A Prospective Population Based Study on Outcome of Juvenile Chronic Arthritis in Costa Rica

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ABSTRACT. ***Objective.*** To study the disease process and outcome in an unselected group of patients with juvenile chronic arthritis (JCA).

Methods. From a population based study in San José, Costa Rica, 47 patients with JCA with disease onset from 1993 through 1995 were investigated after median duration of 4.1 yrs (range 2.9–4.9) (incidence group). Another 49 children with disease onset prior to 1993 and younger than 16 years of age on December 31, 1995 (cross sectional group) were also followed.

Results. In the incidence group, 4/47 children changed subtype during the course of the disease. All did so within 2 years from disease onset, and the same observation was made in the cross sectional group. Uveitis was described at onset in a single case, and no child developed uveitis later. In patients from the incidence group in the process of being transferred to adult rheumatology clinics, 48% were still taking medication. Patients who had involvement of proximal interphalangeal (PIP) joints at onset had an increased risk of being active or stable at followup (RR 12.3, 95% CI 1.4–108.3). A higher chance of no continuing disease activity at followup was observed in children with oligoarticular disease than in the other subtypes (RR 2.8, 95% CI 1.2–6.9).

Conclusion. Uveitis associated with antinuclear antibody positive JCA and psoriatic arthritis in Costa Rican children is uncommon, and the risk of developing uveitis remains low during the course of the disease. Involvement of PIP joints predicts an increased risk of continuing disease. The course of JCA in Costa Rican children is not milder than in Caucasian populations, since 48% of the patients showed persistent disease activity at the transition to adult care. (J Rheumatol 2002;29:174–83)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS EPIDEMIOLOGY OUTCOME COSTA RICA

The outcome of patients with juvenile chronic arthritis (JCA) has been the topic of many discussions. Our hypothesis was to test the reliability of the observation in some reports during the 1980s that, "80% of children with JRA [juvenile rheumatoid arthritis] can expect to be rid of inflammation when they reach adulthood"[1-3]. Several authors have critically challenged this theory[4-8], but there are few studies in unselected populations of patients concerning this issue[5,6] and none from a non-Caucasian setting.

The Costa Rican population has a mixed ancestral origin. At the time of the Spanish conquest, the country was scarcely populated by indigenous groups; many indigenous people died as result of the conquest. The remainder mixed over the centuries with the Spanish settlers, resulting in a population of high consanguinity. There is also a black population in Costa Rica, whose ancestors were "imported" as a labor force at the end of the last century. The current population is a mixture of all these groups.

Studies on outcome in JCA are difficult to evaluate and compare for many reasons: heterogeneity of the disease, differences in diagnostic criteria used, patient selection bias, the multidimensional and transitional nature of outcome, lack of consensus on the methods of assessing outcome, and differences in the length of followup and in the definition of remission[4,9-12]. In addition to these methodological difficulties, some differences between ethnic populations regarding incidence, prevalence, and subtype distribution of JCA have been described in epidemiological studies from different parts of the world[13-20]. The influence of genetic or environmental factors on those differences makes the perception of outcome even broader and more difficult.

The aim of this descriptive study was to investigate the disease process and outcome of JCA longitudinally in an unselected cohort of patients of Hispanic origin recruited from a population based epidemiological study[18]. The EULAR criteria (EULAR Standing Committee on Paediatric Rheumatology, Moscow, 1983) were used for inclusion and for classifying patients at onset and during the

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course of their disease. A cross sectional group of patients with JCA was also investigated and used as a hypothesis generator, and to answer some questions that might require longer disease duration.

In this paper, results from the disease onset and the disease process are presented. The multidimensional evaluation of outcome and the social and financial effects of JCA on this population will be presented in future reports.

MATERIALS AND METHODS

Criteria. The EULAR[21] criteria were used to define cases of JCA and to divide patients into subgroups at onset and followup. The onset type was determined 6 months after onset of symptoms. A diagnosis of JCA requires onset before 16 years of age, disease duration > 3 months, and elimination of diagnostic exclusion criteria. The following subgroups are distinguished according to EULAR: (1) onset with systemic features; (2) onset with polyarthritis in the absence of marked systemic features, ≥ 5 joints affected; (3) onset with arthritis affecting ≤ 4 joints — oligoarticular. Late onset oligoarticular JCA was defined as those cases with disease onset after 6 years of age, and early onset oligoarticular JCA was recognized as those with onset of arthritis below this age limit. Within these groups it is possible to identify children with probable juvenile ankylosing spondylitis (JAS), juvenile psoriatic arthritis (JPsA), and arthritis associated with inflammatory bowel disease (IBD)[21].

