HLA-B27 Predicts a More Chronic Disease Course in an 8-year Followup Cohort of Patients with Juvenile Idiopathic Arthritis

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ABSTRACT. Objective. We investigated associations of HLA-B27 with clinical manifestations and longterm outcome in a near population-based setting among patients with juvenile idiopathic arthritis (JIA).

Methods. We studied clinical and serological data from 410 patients with HLA-B27 results among 440 prospectively collected patients with JIA with 8-year followup data in a Nordic database. The study was structured to be as close to a population-based study as possible.

Results. HLA-B27 was analyzed in 93% of patients, and was positive in 21% of the cohort, in 18.4% of the girls and in 25.9% of the boys. Boys who were HLA-B27-positive had significantly higher age at onset compared to HLA-B27-negative boys and compared to both HLA-B27-negative and positive girls. This difference in onset age in relation to HLA-B27 was not found in girls. HLA-B27 was associated with clinical signs of sacroiliitis, enthesitis, and tenosynovitis in boys, but not in girls. After 8 years of disease, 46 children (11.2%) were classified as having enthesitis-related arthritis (ERA). Boys with ERA had clinical signs of sacroiliitis more often than girls with ERA. HLA-B27-positive children, as well as children with clinical signs of sacroiliitis, enthesitis, and hip arthritis, had higher odds of not being in remission off medication after 8 years of disease.

Conclusion. In this near population-based Nordic JIA cohort we found significant differences between HLA-B27-positive boys and girls in age at disease onset, clinical signs of sacroiliitis, and ERA classification. HLA-B27 was negatively associated with longterm remission status, possibly because of its association with clinical disease characteristics, such as sacroiliitis, rather than being a general marker of persistent disease. (First Release April 1 2013; J Rheumatol 2013;40:725–31; doi:10.3899/jrheum.121257)

Key Indexing Terms: JUVENILE RHEUMATOID ARTHRITIS GENETICS HLA-B27 CHILD JOINTS

Juvenile idiopathic arthritis (JIA) is a heterogeneous disease entity, and the search for more homogeneous disease categories is under way, especially regarding the classification of juvenile spondyloarthropathies. The introduction of the International League of Associations for Rheumatology (ILAR) classification system was an important contribution toward a unified international classification system. However, challenges remain with respect to defining meaningful categories of JIA to be used in further research, clinical practice, and prediction of outcome.

One of the challenges in classification of JIA is to predict sacroiliitis in children, since this condition often presents years after disease onset and is known to be associated with a worse prognosis. Children that later develop sacroiliitis will initially often present with peripheral arthritis and enthesitis and less commonly inflammatory back pain, compared to the axial pattern found in adults. The concept of juvenile spondyloarthropathy (JSpA) refers to a group of rheumatic diseases with onset age < 16 years, characterized by arthritis, enthesitis, inflammatory back pain, and an association with the human leukocyte antigen
rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA, with normal ESR and, if both were present, also a normal CRP, and physician’s global assessment of disease activity indicating no disease activity. To be in clinical remission while off medication the patient must have met the criteria for inactive disease for a minimum of 12 continuous months while taking no antiarthritics and antiuveitis medications17. Remission data based on updated criteria from 2011 were not accessible18.

The Research Ethics Committees in each country had given their approval according to national practice and legislation. Written informed consent had been obtained from children ≥16 years of age and from parents of children aged <16 years.

Statistical methods. Conventional descriptive statistics were used; median and interquartile ranges (IQR) were given. For paired samples, the Wilcoxon signed-rank test was used, and for independent samples the Mann-Whitney U test or Fisher’s exact test, as appropriate. P values on 2-tailed tests <0.05 were considered statistically significant. To measure the effect of HLA-B27 on age at onset and sex, a binary logistic regression analysis was used. The interaction between age at disease onset and sex was included in the model. Binary logistic regression was also used in analyses exploring the association of HLA-B27 and remission status. The OR and 95% CI were calculated to determine the odds of not being in remission while off medication after 8 years of disease in relation to HLA-B27, occurrence of enthesitis, and clinical signs of SI and hip joint arthritis, stratified for sex. We also studied the interaction between HLA-B27 and the other variables. Analyses were carried out using SPSS version 20 (IBM SPSS Statistics).

RESULTS

HLA-B27 data were available for 410 (93.2%) of the 440 patients with longterm followup data in the Nordic database. In the 30 patients for whom HLA-B27 data were not available, sex distribution and prevalence of oligoarticular persistent disease were similar to the 410 study patients, while median age at disease onset was significantly lower (p<0.01).

