

Juvenile Psoriatic Arthritis: Longterm Outcome and Differentiation from Other Subtypes of Juvenile Idiopathic Arthritis

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ABSTRACT. *Objective.* To compare outcomes in patients with juvenile psoriatic arthritis (PsA) with those in patients with other juvenile idiopathic arthritis (JIA) subtypes, and to evaluate characteristics and genetic markers that may differentiate PsA from other subtypes of JIA.

Methods. JIA patients first admitted between 1980 and 1985 were clinically examined after a median of 15 years. Health status was reassessed by the Short Form-36 Health Survey (SF-36) after a median of 23 years. Of 336 JIA patients, 31 (9%) had PsA.

Results. Predictors of PsA were psoriasis in the patient (OR 12.06, $p = 0.004$) or first-degree relative (OR 30.86, $p < 0.001$), dactylitis (OR 10.97, $p < 0.001$), and ankle/toe arthritis (OR 3.04, $p = 0.038$) within the first 6 months. HLA-DRB1*11/12 status (OR 2.69, $p = 0.040$) and onset after age 6 years (OR 4.41, $p = 0.004$) differentiated PsA from either oligoarthritis or polyarthritis. After 15 years, PsA patients had poorer physical health than healthy population controls ($p = 0.001$). After 23 years, the SF-36 physical scores were poorer in PsA patients than in those with either oligoarthritis or polyarthritis ($p < 0.045$). The need for disease-modifying antirheumatic drugs and/or anti-tumor necrosis factor agents was present in 33% of PsA versus 8% in oligoarthritis and 13% in either oligoarthritis or polyarthritis patients ($p < 0.001$ and $p = 0.002$, respectively).

Conclusion. In addition to a history of psoriasis, dactylitis, ankle or toe arthritis, and DRB1*11/12 in children with JIA indicate the likelihood of PsA, a subtype associated with unfavorable outcome. (J Rheumatol First Release Feb 1 2009; doi:10.3899/jrheum.080543)

Key Indexing Terms:

JUVENILE IDIOPATHIC ARTHRITIS PSORIATIC ARTHRITIS OUTCOME ASSESSMENT
PROGNOSTIC FACTORS PEDIATRIC RHEUMATOLOGY
HUMAN LEUKOCYTE ANTIGEN

Onset of arthritis precedes the onset of psoriasis in a significant proportion of children with psoriasis-associated arthritis, often by several years^{1,2}. The Vancouver criteria for juvenile psoriatic arthritis (PsA) were developed to facilitate the diagnosis of PsA before the onset of psoriasis². However, substantial clinical and genetic heterogeneity within PsA has been found¹⁻³. In order to recognize children with a single disease entity, juvenile PsA was classified as a category of juvenile idiopathic arthritis (JIA) by the

International League of Associations for Rheumatology (ILAR)⁴. Modifications of these criteria became necessary due to a large proportion of patients with unclassified arthritis⁵. Only 2 studies have described the characteristics of patients with PsA according to the ILAR criteria^{6,7}. Huemer, *et al* found that in addition to dactylitis, the pattern of joint involvement facilitated the identification of children with PsA and suggested that this factor should be considered as a modification of the ILAR classification⁶. Stoll, *et al* questioned whether the restriction of the diagnosis of PsA according to the ILAR criteria reflects substantial clinical differences compared to the Vancouver criteria⁷.

Several HLA-DRB1, HLA-DPB1, and HLA-B27 genes have been associated with susceptibility to various JIA subtypes. Studies on the HLA associations in PsA have provided conflicting results and no antigen has been consistently raised or decreased^{2,3,8,9}. Few studies have addressed the outcome in PsA; most studies are based on limited patient numbers, and the duration of followup has varied from 2 to 11 years^{1,2,6,9}. Most studies have focused on progression from oligo- to polyarthritis^{1,6,10}, while some authors have included the need for disease-modifying antirheumatic

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drugs (DMARD) and joint erosions as dimensions of outcome^{1,9}. Differences in the classification criteria used make the results difficult to compare. To date, the multidimensional outcomes of PsA have not been assessed.

Our aim was to assess the longterm outcome in juvenile PsA and to compare the outcome in PsA patients with that in those with other JIA subtypes. The health status in PsA patients was compared with that of controls from the general population. We also evaluated patient characteristics, clinical features, and HLA-DRB1 and DPB1 alleles that may differentiate PsA from other subtypes of JIA during the first 6 months of disease.

MATERIALS AND METHODS

Patients and controls. Three hundred thirty-six patients with JIA first admitted to the Division of Pediatric Rheumatology, Rikshospitalet Medical Center, between January 1980 and September 1985 were examined by clinical, laboratory, radiographic, and health status assessments after a median of 14.9 years (range 11.7–25.1, mean 15.0 ± 2.1) of disease duration. Thirty-one patients (9%) had PsA, 23 (7%) systemic arthritis, 95 (28%) persistent oligoarthritis, 42 (13%) extended oligoarthritis, 57 (16%) rheumatoid factor (RF)-negative polyarthritis, 11 (3%) RF-positive polyarthritis, 55 (16%) enthesitis-related arthritis (ERA), and 22 patients (6%) had undifferentiated JIA. Medical records were reviewed for variables related to onset of disease. After a median of 22.8 years of disease duration (range 19.6–31.7, mean 22.9 ± 2.0), a mailed questionnaire was sent to the 336 patients; questionnaires were completed by 28 (90%) PsA patients, 110 (80%) oligoarthritis patients, 45 (66%) polyarthritis patients, 40 (73%) of those with ERA, 17 (74%) with systemic arthritis, and 18 (82%) with undifferentiated arthritis. Characteristics of the total group of JIA patients have been described^{11–13}.