In this study, the diagnosis of JAS required the child to be HLA-B27+ and to have peripheral arthritis combined with radiological evidence of sacroiliitis and/or clinical evidence of sacroiliitis in combination with enthesitis. JPsA was defined as arthritis in combination with psoriasis diagnosed by a dermatologist, or arthritis and a positive family history of psoriasis in parents or siblings, and either dactylitis or nail abnormalities (nail pitting or onycholysis)[22]. To identify a case of arthropathy associated with IBD, an intestinal mucosal biopsy indicating ulcerous colitis or Crohn's disease was required.

The activity of the disease, according to EULAR, is divided into 4 groups: (1) active = increasing number of active joints irrespective of drug therapy; (2) stable = stable number of joints but requiring drug therapy; (3) inactive = no evidence of active synovitis and/or active extraarticular features and without drugs for < 2 years; (4) remission = no evidence of active synovitis and/or active extraarticular features and without drugs for ≥ 2 years.

Study area. This study was conducted in Costa Rica, a tropical Central American country with a population of about 3 million at the time of the study. Epidemiological research in Costa Rica is facilitated by the fact that, although it is a poor country, it is rather more developed socially than economically, distances are short, and the health care system is based on a social security system that de facto covers 100% of the population and provides free health care from primary to tertiary, specialized care. Thus, all children with a long standing complaint of any kind would go to the local doctor at the peripheral clinic or directly to the National Children's Hospital (NCH). All specialized pediatric care in the country takes place at NCH.

Patients were recruited from a population based epidemiological survey of JCA performed in the greater San José urban area during 1993–95[18]. San José is the capital of the country and urban San José consists of the 12 counties that together form this urban area. Further, it has a well developed chain of peripheral clinics belonging to the social security system, with both general practitioners, pediatricians, and special health teams called Equipos Básicos de Atención Integral (EBAIS; Specialized Teams for Basic Integral Health Attention). Personnel from EBAIS periodically visit every household in the area to investigate health problems in children, such as chronic diseases, including JCA. The NCH is located within the catchment area as are the 3 tertiary care hospitals with clinics for adult rheumatology.

Study population. The catchment population consisted of around 350,000 children (170,000 girls, 180,000 boys). This was roughly 30% of all children in Costa Rica (1,200,000). Since the last national population survey was done in 1984 the demographic data have been updated using estimations and projections of the population from the General Bureau of Statistics and Census[23].

Study groups. Two groups of patients were investigated; they were divided according to the methodological differences in the data collection.

Incidence group. This group consisted of patients who had onset of JCA from February 15, 1993, to February 15, 1995. They were collected from a previous prospective population based study[18] and they were followed until December 31, 1997 (outcome point). During this time period they were evaluated at least every 3rd month by the same investigator (OA). One girl with polyarticular onset JCA was excluded from the analysis since she did not complete followup as she had moved out of the country. This group represents an unselected longitudinally followed group of patients.

Cross sectional group. This group consisted of patients who had onset of their disease before February 15, 1993, and who were younger than 16 years of age at December 31, 1995. These patients were found in the previous epidemiological study[18], and the records from 1989–95 were also reviewed for all patients younger than 16 years seen at the Department of Immunology at NCH, and at the 3 departments of adult rheumatology located in the San José urban area. Probably some patients born between 1980 and 1989 and examined at the 4 hospitals during those years, but not later, were not included. Also, before 1990 most children older than 12 years of age were seen at adult departments of rheumatology.

Twenty-four patients out of the 74 who originally constituted the cross sectional group did not come to followup and one patient was excluded, as at time of followup she was reclassified as having overlap syndrome. In 13 of these patients, who did not come to followup, some general data were available in their medical records. Their median (range) age at onset was 8 years (1.6–15.9), the majority of them were oligoarticular onset type (85%), and 10 (77%) were girls.

The cross sectional group were patients collected partly retrospectively and partly prospectively.

The children were called to followup in the 3 months following December 31, 1995 (prevalence point) and all were evaluated by one of us (OA). The general characteristics of the study groups are presented in Table 1.

The cross sectional group had longer disease duration ($p < 0.00001$) and lower age at onset ($p = 0.003$) than the incidence group. There were no differences in median disease duration for girls and boys within each group. Among the cases with oligoarticular disease course, those with late onset predominated both in the incidence (75%) and cross sectional groups (56%).

