Long-Term Outcome and Prognostic Factors in Enthesitis-Related Arthritis

A Case–Control Study

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Objective. To compare the clinical, functional, and radiographic outcomes in patients with enthesitis-related arthritis (ERA) with those in patients with other subtypes of juvenile idiopathic arthritis (JIA) and healthy controls, and to determine genetic markers, patient characteristics, and early disease variables that predict the development of remission, sacroiliitis, and physical limitations in ERA.

Methods. Fifty-five children with ERA who were first admitted to Rikshospitalet Medical Center between 1980 and 1985 were studied. Patients with oligoarthritis or polyarthritis who were admitted during the same period (n = 55) and individuals from a national population registry (n = 55) were matched for sex and age and used as controls. Health status was assessed after a median of 15.3 years of disease (range 11.7–21.9 years) and, in some patients, was reassessed after a median of 23.0 years (range 19.7–29.4 years) of disease, by use of the 36-item Short Form health survey and the Health Assessment Questionnaire. Clinical and radiographic examinations were performed at the 15-year followup visit. Variables relating to the onset of disease were retrospectively obtained by chart review. HLA alleles were determined by genotyping and serologic testing.

Results. Patients with ERA had lower levels of physical functioning, poorer physical health, and more bodily pain compared with patients with oligoarthritis or polyarthritis (after a median of 15.3 and a median of 23.0 years) and normal controls (after a median of 15.3 years). Among patients with ERA, remission occurred in 44%, sacroiliitis was observed in 35%, and reduced spinal flexion was observed in 75%. Predictors of failure to attain disease remission included the following: ankylosing spondylitis (AS) in a first-degree relative, the presence of HLA–DRB1*08, and ankle arthritis within the first 6 months. HLA–DPB1*02 was a protective factor, whereas a persistently elevated erythrocyte sedimentation rate (ESR), and hip arthritis within the first 6 months were risk factors for sacroiliitis. Female sex, a family history of AS, and high numbers of affected joints within the first 6 months predicted poor physical health status after 23 years. Male sex was associated with reduced anterior flexion of the spine.

Conclusion. In this study, patients with ERA had poorer physical outcomes compared with patients with oligoarticular or polyarticular JIA and controls from the general population. A family history of related diseases, sex, the presence of HLA–DRB1*08, the absence of HLA–DPB1*02, a persistently elevated ESR, early hip or ankle arthritis, and high numbers of affected joints were predictors of an unfavorable outcome.

Enthesitis-related arthritis (ERA) is an HLA–B27–associated type of pediatric inflammatory arthritis characterized by the involvement of the entheses and the axial skeleton in addition to the peripheral joints.
category of juvenile idiopathic arthritis (JIA) was defined by the International League of Associations for Rheumatology (ILAR) in order to recognize children with juvenile spondylarthropathy within the first 6 months of disease (1). Among patients with JIA, 11–16% have been found to have ERA (2–5).

Patients with ERA have a clinical picture similar to that of patients meeting traditional definitions of juvenile spondylarthropathy, including juvenile ankylosing spondylitis (AS), seronegative enthesopathy and arthropathy (SEA) syndrome, and undifferentiated juvenile spondylarthropathy (2–5). Few studies have addressed outcome in juvenile spondylarthropathy, and those studies are based on limited patient numbers and have contradictory results (6–10). Reported remission rates have ranged from 17% to 37%, the reported frequency of sacroiliitis has ranged from 9% to 75%, and the occurrence of severe disability has ranged from 4% to 52% (7–9,11–13). Differences in the duration of followup and the classification criteria used may have influenced the results. Thus far, the outcomes in patients with ERA, applying the ILAR criteria, have been described in only 2 studies involving 10–33 patients (8,14).

Over the past decade, advances in understanding of the pathogenesis of juvenile spondylarthropathy have revealed important mechanisms, such as marked expression of tumor necrosis factor α (TNFα) and TNF receptors in the synovia and early osteitis with cell infiltration in the spine (15,16). New opportunities for early effective therapy with anti-TNF agents emphasize the need for early identification of patients at high risk of a poor outcome (17).

We previously described predictors of the development of radiographic sacroiliitis in patients with all subtypes of JIA (18). The aim of the present study was to assess the clinical and radiographic outcome in a cohort of patients with ERA and to determine the role of genetic markers, patient characteristics, and early disease variables that would predict physical disability, failure to achieve disease remission, and the risk of sacroiliitis developing. We also wanted to compare the health status of patients with ERA with that of patients with oligoarticular or polyarticular JIA and healthy controls.

