Spondyloarthritis in a Pediatric Population: Risk Factors for Sacroiliitis

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ABSTRACT. Objective. Pediatric rheumatologists may have an opportunity to diagnose sacroiliitis in its early stages, prior to the development of irreversible radiographic changes. Early diagnosis frequently requires magnetic resonance imaging (MRI), the use of which is limited by expense and requirement for sedation. We set out to identify features of juvenile spondyloarthritis (SpA) associated with the highest risk of sacroiliitis, to identify patients who may be candidates for routine MRI-based screening.

Methods. We reviewed the charts of 143 children seen at Texas Scottish Rite Hospital for Children diagnosed with SpA based on the International League of Associations for Rheumatology criteria for enthesitis-related arthritis or the Amor criteria for SpA. We performed logistic regression analysis to identify risk factors for sacroiliitis.

Results. A group of 143 children were diagnosed with SpA. Consistent with the diagnosis of SpA, 16% had psoriasis, 43% had enthesitis, 9.8% had acute anterior uveitis, and 70% were HLA-B27+.

Fifty-three children had sacroiliitis, of which 11 cases were identified by imaging studies in the absence of suggestive symptoms or physical examination findings. Logistic regression analysis revealed that hip arthritis was a positive predictor of sacroiliitis, while dactylitis was a negative predictor.

Conclusion. Children with SpA are at risk for sacroiliitis, which may be present in the absence of suggestive symptoms or physical examination findings. The major risk factor for sacroiliitis is hip arthritis, while dactylitis may be protective. Routine screening by MRI should be considered in patients at high risk of developing sacroiliitis. (First Release August 1 2010; J Rheumatol 2010;37:2402–8; doi:10.3899/jrheum.100014)

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Juvenile idiopathic arthritis (JIA) is a heterogeneous set of conditions, linked only by the common features of arthritis or enthesitis in a child under age 16 years, lasting for at least 6 weeks. Juvenile spondyloarthritis (SpA) is a subset of pediatric arthritis, characterized by an increased male:female ratio, relatively older age of onset, predilection for the large joints in the lower extremities, high frequency of enthesitis, risk of sacroiliitis, and frequent presence of the HLA-B27 antigen. Under the current International League of Associations for Rheumatology (ILAR) classification system, most cases of pediatric SpA are subsumed by the diagnosis of enthesitis-related arthritis (ERA). In addition, there are 2 widely used adult criteria for the diagnosis of SpA: the European Spondylarthritides Study Group and the Amor criteria; a study in children revealed that the Amor criteria demonstrated better performance characteristics.

In children with SpA, the development of sacroiliitis and frank ankylosing spondylitis (AS) can take up to 5–10 years. Once AS has developed, therapies that are effective at reducing signs and symptoms of inflammation may not prevent further radiographic progression. It is possible, therefore, that early aggressive therapy of sacroiliac (SI) and lumbar inflammation may be the only means to alter the radiographic course of the disease. Thus, those of us in pediatric rheumatology may have a unique opportunity to intervene with therapies that can prevent the development of irreversible damage associated with spinal inflammation. However, since several of the first-line agents used in children and adults with arthritis appear to have minimal effectiveness in the management of axial inflammation, awareness of spinal inflammation is critical to instituting appropriate therapy. Unfortunately, the physical examination maneuvers used to screen for sacroiliitis have
limited sensitivity\textsuperscript{16,17}, and even plain radiography will miss many of the early findings\textsuperscript{18}, underscoring the value of obtaining advanced imaging such as magnetic resonance imaging (MRI) in high-risk individuals.

It is well recognized that children with certain common characteristics of SpA, such as male sex, hip involvement, and enthesitis, are more likely to develop sacroiliitis and AS compared to children with unrelated subtypes of juvenile arthritis\textsuperscript{6,19}. There are, however, few data identifying risk factors for sacroiliitis among pediatric patients with SpA, with 1 study showing that B27 increased the risk of axial inflammation and another failing to identify any predictors\textsuperscript{9,20}. To address this issue, we characterized a cohort of children with SpA followed at a single center and performed logistic regression analysis to identify features predictive of the development of sacroiliitis.

