less than one, and no Samoans were diagnosed with JRA, possibly indicating a protective effect against developing JRA.

Conclusion. This unique retrospective study examined the ethnic variations of expression of certain rheumatic diseases in an isolated region. Results reveal that certain ethnic groups are at risk for ARF and SLE, but are protected against JRA. These findings suggest investigating possible immunogenetic similarities and differences in these illnesses. (J Rheumatol 2002;29:379–83)

Key Indexing Terms:
PEDIATRIC RHEUMATOLOGY EPIDEMIOLOGY ETHNIC GROUPS
JUVENILE RHEUMATOID ARTHRITIS SYSTEMIC LUPUS ERYTHEMATOSUS
ACUTE RHEUMATIC FEVER

Analysis of rheumatic illnesses in geographic areas composed of many different ethnic groups may reveal susceptible populations at risk. Recent studies analyzed large populations of relatively homogenous ethnicities. Bowyer, *et al*[1] published one of the most complete studies to date on pediatric rheumatologic disease, involving 12,939 patients from 25 pediatric rheumatology centers. However, that study consisted of predominately Caucasian patients, which accounted for 80% of the study population. Only 2% of the population were described as Asian or other. Another analysis by Ferguson, *et al*[2] examined the incidence of acute rheumatic fever (ARF) in a multiethnic, multiracial community. That study consisted primarily of African-American and Hispanic children and did not have many patients of Asian or Polynesian descent. Juvenile arthritis has been investigated in several ethnic groups who showed large differences in incidence rates[3]. For example, in separate studies, the incidence of juvenile rheumatoid arthritis (JRA) was very high in Sweden (86 per 100,000), intermediate in Costa Rica (31 per 100,000), and very low in Japan (0.8 per 100,000). High incidences of systemic lupus erythematosus (SLE) in Africans, Asian Indians, a number of North American Indian tribes, and New Zealand Polynesians have been reported in different studies[4-7].

The population in Hawaii is heterogeneous but is composed predominately of Asian, Polynesian, and Caucasian ethnic groups. Asians and Polynesians make up over 60% of the population, based on 1990 census data. The state is also geographically isolated, and this affords a unique opportunity for a single center to investigate the majority of patients in the state. We compared and contrasted rheumatologic diseases

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Supported by a Research Centers in Minority Institutions award, P20 RR11091, from the National Centers for Research Resources, National Institutes of Health. Views expressed here are solely the responsibility of the authors and do not necessarily represent the views of the NCRR/NIH.

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Submitted September 29, 2000; revision accepted August 23, 2001.

among the diverse ethnic populations in an isolated area. This is important because available studies are often difficult to compare with one another due to methodology differences such as varying diagnostic criteria used at diverse centers. Over the years, it has been noted that Polynesians in Hawaii have a high incidence of ARF[8-11], but controversy exists whether Polynesians and Asians are at high risk for developing SLE[12,13]. Our study compared in detail the 3 most common childhood rheumatologic diseases in Hawaii, and the findings indicated high risk of SLE and ARF but not JRA in certain ethnic groups.

MATERIALS AND METHODS

Patient population. Consecutive patients treated at the Pediatric Rheumatology Center in the pediatric tertiary hospital (Kapi'olani Medical Center for Women and Children) in Honolulu were studied. This center is the only civilian clinic for pediatric rheumatologic illnesses in all areas including the neighboring islands. Referrals to this clinic represent the majority of patients 21 years of age and younger in Hawaii who are diagnosed with a rheumatic illness, the remainder being seen by the military health care system. This clinic population is believed to be representative of the population statewide.

Study design. The distributions of the major ethnic groups in Hawaii were compared to the distribution among the respective study outcomes for descriptive purposes. However, prevalence rates of these study outcomes were not estimated in this study. Instead, a case-control design was employed, and odds ratios were calculated to estimate the association of the respective study outcomes with ethnicity. This methodology was selected for 2 reasons. First, the protocol for data collection on ethnicity differs from that employed by the US Census Bureau, precluding the use of this data for estimates of prevalence. Second, differential referral rates may have occurred due to ethnic differences in socioeconomic and cultural factors, which may lead to erroneous estimates of prevalence.

We studied the following ethnic groups in relation to the development of ARF, JRA, and SLE: part-Hawaiian, Samoan, other Pacific Islanders, Filipino, Chinese, Japanese, and Caucasians. Part-Hawaiian ethnicity was defined as those subjects who were of mixed ethnicity but considered their Hawaiian ethnic background as their primary ethnicity. The population represents those patients evaluated at our pediatric rheumatology center over a 6 year period January 1, 1993, to December 31, 1998. The control group included patients with nonrheumatic diagnoses for each of the ethnic groups.

