Early Predictors of Juvenile Sacroiliitis in Enthesitis-related Arthritis

ILARIA PAGNINI, SARA SAVELLI, MARCO MATUCCI-CERINIC, CLAUDIO FONDA, ROLANDO CIMAZ, and GABRIELE SIMONINI

ABSTRACT. ***Objective.*** To identify early predictors of sacroiliac (SI) involvement in a cohort of patients with enthesitis-related arthritis (ERA).

Methods. During a 7-year followup period, all consecutive patients fulfilling the ILAR classification criteria for ERA were enrolled. Data collected included demographic, clinical and laboratory variables at disease onset, at the onset of inflammatory back pain, and at the last available followup visit. Pelvis radiographs and dynamic magnetic resonance imaging (MRI) scans for SI joints were obtained simultaneously in all patients who developed inflammatory back pain.

Results. Fifty-nine children with ERA were studied; 40 male, 19 female; median age at disease onset 9 years 4 months (range 6 yrs 6 mo – 13 yrs 3 mo). At a median interval after disease onset of 1 year 3 months, 21 children reported symptoms of inflammatory back pain. In all cases, radiographs of SI joints were negative, while dynamic MRI revealed acute sacroiliitis in 17 cases. Multivariate analysis showed that the early predictors of SI were the number of active joints ($p < 0.03$) and the number of active entheses ($p < 0.001$) at onset.

Conclusion. In our cohort, roughly 30% of children with ERA/juvenile idiopathic arthritis develop clinical and MRI evidence of sacroiliitis, detectable with dynamic MRI as early as 1 year after disease onset. Additional data from larger case series are needed to assess the specificity and sensitivity of this technique in the early phase of the disease and to confirm the rate of SI involvement reported in this cohort. (First Release September 1 2010; J Rheumatol 2010;37:2395–401; doi:10.3899/jrheum.100090)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS
ENTHESITIS-RELATED ARTHRITIS
SACROILIAC INVOLVEMENT
MAGNETIC RESONANCE IMAGING

Enthesitis-related arthritis (ERA) is a subset of juvenile idiopathic arthritis (JIA)[1], which preferentially affects boys, most frequently in the preadolescent and adolescent age group. HLA-B27 is associated with this subset, even if it is not required for diagnosis. Extraarticular manifestations (gastrointestinal, ocular, mucosal, and cutaneous) occur in a variable proportion of patients. Throughout the disease course, the severity and duration of disease activity may influence disease outcome[2,3,4]. Unlike adult spondyloarthritides, inflammatory back pain is rarely present at onset, even though sacroiliac (SI) and spinal involvement occurs in up to two-thirds of children within 10 years of disease onset[5,6,7]. Since SI radiographic modifications are frequently detected late, attempts have been made to identify sacroiliitis earlier. In adults, it has been shown that magnetic resonance imaging (MRI) can detect sacroiliitis at early stages when radiographs are still negative[8]. In children, dynamic contrast-enhanced MRI is highly sensitive and seems a useful technique for early detection of SI joint changes, considering the absence of exposure to radiation[9,10].

The aim of our study was to determine the rate of SI involvement using clinical examinations, radiographs, and dynamic MRI in a cohort of patients with ERA/JIA followed for a mean period of 3 years, and to identify early predictors of sacroiliitis.

MATERIALS AND METHODS

This was a retrospective chart and imaging review.

From 2000 to 2006, all consecutive patients fulfilling the International League of Associations for Rheumatology classification criteria for ERA[1] attending the Paediatric Rheumatology Clinic of Anna Meyer Childen's Hospital in Florence, were enrolled in the study. Medical records were reviewed and relevant demographic, clinical, laboratory, and imaging data were collected at disease onset, at the onset of symptoms and signs of inflammatory back pain, and at the last available followup visit.

From the Department of Pediatric Rheumatology and Department of Pediatric Radiology, University of Florence, Anna Meyer Children's Hospital; and Department of Rheumatology, University of Florence, Careggi Hospital, Florence, Italy.

I. Pagnini, MD, Pediatric Rheumatology; S. Savelli, MD, Pediatric Radiology, Anna Meyer Children's Hospital; M. Matucci-Cerinic, MD, Professor, Chair of Rheumatology, Careggi Hospital; C. Fonda, MD, Pediatric Radiology; R. Cimaz, MD, Professor, Pediatric Rheumatology; G. Simonini, MD, Pediatric Rheumatology, Anna Meyer Children's Hospital.