The followup for both groups included clinical examination, laboratory investigations, and doctor's assessment of disease activity. A pediatric ophthalmologist followed all patients regularly. Complete ophthalmologic evaluations, including slit lamp examinations, were done every 3 months for antinuclear antibody (ANA) positive cases and every 6 months for the others.

Data related to medication were recorded in both study groups at the time of the followup evaluations.

The flow of patients in the epidemiological and followup studies is shown in Figure 1. The subgroup distribution at onset and at followup and the proportion of girls in each subgroup for the incidence and cross sectional groups are presented separately in Table 1.

In the incidence group, girls were older than boys at onset: 10.7 (1.9–15.9) vs 8.3 (0.9–13.7) years of age (median, range); $p = 0.049$.

The study was approved by the research ethical committee at NCH and all parents and patients older than 10 years of age gave oral informed consent.

Laboratory investigations. C-reactive protein (CRP) was analyzed using standard methods. A value > 10 mg/l was considered abnormal. Serum

Table 1. Number of patients, proportion of girls, median age at onset, median disease duration, disease onset type, subtype at followup, and proportion of girls per subtype in the incidence and cross sectional groups of children with JCA.

	Incidence Group		Cross Sectional Group	
N	47		49	
Girls, %	60		55	
Median age at onset, yrs (range)	10.3 (0.9–15.8)		5.2 (0.8–12.3)	
Median disease duration, yrs (range)	4.1 (2.9–4.9)		6.0 (3–12)	
Onset type	Number (%)	Girls, %	Number (%)	Girls, %
Polyarticular	10 (21)	60	8 (16)	37
Oligoarticular	27 (57)	59	37 (76)	57
Systemic	3 (6)	100	1 (2)	100
JAS	7 (15)	43	3 (6)	67
Subtype at followup				
Polyarticular	14 (30)	57	9 (18)	44
Oligoarticular	24 (51)	62	36 (73)	56
Systemic	2 (4)	100	0	0
JAS	7 (15)	43	4 (8)	75

JAS: juvenile ankylosing spondylitis.

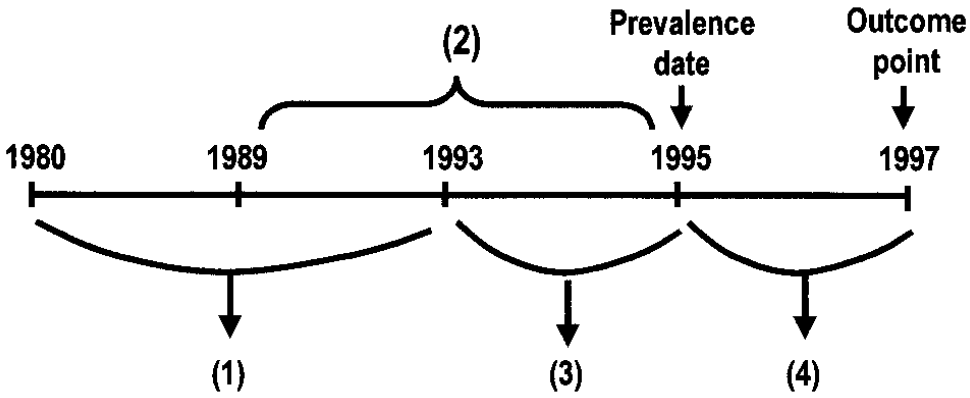

Figure 1. The flow of patients with JCA in the epidemiological and followup studies. 1. Cross sectional group: Patients with onset of disease before February 15, 1993, and younger than 16 years of age at the prevalence date, December 31, 1995. 2. Period of revision of charts for patients with the diagnosis of JCA seen at all centers in the study area with disease onset before February 1993. Number of cases detected = 74. 3. Incidence group: Patients with onset of disease between February 15, 1993, and February 15, 1995; n = 48. 4. Followup period. Number of incidence cases who completed followup = 47. Number of cross sectional cases who completed followup = 49.

immunoglobulin levels were determined by nephelometry. The normal ranges for immunoglobulin levels were set depending on age and sex in accord with published tables[24].

Sera were analyzed for IgM rheumatoid factor (RF) (nephelometry, QM300, Sanofi, Diagnostics Pasteur) and ANA (indirect immunofluorescence using HEp-2 cells). Values > 30 IU/ml for RF and > 1/32 for ANA were considered positive. In the incidence group, a child needed to have at least 2 positive tests 3 months apart during the first 6 months of observation to be judged ANA and RF positive, respectively[25]. In the cross sectional group, a single abnormal value was accepted for classification of the patient as ANA or RF positive.

