Prognostic Factors in Juvenile Rheumatoid Arthritis: A Case-Control Study Revealing Early Predictors and Outcome After 14.9 Years

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ABSTRACT. ***Objective.*** To describe the physical and psychosocial outcome in patients with juvenile rheumatoid arthritis (JRA), compared with subjects in the general population, and to determine patient characteristics, HLA alleles, and disease variables within the first 6 months of disease onset that predict persistent disease, joint erosions, and physical disability.

Methods. A cohort of 268 (85%) of 316 patients with JRA first admitted to the hospital between 1980 and 1985 were examined after a median of 14.9 years (range 11.7–25.1) of disease duration. Controls matched for age, sex, and geographic region were randomly selected from the general population. Patients' medical records were retrospectively reviewed. Clinical examinations and radiographs of the hips, ankles, and affected joints were obtained. HLA-DRB1 and DPB1 alleles were determined by genotyping and HLA-B27 by serologic testing. Physical and psychosocial health status was assessed using the Short-Form Health Survey (SF-36) and the Health Assessment Questionnaire (HAQ).

Results. At followup, 133 patients with JRA (50%) were in remission, 63 (24%) had developed joint erosions, and 93 (36%) had impaired physical functioning (HAQ > 0.0). Patients had greater disability, more bodily pain, and poorer general health than controls. Comparable levels of education, social function, and mental health were found, but the patients had higher rates of unemployment than controls (19% vs 7%; $p < 0.001$). Predictors of persistent disease and joint erosions were: young onset age and large numbers of affected joints, long duration of elevated erythrocyte sedimentation rate (ESR), and positive IgM rheumatoid factor (RF) within the first 6 months. Additionally, persistent disease was predicted by the presence of DRB1*08, and joint erosions were predicted by symmetric arthritis and DRB1*08 and HLA-B27 in combination. DRB1*01 was a predictor of joint erosions in the pauciarticular onset type (n = 163). Predictors of physical disability were: female sex, symmetric arthritis, hip joint involvement, long duration of elevated ESR and IgM RF.

Conclusion. Compared with healthy controls, patients with JRA had impaired physical health and lower employment rates after more than 11 years of disease duration. Elevated ESR, extensive and symmetric arthritis, positive IgM RF, DRB1*08, DRB1*01, HLA-B27 and DRB1*08 in combination, early onset, and female sex were early risk factors for an unfavorable outcome. (J Rheumatol 2003;30:386–93)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS PROGNOSIS RISK FACTORS
DISABILITY RADIOGRAPHS

Juvenile rheumatoid arthritis (JRA) is a chronic inflammatory disorder that affects about 0.1% of children[1]. JRA is a potential cause of longterm impairment, discomfort, and disability, but may also remit with no or minor sequelae[2-5]. Persistent disease after 6–10 years has been found in 23–67% of patients[2,3,6]. The frequency of joint erosions has varied from 25 to 68%[2,6,7], and 5–28% of the patients have been found to have severe disability after 7–10 years[2,6,7]. The variation in results may have been influenced by differences in patient selection, methods for assessing outcome, criteria for remission, and treatment[3,4,6]. Studies of the outcome after more than 10 years of disease are few and rarely include assessments of clinical status and radiographic changes[3,4,6].

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Supported by the Research Council of Norway.

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Submitted March 14, 2002; revision accepted August 23, 2002.

The Health Assessment Questionnaire (HAQ) and the Childhood HAQ are disease-specific instruments that have been used to assess disability in a number of studies of patients with JRA[4-9]. Generic instruments that allow comparison of health status between different diseases and with the normal population have been developed recently[10]. One study compared the health status of 44 JRA patients with that of 102 healthy controls[4].

The use of new and efficacious treatment modalities in JRA emphasize the need for early identification of patients at risk of an unfavorable outcome[11]. HLA polymorphism has been associated with various subtypes of JRA[12,13]. Its influence on the development of disability was studied in 227 American and Italian patients, but no genetic predictors were found[14]. Some clinical and immunological determinants of outcome have been found, but few early predictors have been recognized[3,6,7,15]. The results of previous studies may have been influenced by the small, heterogeneous patient samples[3,6,7,15] or limited assessments of disease outcome[14].

We previously assessed 10-year outcome and predictive factors in 72 patients with JRA or juvenile spondyloarthropathy (SpA) admitted to hospital between 1985 and 1986[6]. The present study includes a cohort of 268 patients with JRA first admitted between 1980 and 1985 and examined after a median of 14.9 years of disease duration. During this period, it was estimated that about 70% of Norwegian children with chronic arthritis were admitted to Rikshospitalet University Hospital[16]. Our aim was to describe the radiographic, physical, and psychosocial outcome in patients with JRA and to compare their functional and social status with that of subjects in the general population. We also wished to identify genetic, demographic, and disease variables at disease onset that predict persistent disease, joint erosions, and disability.

