Gender and Ethnic Origin Have No Effect on Longterm Outcome of Childhood-Onset Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To investigate the associations of gender and ethnic origin with longterm outcome in childhood-onset systemic lupus erythematosus (SLE).

Methods. The study cohort consisted of 51 patients (13 males and 38 females) with childhood-onset SLE followed for ≥ 5 years at the British Columbia Children's Hospital in Vancouver. Fifteen patients were Caucasian, 14 Chinese, 9 East Indian, and 13 patients were of other ethnic backgrounds: none was African-American or Hispanic. Outcome measures assessed retrospectively included Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index score (SDI), SLE-related death, need for dialysis or renal transplantation, and use of intensive immunosuppressive therapy. A SDI ≥ 2 was assigned as poor outcome.

Results. The median age at diagnosis was 10.8 years and the median duration of followup was 7.2 years. Five-year survival was 100%; 10-year survival was 85.7% (12/14 patients). The median SDI score at last followup was 2.0 (range 0–9); 2.0 for male, 1.5 for female; 2.0 for Caucasian and 2.03 for non-Caucasian patients. Twenty-six out of 51 patients (51%) had poor outcome (SDI score > 2). Three female patients required dialysis: 2 had subsequent renal transplants. Thirty patients received intensive immunosuppressive therapy. The SDI scores, mortality, and need for intensive immunosuppressive therapy were not influenced by either gender or ethnic origin.

Conclusion. The median SDI score was high for this cohort with childhood-onset SLE. In contrast to other published data, no association of male gender and/or non-Caucasian ethnicity with poor outcome was found in our study cohort. (J Rheumatol 2004;31:1650–4)

Key Indexing Terms:
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Ethnicity and male gender have been identified as 2 independent prognostic variables affecting mortality and morbidity in adult systemic lupus erythematosus (SLE)[1-3]. In the United States, morbidity and age-adjusted mortality from SLE are increased in adult male patients compared to female patients[4]. Non-Caucasian ethnicity has been identified as a risk factor for decreased survival rates and increased morbidities. This has been clearly documented for adult African Americans and Hispanics living in the United States[1,3-6]. Adult North American Indian patients have also been shown in some studies to have more severe disease than Caucasian patients[7]. It is unclear, however, whether male gender and non-Caucasian ethnicity have any prognostic significance for pediatric patients with SLE. A small study by Wada, *et al* suggested that male pediatric patients with SLE had increased morbidity (central nervous system and renal disease) and decreased survival compared to female patients[8]. Tucker and colleagues reported an association between Hispanic ethnic background and increased renal and cardiopulmonary disease in patients with childhood-onset SLE[9]. Other studies have not confirmed these associations[10-12]. Young age at SLE diagnosis and presence of diffuse proliferative glomerulonephritis (type IV nephritis according to World Health Organization, WHO, classification) have also been identified as poor prognostic indicators in the pediatric age group[9]. However, the associ-

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ation between any of these risk factors and poor prognosis is controversial.

Our primary objective was to determine whether non-Caucasian ethnicity and/or male gender are associated with a worse outcome in children with SLE.

MATERIALS AND METHODS

Patients. Hospital charts were reviewed for all patients who were (a) newly diagnosed with childhood-onset SLE between January 1980 and January 1997; (b) followed at the BC Children's Hospital (BCCH) or at the Mary Pack Arthritis Centre (MPAC), and (c) followed for a minimum of 5 years (or less than 5 years if they had died). All patients fulfilled ACR classification criteria for SLE[13] and were under age 18 years at diagnosis. We had complete followup for 51 of 57 patients (89.5%) who were identified by our search strategy. The 6 patients excluded from the study included 4 patients who were lost to followup or had incomplete records, one patient who had another autoimmune disease, and one patient who also had congenital immunodeficiency. No patient had drug-induced SLE.

Patient data retrospectively collected from the medical records included age at diagnosis, duration of followup, gender, self-reported ethnicity, medication use, presence or absence of renal disease, and type of renal disease. Patients of mixed ethnic background were classified as "other." Four measures of outcome were also recorded:

1. Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index score (SDI) was the primary outcome measure of disease-related morbidity. The SDI has been validated as an instrument for documenting SLE-associated morbidity in both adult and pediatric patients with SLE[10,14,15]. The SDI is an unweighted score that measures damage in 9 different domains: ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, and integument. In addition, development of premature gonadal failure, diabetes, and/or malignancy after SLE is diagnosed is counted as "damage." Damage is considered non-reversible if any given item is present for at least 6 months continuously. Scores range from 0 (no damage) to 47. The SDI score is a continuous variable with higher scores describing increasing damage and by inference a worse outcome. After a review of the literature of SDI use in children and adults with SLE, we considered that permanent damage in 2 organ systems, or significant damage in one organ system, totaling a score > 2, would be considered clinically important as a poor outcome. Therefore a cut-off score of 2 was assigned to separate patients into a good outcome (SDI < 2) or poor outcome group (SDI ≥ 2). SDI scores were determined at last followup for all patients.
2. Requirement for immunosuppressive medications beyond corticosteroids (cyclophosphamide, azathioprine, cyclosporine, and/or mycophenolate mofetil).
3. Renal disease requiring dialysis or transplantation.
4. Mortality related to SLE. Classification as an SLE-related death required at least one of the following: autopsy evidence of SLE related death or death attributed to SLE by clinicians caring for the patient. Data were collected on all deaths in SLE patients followed at either BCCH or MPAC between 1980 and 2001.

Statistical analysis. Demographic characteristics of the patients were summarized using descriptive statistics. The association of gender and ethnicity with each of the outcome measures was examined by Fisher's exact test, and the chi-square test. T tests were used to compare demographic characteristics such as age at onset and length of followup between the SDI-defined good or bad outcome groups. Regression analysis was carried out to assess effects of gender and ethnicity on outcome. All the statistical analyses were performed using SPSS 10.0 software. A p value < 0.05 was considered significant.

RESULTS

Description of patients. Between January 1980 and January 2002, 51 patients with newly diagnosed childhood-onset SLE were seen at the BCCH or MPAC and had been followed for a minimum of 5 years. The median age at diagnosis was 10.8 years, and the median duration of followup was 7.2 years. There were 13 male and 38 female patients, with a M:F ratio of 1:3. There were 15 Caucasian (29.4%) and 36 non-Caucasian (70.6%) patients. Non-Caucasian ethnic groups included Chinese (n = 14), East Indian (n = 9), Filipino (n = 4), North American Indian (n = 3), Fijian (n = 2), Iranian (n = 2), Tanzanian (n = 1), and Bruneian patients (n = 1) (Table 1). When the patients were grouped by either gender or ethnicity, there were no statistically significant differences between the groups for age at presentation, age at last patient visit, or duration of followup (Table 1).

SLICC/ACR Damage Index scores. The mean ± SD SDI score for the entire cohort was 2.08 ± 2.38 (median 2, range 0–9). Twenty-five of 51 patients (49%) had good outcomes (SDI score < 2), and 21 of these (84%) had a SDI score of 0.

Twenty-six of 51 patients (51%) had a poor outcome, with SDI score of ≥ 2. The range of SDI scores in this group was 2–9. Neither gender nor ethnicity was significantly associated with SDI-defined poor outcome (Table 2). Logistic regression did not show any significant influence of sex, ethnicity, age at diagnosis, or length of followup on final SDI scores.

Damage occurred primarily in the musculoskeletal domain (Table 3), with a total of 14 patients (27%) having permanent musculoskeletal damage. Avascular necrosis accounted for the majority of damage in this category (10 patients, 20%). Neuropsychiatric, cardiovascular, peripheral vascular, or integument damage were each identified in 12–14% of patients. Renal damage was found in 10% of patients. The damage accrual by organ system did not differ between the sexes or by ethnic origin (data not shown). One female patient developed premature gonadal failure. There were no malignancies or diabetes in this cohort.

Requirement for intensive immunosuppressive medications in addition to corticosteroids. During the study period, 30 patients (58.8%) received immunosuppressive agents in addition to corticosteroids. A greater percentage of males (69%, 9/13) required the use of immunosuppressive therapy than females (55%, 21/38), but this difference was not statistically significant (Table 4). Five of 6 males with Class IV lupus nephritis, and 9 of 12 females with Class IV or Class V lupus nephritis received intravenous cyclophosphamide pulses. When the use of intensive immunosuppression was analyzed for each ethnic group, no statistically significant differences were found (data not shown).

Requirement for dialysis and/or renal transplant. Kidney biopsies were performed on 25 patients who had clinically suspected renal disease; histologic findings showed WHO Class II glomerulonephritis in 3 patients, Class III in 4

Table 1. Demographic features of patients by gender and ethnicity.

Variables	Total, n = 51	Male, n = 13	Female, n = 38	Caucasian, n = 15	Chinese, n = 14	East Indian, n = 9	Other*, n = 13	p**
Age at presentation, yrs, median	10.7	11.0	10.7	9.7	12.2	10.5	10	NS
Age at last patient visit or at death, yrs, median	19.3	21	18.4	21.5	19.4	17.6	17.4	NS
Duration of followup, yrs, median	7.2	7.6	6.7	7.8	6.3	8.0	7.2	NS

* Filipino (n = 4); North American Indian (n = 3); Fijian (n = 2); Iranian (n = 2); Tanzanian (n = 1); and Brunaian (n = 1). ** $p \leq 0.05$ were considered significant, as determined by analysis of variance for means and by t test.