HLA-B27 was analyzed using serological testing, but only for those who had enthesitis and/or clinical and/or radiological evidence of sacroiliitis and/or family history of spondyloarthropathies.

Radiographic examinations. Radiographic examinations were not performed routinely. Radiographs were taken only in those cases that showed persistent articular involvement at followup, and they were restricted to the affected joint(s). They were all evaluated by the same pediatric radiologist and classified as: normal; stage I = early changes (periarticular soft tissue swelling, periarticular osteoporosis, periosteal new bone formation); or stage II = advanced changes (cartilage destruction, bone destruction, bony ankylosis, large joint subluxation, epiphyseal fracture, vertebral compression fracture)[26].

Statistical methods. The chi-square test was used when comparing fractions. Fisher's exact test was used in 2×2 tables. Correlations were calculated using Spearman's rank correlation coefficient (r_s). Logistic regression was applied to identify predictors for continuing disease activity. Disease activity was dichotomized as active plus stable and inactive plus remission.

Age at onset was divided into 3 groups (0 to 6 years, 6–10, and > 10). Disease duration was split in 2 categories, < 6 years and ≥ 6 years. Odds ratios were calculated as approximations for risk ratios (RR). Limits of significance were set at 0.05 for all tests performed.

RESULTS

The Incidence Group

Data concerning patient's and doctor's delay and joint involvement at onset are presented only for the incidence group. The data from this group are considered reliable and less susceptible to memory bias than in the cross sectional group.

Patient and doctor delay. The delay from onset of symptoms to the first visit to a doctor (patient's delay) was usually short, median 3 months (range 0–32). In 3 patients (6.3%) the delay exceeded one year. The shortest duration was seen in the systemic group (median 1.0 mo, range 1–3), and the longest duration was seen in the JAS group (median 6.0 mo, range 1–32). There was no significant difference between the sexes. The median delay from the first visit to a doctor to the definitive diagnosis of JCA (doctor's delay) was 3.0 months (0–12 mo). In 2 cases (4.2%) the delay exceeded one year. The median doctor's delay was 1.5 months for the polyarticular group, 2 months for the systemic and JAS group, and 3.0 months for the oligoarticular group. There was no significant difference between the sexes.

Joint involvement at onset. The 4 most commonly affected joints during the first 6 months of disease were knee (62%), ankle (36%), and wrist and cervical spine (each 21%).

For patients with oligoarticular JCA, the most common disease pattern was asymmetrical oligoarthritis of the large joints of lower limbs (55%). The 3 joints most commonly affected were knees (70%), ankles (48%), and elbows (15%).

In the polyarticular subgroup the most common onset pattern was symmetrical polyarthritis of the large joints of upper and lower limbs (30%). The joints most often affected at onset were wrists and cervical spine (each 60%), followed by interphalangeal joints (50%). In the JAS group, 4 (57%) patients had asymmetrical oligoarthritis of large joints of lower limbs at onset. The sacroiliac joint and knee were the most commonly affected joints (71%). Six patients had enthesitis (86%).

Data from the disease process. Subgroup distribution at followup. As shown in Table 1, the median disease duration at followup for patients in the incidence group was 4.1 years. There were no significant differences regarding disease duration between JCA disease course subtypes.

Within the incidence group, 8.5% (4/47) of the children changed subgroup. In 27 children classified as having oligoarticular JCA at onset, 24 had an oligoarticular course and 3 turned into polyarticular at followup. Within the 3 cases classified as systemic at onset, 2 had a systemic and one a polyarticular course. The polyarticular group increased from 11 (21%) to 14 (30%); one patient from this group was lost to followup. The JAS group remained stable, with 7 patients at onset and at followup. No case of JPsA or IBD associated arthritis was found. All patients who changed subgroup did so within 2 years from disease onset.

Laboratory investigations at followup. CRP was > 10 mg/l in 14/41 (34%) children. Nine of 23 patients classified as active or stable and 5/24 of those classified as inactive or in remission had elevated CRP levels. Seven of the 14 patients with increased CRP values belonged to the polyarticular group; 6 of them were classified as active or stable. Serum immunoglobulin levels were analyzed in 45/47 children at followup. IgG was elevated in 10 patients. Five of them had polyarticular disease. Six of those patients were classified as active or stable. The majority of patients classified as active or stable at followup where IgG was measured had normal values (16/22). None had selective IgA deficiency.