PATIENTS AND METHODS

Patients and controls. Fifty-five patients with ERA who were 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 disease duration of 15.3 years (range 11.7–21.9 years). Forty of those patients (73%) were reassessed by mailed questionnaires after a median disease duration of 23.0 years (range 19.7–29.4 years). Medical records were reviewed for variables related to the onset of disease. The 55 patients with ERA represented 16% of all new patients with JIA (n = 336) who were admitted during the same period. The characteristics of the total group of patients with JIA and the outcomes in those with juvenile rheumatoid arthritis have previously been described (18,19). Rikshospitalet has the only division of pediatric rheumatology in Norway and serves the whole country.

The patients’ disease subtypes were determined retrospectively according to the ILAR criteria for JIA (1). Patients who were included in the study had ERA, which was defined as the presence of arthritis and enthesitis, or as the presence of arthritis or enthesitis plus at least 2 of the following: sacroiliac joint tenderness or inflammatory lumbosacral pain, HLA–B27, onset (in males) after 6 years of age, acute anterior uveitis, and a history of related disease in a first-degree relative (1). Patients who were IgM rheumatoid factor positive and those with systemic arthritis were excluded. Psoriasis in the patient or a first-degree relative was considered an exclusion criterion in all but 5 patients with signs of spondylarthropathy that implicated exclusion from the group with psoriatic arthritis. These 5 patients had radiographic sacroilitis (n = 3), inflammatory lumbosacral pain (n = 3), enthesitis (n = 3), and/or HLA–B27 positivity (n = 4). It has previously been suggested that when psoriasis is considered to be an exclusion criterion for ERA, no signs of spondylarthropathy should be present (20).

Fifteen (27%) of the patients with ERA did not participate in the reassessment after a median of 23.0 years. Those who did not undergo reassessment were comparable with the participants with regard to sex, disease type, age at onset, and health status after a median of 15.3 years (data not shown).

Two hundred five patients with oligoarticular or polyarticular JIA were used as a comparison group for the assessments after a median of 15.3 years. Of these patients, 55 were randomly selected to serve as matched controls for the health status assessment. The patients with JIA were stratified according to sex and polyarticular versus oligoarticular involvement within the first 6 months. The patients within each group (i.e., male, female, polyarticular onset, oligoarticular onset) were randomly selected from among up to 6 candidates (depending on the numbers of candidates) with an age similar to that of the patients with ERA (±1 year). If fewer than 2 candidates were available, the patient whose age was closest to that of the patient with ERA was selected. A total of 151 patients with oligoarthritis or polyarthritis participated in the reassessment after a median of 23.0 years.

Individuals matched for age, sex, and geographic region (n = 55) were also randomly selected from the national population registry to serve as controls for the health status assessments at the time of the 15-year followup visit. The study was approved by the Regional Ethics Committee for Medical Research.

Clinical examinations and chart reviews. The clinical examinations after a median of 15.3 years of disease included assessments of the numbers of affected (swollen or mobility-
restricted) joints. Arthritis was defined as a joint with swelling not attributable to bony enlargement or limitation of motion in combination with pain or tenderness. Enthesitis was defined as discretely localized tenderness at the point of insertion of ligaments, tendons, joint capsules, or fascia to bone (21). Anterior lumbar flexion was assessed using the modified Schober method (22). Reduced lumbar flexion was defined as values ≤6.5 cm in boys and ≤5.5 cm in girls, based on the mean values minus 2 SD in healthy Mexican adolescents (23). Lateral dorsolumbar flexion was measured as the difference between the fingertips-to-floor distance in the upright position and at maximum lateral flexion (24). A difference in the fingertips-to-floor distance of ≤10% of body height was considered to be abnormal (24). Reduced cervical rotation was defined as values ≤160 degrees. Inflammatory back pain was defined as lumbosacral spinal pain at rest, with morning stiffness that improved with movement (1).

Disease onset was defined by the date on which arthritis was documented by a physician. Remission was defined according to the preliminary criteria for clinical remission in JIA, whereby the patient had no active arthritis, fever, rash, serositis, splenomegalay, generalized lymphadenopathy, or active uveitis, the erythrocyte sedimentation rate (ESR) or C-reactive protein level was normal, and a physician’s global assessment of disease activity indicated that clinical disease quiescence had been present for at least 12 months, during which the patient had not been receiving any antiarthritics or antiuveitis medication (25,26). An elevated ESR was defined as >16 mm/hour.