Age at onset in relation to HLA-B27 and sex. Of the 410 patients (271 girls, 139 boys), 86 (21%) were HLA-B27-positive, 50 girls (18.4%), and 36 boys (25.9%) (Table 1), with no statistical difference between girls and boys (p=0.1).

Median age at onset in the whole cohort was 5.7 years, 7.7 years (IQR 3.1–11.8) in HLA-B27-positive patients and 5.3 years (IQR 2.3–9.2) in HLA-B27-negative patients (p=0.06). The difference in age at onset was primarily due to the difference in boys. We found a significant interaction (p=0.02) between age at onset and sex in a logistic regression analysis of occurrence of HLA-B27, with OR 1.03 (95% CI 1.1–1.1) in girls, and OR 1.20 (95% CI 1.1–1.3) for age in boys.

Cumulative number of joints in relation to HLA-B27 and sex. The cumulative number of affected joints during the disease course showed a significant sex difference; girls had a median 7 (IQR 3–14) and boys median 5 (IQR 2–11) joints involved (p<0.01) during the first 8 years of followup (results not shown). We found no statistical difference in cumulative number of active joints between HLA-B27-positive and negative patients, neither in the total cohort nor stratified by sex. There were no differences in involvement of small joints of the foot in HLA-B27-positive compared to HLA-B27-negative boys or compared to girls.
Association between HLA-B27 and clinical manifestations.
In our study, inflammatory back pain, SI pain, buttock pain, enthesitis, and tenosynovitis were significantly more common in HLA-B27-positive compared to HLA-B27-negative boys (Table 2). In girls, no associations between HLA-B27 and these clinical features were found. Hip joint arthritis was recorded in 99 patients during the course of disease, with no association to HLA-B27 in boys or girls. We also studied the patients with onset of hip joint arthritis within the first year of disease (n = 52, 32 girls, 20 boys), and found no association to HLA-B27. Eighteen patients developed symptomatic uveitis during followup; 11 were HLA-B27-positive, 6 girls and 5 boys.

Clinical signs of sacroiliitis. Fifty children had at least 1 of the following clinical signs of sacroiliitis: inflammatory back pain, pain over the SI joints on palpation, or buttock pain (Table 2). Nine patients had all 3 signs, 13 had 2, and 28 had 1 sign. At least 1 of 3 clinical signs of sacroiliitis occurred in 29 (10.7%) of 271 girls and in 21 (15.1%) of 139 boys (p = 0.16). Patients with clinical signs of sacroilitis more frequently had hip arthritis, irrespective of sex (p < 0.01).

HLA-B27 and clinical manifestations according to ILAR criteria. The prevalence of HLA-B27 in the different JIA categories at the final study visit is presented in Table 3. HLA-B27 was most often found in ERA (72%), but was also found in all other categories, with a frequency of 5%–21%. There were no sex differences in the frequency of HLA-B27 in any of the different JIA categories.

Enthesitis-related arthritis. After 6 months of disease, 31 (7.6%) children were classified as belonging to the ERA category, increasing to 46 (11.2% of the study) after 8 years of disease, 16 girls and 30 boys (Table 3). Median age at disease onset was 8.9 years in girls and 10 years in boys, with no significant sex difference. Although there was a trend toward more HLA-B27-positive boys than girls in the ERA category, 77% versus 62%, this difference was not significant. Similarly, there was no significant sex difference

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Table 1. Age at onset according to sex and HLA-B27 in 410 patients with juvenile idiopathic arthritis (JIA) in the Nordic JIA database.

<table>
<thead>
<tr>
<th></th>
<th>Total Age at Onset, yrs</th>
<th>HLA-B27-positive Age at Onset, yrs</th>
<th>HLA-B27-negative Age at Onset, yrs</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median (IQR)</td>
<td>n</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Girls</td>
<td>271</td>
<td>5.6 (2.3–10.0)</td>
<td>50</td>
<td>6.4 (2.9–10.9)</td>
</tr>
<tr>
<td>Boys</td>
<td>139</td>
<td>5.7 (3.1–9.2)</td>
<td>36</td>
<td>9.3 (5.1–12.3)</td>
</tr>
<tr>
<td>Total</td>
<td>410</td>
<td>5.7 (2.6–9.8)</td>
<td>86</td>
<td>7.7 (3.1–11.8)</td>
</tr>
</tbody>
</table>

* Mann-Whitney U test; HLA-B27-positive versus negative patients. IQR: interquartile range.

Table 2. Association between HLA-B27 and clinical manifestations during 8 years of disease course in 410 patients (271 girls and 139 boys) with juvenile idiopathic arthritis (JIA) in the Nordic JIA database.