MATERIALS AND METHODS

Patients and controls. Two hundred sixty-eight (85%) out of 316 children with JRA first admitted to Rikshospitalet University Hospital between January 1980 and September 1985 were examined after a median of 14.9 years (range 11.7–25.1) of disease duration. Their medical records were retrospectively reviewed for information about the disease onset. The median disease duration prior to admission was 2.7 months (range 0.1–98.9). For patients admitted more than 6 months after disease onset (n = 63), information on the onset was obtained from the charts of their local pediatrician and/or rheumatologist.

Forty-eight (15%) of the 316 first admissions were not included in the study. Seven patients (2%) had died by the time of followup, 23 patients (7%) had left the country or could not be found, and 18 patients (6%) chose not to participate. The participants were comparable to those who did not participate with regard to sex, onset type, age on first visit, and duration of symptoms before admission (data not shown).

Two hundred sixty-eight individuals matched for age, sex, and geographic region were randomly selected from the national population register to serve as controls for the sociodemographic variables and health status. Two hundred ninety-five unrelated healthy individuals, randomly selected from the Norwegian Bone Marrow Donors Registry, were used as controls for the genomic typing. The study was approved by the Regional Ethics Committee for Medical Research.

Classification. JRA was defined as meeting the American College of Rheumatology (ACR) criteria for the classification of JRA[17]. Patients with juvenile SpA at followup (n = 69), defined as having juvenile ankylosing spondylitis, syndrome of seronegative enthesopathy and arthropathy, juvenile psoriatic arthritis, or arthritis associated with inflammatory bowel disease (IBD), were excluded[16]. Onset of disease was defined as the date that arthritis or systemic features were documented by a physician. Pauciarticular JRA was divided into persistently pauciarticular (4 or fewer affected joints during the total period of followup) and extended pauciarticular JRA (4 or fewer affected joints within 6 months of disease duration and more than 4 thereafter). Polyarticular onset JRA (involvement of more than 4 joints within the first 6 months) was subdivided into IgM rheumatoid factor (RF) positive and IgM RF negative polyarthritis.

Clinical examination and chart reviews. Patients were examined by one of the authors (BF, GL, OV, or DS) at followup. The clinical examination included an assessment of number of active (swollen or tender and mobility restricted) and number of mobility restricted joints[17,18]. The examiners were blinded to information about the radiographic and genetic examinations at followup. Symmetric arthritis was defined as arthritis that was predominantly symmetrical.

The definition of remission was based on the preliminary ACR criteria for remission in RA except that the time limit was increased. Thus 5 or more of the following criteria had to have been fulfilled for at least 2 years: morning stiffness not exceeding 15 minutes, no fatigue, no joint pain, no joint tenderness, no swelling in joints or tendon sheaths, and ESR < 20[19]. No antirheumatic medication was to have been given during the last 2 years.

Laboratory variables. Elevated ESR was defined as > 15 mm/h[20]. Positive IgM RF was defined as titers ≥ 1:64 by the Rose-Waaler test measured at least twice. Antinuclear antibody (ANA) titer ≥ 1:32, measured at least twice by indirect immunofluorescence using mouse liver sections as substrate, was considered positive.

Assessments of health status. The HAQ was used to measure physical disability in 258 (96%) of the JRA patients at followup[8]. This 20 item questionnaire measures physical function in 8 areas: dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and activities. Disability was scored from 0 to 3, where 0 means no difficulty with daily activities and 3 means unable to perform these activities[12]. The HAQ has been used in several studies of young adults with JRA[4-6].

Patients (n = 258) and matched controls (n = 258) completed the 36 item Short-Form Health Survey (SF-36) at followup[10]. The SF-36 measures 8 health dimensions: physical functioning (10 items), role limitations due to physical health (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role limitation due to emotional problems (3 items), and mental health (5 items). This generic instrument allows comparisons between the health status of patients with different diseases and controls from the general population. Each dimension was scored from 0 to 100, where 0 means poor and 100 means excellent health[10]. The SF-36 has been evaluated and used in patients with various diseases[4,10], and the questionnaire has been translated and culturally adapted for use by Norwegians[21].

A 14 item version of the Hopkins Symptom Checklist (HSCL) was used to measure mental distress in the patients (n = 258) and controls (n = 258)[22]. The HSCL score ranges from 1 (no mental distress) to 4 (severe mental distress). Scores above 1.75 for females and 1.67 for males are considered to be within the clinical range[23].

