

\*Une promesse pour la vie

**HUMIRA**<sup>®</sup>  
adalimumab



# The Journal of Rheumatology

**The Journal of Rheumatology**

**Volume 37, no. 11**

Spondyloarthritis in a Pediatric Population: Risk Factors for Sacroiliitis

MATTHEW L. STOLL, RAFIA BHORE, MOLLY DEMPSEY-ROBERTSON and MARILYNN PUNARO

J Rheumatol 2010;37;2402-2408

<http://www.jrheum.org/content/37/11/2402>

1. Sign up for our monthly e-table of contents  
<http://www.jrheum.org/cgi/alerts/etoc>
2. Information on Subscriptions  
<http://jrheum.com/subscribe.html>
3. Have us contact your library about access options  
[Refer\\_your\\_library@jrheum.com](mailto:Refer_your_library@jrheum.com)
4. Information on permissions/orders of reprints  
<http://jrheum.com/reprints.html>

*The Journal of Rheumatology* is a monthly international serial edited by Duncan A. Gordon featuring research articles on clinical subjects from scientists working in rheumatology and related fields.

# Spondyloarthritis in a Pediatric Population: Risk Factors for Sacroiliitis

MATTHEW L. STOLL, RAFIA BHOORE, MOLLY DEMPSEY-ROBERTSON, and MARILYNN PUNARO

**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)

## Key Indexing Terms:

SPONDYLOARTHRTIS  
MAGNETIC RESONANCE IMAGING

JUVENILE IDIOPATHIC ARTHRITIS  
PEDIATRICS SACROILIITIS

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<sup>1</sup>. 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<sup>2</sup>. 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)<sup>1</sup>. In addition, there are 2 widely used adult criteria for the diagnosis of SpA: the European Spondylarthritis Study Group and the Amor criteria<sup>3,4</sup>; a study in children revealed that the Amor criteria demonstrated better performance characteristics<sup>5</sup>.

In children with SpA, the development of sacroiliitis and frank ankylosing spondylitis (AS) can take up to 5–10 years<sup>6,7,8,9</sup>. Once AS has developed, therapies that are effective at reducing signs and symptoms of inflammation may not prevent further radiographic progression<sup>10,11,12</sup>. 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<sup>13,14,15</sup>, awareness of spinal inflammation is critical to instituting appropriate therapy. Unfortunately, the physical examination maneuvers used to screen for sacroiliitis have

---

From the Departments of Pediatrics and Clinical Sciences, University of Texas Southwestern Medical Center, and the Departments of Rheumatology and Radiology, Texas Scottish Rite Hospital for Children, Dallas, Texas, USA.

Supported by grant UL1RR024982, “North and Central Texas Clinical and Translational Science Initiative” (Milton Packer, MD, PI) from the National Center for Research Resources, a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical Research.

M.L. Stoll, MD, PhD, Assistant Professor; M. Punaro, MD, Professor, Department of Pediatrics, Division of Rheumatology, UT Southwestern Medical Center, Department of Rheumatology, Texas Scottish Rite Hospital for Children; R. Bhoore, PhD, Assistant Professor, Department of Clinical Sciences, Division of Biostatistics, UT Southwestern Medical Center; M. Dempsey-Robertson, MD, Medical Director, Department of Radiology, Texas Scottish Rite Hospital for Children.

Address correspondence to Dr. M. Stoll, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9063, USA.