The patients' disease subtypes according to the ILAR criteria for JIA were determined at the followup visit after a median of 14.9 years of disease duration based on the clinical examination and chart reviews⁵. Thus, PsA was diagnosed in a child with arthritis and psoriasis, or arthritis and at least 2 of the following: psoriasis in a first-degree relative and dactylitis or nail pitting or onycholysis. Patients with signs of other JIA subtypes were excluded. Psoriasis in a patient or first-degree relative was an exclusion criterion for all other disease subtypes, except for 5 patients with ERA with signs of spondyloarthritis (SpA) that indicated exclusion from the psoriatic arthritis group¹³. It has been suggested that if psoriasis is considered an exclusion criterion for ERA, no signs of SpA should be present¹⁴. At the followup visit, the patients were also classified according to the Vancouver criteria for juvenile PsA².

Individuals matched for age, sex, and geographic region ($n = 279$) were randomly selected from the national population register to serve as controls for the health status assessments at the time of the 15-year followup visit. A family history of psoriasis was not obtained from the controls. Two hundred ninety-five unrelated healthy individuals, randomly selected from the Norwegian Bone Marrow Donors Registry, served as controls for the genomic typing. The whole study was approved by the Regional Ethics Committee for Medical Research.

Clinical examinations and chart reviews. The clinical examinations after a median of 14.9 years' disease duration included assessments of the numbers of affected (swollen or mobility-restricted) joints. Psoriasis in a patient was defined as psoriasis confirmed by a dermatologist. Disease onset was the date that arthritis was documented by a physician.

Remission was defined according to the preliminary criteria for clinical remission in JIA whereby no active arthritis, fever, rash, serositis, splenomegaly, generalized lymphadenopathy or active uveitis was present, the erythrocyte sedimentation rate (ESR) or C-reactive protein level was normal, and the physician's global assessment of disease activity indicated

that clinical disease quiescence had been present for at least 12 months, while the patient had not received any antiarthritis or antiuveitis medication¹⁵. The patients were judged to be in remission regardless of the presence or absence of active psoriasis.

Assessments of health status. The Medical Outcome Study Short Form-36 Health Survey (SF-36) was completed by patients after a median of 14.9 and 22.8 years of disease duration and by controls at the time of the 15-year followup. This 36-item questionnaire measures 2 distinct components: the physical component summary (PCS) scale, consisting of the health dimensions physical functioning, role limitations due to physical health, bodily pain, and general health, and the mental component summary (MCS) scale, consisting of vitality, social functioning, role limitation due to emotional problems, and mental health¹⁶. Low scores indicate that health status is poor and high scores indicate good health. The questionnaire has been translated and culturally adapted for use by Norwegians¹⁷.

The Health Assessment Questionnaire (HAQ) was used to measure physical disability in JIA patients¹⁸. The HAQ is a 20-item questionnaire measuring physical function in 8 areas: dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and activities. The scores range from 0 to 3, where 0 means no difficulty with daily activities and 3, unable to perform these activities. The HAQ has been used in several studies of young adults with JIA¹⁹.

Radiographic examinations. Radiographs of hips (anterior-posterior view), ankles (lateral view), and sacroiliac joints (anterior-posterior view) of all patients were obtained at the 15-year visit. They were independently read by 2 radiologists. The scoring system included grade 0 to 5, where grade 2 to 5 denote definite arthritic changes^{11,13,20}.

Genomic typing for HLA. HLA-DRB1 typing was performed by the non-isotopic method based on polymerase chain reaction (PCR) and hybridization with oligonucleotide probes labeled with biotin^{21,22}. HLA-DPB1 alleles were typed by sequence-specific oligonucleotide probing using PCR^{21,22}. The HLA-DRB1 associations studied included DRB1*01 (also called DR1), DRB1*04 (DR4), DRB1*11/12 (DR5), and DRB1*08 (DR8) alleles. The HLA-DPB1 associations studied included DPB1*02 and DPB1*03 alleles. HLA-B27 was determined by serologic testing.

Statistics. Differences in characteristics between 2 patient groups and between PsA patients and controls were tested with the Student 2-tailed unpaired t test for continuous variables and the chi-square test for categorical variables. Differences between more than 2 patient groups were tested by one-way ANOVA for continuous variables. Changes within a patient group over time were tested by Student 2-tailed paired t test.

In order to identify possible predictors of the diagnosis of PsA in the whole cohort of JIA patients (total $n = 336$) and factors that differentiated patients with PsA from those with either oligoarthritis or polyarthritis (total $n = 236$), logistic regression analyses were performed. The classification of PsA versus all other JIA subtypes and versus either oligoarthritis or polyarthritis was used as the dependent variable. In the PsA group, 68% of patients had oligoarticular onset, which was comparable to the 67% of patients with oligoarticular onset in either the oligoarthritis or the polyarthritis group. First, univariate logistic regression analyses were performed on the relation between PsA and patient characteristics (sex, onset age), genetic markers previously associated with childhood arthritis (HLA-B27, DRB1, and DPB1), and disease variables assessed within the first 6 months of disease duration [onset type, dactylitis, nail pitting, numbers of affected joints, persistently elevated ESR, antinuclear antibody (ANA), small-joint disease, and finger, wrist, hip, knee, ankle or toe involvement]. Psoriasis in a patient or first-degree relative was analyzed as an independent variable in the regression models including all JIA patients, but could not be included in the analyses of factors that differentiated PsA from either oligoarthritis or polyarthritis patients because these factors were exclusion criteria for the classification of oligoarthritis and polyarthritis.

Subsequent multivariate logistic regression analyses with backward deletion of possible predictors were performed to identify early determinants of PsA. Sex, age at onset, and candidate factors that were associated

with the classification of PsA in the univariate tests ($p < 0.10$) were analyzed. Data on the strength of the associations were expressed as odds ratios (OR) and 95% confidence intervals (95% CI). Hosmer-Lemeshow goodness-of-fit statistics were used to assess how well the logistic regression models fit the data (p values > 0.05 were considered to fit).

P values ≤ 0.05 or 1.00 not included in the 95% CI (for the OR) were considered statistically significant. SPSS version 15 software was used for all analyses.