**MATERIALS AND METHODS**

**Patients:** This study took place at Texas Scottish Rite Hospital for Children (TSRHC). It is the major referral center for north Texas and all patient visits and ancillary services at this hospital are free of charge; thus, the patient population is likely to be representative of the general JIA population in Texas. Because TSRHC does not charge patients for its services, it does not use medical codes. This makes it necessary to use a variety of other approaches to identify children diagnosed with SpA. Specifically, we identified children through a clinical database of diagnoses provided by attending physicians and maintained by information services from January 1985 through October 2008. Institutional review board approval was obtained to search and extract data from the database. The database was searched in 2 ways: (1) diagnoses were searched to reflect the different terminology used over the years and included search terms of ankylosing spondylitis, psoriatic arthritis, reactive arthritis, and seronegative enthesitis and arthritis syndrome; and (2) a keyword search was done of all dictated notes for the following terms: acute uveitis, ankylosing spondylitis, B27-related arthritis, enthesis, enthesitis-related arthritis, inflammatory bowel disease, late onset pauci, reactive arthritis, spondyloarthritides, and spondyloarthropathy. A total of 464 medical charts identified in this manner were reviewed, and information was abstracted from 271 patients with documented synovitis or enthesitis lasting at least 6 weeks. We included in the study patients who met either the ILAR criteria for ERA, including patients who met the inclusion criteria for ERA but were excluded on the basis of personal or family histories of psoriasis; or the Amor criteria for SpA\textsuperscript{1,3}. To evaluate for the Amor criteria, we reviewed the charts for specific Amor criteria, assigning points to each criterion as per Amor, et al\textsuperscript{1,3} and including children with a score of at least 6 points\textsuperscript{3}. If the presence or absence of a symptom included in the Amor criteria was not addressed (e.g., alternating buttock pain), it was assumed to be absent.

The following definitions were used in this chart review. Small peripheral joints included the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal of the hands, as well as the corresponding joints of the feet. Large peripheral joints included the hips, shoulders, elbows, wrists, knees, ankles, and subtalar. For the application of the Amor criteria\textsuperscript{3}, oligoarthritis was defined as 4 or fewer joints, consistent with standard pediatric usage. Dactylitis was defined as digital swelling extending beyond the margins of the joints; because dactylitis does not necessarily require the presence of synovitis, the latter was not assumed to be present, unless specifically documented\textsuperscript{21}. Enthesitis was defined as tenderness or swelling at the location of a tendinous insertion into the bone. Iritis counted as a criterion only if it was the acute anterior uveitis (AAU) typical of patients with SpA. A patient or family member was considered to have psoriasis if that diagnosis was made conclusively by a physician, including the attending rheumatologist.

For the diagnosis of sacroiliitis, since neither swelling nor decreased range of motion can ever be detected\textsuperscript{22}, the diagnosis of sacroiliitis was made either on the basis of suggestive findings on physical examination or following a positive imaging study. We did include abnormal MRI, as defined below, as evidence of sacroiliitis under both the Amor and the ILAR criteria. For the ILAR criteria, a patient could be diagnosed with sacroiliitis based on either clinical or imaging findings, while application of the Amor criteria was limited to those with abnormal radiographic or MRI studies. Acute sacroiliitis in an MRI study required the presence of periarticular bone marrow edema; synovial fluid may be present but was not sufficient for diagnosis\textsuperscript{23}. Chronic synovitis in an MRI study was defined by the presence of 1 or more of subchondral sclerosis, bony erosion, periarthritis, fat deposition, or frank ankylosis, but by itself could not establish the diagnosis\textsuperscript{24}. Sacroiliitis on a plain radiograph was given a grade of 0–4, a positive study being one with at least grade 3 unilaterally or grade 2 bilaterally\textsuperscript{24,25}. The official report of each imaging study was reviewed by 2 pediatric rheumatologists to determine whether, based on the report, the study met the above criteria for the diagnosis of sacroiliitis. In cases of disagreement, the actual study was reviewed by a pediatric radiologist with expertise in juvenile arthritis, who made the final determination.