Radiographic examinations. Radiographs of the hips and ankles of 254 patients (95%) were obtained at followup. Pelvic radiographs were taken to exclude patients with sacroiliitis[16]. The radiographs were examined independently by each of 2 radiologists (VJ, KD) blinded to patient identification and without access to earlier radiographic, clinical, or laboratory data. In cases of discrepancies, the radiographs were reexamined jointly by the 2 radiologists and a final conclusion was reached. Radiographs of other affected joints were taken when clinically indicated in 261 patients (97%) during their disease course and/or at followup.

The hips were examined from the anterior-posterior and the ankles from the lateral view. Radiographs of peripheral joints were graded according to the Dale radiographic classification system for JRA: grade 0 (normal joints), grade 1 (juxtaarticular osteoporosis and/or periarticular soft tissue swelling), grade 2 (growth disturbance), grade 3 (growth abnormality and marginal bony erosions), grade 4 (deformation and severe erosions), and grade 5 (gross destruction and deformation)[24]. Joint erosions were defined as being grade 3, 4, or 5.

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[25]. The HLA-DRB1 associations studied were DR1 (DRB1*01), DR4 (DRB1*04), DR5 (DRB*11 and *12), and DR8 (DRB1*08) alleles. HLA-DPB1 alleles were typed by sequence-specific oligonucleotide probing using a PCR as described[26]. The HLA-DPB1 associations studied were DP2 (DRBP*02) and DP3 (DPB1*03) alleles. HLA-B27 was determined by serologic testing[27].

Statistics. Differences between patients and controls were tested with the Student 2 tailed paired t test for normally distributed continuous variables and the McNemar test for categorical variables. Differences between subtypes within the patient group were tested with the chi-square test or, when appropriate, Fisher's exact test for categorical variables, with Bonferroni's correction for multiple comparisons.

To identify risk factors for an unfavorable outcome in JRA, univariate analyses were performed of the relation between outcome and patient characteristics (sex, age at disease onset, and disease duration before admission), genetic markers (HLA-B27, DRB1, DPB1), and disease variables assessed within the first 6 months of disease duration [onset subtype, number of affected joints, symmetric arthritis, affected hips, fingers, wrists, knees and cervical column, uveitis, IgM RF, ANA, ESR on first admission, duration of elevated ESR, and disease duration before the initiation of disease modifying antirheumatic drugs (DMARD)]. Subsequent multivariate analyses were used to identify a set of statistically significant predictors, including onset age, sex, and factors that were statistically significantly associated with unfavorable outcome in the univariate analyses. The missing values for independent variables were replaced using median substitution. All variables had fewer than 5% missing values. Possible interactions between all the independent variables were tested.

Logistic regression analyses were used to analyze factors affecting the risk of persistent JRA, defined as the absence of remission, and the presence of joint erosions at followup. Initial univariate tests were performed on each of the candidate factors separately. Multiple logistic analyses were performed with backward deletion of possible risk factors, based on the likelihood ratio test (removal p value < 0.10). Hosmer-Lemeshow goodness-of-fit statistics were used to assess how well the logistic regression models fitted the data ($p > 0.05$ were considered fit). Data on the strength of the associations were expressed as odds ratios (OR) per unit change of the independent variable and 95% confidence intervals (CI).

Predictors of physical ability were assessed using the SF-36 physical function score as the dependent variable. This score was chosen because of its wide range and normal distribution. Correlations between physical ability at followup and patient characteristics, genetic markers, and early disease variables were expressed as Pearson correlation coefficients. A multiple linear regression analysis was performed with backward deletion of possible predictors.

P values less than 0.05, no overlap between the 95% CI (for comparative groups) or 1.00 not included in the 95% CI (for the OR) were considered statistically significant in comparisons between 2 groups. The SPSS software program version 9.0 was used for all analyses[28].

RESULTS

Demographic and disease characteristics. After a median of 14.9 (range 11.7–25.1) years of disease duration the median age was 22.1 years (range 13.2–31.1) in the JRA patients and 22.2 years (range 13.2–31.2) in controls (p = 0.023). Sixty-four (24%) of the patients and controls were under the age of 18 years and 204 patients and controls (76%) were 18 years or older.

Patient characteristics and disease variables recorded within the first 6 months and within the median of 14.9 years of disease duration are given in Table 1. Twenty-nine patients (11%) had systemic JRA, 106 (40%) had persistently pauciarticular subtype, 57 (21%) had pauciarticular onset and polyarticular course type, 63 (23%) had IgM RF negative polyarthritis, and 13 (5%) had IgM RF positive polyarthritis.