RESULTS

Patient characteristics. The 31 patients with PsA comprised 7 men (23%) and the mean age at the followup visit was 23.3 ± 3.9 years, compared with 84 men (30%) and mean age at followup visit 22.8 ± 4.9 years in the healthy controls (not statistically significant). In patients with PsA, the mean age at disease onset was 11.4 ± 2.4 years in boys and 7.3 ± 3.4 years in girls ($p = 0.006$; Figure 1). The PsA patients were older than those with oligoarthritis and younger than those with ERA (Table 1).

Genetic markers. In patients with PsA HLA-DRB1*08 and HLA-DRB1*11/12 were increased compared with healthy controls (Table 2). HLA-DRB1*11/12 was increased and HLA-B27 was decreased in PsA compared with ERA patients. HLA-DPB1*03 was decreased in PsA patients compared with those with RF-negative polyarthritis. HLA-DRB1*11/12 was present in 4 (50%) of the PsA patients aged ≤ 6 years at disease onset and 5 (22%) of those with onset after the age of 6 (nonsignificant). The frequency of HLA-B27 was comparable in the 2 age groups (data not shown).

Early determinants of PsA. Psoriasis in a first-degree relative (OR 30.86, $p < 0.001$) or in the patient (OR 12.06, $p = 0.004$), dactylitis (OR 10.97, $p < 0.001$), and toe and/or

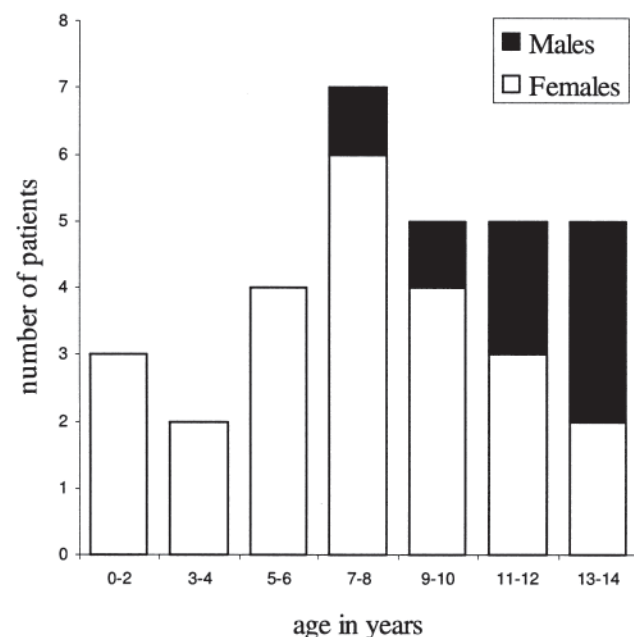


Figure 1. Age distribution at disease onset in boys and girls with juvenile psoriatic arthritis.

ankle involvement (OR 3.04, $p = 0.038$) within the first 6 months were early predictors of PsA in the total cohort of patients with JIA (Table 3). HLA-DRB1*11/12 predicted the development of PsA in 4 patients; however, the association was only statistically significant in the univariate and not in the multivariate analysis. The multivariate regression model supported the data well (chi-square = 2.082, $df = 4$, $p = 0.721$).

Onset after age 6 years (OR 4.41, $p = 0.004$), dactylitis within the first 6 months (OR 14.93, $p < 0.001$), and presence of DRB1*11/12 (OR 2.69, $p = 0.040$) differentiated PsA from either oligoarticular or polyarticular JIA. This regression model also supported the data well (chi-square = 4.130, $df = 3$, $p = 0.248$). Further, PsA was associated with toe and/or ankle arthritis (OR 2.62, $p = 0.022$) and hip involvement (OR 3.39, $p = 0.035$) at disease onset in the univariate, but not the multivariate, analyses. The frequency of hip arthritis in PsA was comparable in boys and girls and in patients aged ≤ 6 years at onset and older children (data not shown). PsA patients and those in either the oligoarthritis or the polyarthritis group had a similar frequency of oligoarticular onset (68% and 67%, respectively).

Patient and disease characteristics in ILAR-included and ILAR-excluded patients with PsA. Eleven (26%) of 42 patients met the Vancouver classification criteria for juvenile PsA, but were excluded from the PsA category under the ILAR criteria for JIA (Table 4).

Psoriasis started before the arthritis in 3 PsA patients (10%) and between the onset of arthritis and the first 6 months of disease duration in 3 patients (10%). Six PsA patients (19%) developed psoriasis between 6 months and median 14.9 years of disease duration. The duration between the onset of arthritis and the onset of psoriasis was median 3.8 years (range 0.2–12.3). Cumulatively, 12 (39%) of the 31 PsA patients developed psoriasis, compared with 4 (33%) of the 11 ILAR-excluded patients that met the Vancouver criteria for PsA, and none of the 22 patients with undifferentiated arthritis (Table 5). Twenty-three (74%) of the ILAR-included PsA patients had a history of psoriasis in a first-degree relative, compared with 1 (8%) ILAR-excluded patient and 19 (86%) of those with undifferentiated arthritis ($p < 0.001$ and p not significant, respectively). None of the ILAR-included and 4 (33%) of the ILAR-excluded patients developed radiographic sacroiliitis ($p < 0.01$). The ILAR-included PsA patients also had statistically significantly less inflammatory back pain and HLA-B27 than the ILAR-excluded patients. Patients with undifferentiated arthritis had less dactylitis, small joint arthritis, ankle or toe arthritis, psoriasis-like rash, and nail pitting than the patients with PsA. Six (26%) of 23 PsA patients with psoriasis in a first-degree relative developed psoriasis, compared with none of 19 patients with undifferentiated arthritis and a family history of psoriasis.

