

## Pediatric rheumatology

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# Systemic features and early prognostic factors in Hispanic and non-Hispanic children from the United States of America and Mexico with systemic juvenile idiopathic arthritis. A multi-center retrospective chart review

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### Abstract

#### Objective

To investigate if the persistence of systemic features is longer in Hispanic children with systemic juvenile idiopathic arthritis (S-JIA) than in non-Hispanic children with S-JIA and to determine early predictors of systemic and articular disease.

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#### Methods

We performed a multi-center retrospective chart review of patients followed in six pediatric rheumatology centers with onset of S-JIA from 1974 to 2004. Patients were included in the study if they had been followed for  $\geq 1$  year after disease onset. Information collected included demographic, clinical, laboratory and treatment data. Systemic features included fever, rash, lymphadenopathy, hepatosplenomegaly, pericarditis, and pleuritis.

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#### Results

Of the 159 S-JIA patients screened, 120 (75%) met our inclusion criteria. There were 65 boys and 55 girls. The mean follow-up period for Hispanic patients was 5.7 years (SD 4.0) and for non-Hispanic patients was 8.6 years (SD 7.2). There was no significant difference in the presence of systemic features between Hispanic and non-Hispanic patients at 0.5, 1, 2, 4, 6, 8, and 10 years of follow-up. Polyarthritis at the 6-month visit was predictive of systemic features (OR 9.7, 95% CI 1.16-81.35,  $p = 0.036$ ) and polyarthritis (OR 5.6, 95% CI 1.42-21.8,  $p = 0.014$ ) at last follow-up.

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#### Conclusion

In children with S-JIA, Hispanics did not demonstrate longer persistence of systemic features than non-Hispanics. Polyarthritis at 6 months strongly predicted the development of persistent systemic features and chronic polyarticular disease.

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#### Key words

Systemic juvenile idiopathic arthritis, predictors of outcome, persistence, polyarthritis, Hispanic, non-Hispanic.

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## Introduction

Systemic juvenile idiopathic arthritis (S-JIA) is an inflammatory disease characterized by extraarticular features including spiking fevers, evanescent rash, and pericarditis (1). Children with S-JIA have a variable course, with half going into remission and the other half developing chronic polyarthritis (1-8). Extraarticular systemic features typically subside within months to a few years (1, 4, 6). However, systemic features have been reported to persist for 10-15 years in up to 25-30% of patients (9-11).

Persistence of systemic disease can result in significant morbidity and mortality. Macrophage activation syndrome (MAS), myocarditis, and secondary amyloidosis are infrequent but potentially fatal consequences of systemically active JIA (12-17). Delayed growth and osteoporosis can also occur (1). Finally, patients are at increased risk of developing aggressive polyarthritis that is often refractory to medical treatment and can result in disabling, destructive arthritis (4, 18, 19).

Recently, there has been improved understanding about the pathogenesis of S-JIA. Several studies have demonstrated that circulating levels of the proinflammatory cytokines tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1, and IL-6 are major mediators of the inflammatory cascade in S-JIA (20-22). These cytokines have been targets for therapy with particularly promising results seen with Anakinra (IL-1 receptor antagonist) and monoclonal antibody to the IL-6 receptor (23, 24). Patients with persistent systemic features may stand to benefit the most from biologic treatments that specifically target cytokines that are mediators of systemic inflammation. It would be critical to identify a high-risk population that would benefit from early treatment with these therapies, with the potential to greatly improve their long-term outcome.

It has been our anecdotal experience that non-Hispanic S-JIA children followed in Cincinnati, Ohio, typically have disappearance of systemic features within two years, while up to 50% of Hispanic S-JIA children followed in Mexico and South America have persistence of systemic features. Possible explanations for

this observation include differences in genetic susceptibility, differences in environmental exposures and referral bias. The purpose of our study was to investigate whether Hispanic children with S-JIA have longer persistence of systemic features than non-Hispanic children with S-JIA. Additionally, we tried to identify, early in the disease course, demographic, clinical and laboratory features in our cohort that were predictive of systemic features, polyarthritis, and disease activity.

## Subjects and methods

### Subjects

We performed a multi-center retrospective chart review of all patients with S-JIA followed in 6 pediatric rheumatology centers. Patients included in the study had onset of S-JIA between 1983 to 2004 at the Children's Hospital Central California in Madera, California, between 1994 to 2004 at 3 centers in Mexico City, Mexico (Hospital General de Mexico, Centro Medico Nacional Siglo XXI, Centro Medico Nacional la Raza) and 1 center in Monterrey, Mexico (Hospital Universitario "Dr. J.E. González", Autónoma de Nuevo León), and between 1974 to 2004 at Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio. The different time frames for data collection reflect the different availability of patient information in the 3 geographic locations. The study was approved by the institutional review boards at the participating centers.