Assessments of health status. The 36-item Short Form health survey (SF-36) (27) was completed by patients with ERA and patients with oligoarticular or polyarticular JIA after a median of 15.5 years and again (by some patients) after a median of 23.0 years, and by controls from the general population after a median of 15.3 years. The SF-36 instrument measures 2 distinct components: the physical component summary scale (PCS), comprising the health dimensions physical functioning, role limitations due to physical health, body pain, and general health, and the mental component summary scale, which comprises the dimensions vitality, social functioning, role limitation due to emotional problems, and mental health. Both of these scales were scored to have an average of 50 and an SD of 10 in the general population in the US. Scores <50 indicate that health status is below average. The SF-36 health survey has been translated and culturally adapted for use by Norwegians (28).

The Health Assessment Questionnaire (HAQ) (29) and the HAQ modified for spondylarthropathy (HAQ-S) (30) were used to measure physical disability in patients with ERA and in controls with other JIA subtypes. The HAQ is a 20-item questionnaire measuring physical function in the following 8 areas: dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and activities. In the HAQ-S, 5 items forming 2 areas, bending and driving, are added to the HAQ (30). Scores for the HAQ and HAQ-S range from 0 to 3, where 0 = no difficulty with daily activities and 3 = unable to perform these activities (29). The HAQ and HAQ-S disability indexes are calculated as the means of the highest scores for each area. The HAQ has been used in several studies of young adults with JIA (8,14,19), and the HAQ-S has been evaluated in adult patients with spondylarthropathy (30).

Radiographic examinations. Radiographs of the hips (anteroposterior view), ankles (lateral view), and sacroiliac joints (anteroposterior view) of all patients were obtained at the 15-year followup visit. Radiographs were independently read by 2 radiologists who were blinded to patient identification, earlier radiographs, and clinical or laboratory data. The scoring system included grades 0–5, with grades 2–5 denoting definite arthritic changes (31,32).

Genomic typing for HLA. HLA–DRBI typing was performed by the nonisotopic method based on polymerase chain reaction (PCR) and hybridization, with oligonucleotide probes labeled with biotin (33,34). HLA–DPB1 alleles were typed by sequence-specific oligonucleotide probing using PCR (33,34). The HLA–DRBI associations studied included the DRBI*01, DRBI*04, and DRBI*08 alleles. The HLA–DPB1 associations studied included the DPB1*02 and DPB1*03 alleles. HLA–B27 was determined by serologic testing. In healthy Norwegian individuals, the frequencies of HLA alleles have been found to be 12% for HLA–B27, 19% for DRBI*01, 34% for DRBI*04, 7% for DRBI*08, 19% for DPB1*02, and 20% for DPB1*03 (18).

Statistical analysis. Differences in characteristics between the 2 patient groups were tested by Student’s unpaired 2-tailed t-test for continuous variables and by chi-square test for categorical variables, with Bonferroni’s correction for multiple comparisons. The significance of differences in health status between patients and matched controls and of changes within a patient group over time was tested by Student’s paired 2-tailed t-test.

In order to identify possible risk factors for unfavorable outcomes in ERA, univariate analyses were performed on the relationship between outcome and patient characteristics (sex, age at onset, family history), genetic markers (HLA–B27, DRBI*04, DRBI*08, DPB1*02), and disease variables assessed within the first 6 months of disease (number of affected joints, duration of elevated ESR, and hip or ankle involvement). Initial tests were performed on each of the candidate factors separately. Logistic regression was used to analyze factors affecting the likelihood of failure to achieve remission and the presence of radiographic sacroiliitis. Pearson’s correlation coefficient was used to analyze possible correlates with the development of physical limitations as measured by the SF-36 PCS after a median of 23.0 years of disease.

Subsequent multivariate regression analyses were performed to identify predictive factors. Sex, age at onset, and candidate factors that were associated (P < 0.10) with the outcome variable in the univariate tests were analyzed. Failure to achieve remission and development of radiographic sacroiliitis were tested using multivariate logistic analyses, with backward deletion of possible predictors. Data on the strength of the associations were expressed as odds ratios (ORs) and 95% confidence intervals. Hosmer-Lemeshow goodness-of-fit statistics were used to assess how well the logistic regression models fit the data (P values less than 0.05 were considered fit). Risk factors for physical limitations (low values on the SF-36 PCS) were tested by linear multiple regression analysis with backward deletion of possible predictors. Data on the strength of the associations were given as the standardized beta.