Clinical and radiographic outcome. After a median of 14.9

Table 1. Characteristics of patients with juvenile PsA and other subtypes of JIA. Values are numbers (%) of patients or mean \pm standard deviation.

| | PsA, n = 31 | Oligoarthritis, n = 137 | Polyarthritis, n = 68 | ERA, n = 55 | Undifferentiated Arthritis, n = 22 | Systemic Arthritis, n = 23 |
|--|----------------|----------------------------|--------------------------|-------------------|---------------------------------------|-------------------------------|
| Male sex | 7 (23) | 29 (21) | 20 (35) | 36 (66)*** | 5 (23) | 10 (59) |
| Age at onset, range 1.7–15.2 yrs | 8.2 \pm 3.6 | 6.0 \pm 4.1** | 8.4 \pm 4.2 | 11.1 \pm 2.8*** | 6.9 \pm 4.7 | 6.2 \pm 4.4 |
| Age at followup visit, range 13.7–31.3 yrs | 23.3 \pm 3.9 | 21.2 \pm 4.6* | 23.1 \pm 4.2 | 26.5 \pm 3.0*** | 22.4 \pm 5.2 | 20.7 \pm 4.5* |
| Onset age > 6 yrs | 23 (74) | 62 (45)** | 35 (61) | 51 (93)* | 11 (50) | 11 (48) |
| Disease duration at followup visit, range 11.7–25.1 yrs | 15.0 \pm 1.8 | 15.2 \pm 2.3 | 14.7 \pm 1.8 | 15.2 \pm 2.3 | 15.5 \pm 2.4 | 14.5 \pm 1.3 |
| Disease duration at postal survey, range 16.1–31.7 yrs [†] | 22.9 \pm 2.0 | 22.8 \pm 2.2 | 22.4 \pm 2.1 | 22.2 \pm 2.5 | 22.6 \pm 2.2 | 21.6 \pm 1.8* |
| Oligoarticular arthritis at onset | 21 (68) | 137 (100)*** | 0*** | 40 (73) | 19 (86) | 16 (70) |
| Polyarticular course | 20 (65) | 42 (31)*** | 68 (100)*** | 37 (67) | 11 (50) | 13 (57) |

*** p < 0.001 versus PsA; ** p < 0.01 versus PsA; * p < 0.05 versus PsA (not statistically significant when corrected for numbers of comparisons). PsA: psoriatic arthritis, ERA: enthesitis-related arthritis. [†] n = 28 PsA, n = 110 oligoarthritis, n = 45 polyarthritis, n = 40 ERA, n = 18 undifferentiated arthritis, n = 17 systemic arthritis.

Table 2. Numbers of patients (%) with various HLA alleles in juvenile PsA compared with other subtypes of JIA and healthy controls.

| | PSA, n = 31 | Persistent Oligoarthritis, n = 95 | Extended Oligoarthritis, n = 42 | RF-negative Polyarthritis, n = 57 | RF-positive Polyarthritis, n = 11 | ERA, n = 55 | Systemic Arthritis, n = 23 | Undifferentiated Arthritis, n = 21 | Controls, n = 295 |
|------------|----------------|---|---------------------------------------|---|---|----------------|----------------------------------|--|----------------------|
| HLA-B27 | 6 (19) | 16 (17) | 5 (12) | 11 (19) | 1 (9) | 47 (85)*** | 2 (9) | 1 (5) | 35 (12) |
| DRB1*01 | 8 (26) | 14 (15) | 18 (43) | 5 (9)* | 5 (46) | 13 (24) | 5 (22) | 3 (14) | 57 (19) |
| DRB1*04 | 6 (19) | 16 (17) | 6 (14) | 15 (26) | 6 (55)* | 20 (36) | 9 (39) | 8 (38) | 99 (34) |
| DRB1*11/12 | 9 (29) | 17 (18) | 7 (17) | 8 (14) | 1 (9) | 6 (11)* | 3 (13) | 2 (10) | 32 (11)** |
| DRB1*08 | 8 (26) | 36 (38) | 12 (29) | 20 (35) | 1 (9) | 16 (29) | 2 (9) | 7 (33) | 20 (7)*** |
| DPB1*02 | 9 (29) | 48 (51)* | 15 (36) | 13 (23) | 1 (9) | 12 (22) | 5 (22) | 7 (33) | 56 (19) |
| DPB1*03 | 4 (13) | 12 (13) | 9 (21) | 24 (42)** | 4 (36) | 15 (27) | 6 (26) | 4 (19) | 59 (20) |

PsA: psoriatic arthritis, ERA: enthesitis-related arthritis, RF: rheumatoid factor. *** p < 0.001 versus PsA; ** p < 0.01 versus PsA; * p < 0.05 versus PsA (not statistically significant when corrected for numbers of comparisons).

years of disease duration, psoriasis, nail pitting, and dactylitis were statistically significantly more frequent in PsA patients than in those with all other JIA subtypes, while ANA was more frequent in PsA patients than in those with ERA (p = 0.029; Table 6). Current remission without medication for at least 12 months was found in 17 PsA patients (55%). The duration of the current remission was median 7.9 years (range 1.6–15.4). Twelve PsA patients (39%) had one or more periods of previous remission, together lasting for a median of 2.8 years (range 0.5–9.0). Radiographic joint erosions were found in 7 PsA patients (23%) compared to 31 (46%) of those with polyarthritis (p = 0.029).

After a median of 22.8 years of disease duration, 10 (33%) patients with PsA still used DMARD and/or anti-tumor necrosis factor (TNF) agents compared with 9 (8%) of those with oligoarthritis and 19 (13%) with either oligoarthritis or polyarthritis (p < 0.001 and p = 0.002, respectively). In the PsA group, 6 patients used methotrexate, one sulfasalazine, and 4 used anti-TNF agents. The need for DMARD and/or anti-TNF agents in ILAR-included PsA patients was comparable with that in ILAR-excluded patients and those with undifferentiated arthritis (data not shown). The remission rate, frequency of joint erosions, and

need for DMARD and/or anti-TNF agents in PsA patients with psoriasis was not significantly different from those without psoriasis (data not shown).