Diagnostic criteria. Diagnostic criteria for the more common rheumatic diseases seen in childhood were based on the most current accepted criteria (Table 1). For ARF, the 1992 American Heart Association guidelines were used[14]. The 1982 revised criteria of Tan, *et al*[15] were used in diagnosing patients with SLE, and the American Rheumatism Association criteria[16] validated in 1986 were used for JRA. The diagnosis of poststreptococcal reactive arthritis (PSRA) was made using clinical criteria summarized from the literature[17]. There is a possibility that this illness is a form of ARF, and thus ARF was studied alone and with the PSRA patients added to the total[18]. Similar to the patients with ARF, most of the patients with PSRA were observed to be Polynesian[17]. For the other rheumatic diseases, criteria similar to those used by Bowyer, *et al*[1], Rosenberg, *et al*[19], and De Nardo, *et al*[20] were followed. Clinical judgement and experience formed the diagnoses for the nonrheumatic conditions made by the pediatric rheumatologist seeing the referral patients. No standardized criteria were available for many of these nonrheumatic illnesses. Some of these children were referred with nonspecific arthralgias, and after consultation were felt to have nonrheumatic symptoms. As with previous studies[1,19,20], many of these nonrheumatic illnesses included orthopedic problems (data not shown).

Table 1. Major childhood rheumatic diseases.

Disease or Condition	N
Juvenile rheumatoid arthritis	118
Pauciarticular	56
Polyarticular RF–	36
Polyarticular RF+	3
Systemic	23
Poststreptococcal disease	83
Reactive arthritis	10
ARF	73
Systemic lupus erythematosus	59

Data collection. Data were collected retrospectively from January 1, 1993, to December 31, 1998, using clinic records. Each patient who registered for a clinic visit was asked by the clinic nurse or pediatric rheumatologist to specify his or her ethnic background. Ethnic classification was based on the predominant ethnicity of each patient. Data were initially compiled on a computer database utilizing the Microsoft Access™ program.

Statistical analysis. Statistical analysis was conducted using the JMP™ statistical software package. To investigate an association between ethnicity and disease frequency, odds ratios were computed for each illness (ARF, JRA, SLE) with Caucasians as the reference group. Logistic regression was used to estimate the OR as an indicator of the strength of the association between ethnicity and the respective study outcomes. Statistical significance was determined using the chi-square test comparing nonrheumatic (control) groups for each ethnicity. Fisher's exact test was used for statistical analysis when the expected numbers of outcomes were exceedingly small.

RESULTS

During this study, 922 patients received care at our pediatric rheumatology center. The most common rheumatic illnesses seen were JRA (18.1%), ARF (12.7%), and SLE (10.3%) (Table 1). A total of 118 children with JRA were seen during this time period. The spondyloarthropathies were classified separately, as in previous studies[1,19,20], and were not included in the JRA population. The next most common illnesses were ARF (n = 73) and SLE (n = 59). These 3 groups were studied in greater detail. Other rheumatic conditions each constituted smaller populations in the different ethnic groups and were not studied.

The remaining 348 patients were felt to have symptoms that were caused by nonrheumatic problems and served as a control group. Many of these children did not have a specific diagnosis other than nonspecific forms of joint pain that were felt to be from nonrheumatic causes. Others represented febrile illnesses that did not reveal a rheumatic cause (data not shown). The number of children in each ethnic group in this nonrheumatic population served as a control to compare OR of different ethnic groups having either ARF, SLE, or JRA.

Odds ratios were calculated to evaluate whether an ethnic group might be at an increased or decreased risk for developing a particular rheumatic illness. Table 2 depicts the OR of patients having ARF, SLE, or JRA based on their dominant ethnicity. Very high OR were found in ARF for part-Hawaiian, Samoan, and other Pacific Islander groups compared with Caucasians (OR 22.5, 120.7, and 60.3, respectively; $p < 0.0005$). These OR did not change significantly when ARF

Table 2. Odds ratios (OR) of having a childhood rheumatic illness based on selected ethnicities.