Physical and psychosocial outcome. At followup, the patients had a mean of 1.7 active joints (95% CI 1.2–2.3) and 5.0 mobility restricted joints (95% CI 3.9–6.1). One patient (0.3%) had developed amyloidosis.

One hundred thirty-three patients with JRA (50%) were in remission without medication that had lasted for a median of 10.7 years (range 2.1–16.3) at the time of the study. One hundred and one patients were in their first period of remission, and 32 patients with current remission had had one or more previous periods of remission. Of 135 patients (50%) with persistent JRA, 61 had had active disease during the entire period of followup, and 74 patients without current remission had had one or more previous periods of remission during their disease course. The remission rate was higher in the patients with persistently pauciarticular than in those with extended pauciarticular and IgM RF positive polyarticular JRA [57% vs 35% (p = 0.009) and 15% (p = 0.005), respectively]. As a group, the patients with systemic JRA had higher remission rates than those with extended

Table 1. Patient and disease characteristics in the cohort of 268 patients with JRA. Values refer to numbers of Patients (%) unless otherwise stated.

	At Disease Onset	Within a Median of 14.9 yrs
Females	193 (72)	
Age, median yrs (range)	7.0 (0.3–15.3)	22.1 (13.2–31.1)
Disease duration, median yrs		14.9 (11.7–25.1)
Subtype		
Systemic	29 (11)	16 (6)
Pauciarticular	163 (61)	106 (40)
Polyarticular	76 (28)	146 (54)
Cumulative no. of affected joints, mean (SD)	5.4 (7.0)	10.6 (12.4)
Knee involvement	202 (75)	229 (85)
Ankle involvement	117 (43)	157 (58)
Finger joint involvement	55 (21)	121 (45)
Wrist involvement	64 (24)	105 (39)
Cervical involvement	24 (9)	73 (27)
Hip joint involvement	17 (6)	54 (20)
Predominantly symmetric arthritis	141 (53)	
ESR, mm/h, mean (SD)	37 (30)	11 (12)
Platelets, mean (SD)	392 (141)	264 (64)
Positive ANA	60 (22)	87 (32)
Positive IgM RF	12 (5)	13 (5)
Uveitis	33 (12)	50 (19)

pauciarthritis and IgM RF negative and RF positive polyarthritis [76% vs 35% ($p < 0.001$), 46% ($p = 0.007$), and 15% ($p < 0.001$), respectively].

Sixty-three (24%) patients with JRA had developed joint erosions after a median of 6.25 years (range 0.30–15.55). Joint erosions were less frequent in those with persistently pauciarticular than in those with extended pauciarticular, IgM RF negative polyarticular, or RF positive polyarticular subtype [5% vs 33% ($p < 0.001$), 40% ($p < 0.001$), and 77% ($p < 0.001$), respectively]. Joint erosions were present in 14% of the patients with systemic onset type compared with 77% of those with IgM RF positive polyarticular onset type ($p < 0.001$). Forty-six (18%) of 254 patients had radiographic arthritis grade 2 to 5 of their hips at followup. Forty-four patients (17%) had radiographic changes grade 2 to 5 of the ankles.

Abnormal HAQ indexes (scores > 0) were found in 93 (36%) patients with JRA, less frequently in those with persistently pauciarticular than in extended pauciarticular, IgM RF negative polyarticular, and IgM RF positive polyarticular JRA [22% vs 47% ($p = 0.001$), 46% ($p = 0.001$), and 75% ($p < 0.001$), respectively]. Thirty-two patients (12%) had a HAQ disability index ≥ 1.

Patients with JRA had poorer physical health than the controls, as indicated by lower scores on the SF-36 subscales (Table 2). More patients than controls were neither working nor studying at the time of study. Patients and controls had comparable levels of vitality, social function, and role limitations due to emotional problems according to the SF-36 (data not shown). Patients with active JRA at followup (n = 130) had more bodily pain, poorer physical functioning, role physical and global health, and higher unemployment rates than controls (mean scores 66.9 vs 80.6, 77.9 vs 95.7, 69.3 vs 85.9 and 64.1 vs 79.6, and 23% vs 7%, respectively; $p < 0.001$). Patients in remission (n = 128) had poorer general health perceptions than controls (mean scores 73.5 vs 79.6; $p = 0.005$), but comparable levels of physical functioning, role physical, bodily pain, and unemployment (data not shown).

Table 2. Outcome of patients with JRA compared with controls.