Health status after a median of 14.9 and 22.8 years of disease duration. After a median of 22.8 years of disease duration, abnormal HAQ disability indexes (scores > 0.12) were found in 14 (45%) PsA patients compared with 62 (30%) of those with either oligoarthritis or polyarthritis (p = 0.098). Two PsA patients (7%) had moderate disability (HAQ scores > 1.25, but \leq 2.0) and none had severe disability (HAQ > 2.0).

The physical functioning as assessed by the mean HAQ and SF-36 PCS scores deteriorated from a median of 14.9 to a median of 22.8 years after onset in patients with PsA (p = 0.033 and p = 0.039, respectively), but not in those with other JIA subtypes (Table 7). After median 14.9 years, the patients with PsA had poorer physical health than individuals from the general population as measured by the SF-36 PCS (p < 0.001), but not poorer than in patients with other subtypes of JIA. After a median of 22.8 years, the SF-36 PCS scores were poorer and the levels of pain intensity were higher in patients with PsA compared with those with either oligoarthritis or polyarthritis (p = 0.045 and p = 0.050,

Table 3. Early determinants for differentiation between juvenile PsA (n = 31) and all other JIA subtypes (n = 305) as well as oligoarticular or polyarticular JIA (n = 205).

| Variables Assessed at Disease Onset | Univariate Analyses* | | | Multivariate Analysis** | | |
|---|----------------------|-------------|---------|-------------------------|-------------|---------|
| | OR | 95% CI | p | OR | 95% CI | p |
| PsA vs all other subtypes (n = 336) | | | | | | |
| Female sex | 1.67 | 0.70–4.01 | 0.249 | | | |
| Onset age ≥ 6 yrs | 1.97 | 0.85–4.55 | 0.112 | | | |
| Psoriasis in first-degree relative | 26.35 | 10.84–64.07 | < 0.001 | 30.86 | 10.68–89.14 | < 0.001 |
| Psoriasis in patient | 14.40 | 4.11–50.51 | < 0.001 | 12.06 | 2.26–64.40 | 0.004 |
| DRB1*11/12 | 2.43 | 1.05–5.61 | 0.038 | 3.09 | 0.86–9.90 | 0.085 |
| Dactylitis | 9.90 | 3.93–24.95 | < 0.001 | 10.97 | 2.96–40.62 | < 0.001 |
| Small-joint arthritis | 2.06 | 0.98–4.33 | 0.050 | | | |
| Toe arthritis | 2.17 | 0.97–4.85 | 0.061 | | | |
| Ankle arthritis | 1.99 | 0.94–4.22 | 0.071 | | | |
| Toe and/or ankle involvement | 2.73 | 1.22–6.13 | 0.015 | 3.04 | 1.07–8.64 | 0.038 |
| Finger arthritis | 2.03 | 0.95–4.33 | 0.067 | | | |
| PsA vs oligo-/polyarthritis (n = 236)*** | | | | | | |
| Female sex | 1.08 | 0.44–2.65 | 0.872 | | | |
| Onset age ≥ 6 yrs | 2.63 | 1.13–6.16 | 0.026 | 4.41 | 1.61–12.12 | 0.004 |
| DRB1*11/12 | 2.13 | 0.90–5.04 | 0.085 | 2.69 | 1.05–6.91 | 0.040 |
| Dactylitis | 3.40 | 3.19–22.10 | < 0.001 | 14.93 | 4.79–47.54 | < 0.001 |
| Ankle arthritis | 1.92 | 0.89–4.12 | 0.096 | | | |
| Toe arthritis | 2.09 | 0.91–4.80 | 0.082 | | | |
| Toe and/or ankle involvement | 2.62 | 1.15–5.96 | 0.022 | | | |
| Hip involvement | 3.39 | 1.09–10.54 | 0.035 | | | |

* DRB1*01, DRB1*04, DPB1*02, DPB1*03, wrist or knee arthritis, nail pitting, ANA, persistently elevated ESR, and cumulative numbers of affected joints within the first 6 months of disease were not associated with diagnosis of PsA in univariate analyses ($p \geq 0.10$, data not shown). ** Results of multiple logistic regression analysis identifying determinants of diagnosis of PsA. Variables associated with PsA in univariate analyses ($p < 0.10$) were included. *** Psoriasis in patient or relative is an exclusion criterion from oligoarthritis and polyarthritis and could not be analyzed as an independent variable in the analyses of factors that differentiated PsA from either oligoarthritis or polyarthritis.

Table 4. Numbers of patients with juvenile PsA according to Vancouver and ILAR criteria and reason for exclusions.

| Vancouver Criteria | Vancouver PsA | PsA | Oligoarthritis | ILAR Category | | Undifferentiated |
|-------------------------------------|---------------|-----|----------------|---------------|------|------------------|
| | | | | Polyarthritis | ERA* | |
| Total no. of patients | 42 | 31 | 2 | 3 | 5 | 1 |
| No. included under ILAR criteria | 31 | 31 | | | | |
| No. excluded under ILAR criteria | 11 | | 2 | 3 | 5 | 1 |
| Reason for exclusion | | | | | | |
| Psoriasis-like rash | 4 | | 1 | 2 | 1 | |
| B27-positive male onset-age > 6 yrs | 3 | | | | 3 | |
| Psoriasis in 2nd-degree relative | 2 | | 1 | 1 | | |
| Meets criteria for AS | 1 | | | | 1 | |
| Positive IgM rheumatoid factor | 1 | | | | | 1 |

* 5 patients excluded from PsA because they met inclusion criteria for ERA had psoriasis in patient or first-degree relative and thus met the criteria for more than one category. However, since they all had signs of spondyloarthritis they were analyzed together with the ERA patients.

respectively), but not compared with ERA patients. The health status in patients with systemic arthritis or undifferentiated JIA or PsA according to the Vancouver but not the ILAR criteria did not differ significantly from those with PsA (data not shown).