Ethnicity (n = controls)	ARF N	ARF OR[a]	ARF CI	ARF + PSRA N	ARF + PSRA OR[a]	ARF + PSRA CI	SLE N	SLE OR[a]	SLE CI	JRA[b] N	JRA[b] OR[a]	JRA[b] CI
Caucasian (n = 69)	1	—	—	1	—	—	3	—	—	32	—	—
Part-Hawaiian (n = 95)	31	22.5[†]	3.0–168.7	36	26.1[†]	3.5–195.4	14	3.4**	0.9–12.3	33	0.8**	0.4–1.4
Samoan (n = 14)	21	120.7[†]	14.8– 982.7	24	118.3[†]	14.8–948.0	6	11.5*	2.5–51.9	0	—[‡]	—
Other Pacific Is. (n = 10)	7	60.3[†]	6.6–554.9	8	55.2[†]	6.2–489.4	2	5.7**	0.8–39.7	7	1.9 **	0.6–5.7
Filipino (n = 50)	12	19.2[†]	2.4–153.2	13	17.9[†]	2.3–141.6	17	9.6[†]	2.7–34.5	9	0.6*	0.3–1.2
Chinese (n = 27)	1	2.6**	0.2–42.3	1	2.6**	0.2–42.3	5	4.3**	1.0–19.1	11	1.0**	0.5–2.2
Japanese (n = 67)	0	—**	—	0	—**	—	10	3,4*	0.9–13.0	12	0.5*	0.2–1.0
Total	73			83			57			104		

[a]Compared with Caucasians. [b]Excluding ankylosing spondylitis. [†]$p < 0.0001$, [‡]$p = 0.001$, * $p < 0.05$, ** not significant. ARF: acute rheumatic fever, PSRA: poststreptococcal reactive arthritis, SLE: systemic lupas erythematosus, JRA: juvenile rheumatoid arthritis.

and PSRA were studied together; this was done to give a better appreciation of ethnicity related to poststreptococcal rheumatic disease (Table 2). Also notable was the lack of Japanese children and the low OR for Chinese children with ARF, although they were overrepresented in the nonrheumatic study population. Due to the existence of research studies involving ARF, the majority of ARF patients with all manifestations are seen in the pediatric rheumatology center even if they do not have arthritis.

For SLE, the highest significant OR were obtained for Samoans (11.5; $p < 0.05$), Filipinos (9.6; $p < 0.0001$), and Japanese (3.4; $p < 0.05$). No significant differences were observed among part-Hawaiians, other Pacific Islanders, or Chinese patients when OR were compared with Caucasians.

In the JRA group, there may have been some protective effect of certain ethnic backgrounds. We found that the Filipinos and Japanese children had OR significantly below one ($p < 0.05$). No Samoan patients with JRA were seen, which is intriguing because these patients were at risk to develop both ARF (OR 120.7) and SLE (OR 11.5). The same finding was noted in Filipinos, a group that showed an increased risk of developing ARF (OR 19.2) and SLE (OR 9.6), and a decreased risk of developing JRA (OR 0.6). It was surprising to find Filipinos and Samoans at risk of developing 2 autoimmune illnesses, ARF and SLE, while seemingly being protected against developing a different one — JRA.

DISCUSSION

Rheumatology encompasses many illnesses that affect multiple organ systems. As our knowledge of these diseases grows, so does the need to expand our understanding of populations at risk. Most population studies of the various rheumatologic conditions to date studied populations that are relatively homogenous, and primarily Caucasian in ethnicity[1,19,20]. This study is unique in that it looks at ethnicity in relation to disease expression of the 3 most common rheumatic diseases seen in Hawaii (ARF, SLE, and JRA). The majority of Hawaii's children affected by rheumatologic disease can be investigated in this diverse population due to the relative isolation of the state. Based on the findings of this study, several conclusions can be drawn.

First, Polynesians and Filipinos were at greater risk for ARF compared to Caucasians, as evidenced by their elevated OR compared to Caucasians. This finding adds support to previous population studies of ARF in Hawaii, which have remained consistent over 40 years[8-11]. In a study from 1966 to 1988, hospitalized children with part-Hawaiian and Samoan ethnicity had the highest rates of rheumatic fever, with part-Hawaiian children and Samoan children being 3 times and 56 times more likely, respectively, to develop ARF than Caucasian children[10]. Our study confirms that this predominance of ARF is still seen in these ethnic groups. We also included outpatient ARF patients in our study, which was not done in the last study[10]. Despite improvements in public health and medical care, our study documents continued risk for these children developing ARF. It implies that children with these particular ethnic backgrounds are at risk, which may be related to genetic predisposition, psychosocial factors, or socioeconomic level. A study is currently investigating whether other risk factors are involved.

Second, we can also conclude that the prevalence of SLE appears to be higher in those of Samoan, Filipino, and Japanese descent, with OR of 11.5, 9.6, 3.4, respectively. This finding is similar to a study that found an increase in SLE prevalence rates of Filipinos and Japanese[12]. However, a more recent study found similar prevalence OR for Filipino, Japanese, and Caucasian ethnic groups, but included all age groups[13]. By combining patients of all ages, this study may have missed associations in the younger age groups. Further, by analyzing only one year of prevalence data, the study may also have missed associations found over greater periods of time. Finally, neither of these studies investigated Samoan patients as a separate ethnic group, and thus may not have seen the increased incidence of SLE in this ethnic group that

we found. We are in the process of studying this further by examining disease prevalence and outcomes, specifically in the population with lupus.