E-mail: Matthew.Stoll@UTSouthwestern.edu

Accepted for publication June 3, 2010.

limited sensitivity<sup>16,17</sup>, and even plain radiography will miss many of the early findings<sup>18</sup>, 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<sup>6,19</sup>. 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<sup>9,20</sup>. 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, enthesitis, enthesitis-related arthritis, inflammatory bowel disease, late onset pauci, reactive arthritis, spondyloarthritis, 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<sup>1,3</sup>. To evaluate for the Amor criteria, we reviewed the charts for specific Amor criteria, assigning points to each criterion as per Amor, *et al* and including children with a score of at least 6 points<sup>3</sup>. 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 metacarpophalangeals, proximal interphalangeals, and distal interphalangeals 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<sup>3</sup>, 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<sup>21</sup>. 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<sup>22</sup>, 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<sup>23</sup>. Chronic synovitis in an MRI study was defined by the presence of 1 or more of subchondral sclerosis, bony erosion, periarticular fat deposition, or frank ankylosis, but by itself could not establish the diagnosis<sup>23</sup>. Sacroiliitis in 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<sup>24,25</sup>. 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 detect whether some of the potential risk factors were correlated with each other. This was done by examining variance inflation factors and variance proportions<sup>26</sup>. Multivariable logistic regression analysis was conducted by constructing a full stepwise sequence<sup>27</sup>. The final multivariable model was selected based on Akaike information criteria to identify risk factors that independently predicted sacroiliitis<sup>28</sup>. 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

Table 1. Clinical features of children with spondyloarthritis. Continuous data are expressed as medians (interquartile range).

Variable	ILAR Only	Criteria Used Amor Only	ILAR and Amor	Total	p
No.	53	33	57	143	NA
Age of onset, yrs	10.8 (9.2–13.0)	3.8 (1.8–8.2)	10.8 (9.1–12.7)	10.2 (7.7–12.4)	< 0.001
Male sex, %	83	30	84	71	< 0.001
Involved joints, %					
Sacroiliitis	32	0	63	37	< 0.001
Silent sacroiliitis	5.9	0/0	28	21	0.082
Any large	96	67	86	85	< 0.001
Large, lower extremity	87	58	86	80	< 0.001
Any small	64	64	42	55	0.037
Total joints	8.0 (3.0–14)	2.0 (1.0–4.0)	4.0 (2.0–9.0)	4.0 (2.0–12.0)	< 0.001
≥ 5 joints, %	66	24	47	49	< 0.001
Extraarticular, %					
Psoriasis	0	52	11	16	< 0.001
Nail pits	8	30	21	18	0.022
Dactylitis	8	85	25	32	< 0.001
Enthesitis	38	6	68	43	< 0.001
Uveitis, %					
Chronic	2	18	0	5	< 0.001
Acute	2	0	23	10	< 0.001
Laboratory findings					
Baseline ESR	29.0 (11.0–55.0)	17.5 (10.5–31.0)	23.0 (11.0–42.0)	22.0 (11.0–45.0)	0.285
Baseline platelet count (× 10 <sup>3</sup> /ml)	357.0 (281.0–466.0)	352.0 (293.0–449.0)	329.0 (270.5–426.0)	346.5 (281.0–431.0)	0.540
ANA, %	26	69	24	36	< 0.001
RF, %	7	4	2	4	0.548
HLA-B27, %	77	30	84	70	< 0.001
Treatment, %					
Methotrexate	51	64	44	51	0.195
Sulfasalazine	8	0	11	7	0.192
Any TNF inhibitor	23	18	39	28	0.064
Any second-line drug	55	70	70	64	0.183
Duration of followup, yrs	3.5 (1.9–5.6)	3.4 (1.4–5.6)	4.0 (1.5–5.7)	3.7 (1.5–5.6)	0.728

ILAR: International League of Associations for Rheumatology; ESR: erythrocyte sedimentation rate; ANA: antinuclear antibody; RF: rheumatoid factor.

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 antinuclear 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<sup>23</sup>. Sclerosis was the most common radiographic finding, followed by erosions and joint space narrowing (including fusion). Importantly,

Table 2. Imaging findings diagnostic of sacroiliitis in children with SpA.