IgM RF was tested in all incidence cases. Four patients were IgM RF positive, 2 classified as oligoarticular and 2 as polyarticular disease type. All RF positive cases were girls. The proportion of active cases at followup between the RF positive and RF negative cases did not show any statistically significant difference.

Three patients were ANA positive, one classified as oligoarticular and 2 as polyarticular disease at followup. Only one was a girl. No case of early onset ANA positive oligoarticular JCA associated with uveitis was found. HLA-B27 was tested only in those patients with clinical suspicion of spondyloarthropathies. Eight of 19 patients tested were positive. All but one of the HLA-B27 positive patients were classified as having JAS at followup. In the HLA-B27 negative group the majority (8/11) had a persistent oligoarticular course.

Radiographic examinations. Twenty-three patients (49%) had radiographic examinations at followup or during the preceding year. Sixty-one percent (14/23) of those examined showed no changes, 35% (8/23) showed stage I changes, and 4% (1/23) had stage II changes. Five of 9 patients who had radiological changes had polyarticular disease at followup.

Uveitis. The median time of ophthalmologic followup was 2 years. Only one single case of uveitis was found: a 7.5 year-old-girl with persistent ANA negative oligoarthritis and unilateral uveitis, which began 7 months before onset of JCA. At the last followup 4.1 years after onset of eye disease, she had bilateral involvement and severely impaired vision. Her joint disease was classified as inactive at that time. No case of acute symptomatic uveitis was found.

Heredity. Six patients reported rheumatic disorders in their parents or siblings: rheumatoid arthritis (RA) in their mothers in 3 cases (2 polyarticular, one oligoarticular), and oligoarticular JCA in one of their siblings in 2 patients with

oligoarticular disease. There was one patient with JAS whose father, mother, and older brother were undergoing treatment for JAS in an adult rheumatology clinic. There were no cases of first-degree relatives with psoriasis.

Disease activity. The total number of patients with active or stable disease at followup in this group was 23 (49%). Of patients in the process of being transferred to adult rheumatology clinics, 48% were still taking medication. The disease activity at followup in the incidence group according to JCA disease course type is presented in Figure 2.

Patients who had involvement of their proximal interphalangeal joints at onset had an increased risk of being active or stable at followup (RR 12.3, 95% CI 1.4–108.3). No such increased risk was found for patients who had involvement of cervical spine, knees, ankles, hips, or wrists at onset.

When data from onset (onset age, subtype at onset, and sex) were analyzed in a logistic regression model to look for predictors for no disease activity (disease activity was dichotomized as active + stable = continuing disease activity and inactive + remission = no disease activity), none was a predictor.

The regression analysis of disease process factors (disease duration, sex, subtype at followup, RF, and ANA) looking for predictors for no disease activity showed that those patients classified as having oligoarticular disease course type had a chance 2.8 times greater (95% CI 1.2–6.9) of being rid of disease activity at followup than those classified within the other subtypes. The rest were not significant covariates.

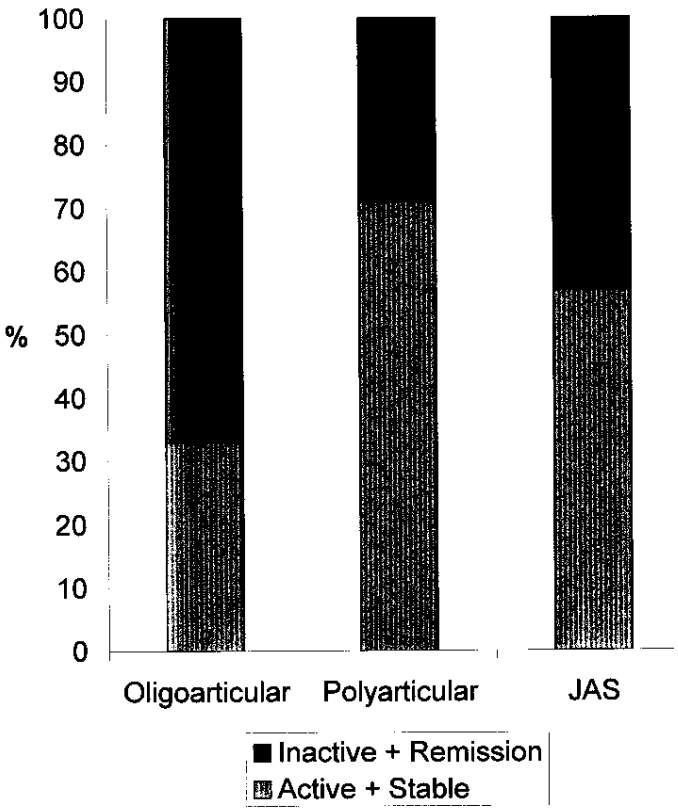

Figure 2. Disease activity at followup by subtype of JCA disease course in the incidence group of children with JCA.