A third conclusion is that Japanese, Filipinos, and Samoans may be protected against JRA. OR values for all these groups are less than one ($p < 0.05$). Surprisingly, no patients with Samoan ancestry developed JRA during that time period, despite having such a high risk of developing ARF. However, these findings should be received cautiously, as the whole JRA population was viewed in total. If the population was subdivided into individual types of JRA, the number of patients became too small to accurately identify OR. Although the number of patients may be viewed as a small population, these findings warrant further study. If these results are confirmed, they would support immunogenetic differences between JRA, SLE, and ARF. Current understanding of cytokine activity of JRA has shown differences among clinical types, identifying the pathogenesis as heterogeneous[21]. To find enough patients in each subtype of JRA may require a multicenter study involving areas with diverse ethnic groups. Further studies on our population with JRA will continue to investigate these findings.

The significance of these conclusions may be illustrated best by looking specifically at the Samoan and Filipino populations. Within this study, both of these groups revealed an increased risk for both SLE and ARF, but a decreased risk for JRA. We are currently studying rheumatic heart disease in these ethnic groups to identify possible risk factors. There are important implications to this finding, as demographic similarities and differences among rheumatic illnesses may give better understanding of the pathogenesis of these diseases. Recent genetic studies have indicated that SLE[22] and JRA[23] are associated with different complexes of genes, and studying different ethnic groups may aid in identifying and substantiating these gene sets.

Limitations of this study included considerations of population and data collection. Although the patients seen in this study represented the majority of the childhood population of Hawaii for rheumatologic disease, it does not include patients seen at the military hospital. In addition, these patients were seen by referral and it is possible that some patients with rheumatic disease may never be referred to the pediatric rheumatology center because of management either by primary care providers or by adult rheumatologists. It is notable that the pediatric rheumatologists use a team approach in evaluating and following patients with rheumatologic disease, making the latter less likely. After being diagnosed at the center, patients with JRA are referred to our JRA program at Shriners Hospital for Children. Many primary care physicians refer their patients to our center because care is provided there at no cost by a multidisciplinary team.

Because our study did not represent the entire state's population, but only the majority, it was decided to use OR to describe risk. Since the study outcomes are relatively rare, the OR provides an accurate estimate of the relative risk, unless the duration of disease is associated with ethnicity. These studies would be more representative of our pediatric rheumatic population using a prospective approach (i.e., relative risk) with the entire state pediatric rheumatic population, and we are currently in discussion with our military colleagues to accomplish this. A prospective approach would also allow estimation of the effect of ethnicity on severity and duration of these illnesses. At any rate, it is felt that the population in this study represents the majority of children in Hawaii and warrants evaluation.

We cannot rule out the possibility that a differential referral bias may have affected estimates of OR based on ethnicity. In particular, referral bias may account for the modest but statistically significant protective effect observed among Filipino and Japanese patients regarding JRA. However, no significant differences were observed in the distribution of nonrheumatic disorders among the control patients (data not shown). This observation suggests that any existing referral bias was small and unlikely to account for the large OR observed for Hawaiian, Samoan, Pacific Islander, and Filipino patients in ARF, or those elevated OR observed for Filipino and Samoan patients in SLE.

Another limitation may be categorizing the ethnicity of patients. Patients were placed in an ethnic group based on their predominant self-identified ethnic background even though they may also represent other ethnic groups. This has been a problem in other studies in Hawaii[8-13]. It makes it difficult to accurately discern ethnic expressions of diseases. Many of the Polynesian cultures did not keep written records of genealogy, so it is difficult to document exact percentages of ethnicity. However, many of the patients seen (especially for Filipinos and Samoans) remain relatively homogenous. Therefore, certain risks based on ethnicity can be studied initially using these data. Other studies have classified patients as part Hawaiian if they had any Hawaiian ethnicity at all[13]. Prospective studies in which a more exact method of defining ethnicity would clarify these data and this is currently being done.

This study revealed an increased incidence of ARF and SLE in those of Polynesian and Filipino ethnic groups. These same groups appear to have a protective effect against JRA. These findings support investigating immunogenetic differences and similarities in patients with ARF, SLE, and JRA. Further study of the epidemiology of these illnesses may also assist our understanding of their pathophysiology.

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