Feature	MRI, n = 20	Radiograph, n = 18
Acute sacroiliitis (MRI only)	20	NA
Bone marrow edema	20	NA
Synovial fluid in SI joint	8	NA
Chronic sacroiliitis	7	18
Subchondral sclerosis	6	16
Bone erosions or irregularity	3	10
Periarticular fat deposition (MRI only)	0	NA
Joint space narrowing (radiograph only)	NA	2
SI ankylosis	1	3

SpA: spondyloarthritis; MRI: magnetic resonance imaging; SI: sacroiliac. NA: not applicable.

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 0.09, 95% CI 0.03–0.30,  $p < 0.0001$ ). This means the odds of getting sacroiliitis in a patient with hip arthritis were 11.45 times higher than that for a patient with no hip arthritis. Similarly, the odds of sacroiliitis in a patient with dactylitis were 0.09 times lower than the odds for a patient without dactylitis. In addition, elevated platelet counts were associated with a slightly decreased risk of sacroiliitis in the

Table 3. Univariate predictors of sacroiliitis.

Risk Factor	OR (95% CI)	p
Male sex	2.26 (1.00, 5.10)	0.0497
B27 positivity	1.29 (0.60, 2.79)	0.5113
Psoriasis	0.21 (0.059, 0.745)	0.0158
Dactylitis	0.124 (0.045, 0.342)	< 0.0001
Enthesitis	1.71 (0.86, 3.40)	0.1256
Acute anterior uveitis	1.31 (0.43, 4.00)	0.6372
Large joint arthritis	0.95 (0.37, 2.47)	0.9152
Lower extremity arthritis	1.31 (0.52, 3.28)	0.5647
Hip arthritis	4.10 (1.44, 11.7)	0.0084
Age of onset	1.20 (1.07, 1.33)	0.0012
Baseline ESR	1.00 (0.99, 1.02)	0.6343
Baseline platelet count	0.998 (0.995, 1.001)	0.1879

ESR: erythrocyte sedimentation rate.

multivariable model, but this finding was not statistically significant (OR 0.99, 95% CI 0.99–1.00,  $p = 0.089$ ). The overall AUC was 0.759, which indicates moderately good ability of the model to predict sacroiliitis based on these 3 risk factors.

**Sensitivity analyses.** As discussed, we included children with either clinical or imaging evidence of sacroiliitis. Because the clinical tools used to diagnose sacroiliitis offer limited sensitivity and specificity<sup>16,17</sup>, 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,  $p = 0.132$ ).

We performed a second sensitivity analysis, in which the 33 children entered into the study exclusively on the basis of the Amor criteria were excluded. This analysis also restricted the definition of sacroiliitis to children with confirmatory imaging studies. In this analysis, the overall findings were essentially unchanged. Hip involvement continued to be a positive predictor of sacroiliitis (OR 7.52, 95% CI 2.10–26.9,  $p = 0.0019$ ) and dactylitis a negative predictor (OR 0.138, 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<sup>4,7,29,30,31</sup>. 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 70%, and involvement of large joints of the lower extremities in 80% (Table 1). These results are consistent with prior descriptions of children with SpA<sup>9,19,29</sup>.

In our study, the Amor criteria did not appear to provide a significantly improved definition of juvenile SpA com-

Table 4. Final adjusted model for prediction of sacroiliitis.

Risk Factor	Estimate ± SE <sup>†</sup>	OR (95% CI)	p
Dactylitis	-2.36 ± 0.59	0.094 (0.030, 0.300)	< 0.0001
Hip arthritis	2.44 ± 0.75	11.45 (2.65, 49.49)	0.0011
Baseline platelet count	-0.0032 ± 0.0019	0.99 (0.99, 1.000)	0.0890