Address correspondence to Dr. I. Pagnini, Rheumatology Unit, Department of Paediatrics, University of Florence, Anna Meyer Children's Hospital, Viale Pieraccini 24, 50139 Florence, Italy. E-mail: dott.pagnini@alice.it

Accepted for publication July 14, 2010.

The following variables were entered into a customized database.

Demographic variables. (1) History of HLA-B27-related disease in a first-degree relative, including ankylosing spondylitis (AS), ERA, inflammatory bowel disease, reactive arthritis (Reiter's syndrome), and acute anterior uveitis. Psoriasis was excluded since it is a mandatory exclusion criterion for ERA diagnosis if present in patient and/or in a first-degree parent; (2) patient's sex; (3) age at onset of disease, defined by the age at diagnosis of ERA.

Clinical variables. (1) Disease duration; (2) assessment of the number and type of affected joints. Active arthritis was defined as a joint with swelling not due to bony enlargement, or limitation of motion in combination with pain or tenderness; (3) assessment of the number and type of affected entheses. Enthesitis was defined as discretely localized tenderness at the point of insertion of ligaments, tendons, joint capsules, or fascia to bone[11], and assessed according to the Maastricht Ankylosing Spondylitis Enthesitis Score (Maseses), but including in addition plantar fascia and calcaneous entheses[12]; (4) inflammatory back pain, defined according to the Assessment of Spondyloarthritis International Society (ASAS) expert criteria[13], as lumbosacral spinal pain persisting at least 3 months in patients with: age at onset < 40 years, insidious onset, improvement with exercise, not improved with rest, pain at night (at least 4 of these 5 requirements need to be present)[13,14]; (5) tenderness of SI joints, compression of pelvis, distraction of the SI joints by Patrick's test[2,13,14]; (6) limited anterior spinal flexion, assessed by the modified Schober test[13]; and (7) limited lateral spinal flexion, according to the ASAS expert criteria[13].

All other variables. (1) Laboratory variables: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and presence of the HLA-B27 allele. (2) Therapy administered at onset and throughout the disease course. (3) Disease activity measures, according to the American College of Rheumatology pediatric criteria[15]. (4) Disease remission indices, according to the preliminary criteria for clinical remission in JIA[16], including no active enthesitis. And (5) assessment of functional health status, measured by the Childhood Health Assessment Questionnaire (CHAQ)[17].

Imaging data. A plain radiograph study of the pelvis and a dynamic MRI study of the SI joints were simultaneously obtained in all patients who, throughout the course of disease, developed inflammatory back pain. The images were assessed independently by 2 pediatric radiologists (CF and SS), each blinded to findings of the other technique.

Assessment of conventional radiographs. Radiographs of the SI joint were scored on the basis of the modified New York criteria for AS[18], where radiographic abnormalities of the SI joints are graded as (1) normal; (2) suspicious changes; (3) minimal abnormality in the form of small areas of erosions or sclerosis without alteration in the joint width; (4) unequivocal abnormalities, i.e., moderate or advanced sacroiliitis consisting of erosions, sclerosis, widening, narrowing, and/or partial ankylosis; and (5) severe abnormality in the form of total ankylosis. The diagnosis of sacroiliitis was defined if grade 2 bilateral sacroiliitis or grade 3 unilateral sacroiliitis was scored.

MRI assessment. With regard to MRI studies of the SI joints, dynamic contrast-enhanced MRI before and after administration of contrast medium was performed as described[8,9].

In all patients MR images were obtained with a 1.5 Tesla unit (Philips Intera; Philips, Eindhoven, The Netherlands) using a pelvic array body coil with the following sequences: semicoronal STIR sequences, semiaxial TSE T1, semicoronal SPIR T1, semiaxial TSE T2, semicoronal dynamic T1 fat-saturated (FS), and semiaxial T1 SPIR after administration of intravenous gadolinium (0.1 mmol/kg). Assessment of the MR examinations included a grading of 0–3 (0 normal, 1 minimal, 2 moderate, 3 severe) of the following findings: erosions, sclerosis (low signal intensity on T1 and/or T1 FS), bone marrow edema (high signal intensity on STIR), contrast enhancement in the bone and in the joint space, and joint space narrowing and/or widening. All assessments and grading were performed at 4 anatomical sites for each SI joint: the sacral and iliac sites of the cartilaginous and ligamentous portions of the joint.