To be included in the study, patients had to meet the International League of Associations for Rheumatology (ILAR) classification criteria for S-JIA (25), and be followed up at the participating center for  $\geq 1$  year after onset of disease. Data was collected from the medical records at the time of diagnosis, at specific time points after disease onset (6 months, 1 year, 2 years, 4 years, 6 years, 8 years, 10 years), and at the most recent clinic visit. Information collected included demographic data (gender, ethnicity, age, disease activity), clinical data (arthritis, fever due to S-JIA [fever], rash due to S-JIA [rash], hepatosplenomegaly, generalized lymphadenopathy [lymphadenopathy], pericarditis, pleuritis, uveitis, myocarditis, macrophage activation

Competing interests: none declared.

syndrome [MAS], amyloidosis), qualitative laboratory data (elevated erythrocyte sedimentation rate [ESR], elevated white blood cell count [WBC], elevated platelet count) and treatment data about medications used at any time during follow-up (nonsteroidal anti-inflammatory drugs [NSAIDs], systemic corticosteroids, disease-modifying antirheumatic drugs [DMARDs], biologics, intravenous gammaglobulin [IVIG]). All of the examiners were highly experienced pediatric rheumatologists.

#### *Assessment of race and ethnicity*

All patients were racially and ethnically classified by the physicians completing the case report form. Ethnic categories were "Hispanic" or "non-Hispanic". In order to potentially assess the role of environmental exposures on phenotypic expression in our Hispanic cohort, Hispanic patients were further geographically classified based on their country of origin and current residence ("Hispanic born in Mexico that resides in Mexico", "Hispanic born in Mexico that resides in the US", or "Hispanic born in the US that resides in the US").

#### *Definition of disease activity*

Disease activity at last follow-up was defined based on recently proposed preliminary criteria for inactive disease and clinical remission of JIA (26). Patients were said to have "inactive disease" if they demonstrated at a point in time all of the following four criteria: 1) no joints with active arthritis (American College of Rheumatology [ACR] definition of active joint is used); 2) no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; 3) no active uveitis since the last slit lamp examination; 4) normal ESR or CRP (if both are tested, both must be normal). We were not able to include the 5<sup>th</sup> criterion, physicians' global assessment of disease activity, since this data was not available. Patients who maintained "inactive disease" for 6 months while on medications for the treatment of JIA were classified as being in clinical remission on medication, while those who maintained "inactive disease" for 12 months while off medications were said to be

in clinical remission off medication. A patient was said to have "active disease" if they did not meet criteria for "inactive disease".

#### *Laboratory variables*

Elevated ESR, WBC, or platelets indicates the blood test exceeded the upper limit of normal for the laboratory performing the analysis; the term elevated was used in order to accommodate different laboratory methodologies and normal range values at the participating sites.

#### *Definition of polyarthritis, MAS and amyloidosis*

Polyarthritis was defined as arthritis in more than 4 joints. The diagnosis of MAS was based on clinical judgment at the participating institution, since validated diagnostic criteria for MAS do not exist at this time. Physicians who recorded that a patient had MAS were required to complete a questionnaire about the histopathologic, clinical, and/or laboratory findings that led to the diagnosis of MAS. A diagnosis of amyloidosis required confirmation by biopsy.

#### *Database*

Data was entered into a database by the first author (MS) using Excel (Microsoft, Redmond, WA, USA). After completion of data entry, 25 charts were randomly selected for review using a random numbers table (27). There were 81 errors out of 2712 possible data points (2.99% error rate). Many of the mistakes were made due to 2 systematic errors discovered in the data entry process. The systematic errors were corrected in the entire database and then another 25 charts were randomly selected. The error rate decreased to 3 errors out of 2480 possible data points (0.12% error rate).

#### *Statistical analysis*

Data was analyzed using SAS 9.1 (SAS, Cary, NC, USA). The primary analysis compared the frequency of systemic features at specific time points during follow-up between Hispanic and non-Hispanic patients with S-JIA using Chi-square statistics or Fisher's

exact test. Differences in the baseline characteristics between Hispanic and non-Hispanic patients were evaluated with the use of the Kruskal Wallis test for continuous variables and with the use of the Chi-square test and Fisher's exact test for categorical variables. The Bonferroni correction was used to adjust the *p* value for multiple comparisons involving the primary analysis. Measures of association were reported as odds ratios (OR) with 95% confidence intervals (95% CI). When there were cells with zero patients present, we added 0.5 to the count of each cell to compute the OR and the 95% CI (28). Secondary analysis evaluated a number of variables at 6 months after disease onset to assess their ability to predict different poor outcomes at last follow-up. Bivariable comparisons were performed with the use of Fisher's exact test and the Chi-square test, in order to screen for potential predictors at the 6 month visit ( $\pm 2$  months). Variables with *p* values  $< 0.20$  were included in a stepwise logistic regression analysis. Both backwards elimination and stepwise selection algorithms were used to identify a final model.