<sup>†</sup> 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  $e^{2.44} = 11.4$  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<sup>3,4,32</sup>, but may have less specificity in pediatric patients, as they define a younger population that is generally not considered to have SpA<sup>33,34</sup>. These findings are in contrast to previous studies, in which the specificity of the Amor criteria in children ranged from 91% to 96%<sup>5,35,36</sup>. 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<sup>37</sup>, but also has significant treatment implications, as axial involvement has not been shown to respond well to traditional disease-modifying agents<sup>14,38</sup>. 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<sup>18</sup>. Since these early findings of sacroiliitis may predict the future development of frank AS<sup>39,40</sup>, 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<sup>9</sup>, 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). Overall, our findings were consistent with those from adult populations, which have identified these conditions as risk factors for AS or severe radiological outcomes among patients with SpA: AAU, limited mobility of the lumbar spine, elevated ESR, B27 positivity, hip arthritis, prolonged disease duration, and male sex<sup>40,41,42,43,44,45,46</sup>. In addition, prior studies among children have shown that the presence of hip arthritis distinguished children who would ultimately develop AS from those with juvenile rheumatoid arthritis<sup>19,43</sup>. The implication of these findings is that children with traditional features of juvenile SpA, including male sex, older age of onset, AAU, and most clearly hip arthritis, should be considered for routine MRI screening for sacroiliitis.

The significance of the findings on dactylitis is uncertain. It could be argued that because dactylitis is commonly found in children with psoriatic arthritis, particularly those with an early age of onset<sup>34</sup>, it might merely serve as a marker for a population that intrinsically is more heterogeneous. Importantly, however, the findings were observed even when the younger Amor population was excluded from the study. In addition, its inclusion in the final multivariable model argues against dactylitis acting exclusively as a confounder, but instead suggests mechanistic differences between the inflammation underlying dactylitis and that underlying axial arthritis. Thus, our data may question some of McGonagle’s hypotheses, according to which all of the articular manifestations of SpA, including dactylitis and sacroiliitis, may be secondary to enthesitis<sup>47,48,49</sup>.

Our study was limited by its retrospective design. Since 2000, we have prospectively collected the core dataset on all arthritis patients seen at TSRHC, and have maintained these data on flow sheets generated at the time of the encounter. However, many of the children included in this study were initially seen before 2000, so the clinical data had to be abstracted entirely from the notes. We may not always have accurate data on the family history. It is and has long been

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 enthesitis, dactylitis, or sacroiliitis 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 sacroiliitis demonstrated by clinical examination or imaging studies; in 11 of those patients, the sacroiliitis 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 sacroiliitis. In addition, prospective studies should be performed to address whether aggressive therapy of relatively early sacroiliitis can halt radiographic progression.