DISCUSSION

In our study, physical health at last assessment in patients with juvenile PsA was poorer than in controls and patients

with either oligoarticular or polyarticular JIA, but not poorer than those with ERA. Physical limitations worsened from a median of 15 to 23 years of disease duration in PsA patients only. The need for DMARD and/or anti-TNF agents after 23 years was greater in patients with PsA than in those with oligoarthritis and tended to be greater than in those with polyarthritis. A history of psoriasis in a patient or first-degree relative, dactylitis, and ankle or toe arthritis within the first 6 months were early predictors of PsA in children

Table 5. Characteristics of ILAR-included patients with juvenile PsA, and patients excluded from the ILAR PsA category. Values are number (%) of patients or mean \pm standard deviation.

| | Included PsA Patients, n = 31 | Vancouver-included, but ILAR-excluded patients [†] , n = 11 | Patients with Undifferentiated Arthritis, n = 22 |
|--|-------------------------------------|--|--|
| Female sex | 7 (23) | 6 (50) | 17 (77) |
| Age at onset, mean \pm SD, yrs | 8.2 \pm 3.6 | 10.2 \pm 4.4 | 7.0 \pm 4.6 |
| Psoriasis in first-degree relative | 23 (74) | 1 (8)*** | 19 (86) |
| HLA-B27 | 6 (19) | 6 (50)* | 1 (5) |
| Variables assessed within first 6 months | | | |
| Psoriasis confirmed by a dermatologist | 6 (19) | 3 (25) | 0* |
| Psoriasis-like rash | 1 (4) | 1 (8) | 0 |
| Nail pitting | 1 (3) | 4 (33)* | 0 |
| Dactylitis | 10 (32) | 4 (33) | 1 (5)** |
| Oligoarthritis | 21 (68) | 6 (50) | 19 (86) |
| Any small joint | 16 (52) | 6 (50) | 4 (18)* |
| Ankle or toe arthritis | 22 (71) | 4 (33)* | 5 (23)** |
| Variables assessed median 15 yrs after onset | | | |
| Psoriasis confirmed by a dermatologist | 12 (39) | 4 (33) | 0** |
| Psoriasis-like rash | 6 (19) | 5 (46) | 0* |
| Nail pitting | 8 (26) | 4 (33) | 0** |
| Dactylitis | 13 (42) | 4 (33) | 1 (5)** |
| Polyarthritis | 20 (65) | 10 (83) | 11 (50) |
| Joint involvement | | | |
| Any small joint | 20 (65) | 9 (75) | 9 (41) |
| Any large joint | 30 (97) | 12 (100) | 20 (91) |
| Hip | 7 (23) | 4 (33) | 2 (9) |
| Knee | 27 (87) | 12 (100) | 17 (77) |
| Ankle | 22 (71) | 8 (67) | 8 (36)* |
| Toe | 13 (42) | 7 (58) | 3 (14)* |
| Elbow | 10 (33) | 8 (67) | 8 (36) |
| Wrist | 13 (42) | 8 (67) | 9 (41) |
| Finger | 19 (61) | 8 (67) | 8 (36) |
| Chronic uveitis | 6 (19) | 0 | 7 (32) |
| Enthesitis | 1 (3) | 2 (17) | 1 (5) |
| Inflammatory back pain | 0 (0) | 4 (33)** | 1 (5) |
| Reduced Schober's test | 4 (13) | 3 (25) | 5 (24) |
| Radiographic sacroiliitis | 0 | 4 (33)** | 1 (5) |

[†] Patients fulfilled the Vancouver but not the ILAR criteria for juvenile PsA. * $p < 0.05$, ** $p < 0.01$ and

*** $p < 0.001$ versus ILAR-included PsA patients.

with all JIA subtypes. Additionally, onset after the age of 6 years and HLA-DRB1*11/12 status differentiated PsA patients from those with either oligoarthritis or polyarthritis. PsA patients were younger at onset, comprised fewer men, and were more often HLA-DRB1*11/12-positive and less often HLA-B27-positive than those with ERA. To date, this is the first description of longterm outcome and early predictors of diagnosis in juvenile PsA according to the ILAR classification criteria.

The patients with PsA were part of a cohort of all new JIA cases who attended hospital during a 5-year period. Being selected from a referral center, our study group probably comprised patients with a more severe disease than patients recruited from the general population. On the other hand, the cohort of JIA patients was previously found to have characteristics comparable to those of JIA patients in epidemiological studies^{11,19,23}. Our results are limited by the low numbers of PsA patients and the retrospective appli-

cation of classification criteria and assessment of variables from disease onset. However, since prospective outcome studies will require many years to carry out, retrospective studies may provide important information on the outcome in PsA patients and the ability of the ILAR criteria to identify disease entities with homogenous features.

Patients with juvenile PsA had more physical limitations, as assessed by the SF-36 PCS, than patients with either oligoarthritis or polyarthritis after a median of 23 years and controls at the time of the 15-year followup. Physical limitations, according to the HAQ and the SF-36, worsened from a median of 15 to 23 years in our PsA patients, but not in patients with other JIA subtypes. The magnitude of the change of the HAQ disability indexes in PsA was in the range for clinically important worsening²⁴. This result is in accord with the tendency to disease progression found in patients with oligoarticular juvenile PsA^{2,8,10}. Although it was statistically significant, one might question whether the

Table 6. Clinical and radiographic outcome in patients with juvenile PsA and other subtypes of JIA. Values are number (%) of patients or mean \pm standard deviation.