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Sex (n) %</th>
<th>HLA-B27-positive</th>
<th>HLA-B27-negative</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50 girls (%)</td>
<td>221 girls (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>36 boys (%)</td>
<td>103 boys (%)</td>
<td></td>
</tr>
<tr>
<td>Inflammatory back pain</td>
<td>Girls (15) 5.5</td>
<td>5/50 (10.0)</td>
<td>10/221 (4.5)</td>
<td>0.16</td>
</tr>
<tr>
<td>Boys (14) 10.1</td>
<td>10/36 (27.8)</td>
<td>4/103 (3.9)</td>
<td>&lt; 0.005</td>
<td></td>
</tr>
<tr>
<td>Sacroiliac pain</td>
<td>Girls (13) 4.8</td>
<td>4/50 (8.0)</td>
<td>9/221 (4.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>Boys (13) 9.3</td>
<td>9/36 (25.0)</td>
<td>4/103 (3.9)</td>
<td>&lt; 0.005</td>
<td></td>
</tr>
<tr>
<td>Buttock pain</td>
<td>Girls (15) 5.5</td>
<td>3/50 (6.0)</td>
<td>12/221 (5.4)</td>
<td>0.74</td>
</tr>
<tr>
<td>Boys (11) 7.9</td>
<td>9/36 (25.0)</td>
<td>2/103 (1.9)</td>
<td>&lt; 0.005</td>
<td></td>
</tr>
<tr>
<td>Any clinical sign of sacroilitis**</td>
<td>Girls (29) 10.7</td>
<td>8/50 (16.0)</td>
<td>21/221 (9.5)</td>
<td>0.20</td>
</tr>
<tr>
<td>Boys (21) 15.1</td>
<td>15/36 (41.7)</td>
<td>6/103 (5.8)</td>
<td>&lt; 0.005</td>
<td></td>
</tr>
<tr>
<td>Enthesitis</td>
<td>Girls (19) 7.0</td>
<td>4/50 (8.0)</td>
<td>15/221 (6.8)</td>
<td>0.48</td>
</tr>
<tr>
<td>Boys (30) 21.6</td>
<td>12/36 (33.3)</td>
<td>8/103 (7.8)</td>
<td>&lt; 0.005</td>
<td></td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>Girls (51) 18.8</td>
<td>12/50 (24.0)</td>
<td>39/221 (17.6)</td>
<td>0.12</td>
</tr>
<tr>
<td>Boys (35) 25.2</td>
<td>14/36 (38.9)</td>
<td>21/103 (20.4)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Hip arthritis</td>
<td>Girls (65) 24.0</td>
<td>14/50 (28.0)</td>
<td>51/221 (23.1)</td>
<td>0.47</td>
</tr>
<tr>
<td>Boys (34) 24.5</td>
<td>12/36 (33.3)</td>
<td>22/103 (21.4)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Arthritis in small joints of feet†</td>
<td>Girls (150) 55.4</td>
<td>28/50 (56.0)</td>
<td>122/221 (55.2)</td>
<td>0.52</td>
</tr>
<tr>
<td>Boys (70) 50.4</td>
<td>20/36 (55.6)</td>
<td>50/103 (48.5)</td>
<td>0.30</td>
<td></td>
</tr>
</tbody>
</table>

* Fisher’s exact test, HLA-B27-positive versus negative JIA patients. ** At least 1 of 3 clinical signs of sacroilitis, inflammatory back pain, sacroiliac pain (pain over the sacroiliac joints at palpation), or buttock pain during disease course. † Arthritis in tarsal, metatarsophalangeal, toe, or subtalar joints during disease course.

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in occurrence of enthesitis or hip joint arthritis in ERA (data not shown). However, 19 of 21 boys with clinical signs of sacroiliitis belonged to the ERA category, while only 8 of 29 girls with those signs were categorized as having ERA. The 2 boys with clinical signs of sacroiliitis not qualifying for ERA both fulfilled inclusion criteria for ERA, but were excluded because of either first-degree heredity for psoriasis or fulfillment of 2 JIA categories. On the other hand, 10 of the 29 girls with clinical signs of sacroiliitis were classified as having undifferentiated arthritis because of first-degree heredity for psoriasis in 8, psoriasis in 1, and positive rheumatoid factor (RF) in 1 patient.

Outcome measures and occurrence of HLA-B27. Of the 410 patients, 204 (49%) were treated with methotrexate (MTX) orally or subcutaneously during disease course. Etanercept was given to 51 patients (12.4%) and infliximab to 31 (7.6%). MTX as well as either or both of etanercept and infliximab was given equally often to HLA-B27-positive and negative patients (p = 0.72 and p = 0.34, respectively).