## REFERENCES

- Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390-2.
- Cabral DA, Malleson PN, Petty RE. Spondyloarthropathies of childhood. *Pediatr Clin North Am* 1995;42:1051-70.
- Amor B, Dougados M, Mijiyawa M. [Criteria of the classification of spondylarthropathies]. *Rev Rhum Mal Osteoartic* 1990;57:85-9.
- Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991;34:1218-27.
- Prieur AM, Listrat V, Dougados M, Amor B. [Criteria for classification of spondylarthropathies in children]. *Arch Fr Pediatr* 1993;50:379-85.
- Flato B, Smerdel A, Johnston V, Lien G, Dale K, Vinje O, et al. The influence of patient characteristics, disease variables, and HLA alleles on the development of radiographically evident sacroiliitis in juvenile idiopathic arthritis. *Arthritis Rheum* 2002;46:986-94.
- Jacobs JC, Berdon WE, Johnston AD. HLA-B27-associated spondylarthritis and enthesopathy in childhood: clinical, pathologic, and radiographic observations in 58 patients. *J Pediatr* 1982;100:521-8.
- Jacobs P. Ankylosing spondylitis in children and adolescents. *Arch Dis Child* 1963;38:492-9.
- Burgos-Vargas R, Clark P. Axial involvement in the seronegative enthesopathy and arthropathy syndrome and its progression to ankylosing spondylitis. *J Rheumatol* 1989;16:192-7.
- van der Heijde D, Landewe R, Baraliakos X, Houben H, van Tubergen A, Williamson P, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. *Arthritis Rheum* 2008;58:3063-70.
- van der Heijde D, Landewe R, Einstein S, Ory P, Vosse D, Ni L, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis Rheum* 2008;58:1324-31.
- van der Heijde D, Salonen D, Weissman BN, Landewe R, Maksymowych WP, Kupper H, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. *Arthritis Res Ther* 2009;11:R127.
- Clegg DO, Reda DJ, Abdellatif M. Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondylarthropathies: a Department of Veterans Affairs cooperative study. *Arthritis Rheum* 1999;42:2325-9.
- Haibel H, Brandt HC, Song IH, Brandt A, Listing J, Rudwaleit M, et al. No efficacy of subcutaneous methotrexate in active ankylosing spondylitis: a 16-week open-label trial. *Ann Rheum Dis* 2007;66:419-21.
- Haibel H, Rudwaleit M, Braun J, Sieper J. Six months open label trial of leflunomide in active ankylosing spondylitis. *Ann Rheum Dis* 2005;64:124-6.
- Spadaro A, Iagnocco A, Baccano G, Ceccarelli F, Sabatini E, Valesini G. Sonographic-detected joint effusion compared to physical examination in the assessment of sacroiliac joints in spondyloarthritis. *Ann Rheum Dis* 2009;68:1559-63.
- Williamson L, Dockerty JL, Dalbeth N, McNally E, Ostlere S, Wordsworth BP. Clinical assessment of sacroiliitis and HLA-B27 are poor predictors of sacroiliitis diagnosed by magnetic resonance imaging in psoriatic arthritis. *Rheumatology* 2004;43:85-8.
- Bollow M, Biedermann T, Kannenberg J, Paris S, Schauer-Petrowski C, Minden K, et al. Use of dynamic magnetic resonance imaging to detect sacroiliitis in HLA-B27 positive and negative children with juvenile arthritides. *J Rheumatol* 1998;25:556-64.
- Burgos-Vargas R, Vazquez-Mellado J. The early clinical recognition of juvenile-onset ankylosing spondylitis and its differentiation from juvenile rheumatoid arthritis. *Arthritis Rheum* 1995;38:835-44.
- Sonkar GK, Usha D, Singh S. Is HLA-B27 a useful test in the diagnosis of juvenile spondyloarthropathies? *Singapore Med J* 2008;49:795-9.
- Healy PJ, Groves C, Chandramohan M, Helliwell PS. MRI changes in psoriatic dactylitis — extent of pathology, relationship to tenderness and correlation with clinical indices. *Rheumatology* 2008;47:92-5.
- Brunner HI. More may not be better — but is less enough? [editorial]. *J Rheumatol* 2009;36:7-8.
- Rudwaleit M, Jurik AG, Hermann KG, Landewe R, van der Heijde D, Baraliakos X, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009;68:1520-7.
- van Tubergen A, Heuft-Dorenbosch L, Schulpen G, Landewe R, Wijers R, van der Heijde D, et al. Radiographic assessment of sacroiliitis by radiologists and rheumatologists: does training improve quality? *Ann Rheum Dis* 2003;62:519-25.
- van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.