| | PsA, n = 31 | Oligoarthritis, n = 137 | p vs PsA | Polyarthritis, n = 68 | p vs PsA | ERA, n = 55 | p vs PsA |
|--|-----------------|----------------------------|----------|--------------------------|----------|-----------------|----------|
| Variables assessed within first 15 yrs after onset | | | | | | | |
| Psoriasis confirmed by a dermatologist | 12 (39) | 0 | < 0.001 | 0 | < 0.001 | 1 (2) | < 0.001 |
| Nail pitting | 7 (23) | 4 (3) | < 0.001 | 2 (3) | < 0.001 | 4 (7) | 0.041 |
| Dactylitis | 13 (42) | 9 | < 0.001 | 2 (3) | < 0.001 | 3 (6) | < 0.001 |
| Enthesitis | 1 (3) | 1 (0) | NS | 1 (0) | NS | 24 (44) | 0.001 |
| Positive ANA | 10 (32) | 51 (37) | NS | 19 (28) | NS | 7 (13) | 0.029 |
| Uveitis | 6 (19) | 27 (20) | NS | 11 (16) | NS | 11 (20) | NS |
| Variables assessed median 15 yrs after onset | | | | | | | |
| Total cumulative no. of affected joints | 12.7 \pm 13.2 | 5.2 \pm 6.1 | 0.004 | 22.5 \pm 13.2 | 0.001 | 11.6 \pm 12.6 | NS |
| No. of mobility-restricted joints, range 0-68 | 3.4 \pm 8.2 | 2.3 \pm 5.2 | NS | 9.7 \pm 11.6 | 0.009 | 4.6 \pm 9.0 | NS |
| Remission without medication at least 1 yr | 17 (55) | 74 (54) | NS | 29 (43) | NS | 24 (44) | NS |
| Inactive disease* | 20 (65) | 93 (70) | NS | 32 (47) | NS | 27 (49) | NS |
| Hips, radiographic grade \geq 2 | 6 (19) | 16 (12) | NS | 21 (31) | NS | 14 (26) | NS |
| Ankles, radiographic grade \geq 2 | 5 (16) | 23 (17) | NS | 25 (37) | 0.038 | 12 (22) | NS |
| Peripheral joints, grade 3-5 | 7 (23) | 18 (13) | NS | 31 (46) | 0.029 | 14 (26) | NS |
| Radiographic sacroiliitis | 0 | 0 | NS | 0 | NS | 19 (36) | < 0.001 |
| Using antirheumatic drugs 23 yrs after onset** | | | | | | | |
| Still on DMARD | 8 (29) | 9 (8) | 0.003 | 8 (18) | NS | 7 (13) | NS |
| On anti-TNF agents | 4 (14) | 4 (3) | 0.050 | 4 (9) | NS | 3 (8) | NS |
| On DMARD and/or anti-TNF agents | 10 (33) | 9 (8) | < 0.001 | 10 (22) | NS | 9 (18) | NS |
| On NSAID | 8 (29) | 25 (23) | NS | 8 (18) | NS | 14 (35) | NS |
| On prednisolone | 4 (14) | 2 (2) | 0.016 | 3 (7) | NS | 1 (3) | NS |

* Remission with or without medication for at least 6 months, ** n = 28 for PsA, n = 40 for ERA, n = 110 for oligoarthritis, n = 45 for polyarthritis. PsA: psoriatic arthritis, ERA: enthesitis related arthritis, NS: not statistically significant, ANA: antinuclear antibodies, DMARD: disease modifying antirheumatic drugs, TNF: tumor necrosis factor, NSAID: nonsteroidal antiinflammatory drugs.

Table 7. Health status after a median of 14.9 years and 22.8 years of disease duration in patients with juvenile PsA, patients with other JIA subtypes, and controls. Values are mean (95% confidence interval).

| | PsA | Oligo- or Polyarthritis | p vs PsA | ERA | p vs PsA | Controls | p vs PsA |
|------------------------|------------------|-------------------------|----------|------------------|----------|------------------|----------|
| Disability (HAQ) | | | | | | | |
| 15 yrs after onset | 0.21 (0.06–0.36) | 0.27 (0.20–0.34) | NS | 0.38 (0.23–0.53) | NS | | |
| 23 yrs after onset | 0.37 (0.18–0.56) | 0.27 (0.20–0.34) | NS | 0.31 (0.14–0.47) | NS | | |
| p for change over time | 0.033 | NS | | NS | | | |
| Health status (SF-36) | | | | | | | |
| Physical summary score | | | | | | | |
| 15 yrs after onset | 49.9 (46.1–53.7) | 50.4 (49.1–51.8) | NS | 46.4 (42.5–50.3) | NS | 54.5 (53.7–55.4) | 0.001 |
| 23 yrs after onset | 46.3 (41.7–50.8) | 50.6 (49.0–52.2) | 0.045 | 48.6 (44.6–52.6) | NS | | |
| p for change over time | 0.039 | NS | | NS | | | |
| Mental summary score | | | | | | | |
| 15 yrs after onset | 52.6 (49.8–55.4) | 52.7 (51.4–54.0) | NS | 51.2 (48.1–54.4) | NS | 49.9 (48.7–51.0) | NS |
| 23 yrs after onset | 51.6 (47.0–56.2) | 51.2 (49.5–52.8) | NS | 47.3 (43.9–50.7) | NS | | |
| Pain* | | | | | | | |
| 15 yrs after onset | 2.40 (1.91–2.90) | 2.26 (2.08–2.44) | NS | 2.88 (2.47–3.30) | NS | 2.04 (1.90–2.18) | NS |
| 23 yrs after onset | 2.79 (2.26–3.31) | 2.27 (2.07–2.48) | 0.050 | 2.85 (2.40–3.30) | NS | | |

N = 31 for PsA, n = 205 for oligo- or polyarthritis, and n = 55 for ERA at 15 years and n = 28 for PsA, n = 155 for JIA and n = 40 for ERA at 23 years followup. Controls were selected from the general population, matched for sex age and region for the total cohort of JIA patients. * Likert scale, range 1 (no bodily pain) to 6 (very strong bodily pain). PsA: psoriatic arthritis, ERA: enthesitis-related arthritis, HAQ: Health Assessment Questionnaire, range 0 (no disability) to 3 (very severe disability); SF-36: Short Form-36 Health Survey; values < 50 indicate physical or mental health poorer than average. NS: not statistically significant.