CHAQ or HAQ was assessed in 335 patients (81.7%) after 8 years of disease and a value > 0 was statistically not more common in HLA-B27-positive compared to negative patients (p = 0.77).

Predictors of remission. After 8 years of disease, 237 (59.4%) of the 399 patients with available outcome data were not in clinical remission while off medication at the final study visit. The odds of not being in remission off medication were twice as high for HLA-B27-positive compared to those HLA-B27-negative when we adjusted for sex (OR 2.2, 95% CI 1.3–3.8; Table 4). The odds of not being in remission were high also for patients with enthesitis, clinical signs of sacroiliitis, and hip arthritis during the course of disease. Adjustments for sex did not weaken the results, and after adjustment for HLA-B27 the results were slightly attenuated, but still remained significant. The OR of not being in remission while off medication, associated with HLA-B27, was attenuated when we adjusted for sex and clinical signs of sacroiliitis, enthesitis, and hip arthritis (OR 1.8, 95% CI 1.0–3.1; p = 0.04). In the analyses of remission we did not find any interaction between sex and HLA-B27 or between sex and enthesitis or clinical signs of sacroiliitis or hip arthritis.

ILAR categories, outcome, and occurrence of HLA-B27. Fewer patients with ERA were in remission after 8 years of disease compared to other categories of JIA (p = 0.038). Occurrence of HLA-B27 did not influence remission status in patients within the ERA category or in other categories such as polyarticular RF-negative, extended, or persistent oligoarticular disease.

DISCUSSION
In this prospectively collected cohort of Nordic patients with JIA followed for a median of 8 years, we found significant differences between boys and girls with HLA-B27, both in age distribution and in association with clinical manifestations. Girls and boys with clinical signs of sacroiliitis were categorized differently, according to the ILAR classification. Also, HLA-B27, as well as clinical signs of sacroiliitis, enthesitis, and hip arthritis, was associated with higher odds of not being in remission while off medication after 8 years of disease, irrespective of sex.

The strength of the study is the near population-based cohort structure and long-term followup. A limitation is that clinical signs of sacroiliitis and hip arthritis were not confirmed by radiology. The number of patients in some of the ILAR categories was also rather low, limiting the value of the analyses.

Application of the remission criteria according to Wallace, et al to patients with ERA can be questioned. Patients with ERA and JPsA were not included in the preliminary criteria17. To date there are no specific remission criteria intended for ERA.

In our study, the prevalence of HLA-B27 was 21%, which is higher compared to findings from other studies on...
The background prevalence of HLA-B27 is high in the northernmost parts of the Nordic countries, about 16% in the population of northern Norway, Sweden, and Finland, and 8%–10% in those living in the southern and central parts of these countries, as well as in Denmark. One of our findings was the higher age of onset in HLA-B27-positive boys compared to boys without the antigen. This is in agreement with earlier studies showing a higher age at onset in HLA-B27-positive patients with JIA, without presenting data on the sexes separately or with a smaller study cohort. One could speculate, like Murray and coauthors, that HLA-B27 protects boys from getting JIA in earlier age groups, or as the ILAR categorization tends to suggest, that the association of HLA-B27 in older boys defines a distinct subgroup of JIA.

The number of cumulative joints did not show any association with HLA-B27 in this study. In our earlier study on 3-year followup of a subgroup of this cohort, HLA-B27-positive boys had a higher risk of more joint involvement with increasing age at onset. They also had more involvement of small joints of the foot compared to HLA-B27-negative boys and also compared to girls, irrespective of HLA-B27 status. We could not confirm these results in this larger cohort followed for 8 years, emphasizing the importance of the size of the study cohort and the length of the followup.

The HLA-B27-positive patients in our study did not have more active joints compared to other patients, but enthesitis and clinical signs of sacroiliitis were overrepresented, at least in boys. Accordingly, we found that clinical signs of sacroiliitis were associated with HLA-B27 in boys, but not in girls. Because we lack radiologic verification of these results, we cannot rule out that these sex differences were not influenced by what the clinicians expected to find. This possible limitation of the clinical data is supported by some studies in adults, where spondylitis is diagnosed after a longer time of symptoms in women compared to men. However, clinical signs of sacroiliitis in our study were as common in girls as in boys, and further, many of the girls with clinical signs of sacroiliitis had heredity for psoriasis. This is in accord with our results where heredity for psoriasis was an important reason why girls with clinical signs of sacroiliitis were classified as having undifferentiated arthritis and not ERA. This finding emphasized a possible weakness in the ILAR criteria, where psoriasis in a first-degree relative is an exclusion criterion for ERA; and similarly, ERA-associated clinical features in a first-degree relative exclude the JPsA category.