P values less than 0.05 were considered significant. SPSS software was used for all analyses (35).
RESULTS

Patient and disease characteristics. The characteristics of and radiography findings for the patients are shown in Table 1. The percentage of males and the mean age at onset were higher in patients with ERA than in controls with oligoarticular or polyarticular JIA (65% versus 24% and 11.1 years [range range 2.1–15.2] versus 6.8 years [range range 0.3–15.3]; both \( P < 0.001 \)).

Among patients with ERA, the remission rate after 15 years was 44%, and the frequency of radiographic sacroiliitis after 15 years was 35%. Calcaneal destruction and/or ossification at the site of insertion of the plantar fascia or the Achilles tendon was present in 22% of the patients with ERA, compared with 9% of those with oligoarthritis or polyarthritis (\( P = 0.012 \)). Spinal anterior and/or lateral flexion was reduced in 75% of the patients with ERA, compared with 49% of those with other JIA subtypes (\( P < 0.001 \)).

Among the patients with ERA, abnormal results of a Schober test were observed in 15 (79%) of 19 patients with radiographic sacroiliitis versus 16 (44%) of 36 patients without sacroiliitis (\( P = 0.024 \)) and in 24 (67%) of 36 males versus 7 (37%) of the 19 females (\( P = 0.034 \)).

After a median of 23.0 years of disease duration, 18 (45%) of 40 patients with ERA compared with 40 (26%) of 151 patients with oligoarthritis or polyarthritis were still receiving antirheumatic drugs (\( P = 0.024 \)). Seven of the patients with ERA were being treated with disease-modifying antirheumatic drugs, 3 patients were receiving anti-TNF agents, and 14 patients were being treated with nonsteroidal antiinflammatory agents.

Genetic markers. The frequency of genetic markers among patients with different JIA subtypes is shown in Table 2. HLA–B27 was positive in 85% of the patients with ERA and in 9–19% of those with other JIA subtypes (\( P < 0.001 \)). HLA–DPB1*02 was less frequent in patients with ERA than in those with persistent oligoarthritis (\( P < 0.001 \)), and the prevalence of HLA–DRB1*04 was increased in the patients with ERA compared with those with persistent oligoarthritis (\( P = 0.007 \)).

Health status after a median of 15.3 years and a median of 23.0 years of disease. For analyses of health status, 55 age- and sex-matched controls were randomly selected from both the comparison group with oligo-
arthritis or polyarthritis and the general population. The JIA controls were also matched for oligoarticular versus polyarticular involvement within the first 6 months.

Abnormal HAQ disability indexes (scores >0) were observed in 28 (51%) of the 55 patients with ERA, compared with 18 (33%) of the 55 controls with oligoarthritis or polyarthritis, after a median of 15.3 years ($P = 0.035$). The mean HAQ and HAQ-S disability indexes were higher in patients with ERA than in those with oligoarthritis or polyarthritis after 15.3 and 23.0 years (Table 3). At the 15-year followup, patients with ERA had poorer physical health as measured by the SF-36 PCS compared with the patients with oligoarthritis or polyarthritis and the normal controls ($P < 0.001$).

Scores for the SF-36 PCS were also lower in patients with ERA than in those with oligoarthritis or polyarthritis after a median of 23.0 years ($P = 0.004$). The intensity of pain was greater in patients with ERA compared with controls with other JIA subtypes ($P < 0.001$ after 15.3 years and $P = 0.007$ after 23.0 years) and normal controls ($P = 0.001$ after 15.3 years).

**Prognostic factors.** Predictors of failure to achieve remission and the development of sacroiliitis in patients with ERA were identified by multiple logistic regression analyses. Patient characteristics, genetic variables, and disease characteristics assessed within the first 6 months that were associated with the outcome variable ($P < 0.10$) were tested as possible predictors.

### Table 2. Prevalence of HLA alleles in patients with ERA compared with other subtypes of JIA*

<table>
<thead>
<tr>
<th>Allele</th>
<th>ERA (n = 55)</th>
<th>Persistent oligoarthritis (n = 95)</th>
<th>Extended oligoarthritis (n = 42)</th>
<th>RF-negative polyarthritis (n = 57)</th>
<th>RF-positive polyarthritis (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA–B27</td>
<td>47 (85)</td>
<td>16 (17)†</td>
<td>5 (12)‡</td>
<td>11 (19)†</td>
<td>1 (9)†</td>
</tr>
<tr>
<td>DRB1*01</td>
<td>13 (24)</td>
<td>14 (15)</td>
<td>18 (43)‡</td>
<td>5 (9)‡</td>
<td>5 (45)</td>
</tr>
<tr>
<td>DRB1*04</td>
<td>20 (36)</td>
<td>16 (17)‡</td>
<td>6 (14)‡</td>
<td>15 (26)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>DRB1*08</td>
<td>16 (29)</td>
<td>36 (38)</td>
<td>12 (29)</td>
<td>20 (35)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>DPB1*02</td>
<td>12 (22)</td>
<td>48 (51)†</td>
<td>15 (36)</td>
<td>13 (23)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>DPB1*03</td>
<td>15 (27)</td>
<td>12 (13)‡</td>
<td>9 (21)</td>
<td>24 (42)</td>
<td>4 (36)</td>
</tr>
</tbody>
</table>