Plain radiographs of the SI joints generally consisted of both anteroposterior and either lateral or oblique views, although not all studies specified the exact views. MRI studies generally consisted of 4–5 mm coronal T1-weighted spin-echo and short-tau inversion recovery (STIR) images, as well as axial fat suppressed T2-weighted fast spin-echo (FSE) images. Contrast medium was not administered.

**Statistical analysis:** Demographics and clinical characteristics of the patients were summarized using descriptive statistics. Categorical data were summarized through frequencies and percentages, and continuous data through medians and intraquartile ranges. Categorical data were compared with the asymptotic chi-square, exact chi-square test, or Fisher’s exact test, as appropriate; continuous data were compared with the non-parametric Kruskal-Wallis test. To identify which patients might be at increased risk of sacroiliitis, we performed logistic regression analysis. Variables input into the model were baseline values for erythrocyte sedimentation rate (ESR) and platelet count, large joint arthritis, lower extremity arthritis, hip arthritis, sex, B27 status, psoriasis, dactylitis, enthesitis, AAU, and age of onset. Univariate logistic regression analyses were first done to identify significance of each factor in predicting the risk of sacroiliitis. Multicollinearity diagnostics for a multivariable regression model were then done to determine whether some of the potential risk factors were correlated with each other. This was done by examining variance inflation factors and variance proportions\textsuperscript{26}. Multivariable logistic regression analysis was conducted by constructing a full stepwise sequence\textsuperscript{27}. The final multivariable model was selected based on Akaike information criteria to identify risk factors that independently predicted sacroiliitis\textsuperscript{28}. The c-statistic showing area under the curve (AUC) of the predictive logistic regression model was also calculated. Statistical analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA) and SPSS Version 16 software (SPSS, Chicago, IL, USA).

**Sensitivity analysis:** In the primary analysis, sacroiliitis was determined to be present based on either typical findings on physical examination or abnormal imaging studies, as described. We performed a sensitivity analysis in which the diagnosis of sacroiliitis was limited to patients with abnormal imaging studies, and a second sensitivity analysis that excluded patients meeting only the Amor criteria for SpA.

**RESULTS**

**Clinical features of spondyloarthritis:** A total of 143 children were diagnosed with SpA based on the ILAR or Amor criteria, modified as discussed (Table 1). Fifty-three children were diagnosed exclusively based on the ILAR criteria, 33 exclusively by the Amor criteria, and 57 met both sets of
criteria. These numbers include 10 patients who met the inclusion criteria for ERA but were diagnosed with undifferentiated arthritis because of a personal (n = 6) or first-degree family history (n = 4) of psoriasis; 8 of those 10 patients also met the Amor criteria for SpA (data not shown). Overall, 37% of the SpA population had clinical or imaging evidence of sacroiliitis involvement. In addition, 16% had psoriasis, 43% had enthesitis, 9.8% had AAU, and 70% were HLA-B27+. About one-third had a positive anti-nuclear antibody. A positive rheumatoid factor was determined in 4.2%, although none of them had a second positive test that would have disqualified them under the ILAR criteria. Tumor necrosis factor (TNF) inhibitors were used to treat nearly one-third of the patients, while almost two-thirds were treated with at least 1 second-line agent, most commonly methotrexate.

Comparison of the 3 groups of patients (Amor only, ILAR only, and both) revealed that the Amor-only group were significantly younger than the remainder of the subjects, and were also less likely to be males, to have large joint involvement, enthesitis, acute anterior uveitis, or sacroiliitis, or to be B27+ (Table 1). They were more likely to have oligoarticular disease, dactylitis, or psoriasis. There were no differences in baseline laboratory values, treatment decisions, or duration of followup.