Variables Assessed After Median of 14.9 Years of Disease Duration	Patients, n = 258	Controls, n = 258
Physical disabilities, No. (%) with HAQ > 0	93 (36)	
Physical functioning, mean SF-36 (SD)	85.2 (18.4)***	95.7 (10.3)
Role physical, mean SF-36 (SD)	78.9 (32.9)**	85.9 (26.6)
Bodily pain, mean SF-36 (SD)	75.6 (23.5)**	80.6 (21.0)
General health, mean SF-36 (SD)	69.9 (22.5)***	79.6 (19.4)
Mental health, mean SF-36 (SD)	82.4 (16.2)*	79.3 (13.6)
Mental distress, n (%) with abnormal HSCL	34 (13)	36 (14)
Education level, mean years (SD)	11.9 (2.6)	11.6 (2.5)
Out of work and school/university, n (%)	50 (19)**	17 (7)
Full time student or employee, n (%)	191 (74)*	226 (88)
Disability or unemployment pension, n (%)	50 (19)**	10 (4)

HAQ: Health assessment questionnaire, range 0 (no disability) – 3 (unable to perform physical activities). SF–36: Short Form Health Survey, range 0 (poor health) – 100 (excellent health). Scores for vitality, social functioning, and emotional role limitations were comparable in patients and controls (data not shown). HSCL: Hopkins Symptom Checklist, range 1 (no mental distress) – 4 (severe mental distress). Scores ≥ 1.75 for girls and ≥ 1.67 for boys are considered abnormal. *$p < 0.05$ controls; **$p < 0.01$ controls; ***$p < 0.001$ controls.

Treatment. Two hundred and three patients (76%) were treated with one or more DMARD. The treatment had been started after a median of 0.4 years (range 0.1–13.0) of disease duration. The median cumulative number of DMARD was 2.0 (range 1.0–7.0) and the median duration of treatment was 3.4 years (range 0.1–17.7). Antimalarials were the most frequently used drugs (n = 184), followed by methotrexate (n = 82), gold (n = 82), penicillamine (n = 39), azathioprine (n = 25), sulfasalazine (n = 11), and cyclosporine (n = 6).

Genetic markers. Compared with controls, the frequency of HLA*DR08 was increased in patients with persistent and extended pauciarthritis and IgM RF negative polyarthritis (7% vs 36%, 39%, and 32%, respectively; $p < 0.001$). The frequency of DRB1*01 was higher in the patients with extended pauciarticular JRA than in controls (40% vs 19%; $p < 0.001$). DPB1*02 was increased in persistent and extended pauciarthritis (51% and 42%, respectively, vs 19% in controls; $p < 0.001$). DPB1*03 was increased in IgM RF negative polyarthritis (41% vs 20% in controls; $p < 0.001$).

Predictive factors. Young age at onset, DRB1*08, positive IgM RF, long duration of elevated ESR, and large number of affected joints within the first 6 months were risk factors for the absence of remission at followup (Table 3). These 5 predictive factors explained 23% of the variance. The regression model fitted the data well (chi-square 7.07, df 8, $p = 0.53$). When combinations of candidate factors were tested, the numbers of affected joints multiplied by the duration of elevated ESR was selected as a predictor of persistent disease (OR 1.02, 95%CI 1.01–1.03, $p = 0.001$). No other interaction term was included.

Development of joint erosions was associated with the absence of DPB1*02 and most disease activity variables assessed within the first 6 months (Table 4). Early onset, large numbers of affected joints, positive IgM RF, long duration of elevated ESR, and symmetric arthritis were predictors of joint erosions. These factors explained 34% of the variance. The regression model fit was good (chi-square 3.99, df 8, $p = 0.86$). The presence of HLA-B27 and DR8B1*08 in combination increased the risk of joint erosions (OR 2.72, 95% CI 1.03–7.15, $p = 0.043$). So did the combination of numbers of affected joints and duration of elevated ESR (OR 1.02, 95% CI 1.08–1.44, $p < 0.001$).

Predictors of physical disability were: female sex, symmetric arthritis, early hip joint involvement, long duration of elevated ESR, and positive IgM RF (Table 5). These

Table 3. Patient characteristics, early disease variables, and HLA alleles predicting persistent JRA 14.9 years after disease onset (n = 268).