In order to calculate the sample size, we estimated a 25% difference in the persistence of systemic features between Hispanic and non-Hispanic patients. Under this assumption, a sample size of 110 patients (55 Hispanic patients and 55 non-Hispanic patients) was needed to detect a 25% difference in the frequency of systemic features between the two populations at the different time points with a power of 80%, using a two-sided alpha level of 0.05.

## **Results**

### *Study population characteristics*

Of the 159 S-JIA patients screened, 120 (75%) met our inclusion criteria. Fourteen patients were excluded because of follow-up for less than 1 year, 9 were excluded for failure to meet S-JIA ILAR criteria, and 16 were excluded because of incomplete records. We performed a separate analysis on the available data of 4/16 patients with incomplete records. We found no differences between the study patients and the non-study patients.

**Table I.** Demographic, clinical, laboratory and treatment data in non-Hispanic and Hispanic patients with S-JIA\*.

|                                                 | Ohio<br>non-Hispanic<br>(n = 41) | California<br>non-Hispanic<br>(n = 14) | California<br>Hispanic<br>(n = 17) | Mexico<br>Hispanic<br>(n = 48) | <i>p</i> <sup>†</sup> |
|-------------------------------------------------|----------------------------------|----------------------------------------|------------------------------------|--------------------------------|-----------------------|
| Descriptive data                                |                                  |                                        |                                    |                                |                       |
| Age at onset, years <sup>‡</sup>                | 6.71 ± 4.37                      | 6.43 ± 4.30                            | 6.28 ± 4.48                        | 4.90 ± 3.84                    | 0.212                 |
| Follow-up, years <sup>‡</sup>                   | 8.62 ± 7.47                      | 8.51 ± 6.57                            | 7.80 ± 4.81                        | 4.91 ± 3.33                    | 0.045                 |
| Male:Female ratio                               | 1.4:1                            | 1.3:1                                  | 1.4:1                              | 0.9:1                          | 0.744                 |
| Clinical data at onset                          |                                  |                                        |                                    |                                |                       |
| Arthritis                                       |                                  |                                        |                                    |                                | < 0.001               |
| Oligoarticular                                  | 10 (24)                          | 5 (36)                                 | 7 (41)                             | 4 (8)                          |                       |
| Polyarticular                                   | 25 (61)                          | 5 (36)                                 | 6 (35)                             | 44 (92)                        |                       |
| None                                            | 6 (15)                           | 4 (29)                                 | 4 (24)                             | 0 (0)                          |                       |
| Fever                                           | 41 (100)                         | 13 (93)**                              | 17 (100)                           | 47 (98)**                      | 0.240                 |
| Rash                                            | 32 (78)                          | 11/13 (85)                             | 15 (88)                            | 38 (79)                        | 0.858                 |
| Hepatosplenomegaly                              | 14 (34)                          | 2/8 (25)                               | 2/15 (13)                          | 14 (29)                        | 0.513                 |
| Lymphadenopathy                                 | 13 (32)                          | 4/7 (57)                               | 11/15 (73)                         | 23 (48)                        | 0.039                 |
| Pericarditis                                    | 3 (7)                            | 1/12 (8)                               | 1/15 (7)                           | 4 (8)                          | 1                     |
| Pleuritis                                       | 1 (2)                            | 1/13 (8)                               | 1/15 (7)                           | 0 (0)                          | 0.106                 |
| Myocarditis                                     | 1 (2)                            | 1/13 (8)                               | 1/16 (6)                           | 3 (6)                          | 0.607                 |
| Uveitis                                         | 0 (0)                            | 0 (0)                                  | 0 (0)                              | 0 (0)                          | NA                    |
| MAS                                             | 3 (7)                            | 2 (14)                                 | 0 (0)                              | 0 (0)                          | 0.039                 |
| Amyloidosis                                     | 0 (0)                            | 0 (0)                                  | 0 (0)                              | 0 (0)                          | NA                    |
| Corticosteroid use                              | 14 (34)                          | 1/13 (8)                               | 7/16 (44)                          | 30/46 (65)                     | 0.001                 |
| Laboratory data at onset                        |                                  |                                        |                                    |                                |                       |
| Elevated ESR                                    | 36/36 (100)                      | 6/7 (86)                               | 12/13 (92)                         | 35/39 (90)                     | 0.138                 |
| Elevated WBC                                    | 23/38 (61)                       | 6/7 (86)                               | 7/13 (54)                          | 34/38 (90)                     | 0.007                 |
| Elevated Platelets                              | 22/38 (58)                       | 5/7 (71)                               | 11/13 (85)                         | 27/38 (71)                     | 0.329                 |
| Medications used during follow-up               |                                  |                                        |                                    |                                |                       |
| NSAIDs                                          | 41 (100)                         | 14 (100)                               | 17 (100)                           | 48 (100)                       | NA                    |
| Corticosteroids                                 | 36 (88)                          | 10 (71)                                | 16 (94)                            | 45 (94)                        | 0.125                 |
| DMARDs                                          | 37 (90)                          | 13 (93)                                | 17 (100)                           | 43 (90)                        | 0.668                 |
| Biologics§                                      | 25 (61)                          | 6 (43)                                 | 7 (41)                             | 21 (44)                        | 0.325                 |
| IVIG                                            | 10 (24)                          | 2 (14)                                 | 1 (6)                              | 2 (4)                          | 0.024                 |
| Disease activity at last follow-up <sup>‡</sup> |                                  |                                        |                                    |                                |                       |
| Active                                          | 20 (49)                          | 6 (43)                                 | 5 (29)                             | 12 (25)                        | 0.003                 |
| Inactive                                        | 9 (22)                           | 1 (7)                                  | 7 (41)                             | 4 (8)                          |                       |
| CR on medications                               | 7 (17)                           | 7 (50)                                 | 4 (24)                             | 25 (52)                        |                       |
| CR off medications                              | 5 (12)                           | 0 (0)                                  | 1 (6)                              | 7 (15)                         |                       |