26. Myers RH. Classical and modern regression with applications. Belmont, CA: Duxbury Press; 1989.
27. Shtatland ES, Kleinman K, Cain EM. Stepwise methods in using SAS PROC LOGISTIC and SAS ENTERPRISE MINER for prediction. In: SAS Users Group International 28th Proceeding, Paper 258-28; 2003. Cary, NC: SAS Institute Inc.; 2003.
28. Shtatland ES, Kleinman K, Cain EM. A new strategy of model building in PROC LOGISTIC with automatic variable selection, validation, shrinkage and model averaging. In: SAS Users Group International 29th Proceeding, Paper 191-29; 2004. Cary, NC: SAS Institute Inc.; 2004.
29. Rosenberg AM, Petty RE. A syndrome of seronegative enthesopathy and arthropathy in children. *Arthritis Rheum* 1982;25:1041-7.
30. Petty RE, Malleson P. Spondyloarthropathies of childhood. *Pediatr Clin North Am* 1986;33:1079-96.
31. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. *Ann Rheum Dis* 2002;61 Suppl 3:iii8-18.
32. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.
33. Stoll ML, Nigrovic PA. Subgroups within juvenile psoriatic arthritis: a review of the literature. *Clin Dev Immunol* 2006;13:377-80.
34. Stoll ML, Zurakowski D, Nigrovic LE, Nichols DP, Sundel RP, Nigrovic PA. Patients with juvenile psoriatic arthritis comprise two distinct populations. *Arthritis Rheum* 2006;54:3564-72.
35. Kasapcopur O, Demirli N, Ozdogan H, Apelyan M, Caliskan S, Sever L, et al. Evaluation of classification criteria for juvenile-onset spondyloarthropathies. *Rheumatol Int* 2005;25:414-8.
36. Joos R, Dehoorne J, Hoffman I, Mielants H, Verbruggen G, Elewaut D. Sensitivity and specificity of criteria for spondyloarthritis in children with late onset pauciarticular juvenile chronic arthritis as well as their characteristics. *Clin Exp Rheumatol* 2009;27:870-6.
37. Boonen A, van der Linden SM. The burden of ankylosing spondylitis. *J Rheumatol* 2006;33 Suppl 78:4-11.
38. Chen J, Liu C. Is sulfasalazine effective in ankylosing spondylitis? A systematic review of randomized controlled trials. *J Rheumatol* 2006;33:722-31.
39. Bennett AN, McGonagle D, O'Connor P, Hensor EM, Sivera F, Coates LC, et al. Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. *Arthritis Rheum* 2008;58:3413-8.
40. Huerta-Sil G, Casasola-Vargas JC, Londono JD, Rivas-Ruiz R, Chavez J, Pacheco-Tena C, et al. Low grade radiographic sacroiliitis as prognostic factor in patients with undifferentiated spondyloarthritis fulfilling diagnostic criteria for ankylosing spondylitis throughout follow up. *Ann Rheum Dis* 2006;65:642-6.
41. Mau W, Zeidler H, Mau R, Majewski A, Freyschmidt J, Stangel W, et al. Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year followup. *J Rheumatol* 1988;15:1109-14.
42. Spencer DG, Park WM, Dick HM, Papazoglou SN, Buchanan WW. Radiological manifestations in 200 patients with ankylosing spondylitis: correlation with clinical features and HLA B27. *J Rheumatol* 1979;6:305-15.
43. Boonen A, Cruyssen BV, de Vlam K, Steinfeld S, Ribbens C, Lenaerts J, et al. Spinal radiographic changes in ankylosing spondylitis: association with clinical characteristics and functional outcome. *J Rheumatol* 2009;36:1249-55.
44. Brophy S, Mackay K, Al-Saidi A, Taylor G, Calin A. The natural history of ankylosing spondylitis as defined by radiological progression. *J Rheumatol* 2002;29:1236-43.
45. Doran MF, Brophy S, MacKay K, Taylor G, Calin A. Predictors of longterm outcome in ankylosing spondylitis. *J Rheumatol* 2003;30:316-20.
46. Lee W, Reveille JD, Davis JC Jr, Learch TJ, Ward MM, Weisman MH. Are there gender differences in severity of ankylosing spondylitis? Results from the PSOAS cohort. *Ann Rheum Dis* 2007;66:633-8.
47. McGonagle D. Imaging the joint and entheses: insights into pathogenesis of psoriatic arthritis. *Ann Rheum Dis* 2005;64 Suppl 2:ii58-60.
48. McGonagle D, Gibbon W, Emery P. Classification of inflammatory arthritis by enthesitis. *Lancet* 1998;352:1137-40.
49. Benjamin M, McGonagle D. The anatomical basis for disease localisation in seronegative spondyloarthropathy at entheses and related sites. *J Anat* 2001;199:503-26.