Characteristics and Disease Variables Assessed Within the First 6 Months	Univariate Analysis * OR (95% CI)	p	Multiple Regression Analysis *† OR (95% CI)	p
Female sex	1.66 (0.96–2.85)	0.066		
Onset age, yrs	0.91 (0.86–0.97)	0.003	0.90 (0.85–0.96)	0.001
Onset type				
Pauciarticular	Referent group			
Polyarticular	1.40 (0.81–2.43)	0.232		
Systemic	0.31 (0.12–0.76)	0.010		
DRB1*08	2.39 (1.40–4.10)	0.001	2.25 (1.27–3.96)	0.005
HLA-B27	1.96 (1.05–3.66)	0.035		
No. of affected joints, range 0–69	1.05 (1.01–1.10)	0.010	1.05 (1.01–1.09)	0.049
Months of elevated ESR, > 15 mm/h, range 0–6	1.22 (1.10–1.34)	< 0.001	1.15 (1.03–1.28)	0.012
Uveitis	2.53 (1.15–5.54)	0.021		
Positive IgM RF	5.28 (1.13–24.58)	0.034	5.78 (1.11–30.07)	0.037
Positive ANA	2.17 (1.19–3.94)	0.011		

OR: Adjusted odds ratio per unit change of the variable. *Results of logistic regression analyses with the absence of remission for at least 2 years without medication as the dependent variable. Persistent JRA was present in 135 patients (50%). Disease duration before admission and before initiation of DMARD, HLA–DR1, DR4, DR5, DP2 and DP3, the presence of symmetric arthritis, involvement of hips, knees, fingers, wrists and neck, and ESR on first admission were not significantly associated with persistent JRA (data not shown). †Final model including sex, onset age, and variables significantly associated with persistent disease as independent variables.

Table 4. Patient characteristics, early disease variables, and HLA genes as predictors of the developement of joint erosions within 14.9 years in JRA (n = 268).

Characteristics and Disease Variables Assessed Within the First 6 Months	Univariate Analysis* OR (95%CI)	p	Multivariate Analysis*† OR (95%)	p
Female sex	0.90 (0.51–1.8)	0.896		
Onset age, yrs	0.99 (0.92–1.05)	0.672	0.91 (0.84–0.99)	0.045
Onset type				
Pauciarticular	Referent group			
Polyarticular	4.94 (2.65–9.24)	< 0.001		
Systemic	0.93 (0.30–2.90)	0.896		
DPB1*02	0.44 (0.23–0.84)	0.013		
No. of affected joints, range 0–69	1.14 (1.09–1.19)	< 0.001	1.09 (1.04–1.15)	0.001
Hip joint involvement	4.08 (1.50–11.09)	0.006		
Symmetric involvement	4.30 (2.24–8.29)	< 0.001	2.32 (1.06–5.05)	0.035
Finger joint involvement	3.86 (2.13–7.00)	< 0.001		
Wrist involvement	3.71 (2.01–6.85)	< 0.001		
Cervical involvement	4.11 (1.71–9.84)	0.002		
Months of elevated ESR, > 15 mm/h, range 0–6	1.35 (1.18–1.54)	< 0.001	1.29 (1.12–1.49)	0.002
ESR on first admission, mm/h	1.01 (1.00–1.02)	0.027		
Positive IgM RF	19.05 (4.05–89.58)	< 0.001	10.95 (1.86–64.59)	0.008

OR: Adjusted odds ratio per unit change. *Results of logistic regression analyses with joint erosions (radiographic arthritis grade 3–5) as the dependent variable. Sixty–three patients (24%) had developed joint erosians. Disease duration before admission and before initiation of DMARD, HLA–B27, DR1, DR4, DR5, DR8 and DP3, involvement of knees, uveitis, and ANA were not significantly associated with persistent disease (data not shown). †Final model including sex, onset age, and variables significantly associated with joint erosions as independent variables.

5 variables explained 13% of the variation in the physical functioning scores. When interaction terms were included, the combination of onset subtype and positive IgM RF increased the risk for disability (beta – 0.138, p = 0.027).

In the pauciarticular onset type (n = 163), early onset and a high ESR value on first admission were predictors of persistent disease (Table 6). Early onset, presence of DRB1*01, and long duration of elevated ESR were predictors of joint erosions, while knee joint involvement was a protective factor. Predictors of disability were early onset, persistently elevated ESR, and hip joint involvement within the first 6 months.

In the polyarticular onset type (n = 76), early onset, duration of elevated ESR, and presence of IgM RF were predictors of persistent disease. Duration of elevated ESR, IgM RF, and cervical involvement were predictors of joint erosions. Predictors of disability in polyarticular onset were female sex and the presence of IgM RF.

Table 5. Patient characteristics, early disease variables, and HLA genes as predictors of physical function after 14.9 years of disease duration in JRA (n = 258).