* Values are the number (%). ERA = enthesitis-related arthritis. JIA = juvenile idiopathic arthritis; RF = rheumatoid factor.
† $P < 0.001$ versus ERA.
‡ $P < 0.05$ versus ERA ($P$ not significant when corrected for the number of comparisons).
§ $P < 0.01$ versus ERA.

### Table 3. Health status after a median of 15.3 years and 23.0 years of disease in patients with ERA, controls with oligoarticular or polyarticular JIA, and controls from the general population*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients with ERA</th>
<th>Patients with oligoarthritis or polyarthritis</th>
<th>$P$, vs. ERA</th>
<th>Normal controls</th>
<th>$P$, vs. ERA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ disability index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 15 years</td>
<td>0.38 (0.23–0.53)</td>
<td>0.16 (0.07–0.24)</td>
<td>0.010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 23 years</td>
<td>0.31 (0.14–0.47)</td>
<td>0.13 (0.03–0.22)</td>
<td>0.047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAO-S disability index after 15 years</td>
<td>0.44 (0.44–0.59)</td>
<td>0.18 (0.08–0.29)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 physical component summary score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 15 years</td>
<td>46.4 (42.5–50.3)</td>
<td>52.4 (50.2–54.6)</td>
<td>&lt;0.001</td>
<td>54.3 (52.7–55.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After 23 years</td>
<td>48.6 (44.6–52.6)</td>
<td>55.8 (53.0–58.5)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 mental component summary score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 15 years</td>
<td>51.2 (48.1–54.4)</td>
<td>55.8 (54.0–57.7)</td>
<td>0.007</td>
<td>51.3 (48.1–52.9)</td>
<td>0.698</td>
</tr>
<tr>
<td>After 23 years</td>
<td>47.3 (43.9–50.7)</td>
<td>52.3 (49.7–54.9)</td>
<td>0.042</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body pain score (range 1–6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 15 years</td>
<td>2.88 (2.47–3.30)</td>
<td>2.09 (1.76–2.42)</td>
<td>0.001</td>
<td>1.97 (1.73–2.21)</td>
<td>0.001</td>
</tr>
<tr>
<td>After 23 years</td>
<td>2.85 (2.40–3.30)</td>
<td>2.00 (1.63–2.37)</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Values are the mean (95% confidence interval). Fifty-five patients were included in the 15-year followup assessment, and 40 patients were included in the 23-year followup assessment. Controls were matched for sex, age, and oligoarticular versus polyarticular onset, when appropriate. Values <50 for the 36-item Short Form health survey (SF-36) mean physical or mental summary scores are below the average value for the normal US population. For body pain, a Likert scale was used, where 1 = no pain and 6 = very strong pain. Changes from the 15-year assessment to the 23-year assessment were not statistically significant. ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; HAQ = Health Assessment Questionnaire, where 0 = no disability and 3 = very severe disability; HAQ-S = HAQ modified for spondyloarthropathy.
Predictors of failure to achieve remission after a median of 15.3 years of disease duration were as follows: a family history of AS in a first-degree relative (OR 5.31, \( P = 0.025 \)), the presence of HLA–DRB1*08 (OR 7.94, \( P = 0.014 \)), and arthritis in ankle joints within the first 6 months (OR 8.65, \( P = 0.004 \)) (Table 4). The regression model supported the data well (\( R^2 = 0.340 \), \( P = 0.638 \)). Furthermore, failure to achieve remission was associated with female sex (OR 4.69, \( P = 0.018 \)) and younger age at disease onset (OR 0.77 per year, \( P = 0.046 \)) in the univariate analysis but not in the multivariate analysis. The same predictors were identified when the 5 patients who had psoriasis (or psoriasis in a first-degree relative) were excluded (data not shown).