Table 2. SLICC/ACR Damage Index scores (SDI) in cohort by gender and ethnicity. Except where indicated otherwise, values are the mean ± SD. Good outcome was defined as SDI score < 2; poor outcome as SDI score ≥ 2.

Variables	Total, n = 51	Male, n = 13	Female, n = 38	Caucasian, n = 15	Chinease, n = 14	East Indian, n = 9	Other*, n = 13	p**
SDI score at last patient visit or death	2.08 ± 2.38	2.15 ± 2.08	2.05 ± 2.50	2.20 ± 2.14	1.64 ± 2.21	2.67 ± 3.16	2.00 ± 1.71	NS
Patients with good outcome, %	49.0	46.2	50.0	46.7	57.1	44.4	46.2	NS
Patients with poor outcome, %	51.0	53.8	50	53.3	42.9	55.6	53.8	NS

* As defined in Table 1. ** $p \leq 0.05$ was considered significant, as determined by analysis of variance for means and by t test.

Table 3. Organ system damage accrual as defined by SLICC/ACR Damage Index Score (SDI), by gender.

Organ System	Total (n = 51)	Males (n = 13)	Females (n = 38)	p
Ocular, n (%)	6 (12)	1 (8)	5 (13)	NS
Neuropsychiatric, n (%)	7 (14)	2 (15)	5 (13)	NS
Renal, n (%)	5 (10)	2 (15)	3 (8)	NS
Pulmonary, n (%)	2 (4)	0 (0)	2 (5)	NS
Cardiovascular, n (%)	6 (12)	2 (15)	4 (11)	NS
Peripheral vascular, n (%)	6 (12)	1 (8)	5 (13)	NS
Gastrointestinal, n (%)	2 (4)	0 (0)	2 (5)	NS
Musculoskeletal, n (%)	14 (27)	3 (23)	11 (29)	NS
Avascular necrosis, n (%)	10 (20)	3 (23)	7 (18)	NS
Integument, n (%)	6 (12)	1 (8)	5 (13)	NS
Diabetes, n (%)	0 (0)	0 (0)	0 (0)	NS
Gonadal failure, n (%)	1 (2)	0 (0)	1 (3)	NS
Malignancy, n (%)	0 (0)	0 (0)	0 (0)	NS

Table 4. Requirement for intensive immunosuppressive therapy (IT), defined as requirement for azathioprine, or cyclophosphamide, cyclosporine, and/or mycophenolate mofetil in addition to corticosteroids, by gender.

Variable	Total, n = 51	Male, n = 13	Female, n = 38	p
Patients receiving any IT, n (%)	30 (59)	9 (69)	21 (55)	NS
Azathioprine, n (%)	27 (53)	7 (54)	20 (53)	NS
Cyclophosphamide, n (%)	15 (29)	6 (46)	9 (24)	NS
Cyclosporine, n (%)	4 (8.0)	0 (0)	4 (11)	NS
Mycophenolate mofetil, n (%)	3 (6.0)	1 (8)	2 (5)	NS

patients, Class IV in 14 patients, and Class V in 4 patients. Three female patients (2 Caucasian and one East Indian) required dialysis due to end stage renal disease, and 2 of these patients subsequently went on to renal transplantation. No male patient required dialysis or renal transplantation, but this gender difference was not statistically significant.

Survival. Survival at 5 years of followup was 100%, and after 10 years, survival was 85.7% (12 of the 14 patients followed for 10 years or longer). No patient died within 5 years of followup. Deaths occurred in 5 female patients from sepsis (n = 2), pulmonary hemorrhage as a part of catastrophic antiphospholipid syndrome (n = 2), and suicide (n = 1); one male patient died from a hypertensive cerebrovascular accident. All deaths were classified as SLE-related deaths. The mean SDI score (± SD) for the patients who died (5.33 ± 2.94) was significantly higher than the SDI score (± SD) for the patients who survived (1.64 ± 1.96) (p = 0.027).

DISCUSSION

The demographics of this cohort of patients with childhood-onset SLE, with a high frequency of male and non-Caucasian patients other than African-American and Hispanic, has provided a unique opportunity to examine the effects of gender and race on outcome in pediatric onset SLE. The ratio of female to male children with SLE in our cohort is similar to many previous reports (3 females to 1 male) from other pediatric centers[9,11,12,16]. The reason for a higher number of males with SLE presenting in childhood is unknown, but may be related to the interplay between inher-

ited predisposition to developing SLE, environmental factors, and post-pubertal hormonal factors.