The ERA category included many of the HLA-B27-positive patients in our study, but the antigen was also found in all other ILAR categories. This is mainly in accord with other studies. However, the higher background prevalence of HLA-B27 in the northernmost parts of the Nordic countries must be considered.

The ILAR classification criteria for ERA (Table 5) include the clinical signs of sacroiliitis such as inflammatory back pain, sacroiliac (SI) pain (pain over the SI joints at palpation), or buttock pain during disease course. Data available for 397 patients. JIA: juvenile idiopathic arthritis.

### Table 4. OR (95% CI) for not being in remission off medication after 8 years of disease in relation to HLA-B27 and clinical characteristics in 399 patients with available outcome data from the Nordic JIA database.

<table>
<thead>
<tr>
<th>Total Cohort</th>
<th>N</th>
<th>N (%)</th>
<th>OR (95% CI)</th>
<th>p</th>
<th>OR (95% CI)</th>
<th>p</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B27-positive</td>
<td>82</td>
<td>(73.2)</td>
<td>2.2 (1.3–3.7)</td>
<td>0.005</td>
<td>2.2 (1.3–3.8)</td>
<td>0.004</td>
<td>——</td>
<td>——</td>
</tr>
<tr>
<td>Any clinical sign of sacroiliitis†</td>
<td>50</td>
<td>(84.0)</td>
<td>4.1 (1.9–9.1)</td>
<td>&lt; 0.001</td>
<td>4.3 (1.9–9.4)</td>
<td>&lt; 0.001</td>
<td>3.6 (1.6–8.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Enthesitis††</td>
<td>38</td>
<td>(76.3)</td>
<td>2.4 (1.1–5.2)</td>
<td>0.028</td>
<td>2.5 (1.1–5.4)</td>
<td>0.022</td>
<td>2.2 (1.0–4.8)</td>
<td>0.051</td>
</tr>
<tr>
<td>Hip arthritis</td>
<td>96</td>
<td>(72.9)</td>
<td>2.2 (1.3–3.6)</td>
<td>0.002</td>
<td>2.2 (1.3–3.6)</td>
<td>0.002</td>
<td>2.1 (1.3–3.5)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

* Adjusted for sex. ** Adjusted for sex and HLA-B27. † At least 1 of 3 clinical signs of sacroiliitis, inflammatory back pain, sacroiliac (SI) pain (pain over the SI joints at palpation), or buttock pain during disease course. †† Data available for 397 patients. JIA: juvenile idiopathic arthritis.
Table 5. Enthesitis-related arthritis according to the International League of Associations for Rheumatology classification criteria2.

Definition: arthritis and enthesitis, or arthritis, or enthesitis, with at least 2 of the following:
1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain.
2. The presence of HLA-B27 antigen.
3. Onset of arthritis in a male over 6 years of age.
4. Acute (symptomatic) anterior uveitis.
5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroilitis with inflammatory bowel disease, Reiter’s syndrome, or acute anterior uveitis in a first-degree relative.

Exclusions:
Psoriasis or a history of psoriasis in the patient or first-degree relative.
The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart.
The presence of systemic JIA in the patient.

JIA: juvenile idiopathic arthritis.

different followup times4,5. A higher disease activity in patients with HLA-B27 has been suggested in children37 as well as in adults38. Interestingly, we could not find a worse outcome depending on HLA-B27 within the 4 most common categories of JIA, and we could not find higher use of disease-modifying antirheumatic drugs (including tumor necrosis factor blockers) in HLA-B27-positive compared to HLA-B27-negative patients. HLA-B27, though, was associated with clinical signs of ERA, signs that in themselves were associated with a bad outcome. Other authors have published data supporting difficulties in achieving remission in treatment of patients with ERA and less effectiveness of MTX and tumor necrosis factor inhibitors compared to other JIA categories39-41.

Our study supports an important role for HLA-B27 in characterizing subsets of patients with JIA, especially boys, who tend to develop JIA at a later age than girls and to develop clinical signs of sacroiliitis, enthesitis, and tenosynovitis more often during the disease course. In addition, HLA-B27, clinical signs of sacroiliitis, and hip arthritis seem to predict a more severe outcome in JIA, irrespective of sex. The severe outcome associated with HLA-B27 in our study seemed, however, to be associated with clinical characteristics in ERA.

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