In patients with ERA, the presence of HLA–DPB1*02 protected against the development of radiographic sacroiliitis (OR 0.38, \( P = 0.013 \)), while hip arthritis within the first 6 months (OR 6.73, \( P = 0.034 \)) and an elevated ESR for at least 6 months (OR 4.09, \( P = 0.042 \)) predicted the development of sacroiliitis (Table 5). The regression model supported the data well (\( R^2 = 0.440 \), \( P = 0.354 \)). Additionally, HLA–DRB1*04 was associated with the development of sacroiliitis in the univariate analysis (OR 4.13, \( P = 0.019 \)). When the 5 patients with a history of psoriasis (or psoriasis in a first-degree relative) were excluded, HLA–DPB1*02 negativity and hip arthritis, but not an elevated ESR, were predictors of sacroiliitis (data not shown).

Predictors of poor physical health after a median of 23.0 years, as measured by the SF-36 PCS, were analyzed by multiple linear regression analysis (Table 6). Female sex, AS in a first-degree relative, and a high number of affected joints within the first 6 months predicted physical limitation (standardized \( \beta = -0.403 \), \( P = 0.003 \); \( \beta = -0.379 \), \( P = 0.005 \); and \( \beta = -0.325 \), \( P = 0.012 \), respectively). These 3 variables explained 45% of the variation in the PCS scores. Furthermore, HLA–DRB1*08 correlated with physical limitations in the univariate analysis (\( r = -0.349 \), \( P = 0.027 \)). The same predictors were identified when separate analyses excluding the 5 patients with a history of psoriasis (or psoriasis in a first-degree relative) were performed (data not shown).

<table>
<thead>
<tr>
<th>Table 4. Predictors of failure to achieve remission after a median of 15.3 years of disease in 55 patients with ERA*</th>
<th>Univariate analysis</th>
<th>Multivariate analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
<td>( P )</td>
</tr>
<tr>
<td>Female sex</td>
<td>4.69</td>
<td>1.30–16.93</td>
</tr>
<tr>
<td>Age at onset, years</td>
<td>0.77</td>
<td>0.60–0.99</td>
</tr>
<tr>
<td>Family history of AS in first-degree relative</td>
<td>3.55</td>
<td>1.04–12.08</td>
</tr>
<tr>
<td>DRB1*08</td>
<td>5.06</td>
<td>1.24–20.59</td>
</tr>
<tr>
<td>Ankle arthritis within the first 6 months</td>
<td>6.92</td>
<td>1.91–25.13</td>
</tr>
</tbody>
</table>

* HLA–B27, HLA–DRB1*04, HLA–DPB1*02, duration of an elevated erythrocyte sedimentation rate, numbers of affected joints, and hip arthritis within the first 6 months were not associated with failure to achieve remission (\( P \geq 0.10 \)). ERA = enthesitis-related arthritis; OR = odds ratio; 95% CI = 95% confidence interval; AS = ankylosing spondylitis.
† Results of multiple logistic regression analysis, including variables associated with failure to achieve remission in the univariate analysis (\( P < 0.10 \)).

<table>
<thead>
<tr>
<th>Table 5. Risk factors for development of sacroiliitis within a median of 15.3 years in 55 patients with ERA*</th>
<th>Univariate analyses</th>
<th>Multivariate analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
<td>( P )</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.78</td>
<td>0.53–6.04</td>
</tr>
<tr>
<td>Age at onset, years</td>
<td>1.04</td>
<td>0.85–1.28</td>
</tr>
<tr>
<td>HLA–DRB1*04</td>
<td>4.13</td>
<td>1.26–13.46</td>
</tr>
<tr>
<td>HLA–DPB1*02</td>
<td>0.13</td>
<td>0.02–1.07</td>
</tr>
<tr>
<td>Hip arthritis within the first 6 months</td>
<td>3.62</td>
<td>0.96–13.64</td>
</tr>
<tr>
<td>Elevated ESR for at least 6 months</td>
<td>2.75</td>
<td>0.88–8.64</td>
</tr>
</tbody>
</table>

* Ankylosing spondylitis in a first-degree relative, HLA–DRB1*08, numbers of affected joints, and ankle arthritis within the first 6 months were not associated with the development of sacroiliitis in the univariate analysis (\( P \geq 0.10 \)). ERA = enthesitis-related arthritis; OR = odds ratio; 95% CI = 95% confidence interval; ESR = erythrocyte sedimentation rate.
† Results of multiple logistic regression analysis, including variables associated with radiographic sacroiliitis in the univariate analysis (\( P < 0.10 \)).
DISCUSSION