Risk factors for sacroiliitis. In our study, 53 children were diagnosed with sacroiliitis based upon clinical or imaging criteria (radiograph or MRI), 32 of whom had abnormal imaging studies. Among those 32, 20 had abnormal MRI studies, and 18 had abnormal plain radiographs (6 had both). Specific imaging findings are summarized in Table 2. All 20 of the patients with sacroiliitis detected by MRI had bone marrow edema seen as decreased signal intensity on the T1-weighted images and increased signal intensity on the fluid-sensitive T2 and STIR images; 8 (40%) also had synovial fluid. Seven (35%) had evidence of chronic changes at the first abnormal MR study, as evidenced by the presence of sclerosis, erosions, or joint space pseudo-widening, although these chronic findings by themselves were not sufficient for the diagnosis of sacroiliitis. Sclerosis was the most common radiographic finding, followed by erosions and joint space narrowing (including fusion). Importantly,
11 children lacked any documented history of back pain or stiffness, and had normal examinations of the SI joints at the time of the study. In these 11 patients, the sacroiliitis was detected either incidentally on dedicated images of the hips, in which case they were followed by dedicated imaging studies of the SI joints, or as a screening tool in light of the diagnosis of SpA.

We performed regression analysis to evaluate risk factors for sacroiliitis among children with SpA. The univariate regression analysis revealed that risk factors for sacroiliitis were male sex, hip arthritis, and older age of onset, while psoriasis and dactylitis were associated with a decreased risk (Table 3). In the multivariable model (Table 4), hip arthritis was the only significant positive risk factor for sacroiliitis (OR 11.45, 95% CI 2.65–49.49, p = 0.001), and dactylitis was the only significant negative predictor (OR 0.128, 95% CI 0.025–0.776, p = 0.0246). Unexpectedly, large joint arthritis entered this model as a weak negative predictor (OR 0.228, 95% CI 0.052–0.997, p = 0.0495).

**DISCUSSION**

We reviewed the charts of 143 children meeting the ILAR or Amor criteria for SpA. Although SpA is difficult to define, suggestive features in both adults and children include axial disease, AAU, male sex, oligoarthritis predominantly involving the lower extremities, enthesitis, psoriasis, and dactylitis.4,7,9,20,29. As a group, many of our patients with SpA did indeed have suggestive features, including sacroiliitis in 37%, AAU in 9.8%, male sex in 71%, enthesitis in 43%, dactylitis in 32%, psoriasis in 16%, B27 positivity in 26.9%, and involvement of large joints of the lower extremities in 80% (Table 1). These results are consistent with prior descriptions of children with SpA.9,19,29.

In our study, the Amor criteria did not appear to provide a significantly improved definition of juvenile SpA compared with either clinical or imaging evidence of sacroiliitis. Because the clinical tools used to diagnose sacroiliitis offer limited sensitivity and specificity,16,17 we performed a sensitivity analysis that included only cases of sacroiliitis that were detected by imaging studies. This did not affect inclusion under the Amor criteria, which already restricted the definition of sacroiliitis to patients with abnormal imaging studies, but did affect inclusion under the ILAR criteria. Under the sensitivity analysis, the number of patients included in this study was only 134, with their overall clinical features similar to those included in the primary analysis (data not shown). We repeated the regression analysis, using data on only those 134 children who were confirmed with imaging studies (32 cases with evidence of sacroiliitis and 102 with no evidence of sacroiliitis). The results were similar to those obtained with the primary analysis, except that baseline platelet count was no longer included in the multivariable model, while AAU was included, but was not statistically significant (OR 2.89, 95% CI 0.73–11.46, p = 0.132).

**Sensitivity analyses.** As discussed, we included children with either clinical or imaging evidence of sacroiliitis. The overall AUC was 0.759, which indicates moderately good ability of the model to predict sacroiliitis based on these 3 risk factors.
years in children with SpA, repeat imaging studies should be considered periodically. Axial disease often occurs after a lag time of 5–10 years in children with SpA, repeat imaging studies should be considered periodically.