\*Except for descriptive data, values are the number (%). Ratios are provided for cells with missing data. S-JIA: systemic juvenile idiopathic arthritis; NA: Not Applicable; MAS: Macrophage Activation Syndrome; ESR: erythrocyte sedimentation rate; WBC: white blood cells; NSAIDs: nonsteroidal anti-inflammatory drugs; DMARDs: disease-modifying antirheumatic drugs; IVIG: intravenous gammaglobulin; CR: clinical remission.

\*\*One child from California and one child from Mexico had arthritis without fever at onset; by 6 months after disease onset, they both demonstrated fever, rash, and hepatosplenomegaly, thus fulfilling the ILAR classification criteria for S-JIA (25).

<sup>†</sup>*p* values were calculated with the use of the Kruskal-Wallis test for continuous variables and with the use of the Chi-square test and Fisher's exact test for categorical variables.

<sup>‡</sup>Plus-minus values are means ± SD.

<sup>§</sup>Biologics include Infliximab, Etanercept, Adalimumab, and Anakinra.

<sup>‡</sup>Disease activity at last follow-up was defined based on preliminary criteria for inactive disease and clinical remission of JIA (26). "Inactive disease" required demonstrating at a point in time all of the following four criteria: 1) no joints with active arthritis; 2) no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; 3) no active uveitis; 4) normal ESR or CRP (if both are tested, both must be normal). Patients who maintained "inactive disease" for 6 months while on medications for the treatment of JIA were classified as being in clinical remission on medication, while those who maintained "inactive disease" for 12 months while off medications were said to be in clinical remission off medication. A patient was said to have "active disease" if they did not meet criteria for "inactive disease".

Demographic, clinical, laboratory and treatment data for Hispanic and non-Hispanic patients are shown in Table I. There were 65 boys and 55 girls. The Hispanic (n = 65) and non-Hispanic (n = 55) arms were well-balanced. Of the non-Hispanic patients, 49 were Cauca-

sian, 5 were Black and 1 was Asian. Of the Hispanic patients, 48 were born in Mexico and now reside in Mexico, 16 were born in the US and now reside in the US, and only 1 patient was born in Mexico and now resides in the US. California was the only clinical site that

had both Hispanic and non-Hispanic patients.