In the present study, patients with ERA had higher levels of physical disability, more bodily pain, and poorer physical health compared with controls from the general population and patients with oligoarthritis or polyarthritis, after a median disease duration of 15.3 and 23.0 years. Most patients with ERA had reduced spinal mobility, one-third had radiographic sacroiliitis, and more than half of the patients failed to achieve disease remission. An unfavorable outcome was predicted by a family history of AS, the presence of HLA–DRB1*08, the absence of HLA–DPB1*02, a persistently elevated ESR, early hip or ankle involvement, and a high number of affected joints within the first 6 months. Female sex was a predictor of poor patient-assessed physical health, while male sex was associated with reduced anterior spinal flexion. This is the first study of the long-term multidimensional outcome and prognostic factors in ERA.

These patients with ERA were part of a cohort of all new patients with JIA who were admitted to the hospital during a 5-year period. Because they were selected from a referral center, patients in our study group probably had more severe disease compared with that in patients recruited from the general population. However, the homogeneous public health system in Scandinavia, with regular free check-ups for all children, may facilitate admission of most children with chronic disease (36). The cohort of patients with JIA has previously been shown to have characteristics comparable with those of patients in epidemiologic studies (9,18,36). Our results are limited by the retrospective application of classification criteria and assessment of variables from disease onset. However, because prospective outcome studies will require many years to carry out, retrospective studies may provide important information on the ability of the ILAR criteria to identify disease entities with homogeneous outcomes.

Patients with ERA had more physical limitations compared with age- and sex-matched patients with other JIA subtypes (after a median of 15.3 and 23.0 years) and controls from the general population (after a median of 15.3 years). Our results indicate that patients with ERA have a poorer physical outcome than other JIA patients with similar joint involvement at the time of disease onset. Limitations in the numbers of patients did not allow comparisons between patients with ERA and those with oligoarthritis and polyarthritis separately. Studies of larger patient populations are needed in order to compare patients with ERA with patients with each of the other JIA subtypes. The finding of a relatively high level of disability in juvenile spondylarthropathy may be supported by a recent study demonstrating more functional impairment in juvenile AS than in adult AS (13). The mean HAQ indexes in our patients tended to be higher than the indexes observed in 33 patients with ERA who were assessed after 16 years by Minden et al (8). In contrast, slightly poorer HAQ and SF-36 PCS scores than ours were observed by Foster et al in 10 patients with ERA (14).

The remission rate among our patients with ERA was higher than that reported by Minden et al (8). In studies of juvenile spondylarthropathy, the frequency of remission has ranged from 17% to 37% (7,9). Differences in the definition of remission may have influenced the results. Previous studies have used criteria for remission that were developed for adult patients with rheumatoid arthritis (RA). The new criteria for remission in JIA used in the present study have been evaluated for oligoarthritis and polyarthritis but not for ERA (26).

### Table 6. Correlates of physical health after a median of 23.0 years of disease in 40 patients with ERA*

<table>
<thead>
<tr>
<th>Pearson’s correlation coefficient†</th>
<th>Multiple regression analysis†</th>
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<tbody>
<tr>
<td>Female sex</td>
<td>-0.466 0.002</td>
<td>-0.403 0.003</td>
</tr>
<tr>
<td>Age at onset, years</td>
<td>0.254 0.114</td>
<td>0.114</td>
</tr>
<tr>
<td>Family history of AS in first-degree relative</td>
<td>-0.450 0.004</td>
<td>-0.379 0.005</td>
</tr>
<tr>
<td>HLA–DRB1*08</td>
<td>-0.349 0.027</td>
<td>-0.325 0.012</td>
</tr>
<tr>
<td>Number of affected joints within 6 months</td>
<td>-0.294 0.065</td>
<td>-0.304 0.056</td>
</tr>
<tr>
<td>Hip arthritis within the first 6 months</td>
<td>-0.294 0.065</td>
<td>-0.304 0.056</td>
</tr>
</tbody>
</table>

* Other HLA alleles, ankle arthritis, and an elevated erythrocyte sedimentation rate within the first 6 months did not correlate with the physical component summary score of the 36-item Short Form health survey (P ≥ 0.10; data not shown). ERA = enthesitis-related arthritis; AS = ankylosing spondylitis.
† Results of final multiple linear regression analysis identifying predictors of poor physical health. Correlates with physical limitations in the univariate analyses (P < 0.10) were included.
Further evaluation of criteria for remission is needed in order to determine reliable frequencies of failure to achieve remission in ERA.