There were no significant differences in the number of patients active or stable at followup in either boys or girls. We found no differences in the number of patients active or stable at followup in the 3 groups of age at onset (< 6 years, 6–10, and ≥ 6), neither boys nor girls.

The Cross Sectional Group

As this group of patients is a selected sample of prevalence cases in the study area, only selected data at followup and for the disease process are presented. The disease course type and the fraction of girls per subtype in the cross sectional group of patients are presented in Table 1.

Data from the disease process. The median disease duration at followup for the patients in the cross sectional group was 6.0 years (Table 1). There was no significant difference regarding disease duration between the different JCA disease course subtypes.

Only 2 of the 49 children followed in this group changed subgroup. One patient changed from oligoarthritis to polyarthritis and one child with oligoarthritis was classified as having JAS at followup. All changes of subgroup occurred within 2 years after disease onset.

Laboratory findings. CRP > 10 mg/l was found in 28% (13/46) of the children. There was no correlation between CRP and disease activity. Seven of the 13 patients with increased CRP values belonged to the polyarticular group. With the exception of the polyarticular group, the majority of patients in the other subgroups had negative CRP values. Serum immunoglobulin levels were analyzed in 43/49 children at followup. IgG was elevated in 11 patients. Within the polyarticular group, the majority of patients evaluated (6/8) had elevated IgG levels. This was not noted in the other JCA subgroups. Eight of the 11 patients with elevated IgG were classified as active or stable at followup. Three patients had selective IgA deficiency.

Eight patients were RF positive, 3 of them were girls. Five had a polyarticular disease course type and it was oligoarticular in 3. Symmetrical polyarthritis at followup was seen in 2 RF positive cases, one girl and one boy. Five patients who were RF positive were still taking medication after median disease duration of 6.5 years (range 5.7–12 yrs). Only 3 patients were ANA positive, all were boys and were classified as oligoarticular disease course type. Only one had arthritis onset before 6 years of age. No case of early onset ANA positive oligoarticular JCA associated with uveitis was found. Four of 13 children tested were HLA-B27 positive, all were classified as having JAS at followup.

In the HLA-B27 negative group the majority (7/9) had a persistent oligoarticular course.

Radiological findings at followup. Only 35% of cases were examined. Seventy percent of those examined showed no changes. Four patients (23.5%) showed stage I and one patient stage II changes.

Uveitis. In the cross sectional group, 3 patients developed uveitis at some time during the disease course; all of them were classified as oligoarticular JCA, ANA and HLA-B27 negative, and all had asymptomatic onset of uveitis. Two were boys and one was a girl. The girl had uveitis in connection with arthritis onset. In one of the boys the time of onset of uveitis was unknown. He already had mild sequelae in one eye at the first ophthalmologic evaluation and remained asymptomatic at followup. The other boy developed a bilateral uveitis 7 months after arthritis onset and required ophthalmologic surgery.

Disease activity. The total number of patients with active or stable disease at followup in this group was 27 (55%). The proportion of patients with continuing disease activity at followup was 47% (17/36), 67% (6/9), and 100% (4/4) for the oligoarticular, polyarticular, and JAS disease course types, respectively.

Medication. Beginning as late as 1990 a uniform medical treatment policy was developed. It called for first-line treatment with a nonsteroidal antiinflammatory drug (NSAID) followed by methotrexate (MTX) if the initial response was unsatisfactory. Before 1990 MTX was rarely used, and medication was based mainly on NSAID and oral steroids.

Medication in the incidence group. The medication used by this group is summarized in Table 2. Four of 14 patients who received MTX within the first year after disease onset were still classified as active at followup, while the rest showed no signs of activity of JCA. All but one were still taking MTX at followup. No patient used intravenous immunoglobulin or cyclosporin A during the first 12 months of the disease. Nine out of 11 (82%) of the patients with polyarticular disease who were still taking medication at followup received MTX. In the oligoarticular group, 8/25 (32%) patients were taking medication at followup. All of them were receiving NSAID only. Seven patients (15%) received intraarticular corticosteroid injections at some time during the disease course. All the injections were given in the knee joint, except in 2 cases.