Characteristics and Disease Variables Assessed Within the First 6 Months	Correlation with SF-36 Physical Function Scale (Pearson R)*	p	Linear Multiple Regression Analyses Standardized beta	p
Female sex	–0.134	0.028	–0.162	0.008
Onset age, yrs	–0.105	0.086		
Onset type				
Pauciarticular	Referent group	0.001		
Polyarticular	–0.207	0.002		
Systemic	0.100	0.175		
No. of affected joints, range 0–69	–0.204	0.001		
Symmetric arthritis	–0.192	0.002	–0.152	0.012
Hip joint involvement	–0.143	0.020	–0.132	0.027
Finger joint involvement	–0.128	0.036		
Months of elevated ESR, > 15 mm/h, range 0–6	–0.188	0.003	–0.163	0.007
Positive IgM RF	–0.203	0.001	–0.167	0.006

*Disease duration before admission and before initiation of DMARD, HLA alleles, involvement of knees, wrists and neck, uveitis, ESR on first admission, and ANA did not correlate with the level of disability (data not shown). †Results of the final model identifying predictors of the degree of physical disability (SF-36 physical functioning score). Sex, onset age, and significant correlates in the univariate analyses were included as independent variables.

Table 6. Predictors of unfavorable outcomes in subtypes of JRA.

Characteristics and Disease Variables Assessed Within the First 6 Months	Outcome Variable Assessed After 14.9 Years: Persistent Disease* OR (95% CI)	p	Joint Erosions* OR (95% CI)	p	Physical Function† Standardized beta	p
Pauciarticular onset type						
Onset age, yrs	0.86 (0.79–0.94)	< 0.001	0.84 (0.73–0.96)	0.010	–0.188	0.015
ESR on first admission, mm/h	1.02 (1.00–1.03)	0.027				
Months of elevated ESR, range 0–6			1.26 (1.02–1.56)	0.033	–0.208	0.008
DRB1*01			2.92 (1.05–8.09)	0.039		
Knee joint involvement			0.15 (0.04–0.51)	0.003		
Hip joint involvement					–0.173	0.025
Polyarticular onset type						
Onset age, yrs	0.84 (0.71–1.00)	0.050				
Female sex					–0.348	0.003
Months of elevated ESR, range 0–6	1.45 (1.13–1.86)	0.003	1.39 (1.10–1.76)	0.007		
Positive IgM RF	12.71 (1.60–100.81)	0.016	15.57 (2.16–112.26)	0.006	–0.235	0.049
Cervical involvement			8.82 (1.46–53.42)	0.018		

*Results of the final model in multiple logistic regression analyses identifying predictors of persistent disease and joint erosians (n = 163 for pauciarticular onset and n = 76 for polyarticulat onset). Sex, onset age, patient characteristics, HLA alleles, and early disease variables significantly associated with the dependent variable were included as independent variables.†Results of the final model in multiple linear regression analyses identifying predictors of disability according to the SF-36 functioning scale (n = 159 for pauciarticular onset and n = 70 for polyarticulat onset).

DISCUSSION

Longterm physical, psychosocial, and radiographic outcome and predictors of outcome are described in this case-control study of 268 patients with JRA. To our knowledge, this is the first study of the influence of HLA-DRB1 and DPB1 genes on the development of joint erosions and remission in JRA. DR8 was identified as a predictor of persistent disease, and DR8 in combination with HLA-B27 was a predictor of development of joint erosions. DR8 has been associated with susceptibility to pauciarticular and RF negative polyarticular JRA, but not with RF positive polyarticular or systemic sybtypes[12,13], and these results merit further investigation.

The finding that DR1 was a predictor of joint erosions in pauciarticular JRA fits well with the fact that DR1 is associated with a polyarticular course type in patients with pauciarticular onset JRA[13]. This subtype has been found to be associated with joint erosions and disability[6,7,13]. DP2 had a protective influence on the risk of joint erosions in the present cohort of JRA patients. DP2 is a well known correlate of pauciarticular JRA[12,13,29], a subtype that tends to have a good prognosis[5,30]. However, the numbers and symmetry of affected joints and not the absence of DP2 predicted joint erosions in our multivariate analysis, which suggests that the joint pattern is more important than the absence of DP2 for

the development of joint erosions. HLA-B27 was associated with persistent disease in our patients with JRA, as was recently found in 171 German and 190 Finnish patients with juvenile chronic arthritis[30,31]. On the other hand, HLA-B27 was not a predictive factor in our multivariate analyses, and in another study no association between HLA-B27 and severe disability was found[32]. Genetic markers were found not to be predictors of disability in the present cohort, as in American and Italian patients with JRA[14].