Patients were followed for similar periods of time in Ohio and California, but Hispanic patients from Mexico had a shorter mean length of follow-up. There were differences in the number

of joints involved at disease onset, with 92% of Hispanic patients from Mexico having polyarthritis at onset. During follow-up, all patients used NSAIDs and a majority used DMARDs and systemic corticosteroids. The frequency of biologic use was similar between non-Hispanic (56%) and Hispanic patients (43%). At last follow-up, 47% of non-Hispanic patients had “active disease” while 26% of Hispanic patients had “active disease” (see definition for “active disease” in Table I). MAS was reported at onset in 5 non-Hispanic patients, all of whom demonstrated hemophagocytosis on bone marrow biopsy, but was not reported in any Hispanic patients at onset or during follow-up. Amyloidosis was not reported in any patients at onset, while 1 non-Hispanic patient developed amyloidosis in subsequent follow-up, which was confirmed by liver biopsy. There were no reports of uveitis occurring at onset or in follow-up.

#### Systemic features

There was no significant difference in systemic features between Hispanic and non-Hispanic patients during follow-up (Table II). Nine out of twenty-two (41%) non-Hispanic patients demonstrated persistence of systemic features at 10 years of follow-up, while 0/8 Hispanic patients demonstrated systemic features at 10 years of follow-up.

We performed a subset analysis of pa-

tients followed only in California in order to limit variations that might arise between different treatment centers and geographic locations. The results were similar, with no significant difference in systemic features between Hispanic and non-Hispanic patients during follow-up. We considered the possibility that patients who had onset of S-JIA after 1990 may have had less persistence of systemic features compared to patients who had onset prior to 1990 due to potential influences on outcome that may have occurred during this long time interval. We performed a subset analysis by excluding patients with onset of S-JIA before 1990 (12 non-Hispanic and 2 Hispanic patients were excluded). Of the 12 non-Hispanic patients excluded, only 2 had their 10-year follow-up before 1990. The results were not significantly different, with 30% of non-Hispanic patients demonstrating systemic features at 10 years of follow-up.

#### Prognostic factors

We wanted to determine if there were factors at 6 months of disease duration that could predict unfavorable outcomes at last follow-up. Factors evaluated for predictive ability included descriptive data (age of onset, duration of follow-up, and gender), clinical data (arthritis, fever, rash, hepatosplenomegaly, lymphadenopathy, pericarditis, pleuritis, myocarditis, and corticosteroid use)

and laboratory data (elevated ESR, elevated WBC, and elevated platelets). Outcomes at last follow-up included the presence of systemic features, polyarthritis, or “active disease”.

We compared patients' values at 6 months in those that had  $\geq 1$  systemic features at last follow-up (group 1) with those that did not (group 2) (Table III). Patients in group 1 had almost twice the incidence of polyarthritis compared to group 2 (90% vs. 47%, respectively) and more than twice the mean length of follow-up compared to group 2 (12.44 years vs. 6.07 years, respectively). The average follow-up for the 2 groups was approximately 6 years. The independent variables included in the model were length of follow-up ( $< 6$  years or  $\geq 6$  years), polyarthritis, fever, rash, and hepatosplenomegaly. Polyarthritis at the 6-month visit was the only statistically significant predictor of persistent systemic features at last follow-up (odds ratio [OR] 9.7, 95% confidence interval [95% CI] 1.16-81.35,  $p = 0.036$ ). Additional analysis of the predictive ability of polyarthritis, while controlling for ethnicity (Hispanic and non-Hispanics), did not demonstrate any significant effect (Breslow-Day test for homogeneity of the odds ratios  $p = 0.1538$ ).

We compared patients' values at 6 months in those that had polyarthritis at last follow-up (group 1) with those that did not (group 2) (Table III). There were significant differences between the groups in length of follow-up, arthritis, hepatosplenomegaly, and elevated WBC count. Patients in group 1 had almost twice the incidence of polyarthritis compared to group 2 (85% vs. 43%, respectively) and more than twice the mean length of follow-up as group 2 (11.3 years vs. 5.4 years, respectively). The average follow-up for the 2 groups was approximately 6 years. Length of follow-up ( $< 6$  years or  $\geq 6$  years), polyarthritis, fever, hepatosplenomegaly, and elevated WBC count were included in the model. Polyarthritis at the 6-month visit was the only statistically significant predictor of polyarthritis at last follow-up (odds ratio 5.6, 95% CI 1.42-21.8,  $p = 0.014$ ). Additional analysis of the predictive ability of polyarthritis,

**Table II.** Presence of  $\geq 1$  systemic features at different time points during follow-up in Hispanic and non-Hispanic patients with S-JIA\*.