Medication in the cross sectional group. No patient from this group received MTX in the first year after disease onset (Table 2). At followup, 7 (14%) patients were taking MTX. The majority of patients using MTX at the last visit belonged to the polyarticular group (71%).

Two patients used slow acting antirheumatic drugs (one hydroxychloroquine, one oral gold). No patient received penicillamine, sulfasalazine, cyclosporin A, or intravenous immunoglobulin. There were no significant differences in the use of oral steroids at onset or in chronic dependence on steroids compared with the incidence group.

Six of the patients (12%) received intraarticular corticosteroid injections at some time during the disease course. All injections were given in the knee joint.

DISCUSSION

Over the past decade, the goals of studying outcome in JCA have expanded to include questions such as the identification of factors to support the selection of therapies early in the disease course, how to minimize side effects from therapy, how to maintain function and quality of life, and cost-effectiveness.

Lately, significant improvements have been made in recognizing biological differences between JCA subtypes[27,28]. These findings underline the need to also eluci-

Table 2. Treatment at the first year after disease onset and at followup in the incidence and cross sectional groups.

Medication	Incidence Group, n = 47		Cross Sectional Group, n = 49	
	n	%	n	%
First year after disease onset				
No medication	1	2	0	0
NSAID only	34	72	41	84
Oral steroids	11	23	8	16
Methotrexate	14	30	0	0
SAARD	0	0	2	4
At followup				
No medication	22	51	22	45
NSAID only	13	28	20	41
Methotrexate only	5	11	3	6
Methotrexate + NSAID or oral steroids	6	14	4	8
SAARD	0	0	0	0
Chronic dependence on steroids	3	6	2	4

NSAID: nonsteroidal antiinflammatory drugs, SAARD: slow acting antirheumatic drugs.

Table 3. Reports on followup of patients with JCA: number of patients (percentages) with continuing disease activity at followup by type of study, location, and duration of followup.

Study (year)	Type of Study	Location	Years of Followup, Median	Percentage of Patients with Continuing Disease Activity at Followup
Calabro[37,38] (1968, 1989)	Prospective, Clinic based	New Jersey, USA	7–10, 25	43, 9
Hanson[39] (1977)	Clinic based	California, USA	10	55
Karup Pedersen[3] (1987)	Retrospective, Hospital based	Copenhagen, Denmark	3–30 (mean 10)	35
Levinson[4] (1991)	Prospective, Clinic based	Cincinnati, USA	15–20	45
Andersson-Gäre[5] (1995)	Prospective, population based	Southwestern Sweden	2–22 (7)	49
Soesbergen[40] (1997)	Retrospective	Amsterdam, Netherlands	0.2–28.2 (mean 7.8)	71
Flatø[41] (1998)	Prospective, clinic based	Oslo, Norway	10	36
Minden[42] (2000)	Retrospective, clinic based with a population based cohort	Berlin, Germany	1–15 (mean 7.4)	55
Present study	Prospective, population based	San José, Costa Rica	Incidence group: 2.9–4.9 (4.1)	49
			Cross sectional group: 3–12 (6)	55

date possible differences in outcome for each JCA subtype in various settings.

Costa Rica is a transitional society with very good basic health indexes, and is now facing the problem of how to handle chronic disorders such as JCA[29,30]. The Costa Rica care system provides excellent opportunities for population based studies, and certain differences from Caucasian populations have been described in studies on epidemiology of JCA in this population[18,31]. A 2 year population based prospective study on incidence and prevalence of JCA in Costa Rica showed lower rates than those reported in other studies with comparable designs[18,32-35]. The incidence rates of ANA positive oligoarticular JCA and of uveitis in ANA positive cases were substantially lower in Costa Rica[17,18,33]. A similar lack of ANA positive cases and uveitis associated with arthritis in young girls has been reported in India[19] and South Africa[36]. In our setting, no case of JPsA was found and no heredity for psoriasis was observed. All these findings point to biological differences in this Latin American population in comparison with other populations[33-35].

Table 3 summarizes some followup studies of children with JCA. The present survey is to our knowledge the first population based prospective study on outcome of JCA in a non-Caucasian population. The length of the followup period in the cross sectional group was similar to other studies[5,42], while it was shorter in the incidence group. Still, reporting the data from the incidence group now was considered important, since at the last followup evaluation 50% of the cohort was in the process of being transferred to adult rheumatology clinics, where the chance of further followup by the authors would diminish. In addition, it has been shown that JCA subtype switching and the development of uveitis usually occur early in the disease course[43-45].