MRI are expensive and do require sedation in some children; thus, it may be of benefit to identify a set of high-risk children with SpA who would most benefit from MRI screening. Therefore, we performed logistic regression analysis to look for predictors of sacroiliitis, finding that children with hip disease were at increased risk of sacroiliitis, while dactylitis was associated with a statistically significant reduced risk in the multivariable model (Table 4).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Estimate ± SE</th>
<th>OR (95% CI)</th>
<th>p</th>
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<tbody>
<tr>
<td>Dactylitis</td>
<td>-2.36 ± 0.59</td>
<td>0.094 (0.030, 0.300)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hip arthritis</td>
<td>2.44 ± 0.75</td>
<td>11.45 (2.65, 49.49)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Baseline platelet count</td>
<td>-0.0032 ± 0.0019</td>
<td>0.99 (0.99, 1.00)</td>
<td>0.0890</td>
</tr>
</tbody>
</table>

The estimates and their SE can be used to compute the OR and CI for a given risk factor as well as to predict the odds of sacroiliitis for patients with different combinations of risk factors. OR is equal to the exponential value of the estimate, e.g., the odds of sacroiliitis for patients with hip arthritis is e2.44 = 11.4 times that for patients without.

pared to the ILAR criteria. Specifically, patients defined by the Amor criteria as having SpA but not included under the ILAR criteria were typically females and were less likely to have large joint arthritis, sacroiliitis, or AAU (Table 1). They may have been enrolled on the basis of oligoarticular arthritis, dactylitis, and psoriasis. These features are generally consistent with SpA in adult patients, but may have less specificity in pediatric patients, as they define a younger population that is generally not considered to have SpA.

These findings are in contrast to previous studies, in which the specificity of the Amor criteria in children ranged from 91% to 96% to 96% to 96% to 96% to 96%. Until a biological “gold standard” is defined, further studies may be warranted to define the role of the Amor and other sets of adult classification criteria in pediatric patients.

Arguably, the most important reason to identify whether a child has SpA is to characterize that child’s risk of developing sacroiliitis. This complication is not only associated with increased morbidity and rarely even mortality among adult patients, but also has significant treatment implications, as axial involvement has not been shown to respond well to traditional disease-modifying agents. It is therefore of particular interest that 11 children were diagnosed incidentally with sacroiliitis, 8 with plain radiographs, and 7 with MRI (4 had both); by definition, sacroiliitis was detected in these 11 patients in the absence of any documented complaints of back pain (inflammatory or otherwise) or stiffness, or any abnormalities of the SI joint on physical examination. The findings of silent sacroiliitis in these patients are consistent with the findings of Bollow, et al, who reported that while the presence of back pain in children with SpA was a risk factor for MRI-demonstrated sacroiliitis, the latter was detected in almost 20% of patients who did not report a history of back pain. Since these early findings of sacroiliitis may predict the future development of frank AS, there may be a value in obtaining routine MRI imaging of the SI joints at baseline. In addition, because axial disease often occurs after a lag time of 5–10 years in children with SpA, repeat imaging studies should be considered periodically.

MRI are expensive and do require sedation in some children; thus, it may be of benefit to identify a set of high-risk...
our practice to document family histories of AS, psoriasis, and other inflammatory conditions at the first visit, but this documentation was not always performed, and we typically are unable to validate those diagnoses. We do not routinely collect information on some of the variables included in the Amor criteria. Any variables not mentioned were assumed to be negative, so it is possible that there are additional patients in the larger database who might have been included under the Amor criteria had we elicited information on features such as alternating buttock pain. Finally, the potential for ascertainment bias exists; thus, for example, the clinician might be more likely to look closely for enthesisitis, dactylitis, or sacroilitis in a child clinically suspected of having SpA.

We studied a cohort of children diagnosed with SpA over a 23-year period at a single children’s hospital. Over one-third of these children had sacroilitis demonstrated by clinical examination or imaging studies; in 11 of those patients, the sacroilitis was silent, present only on the imaging studies. This finding suggests that routine screening of children with SpA may be of use in identifying those who might benefit from more aggressive therapy early in the disease course, while identifying children with axial disease based on the historical features of inflammatory back pain or even suggestive physical examination findings may miss the diagnosis of axial disease. Additional research is needed to validate our findings on factors that in this study were shown to predict sacroilitis. In addition, prospective studies should be performed to address whether aggressive therapy of relatively early sacroilitis can halt radiographic progression.

REFERENCES