| Follow-up <sup>§</sup> | Hispanic<br>(n = 65) | non-Hispanic<br>(n = 55) | $p^{\dagger}$      | OR<br>(95% CI)  |
|------------------------|----------------------|--------------------------|--------------------|-----------------|
| 6 months               | 28/58 (48)           | 25/51 (49)               | 1                  | 1.0 (0.5-2.1)   |
| 1 year                 | 20/58 (34)           | 24/51 (47)               | 0.241              | 0.6 (0.3-1.3)   |
| 2 years                | 18/49 (37)           | 21/46 (46)               | 0.410              | 0.7 (0.3-1.6)   |
| 4 years                | 9/31 (29)            | 12/33 (36)               | 0.601              | 0.7 (0.3-2.1)   |
| 6 years                | 5/23 (22)            | 11/27 (41)               | 0.225              | 0.4 (0.1-1.4)   |
| 8 years                | 1/15 (7)             | 11/24 (46)               | 0.013 <sup>‡</sup> | 0.1 (0.01-0.8)  |
| 10 years               | 0/8 (0)              | 9/22 (41)                | 0.067              | 0.1 (0.004-1.6) |
| >10 years              | 1/10 (10)            | 5/20 (25)                | 0.633              | 0.3 (0.03-3.3)  |

\*Values are proportion of patients with available data with  $\geq 1$  systemic features (%).

Systemic features include fever and rash due to S-JIA, hepatosplenomegaly, generalized lymphadenopathy, pericarditis, and pleuritis. Follow-up is months or years after onset of disease. OR: odds ratio; 95% CI = 95% confidence interval.

<sup>†</sup>Fisher's exact test.

<sup>‡</sup>Adjusted  $p$  value is 0.104 after Bonferroni's correction for multiple comparisons.

<sup>§</sup>Mean duration of follow-up was 8.6 years in non-Hispanics and 5.7 years in Hispanics.