The references cited in Table 3 are difficult to compare due to methodological differences and differences in the length of followup, but especially because of disagreements in the definition of remission. Thus we preferred to present the percentages of patients with continuing disease activity rather than the proportion of those in remission. The definition of "continuing disease activity," here defined as active or stable disease according to EULAR (EULAR Standing Committee on Paediatric Rheumatology, Moscow, 1983), differs in the articles cited. The EULAR disease activity criteria used in this report have been criticized, since the need of ongoing medication is based on a physician's recommendation and may not reflect the real activity of the disease. Another consideration is that flares may occur late as well as early after the onset of remission[46]. However, the

EULAR criteria set was used in the present study because it allowed us to make comparisons with methodologically similar published material.

Our findings support previous observations[4,5,39,41,42] that oppose the paradigm that "80% of children can expect to be rid of inflammation when they reach adulthood"[1]. In our incidence group, about half the patients were classified as having active or stable disease at the last followup evaluation. Among patients older than 13 years of age, who are in the process of being transferred to adult rheumatology clinics, the percentage of patients still taking medication was 48%. We attempted to determine predictors at onset for continuing disease activity at followup in our population. Regarding disease process factors (disease duration, sex, disease course type, RF, ANA), we found that the persistent oligoarticular group had the most favorable outcome, with a 2.8 times greater chance than the other disease course types of being rid of disease activity at followup. This is in accord with previous reports[4,5,41,42,47].

We found that patients who had involvement of their proximal interphalangeal joints at onset had an increased risk of continuing disease activity at followup. These joints are mainly affected in polyarticular cases. In previous reports, polyarticular JCA at onset has been related with a high risk of continuing disease activity at followup[5,42]. Other covariates such as female sex, long disease duration, and IgM RF positivity described in other studies[5,41] were not found to be significant in this report, probably because of the small number of cases involved. As pointed out in some publications[48,49], the disease definition of juvenile arthritis must take into consideration not only onset types, but also disease course types, since many patients change patterns of disease[5,50,51]. In our study, the percentage of patients who changed subgroup from onset to followup was low (8.5%). Reports from Norway[41] and Sweden[5] showed percentages of subtype switching during the disease course of 21% and 37%, respectively. The differences compared with our material can be explained by the scarcity of extended oligoarticular cases and the lack of JPsA or IBD in our population. Another factor was the shorter disease duration in our group compared with the Scandinavian studies. However, since in the cross sectional group no change of subgroup was found after 2 years of disease onset, the influence of the disease duration is probably less. In agreement with this observation, Guillaume, *et al* reported recently that most cases of polyarticular progression occurred during the first 2 years of disease[43].

Andersson-Gäre and Fasth demonstrated in Caucasian children that 6% of their patients classified at onset as having oligoarticular JCA later turned into JAS, JPsA, or arthritis associated with IBD[5]. This was not observed in the present study, where only one patient from the cross sectional group had turned into JAS at followup. The difference with the Swedish report may be explained by the absence of cases of JPsA in our population and the stricter definition of JAS used in this study. It is possible that in the longterm followup of our patients with oligoarticular course more cases of JAS will emerge. Some of these issues will be clarified through further immunogenetic studies.

In our population, there was a lack of the typical ANA positive early onset JCA in girls; consequently, uveitis associated with arthritis is rare[18]. From our data, we also show that the risk of developing uveitis remained low throughout the course of the disease.

The value of laboratory investigations in the evaluation of disease activity and prediction of functional outcome in JCA is controversial[5,52,53]. We found that they did not give much guidance on group levels of disease activity or subtype. Few cases had positive ANA or RF, and few had elevated levels of activity indicators such as CRP or immunoglobulins.

The absence of uniform treatment policies during the whole study period makes it difficult to analyze the effects of medication on the natural history of JCA. Since 1990, MTX has been used in Costa Rican children with JCA. In the incidence group it was introduced early in the course of the disease. The prescription of MTX changed through time in our population, with a wider and earlier use in recent years. The influence of this changing pattern in medication on disease outcome could not be measured in the present material.

This report confirms our previous observation of the differences in the clinical spectrum of JCA between our Costa Rican population and Caucasian children. These differences are reflected in a different pattern of age distribution, differences in subtype distribution, and also low frequency of uveitis and ANA positivity during the disease course. The prognosis regarding continuing disease activity at followup is more favorable for the patients with oligoarticular course. Involvement of proximal interphalangeal joints gives an increased risk of continuing disease. The course of JCA in Costa Rican children is not milder than in Caucasian populations, since half the patients in this study showed persistent disease activity at the time of transition to adult care.

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