Duration of elevated ESR during the first 6 months had a consistent influence on the risk of unfavorable outcomes in our study, while a high ESR value on first admission had a weak or no influence on the prognosis. Ruperto, *et al* suggested that elevated ESR at disease onset was a predictor of reduced quality of life, but not of disability[14]. High ESR values on first examination predicted the development of joint erosions in a study of pauciarticular JRA by Guillaume, *et al*[33].

The identification of IgM RF as a predictor of severe JRA, especially in the polyarticular onset type, is in accord with previous findings[6,7]. A large number of affected joints within the first 6 months was more important for the risk of persistent disease and joint erosions than the onset type. Hip joint involvement was a risk factor for disability, while knee joint involvement was protective for joint erosions in the pauciarticular onset type. Hip involvement has been found to result in poor functional capacity in JRA[34].

In contrast to most previous findings, we found that early onset increased the likelihood of an unfavorable outcome in JRA[3,7,14,30]. There might have been fewer patients with early onset pauciarticular JRA, which is supposed be a benign disease, in the present cohort of patients admitted to hospital than in other, epidemiological studies[3,7,30]. The frequency of pauciarticular onset was lower in the present cohort than in some recent population or practitioner based patient samples[4,30]. However, the age of onset, sex, and proportion of patients with pauciarticular onset in our study were similar to those in Scandinavian epidemiological studies[3,35]. The health care system in Scandinavia, with regular free checkups of all children, probably leads to hospital admission of most children with chronic rheumatic disease[3]. Careful exclusion of patients with juvenile SpA, who are older at disease onset and might have a more severe outcome than patients with JRA, might also have influenced our results[36]. Our results are in accord with a few studies suggesting that young age of onset is associated with a poor prognosis[37,38].

The assessment of early disease characteristics was limited by the retrospective design of this study. Twenty-four percent of the patients were admitted after the first 6 months of disease duration. However, information was obtained from the local pediatrician or rheumatologist as the health care system in Scandinavia makes it possible to collect medical data from different sources.

The results of the multivariate analyses are limited because some of the predictive factors had an OR close to one per unit change or a wide CI. The variance explained by the models was low, indicating that other factors than those identified here are important determinants of outcome in JRA.

Correlates with physical function were obtained using the SF-36[10]. The HAQ or the Childhood HAQ has been used in previous analyses, but HAQ disability indexes close to zero in the majority of the patients with JIA make analyses of predictive factors difficult[5-7]. The normal distribution and wide range of SF-36 scores might have made predictors of disability easier to observe in this study than in previous reports[5-7].

In spite of similar levels of education, the patients had poorer physical function, general health, and employment status at followup than the controls. This result cannot be explained by the small age difference between patients and controls, since the number of patients under the age of 18 was equal among patients and controls. The large numbers of patients in our cohort made an age difference of 0.1 years statistically significant even though this small difference was not clinically significant. Our results are in accord with the only previous controlled study of 44 patients with JRA, and emphasize the importance of early vocational guidance in JRA patients[4].

After a median of 14.9 years, 50% of the JRA patients were in remission without medication for a period that had lasted for at least 2 years. This figure is in the same range as the remission rates found in most recent studies[3,6,30,39]. Joint erosions were found in 24% of our patients, in contrast to reports of up to 68% between 1966 and 1991[2]. However, our results are in accord with the figure of 25–27% with erosive disease found in recent studies[3,6,30]. The larger numbers of patients receiving DMARD, particularly methotrexate, and the inclusion of more representative patient samples in recent than in earlier studies may explain the difference in the results. However, the frequency of joint erosions may have been underestimated in our study because radiographs of affected joints other than hips and ankles were only taken when clinically indicated, and were not obtained and blindly examined for all patients.

The 36% frequency of abnormal physical functioning presented here is in agreement with the most recent reports using the HAQ or the Childhood HAQ[4-6], although a higher frequency was found by Gare, *et al*[7]. The HAQ was completed by all our patients, including the 64 adolescents under age 18. In contrast to the Childhood HAQ, the HAQ does not include questions on activities relevant to children of all ages. Thus, we may have underestimated the degree of disability.

We conclude that patients with JRA had poorer physical health and were less likely to be employed than age and sex matched controls from the general population. The most consistent early predictors of an unfavorable outcome were

persistent elevation of ESR, the presence of IgM RF, and extensive joint involvement. Further, young age of onset, female sex, and the presence of DR8 or DR1 were risk factors for a poor prognosis. Prospective testing of these predictors is needed to establish a set of reliable criteria for the early recognition of children with severe JRA who need aggressive and innovative treatment regimes.

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