**Table III.** Demographic, clinical and laboratory data in S-JIA patients 6 months after disease onset\*.

|                                  | 0 systemic<br>features at last<br>follow-up<br>(n = 89) | ≥ 1 systemic<br>features at last<br>follow-up<br>(n = 10) | <i>p</i> <sup>†</sup> | No polyarthritis<br>at last<br>follow-up<br>(n = 77) | Polyarthritis<br>at last<br>follow-up<br>(n = 20) | <i>p</i> <sup>†</sup> | "No active<br>disease" at<br>last follow-up<br>(n = 61) | "Active<br>disease" at<br>last follow-up<br>(n = 38) | <i>p</i> <sup>†</sup> |
|----------------------------------|---------------------------------------------------------|-----------------------------------------------------------|-----------------------|------------------------------------------------------|---------------------------------------------------|-----------------------|---------------------------------------------------------|------------------------------------------------------|-----------------------|
| <b>Descriptive data</b>          |                                                         |                                                           |                       |                                                      |                                                   |                       |                                                         |                                                      |                       |
| Age at onset, years <sup>‡</sup> | 6.35 ± 4.25                                             | 6.08 ± 4.54                                               | 0.866                 | 6.45 ± 4.28                                          | 6.17 ± 4.24                                       | 0.820                 | 5.88 ± 4.16                                             | 7.04 ± 4.35                                          | 0.178                 |
| Follow-up, years <sup>‡</sup>    | 6.07 ± 4.90                                             | 12.44 ± 8.68                                              | 0.015                 | 5.40 ± 3.79                                          | 11.30 ± 8.15                                      | 0.001                 | 6.34 ± 5.17                                             | 7.33 ± 6.42                                          | 0.690                 |
| Male:female ratio                | 1.3:1                                                   | 1.5:1                                                     | 1                     | 1.6:1                                                | 0.8:1                                             | 0.214                 | 1.3:1                                                   | 1.4:1                                                | 1                     |
| <b>Clinical data</b>             |                                                         |                                                           |                       |                                                      |                                                   |                       |                                                         |                                                      |                       |
| Arthritis                        |                                                         |                                                           | 0.034                 |                                                      |                                                   | 0.003                 |                                                         |                                                      | 0.296                 |
| Oligoarticular                   | 26/89 (29)                                              | 1/10 (10)                                                 |                       | 26/77 (34)                                           | 1/20 (5)                                          |                       | 16/61 (26)                                              | 11/38 (29)                                           |                       |
| Polyarticular                    | 42/89 (47)                                              | 9/10 (90)                                                 |                       | 33/77 (43)                                           | 17/20 (85)                                        |                       | 29/61 (48)                                              | 22/38 (58)                                           |                       |
| None                             | 21/89 (24)                                              | 0/10 (0)                                                  |                       | 18/77 (23)                                           | 2/20 (10)                                         |                       | 16/61 (26)                                              | 5/38 (13)                                            |                       |
| Fever                            | 31/86 (36)                                              | 6/9 (67)                                                  | 0.147                 | 26/75 (35)                                           | 11/19 (58)                                        | 0.073                 | 23/58 (40)                                              | 14/37 (38)                                           | 1                     |
| Rash                             | 26/84 (31)                                              | 5/9 (56)                                                  | 0.154                 | 23/74 (31)                                           | 8/18 (44)                                         | 0.405                 | 19/56 (34)                                              | 12/37 (32)                                           | 1                     |
| Hepatosplenomegaly               | 8/82 (10)                                               | 3/9 (33)                                                  | 0.074                 | 6/72 (8)                                             | 5/18 (28)                                         | 0.039                 | 4/55 (7)                                                | 7/36 (19)                                            | 0.101                 |
| Lymphadenopathy                  | 12/82 (15)                                              | 1/9 (11)                                                  | 1                     | 10/72 (14)                                           | 3/18 (17)                                         | 0.719                 | 7/55 (13)                                               | 6/36 (17)                                            | 0.761                 |
| Pericarditis                     | 1/84 (1)                                                | 0/10 (0)                                                  | 1                     | 1/74 (1)                                             | 0/18 (0)                                          | 1                     | 0/57 (0)                                                | 1/37 (3)                                             | 0.394                 |
| Pleuritis                        | 1/85 (1)                                                | 0/10 (0)                                                  | 1                     | 1/74 (1)                                             | 0/19 (0)                                          | 1                     | 1/57 (2)                                                | 0/38 (0)                                             | 1                     |
| Myocarditis                      | 1/88 (1)                                                | 0/10 (0)                                                  | 1                     | 1/76 (1)                                             | 0/20 (0)                                          | 1                     | 0/61 (0)                                                | 1/38 (3)                                             | 0.389                 |
| Corticosteroid use               | 56/86 (65)                                              | 7/9 (78)                                                  | 0.713                 | 48/74 (65)                                           | 14/20 (70)                                        | 0.793                 | 37/58 (64)                                              | 26/37 (70)                                           | 0.657                 |
| <b>Laboratory data</b>           |                                                         |                                                           |                       |                                                      |                                                   |                       |                                                         |                                                      |                       |
| Elevated ESR                     | 47/76 (62)                                              | 4/6 (67)                                                  | 1                     | 40/67 (60)                                           | 11/14 (79)                                        | 0.234                 | 31/51 (61)                                              | 20/31 (65)                                           | 0.817                 |
| Elevated WBC                     | 29/78 (37)                                              | 2/6 (33)                                                  | 1                     | 22/69 (32)                                           | 9/14 (64)                                         | 0.033                 | 17/52 (33)                                              | 14/32 (44)                                           | 0.356                 |
| Elevated Platelets               | 38/79 (48)                                              | 2/6 (33)                                                  | 0.679                 | 32/70 (46)                                           | 8/14 (57)                                         | 0.561                 | 24/53 (45)                                              | 16/32 (50)                                           | 0.883                 |

\*Values are proportion of patients with available data (%). Systemic features at last follow-up include fever and rash due to S-JIA, hepatosplenomegaly, generalized lymphadenopathy, pericarditis, and pleuritis. Polyarthritis indicates arthritis in more than 4 joints. "No active disease" refers to patients that had inactive disease, clinical remission on medication or clinical remission off medication at last follow-up (see reference 26 for definitions of inactive disease and clinical remission in JIA). ESR: erythrocyte sedimentation rate; WBC: white blood cells.

<sup>†</sup>*p* values were calculated with the use of the Kruskal-Wallis test for continuous variables and with the use of the Chi-square test and Fisher's exact test for categorical variables.

<sup>‡</sup>Values are mean ± SD.

while controlling for ethnicity (Hispanic and non-Hispanics), did not demonstrate any significant effect (Breslow-Day test for homogeneity of the odds ratios  $p = 0.6872$ ).

We considered the possibility that increased follow-up in the poor outcome groups above could have affected the predictive ability of our criteria. After further analysis, we observed that 4 patients in each of the poor outcome groups had more than 20 years of follow-up. When we excluded these patients from the analysis, polyarthritis at 6 months remained the only predictive factor for systemic features and polyarthritis.

We compared patients' values for prognostic factors at 6 months in those that had "active disease" at last follow-up with those that did not (Table III). No statistically significant differences emerged between the groups, with only hepatosplenomegaly displaying a trend towards significance (odds ratio 3.1, 95% CI 0.83-11.41,  $p = 0.105$ ).