change in the SF-36 PCS is clinically significant. The minimal important difference of the SF-36 has not been determined, but the responsiveness seems to be comparable with that of the HAQ in adults with RA²⁵. The low frequency of

moderate or severe disability in our PsA patients is in agreement with results from Hamilton, *et al* (7% in functional class III or IV), but contrasts with the higher frequency found by Robertson, *et al* (30% in functional class III or

IV)^{8,9}. The longterm need for treatment with DMARD and/or anti-TNF agents, as associated with PsA in our study, is a marker of disease severity. It cannot be completely ruled out whether skin disease influenced the indication for these drugs in our patients with PsA. However, the substantial need for DMARD is in accord with most previous studies of juvenile PsA^{1,8,9}.

About half of our PsA patients were in remission after 15 years and 65% had inactive disease. Almost one-fourth had developed joint erosions. The rate of erosive disease was comparable with that found by Southwood, *et al*² after a median of 6 years, and lower than the results after 9 years described by Hamilton, *et al*⁹. The frequency of inactive disease has ranged from 34% to 60%^{1,2,8,10}. Differences in the definition of remission or inactive disease will have influenced the results. The new criteria for remission in JIA used in our study have not previously been used in PsA¹⁵.

None of our patients with PsA had developed radiographic sacroiliitis or inflammatory back pain even though all patients were radiographically assessed after a median of 15 years. However, 5 patients with psoriasis or a family history of psoriasis in a first-degree relative, including 3 patients with radiographic sacroiliitis, were excluded from the PsA group because of signs of SpA¹⁴. One-third of the patients that fulfilled the Vancouver but not the ILAR criteria for PsA had radiographic sacroiliitis, and one-fourth had inflammatory back pain. Compared to the Vancouver classification, the ILAR classification restricted the diagnosis of PsA particularly in patients with juvenile SpA. This reduction of numbers of patients available for studies of juvenile PsA may not reflect substantive clinical differences, according to one study⁷. On the other hand, it has been suggested that children with signs of SpA should be included in the ERA group rather than excluded from ERA because of a family history of psoriasis¹⁴. A low frequency of SpA in juvenile PsA has been found in one study⁸. However, frequencies up to 47% have been described by others^{1,2}. Incomplete radiographic assessments and a short disease duration may have influenced the low frequency of SpA found in the first study⁸.

Psoriasis in a first-degree relative predicted juvenile PsA with the highest OR in our study. Psoriasis in the patient added independent contribution to the correct classification of PsA patients. These results emphasize the importance of psoriasis in both the patient and a first-degree relative as an inclusion criterion for juvenile PsA^{5,8}. Dactylitis at onset was an important determinant for early differentiation of PsA from oligo- or polyarticular JIA in our study, as suggested by others^{6,10}.

HLA-DRB1*11/12 was increased in patients with PsA compared with controls from the general population and ERA patients in our study. Further, this factor was higher in PsA than in all other JIA subtypes and differentiated PsA from either oligoarthritis or polyarthritis. Ansell, *et al* found

an increase of DR5 in 26 patients with juvenile PsA with early onset³. An increase of DR5 has also been found in pauciarticular juvenile rheumatoid arthritis, particularly in those with uveitis^{26,27}. However, no increase of DR5 was found in 50 juvenile PsA patients studied by Robertson, *et al*⁸ and 28 patients studied by Hamilton, *et al*⁹. The ILAR criteria for classification of JIA were applied in our study, while the Vancouver criteria for juvenile PsA were used in previous studies^{2,5}. Our study is limited by the small sample size, and further studies from different populations are needed in order to evaluate whether the ILAR criteria identify a group of PsA patients with specific HLA associations.

Toe or ankle arthritis within the first 6 months was a determinant for PsA in our study and PsA was associated with small-joint arthritis in the univariate, but not the multivariate analysis. These results are in line with the previous finding that small-joint disease is more frequent in oligoarticular PsA than in other oligoarticular JIA⁶.

We found that onset after age 6 years differentiated PsA from either oligoarthritis or polyarthritis. The mean age of onset was higher than in most previous studies and variations in the results may have been influenced by the different classification criteria used^{2,6,8,10}. The presence of psoriasis-like rash is included in the Vancouver but not in the ILAR criteria^{2,5}. This may have influenced the higher age at onset in our study, because skin lesions may be more subtle or atypical in younger children^{7,28}. On the other hand, exclusion of patients with signs of juvenile SpA according to the ILAR criteria⁵ should have decreased the mean age of onset in our patients. One might question whether our PsA group still comprised patients, particularly boys with late-onset disease, that may have had juvenile SpA. However, in addition to the absence of sacroiliitis, there was no increase of HLA-B27, enthesitis, or hip arthritis in our patients with late-onset PsA. Recently it was suggested that juvenile PsA according to the Vancouver criteria comprises 2 distinct populations, one characterized by early onset, female sex, and positive ANA, and another with older patients and a tendency to have axial joint disease¹⁰. The lack of a peak of girls with early-onset arthritis and a lower frequency of ANA in our PsA patients compared to those previous studies may suggest that the ILAR criteria include fewer girls with early-onset ANA-positive arthritis, a patient group that also may have features in common with early-onset pauciarticular juvenile rheumatoid arthritis^{2,6,8,10,26}.

Patients with juvenile PsA shared characteristics and genetic markers that were different from other JIA subtypes. Longterm disease progression with worsening of physical limitations was found in patients with PsA, but not in those with other JIA subtypes. However, there was considerable overlap between PsA and other JIA subtypes, particularly regarding joint distribution, remission rates, and the development of joint erosions. Further prospective studies of large patient populations are needed in order to evaluate

whether the ILAR criteria classify a PsA group that represents a relatively homogenous disease entity.

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