The frequency of sacroiliitis in our patients with ERA is consistent with the results reported by Minden et al (8). Higher frequencies of sacroiliitis have previously been observed in most studies of the SEA syndrome and unspecified juvenile spondylarthropathy (6,10,11), but a low rate was found in one small study group (12). Limited study samples and differences in the classification criteria used make the results difficult to compare. Conventional radiography, as used in the present study, is considered to be the gold standard for the demonstration of sacroiliitis (37). However, computed tomography and contrast-enhanced magnetic resonance imaging are more sensitive techniques for detecting early sacroiliitis (16,38,39), and the use of these methods may have revealed a higher frequency of sacroiliitis in patients with ERA.

Reduced spinal mobility occurred in three-fourths of our patients with ERA, and almost half of them experienced inflammatory back pain. Spinal signs and symptoms occurred with slightly less frequency than that in 2 previous studies of juvenile spondylarthropathy (6,8,13), but the frequency was similar to that in another study (40). The frequency of reduced spinal mobility was higher in patients with sacroiliitis than in those without sacroiliitis, in the present study and in a previous study (6), and differences in the classification of patients may have influenced the results. Furthermore, the frequency of reduced spinal mobility in our study is limited by the lack of control groups of similar age and sex who were derived from a Caucasian population.

The male preponderance, late age at onset, high frequency of HLA–B27, low frequency of antinuclear antibodies, and increased occurrence of sacroiliac and calcaneal changes in ERA were significantly different from the same characteristics of patients with oligoarthritis and polyarthritis. Thus, patients with ERA represented a group with distinct patient and disease characteristics.

In the present study, AS in a first-degree relative predicted failure to attain remission and physical limitations. An association between a family history of AS and the development of juvenile AS is well known (6,18). Differences in disease severity between familial and sporadic juvenile spondylarthropathy need to be further explored.

HLA–DRB1*08 was a predictor of failure to attain remission and a correlate to physical limitation in ERA. We previously demonstrated that HLA–DRB1*08 was a predictor of persistent disease in juvenile RA (JRA) (19). HLA–DRB1*08 has been found to be more prevalent in patients with juvenile spondylarthropathy than in HLA–B27–positive individuals in Norwegian Caucasian and Mexican Mestizo populations (41,42). Our results indicate that HLA–DRB1*08 (or genes in linkage disequilibrium) may be a marker of persistent disease activity in various JIA subtypes, but further investigations in different populations are needed. HLA–DPB1*02, a well-known correlate of oligoarthritis, protected against the development of sacroiliitis in ERA, as was previously demonstrated for JIA (18).

In our patients with ERA, female sex was a predictor of patient-assessed physical limitations and was associated with failure to attain remission. In contrast, male sex was associated with reduced anterior spinal flexion. In the total cohort of patients with JIA, males had an increased risk of the development of sacroiliitis (18). Male sex is part of the criteria for the classification of ERA (1), and one might question whether more males with mild disease than females with mild disease were included. Furthermore, the new criteria for remission in JIA do not include signs of axial involvement, a feature that was more frequent in males with ERA than in females with ERA (26). Our results are consistent with previous identifications of female sex as a predictor of disability in JRA and seronegative polyarticular JIA (19,43,44).

Early ankle arthritis predicted failure to achieve remission. Recently, Burgos-Vargas et al reported that midfoot involvement was associated with active disease in juvenile spondylarthropathy (45). In the present study, information from the time of disease onset was obtained by chart reviews and did not allow differentiation between tarsal and ankle involvement. Hip arthritis within the first 6 months predicted the development of sacroiliitis in ERA, as previously demonstrated in JIA (18). This result is in accordance with the association between hip joint involvement and juvenile AS observed by other investigators (6,46). In our patients, a large cumulative number of affected joints at the time of disease onset predicted poor physical health, and a persistently elevated ESR predicted the development of sacroiliitis, suggesting that the level of disease activity early in the disease course is a marker of disease severity.

ERA was associated with increased frequency of spinal involvement and represented a disease entity with distinct characteristics and outcomes. More than half of the patients still had significant disease when they reached adulthood, and the physical outcome was
poorer in patients with ERA than in those with oligoarthritis or polyarthritis and healthy controls. Our results may emphasize the need for aggressive treatment of juvenile spondylarthropathy, especially in patients with a family history of similar disease, the presence of HLA–DRB1*08, the absence of HLA–DPB1*02, early hip or ankle arthritis, high numbers of affected joints, and a persistently elevated ESR within the first 6 months.

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REFERENCES