## Discussion

The results of this multi-center retrospective study of 120 patients with S-JIA show that Hispanics did not have longer persistence of systemic features than non-Hispanics. In fact, while Hispanic patients demonstrated a decrease in systemic features over time, 40% of non-Hispanic patients demonstrated persistence of systemic features with or without arthritis at 10 years of follow-up. Non-Hispanic patients had an increased mean length of follow-up (8.6 years) compared to Hispanic patients (5.7 years), which was primarily due to differences in availability of patient information. Increased length of follow-up in non-Hispanic patients may have led to the inclusion of a larger number of chronically relapsing systemically active patients compared to Hispanic patients. However, it is striking that among Hispanic patients, only 1 out of 15 had systemic features at 8 years of

follow-up, and 0 out of 8 had systemic features at 10 years of follow-up. In spite of the small number of Hispanic patients at these specific time points, the evidence appears strong that Hispanic patients failed to demonstrate persistence of systemic features.

Because our patients were followed in centers in Mexico, California, and Ohio, we were concerned that differences in physician practice habits, referral patterns, access to medical care, and environmental exposures might have affected the results. The pediatric rheumatology center in California was the only site that had both Hispanic and non-Hispanic patients and was useful in comparing systemic features between the two groups while limiting confounding by clinical center and geographic location. The results were similar for patients followed in California, with Hispanic patients demonstrating fewer systemic features over time and 40% of non-Hispanic patients

demonstrating persistence of systemic features at 8 years of follow-up. In order to make sure that environmental differences were controlled as much as possible, the one patient born in Mexico that resided and was followed in California was excluded from the analysis. The results remained similar.

By 6 months after disease onset, significant differences in prognostic factors between the two groups began to emerge. After logistic regression, polyarthritis at 6 months was the only factor predictive of systemic or polyarticular disease. Specifically, patients with polyarthritis at 6 months had approximately 10 times the odds of systemic features at last follow-up and approximately 6 times the odds of polyarthritis at last follow-up compared to patients without polyarthritis. Amongst the patients with polyarthritis at 6 months that had presence of systemic features or polyarthritis at last follow-up, there were approximately twice as many non-Hispanic patients compared to Hispanic patients.

Similar to our findings, Sandborg *et al.* concluded that an active joint count and elevated platelet count at 3 months was predictive of joint damage at 2 years after diagnosis (29).

In contrast to our findings, Schneider *et al.* reported that the presence of persistent systemic features (fever or requirement for corticosteroids) and thrombocytosis at 6 months predicted the development of destructive polyarthritis (30), while Spiegel *et al.* reported that the same prognostic factors at 6 months predicted the development of a poor functional outcome (as measured by a Child Health Assessment Questionnaire [CHAQ] score  $\geq 0.75$  or the occurrence of a disease-associated death) (31).

We were unable to identify a predictive factor for "active disease". We expected polyarthritis to predict future development of "active disease" since the outcomes "polyarthritis" and "systemic features" are part of the criteria for disease activity in JIA and both outcomes shared the same predictive factor. However, the group with "active disease" includes patients with oligoarticular arthritis and patients with an elevated ESR or CRP. Inclusion of these

additional patients probably affected the results.

There were some potential limitations to this study. Ideally, a prospective study design should be used to assess long-term outcomes and prognostic factors. However, because JIA is a rare disease and S-JIA accounts for only 10% of all JIA cases (1), we needed to use a retrospective, multi-center approach to identify a sufficient number of patients in our study. As a result, there was missing data for some of the patients in the study population. Sixteen patients were excluded because of incomplete records. We were concerned that the exclusion of this group could potentially lead to sampling bias. Therefore, we performed a separate analysis on the available data of 4/16 patients to permit comparison with the study population. There was no difference between the two groups.

Clinically important events may have been missed because the study only collected data at specific time points during follow-up. This is a source of possible reporting bias. This may have led to under-reporting of rare events like MAS. The assessment of the incidence of systemic features may have been confounded by various influences on outcome over the past 30 years. We performed a subset analysis by excluding patients with onset of S-JIA before 1990. The results were not significantly different, with 30% of non-Hispanic patients demonstrating persistence of systemic features at 10 years of follow-up.

In conclusion, this study shows that in children with S-JIA, Hispanics have fewer systemic features over time while 40% of non-Hispanics have persistence of systemic features during follow-up. S-JIA patients with polyarthritis at 6 months are at high risk for development of systemic disease and polyarthritis. It will now be important to prospectively study an inception cohort of non-Hispanic and Hispanic children with S-JIA to see if these results can be duplicated. It is possible that children with S-JIA that demonstrate polyarthritis at 6 months may need early, more aggressive therapy in order to decrease their risk of chronic systemic and articular disease.

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