Male gender has been reported to be associated with reduced survival[1,4] and worse outcome[2,17] in patients with SLE. In contrast to these studies, we did not find either poor outcome or increased mortality among our male patients with SLE as compared to the female patients. Although only female patients developed end stage renal disease requiring dialysis or renal transplantation, this difference was not significant perhaps due to the small numbers in our study.

Non-Caucasian ethnic background has previously been associated with a poor prognosis in both adult and pediatric patients with SLE[6,16,18-21]. However we did not find this association in our ethnically diverse group. A possible explanation for the lack of association between ethnicity and outcome is that our patient population did not include representation from African-American, Afro-Caribbean, or Hispanic populations, the ethnic groups in which a poorer outcome has been shown in previous studies[4,5,12,20-22]. Of particular interest in our study is the finding that all 3 patients of North American Indian origin in our cohort had elevated SDI scores (range 2–9), and one of these patients died. This finding is consistent with the findings of a population study in Manitoba, Canada by Peschken and Esdaile[7], where SLE was found to be nearly twice as prevalent in North American Indians as in the Caucasian population of Manitoba, and their SDI scores at 2 and 8 years after diagnosis were significantly higher than the Caucasian patients. Taken together, our data suggest that North American Indian children who develop SLE may be at particular risk for poor outcome.

Although some previous studies of outcome in adult onset SLE have suggested that increased mortality and poor outcome in African-American patients may be related to inadequate access to healthcare and lower socioeconomic status[22], this continues to be controversial. Low socioeconomic status, independent of ethnic background, has been identified as a prognostic variable for poor outcome[1,4,7] and differentiating low socioeconomic status from poor access to health care is difficult in many studies. Petri, *et al*[5] showed that morbidity of SLE was not associated with black race in a US-based cohort study, but morbidity was associated with physician-assessed poor compliance and type of medical insurance. One study performed in the UK, where there is universal access to healthcare, showed increased organ damage among non-Caucasian adult patients irrespective of education level (a surrogate marker for socioeconomic status)[23]. Although we did not determine the socioeconomic status of the families of the patients included in our study, the universal access to healthcare in the Canadian health care system may have been a factor promoting similar outcomes in different ethnic groups. A similar suggestion has been made regarding patients with childhood-onset lupus by Brunner, *et al*[10], who concluded that non-white race was not a risk factor for development of disease damage in a cohort of children with SLE in Toronto.

As a group, the children and young adults in our study accumulated more disease damage than is usual in patients with adult onset SLE. The median SDI score was 2.10 after an average disease duration of 8.5 years, which is similar to a previously reported mean SDI score of 1.76 in childhood-onset SLE patients followed in Toronto after an average disease duration of 3.3 years[10]. Studies reporting outcome of adult patients with SLE using the SDI show a slower rate of accumulation of damage than we and others have seen in pediatric patients. In 3 large cohort studies of adult patients with SLE from the UK, Toronto, and Montreal (number of patients = 1080 total), mean SDI scores at followup ranged from 1.2–1.8, with mean disease durations of 8–10 years[15,24,25].

Although the SDI has been tested for validity and reliability in a single-center pediatric SLE cohort, there remain some questions about whether modifications should be made to the SDI to incorporate areas of specific impact in pediatrics, such as growth and development. Inclusion of items that record growth retardation and pubertal delay as damage, and incorporation of specific pediatric definitions for items such as cognitive disturbance and end stage renal disease may improve damage assessment in children with SLE[26].

The dramatically improved survival for childhood-onset SLE over the last few decades is supported by our study. In our cohort, survival at 5 years was 100% and at 10 years 85.7%. This is consistent with other reports on outcome of childhood SLE from North America[9,16,27].

A potential limitation of our study is the relatively small sample size. Although this is the second-largest reported cohort of childhood SLE patients in Canada, the numbers in each ethnic subgroup were too small to disprove the null hypothesis. Because the study was carried out at a single center, there is less of the variation in treatment than would be expected from a multicenter study; this could account for some of the differences from comparable studies. This single center cohort is probably a very good approximation of the population of British Columbia, since virtually all children and youth with the onset of SLE before age 18 years are seen by our clinic either alone or in conjunction with another subspecialty clinic such as nephrology.

Assessment of risk factors for decreased survival and for permanent damage guides treatment decisions in childhood-onset SLE. Our results support the concept that neither gender nor ethnic origin alone predict a worse longterm outcome for childhood-onset SLE, and that in general, childhood-onset SLE has a more aggressive course than that described for adult SLE. Although the survival in this pediatric cohort was very good, over 50% of the patients developed chronic damage in 2 separate organ systems or significant damage in one organ system. Although patients

who died had a high SDI score around the time of death, it is not known whether earlier or sequential measurements of SDI in these patients would have predicted this outcome. Routine and sequential use of the SDI in pediatric lupus care may provide a rate of change of disease damage that is predictive of severe disability or death; this concept warrants further study.

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