Gadolinium contrast enhancement in the bone and joint space was objectively and quantitatively measured by determining the maximum percentage increase in signal intensity of the intraarticular space and/or the juxtaarticular bone marrow (an enhancement rate > 25% was considered indicative for acute sacroiliitis) and by obtaining a time-intensity curve of the dynamic examination (an enhancement with plateau was considered a specific sign for bone marrow osteitis)[19]. As reported[20], acute/active sacroiliitis on MRI was defined if bone marrow edema on STIR or bone marrow osteitis on T1 post-gadolinium were detected and located in subchondral or periarticular bone marrow. In addition, if only one signal for each MRI slice was present, lesion was considered active if present on at least 2 consecutive slices; if more than one signal on a single slice was detected, one slice was considered sufficient.

An overall score for joint destruction was calculated as a sum of the scores of erosions, sclerosis, and joint space width, for one or both joints (0–60 for bilateral sacroiliitis and 0–30 for monolateral sacroiliitis). An overall score for inflammatory activity was calculated as a sum of the score of the bone marrow edema, gadolinium enhancement in the bone marrow, and gadolinium enhancement in the joint space for one or 2 joints (0–60 for bilateral and 0–30 for monolateral sacroiliitis). An overall score of sacroiliitis with regard to joint destruction and inflammatory activity (0–120 for bilateral, 0–60 for monolateral sacroiliitis) was calculated as a sum of all scores. Using the overall score, monolateral and bilateral sacroiliitis was finally graded 0–4 corresponding to the New York criteria, in accord with the Aarhus criteria accepted by OMERACT RAMRIS[21]. As noted, 2 radiologists blinded to radiographic features independently reviewed and scored MRI images according to these criteria.

The study was approved by the Institutional Review Board of Anna Meyer Children's Hospital, Florence.

Statistical analysis. All results are expressed as mean and SD, or median and range. Mann-Whitney U test, Wilcoxon signed-rank test for paired samples, and Fisher exact test, when appropriate, were used to compare data. For imaging data, the kappa test for agreement and McNemar test for disagreement were used to estimate interobserver variation. In cases of disagreement between the 2 readers, the lowest imaging classification score was considered for the purposes of the study. Pearson and Spearman correlation tests were used to determine correlation coefficients for different variables (time from disease onset and onset of inflammatory back pain, laboratory variables, therapy at onset and throughout the disease course, disease activity indexes). Multiple stepwise regression was performed to determine variables, including disease severity indicators, that could correlate independently with active SI involvement as judged by MRI. The predictors used in the final model were those showing a significant correlation with SI involvement in the univariate analysis. Nonparametric tests were used, where necessary, due to the small size of our groups and to the skewness of data. Levels of $p < 0.05$ were considered statistically significant. All analyses were performed on SPSS for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Fifty-nine children with ERA were included in the analysis: 40 male, 19 female, median age at disease onset 9 years 4 months, (range 6 yrs 6 mo to 13 yrs 3 mo). This represents 28% of the total cohort of patients with JIA followed in our center in the same period. Thirty-nine patients (66.1%, 26 male, 13 female) were HLA-B27-positive; a family history positive for HLA-B27-related diseases was present in 21/59 subjects (35.6%). At disease onset the knees were the joints most frequently affected (65% of patients), followed by the midfoot (58%) and the ankles (48%), with a median number of 2 involved joints per patient (range 1–7). Entheses involved were plantar fascia/calcaneous (38% of children),

followed by the Achilles tendon (28% of children), with a median number of 1 involved enthesis per child (range 1–6). At disease onset, median ESR value was 40 mm/h (range 8–68) and median CRP was 1.1 mg/dl (range 0.7–3.8); the median CHAQ value was 1.4 (range 0.8–1.8). Initially, all patients received nonsteroidal antiinflammatory drugs, and most of them needed disease-modifying antirheumatic drug (DMARD): sulfasalazine (30–50 mg/kg/day) in 39 cases and methotrexate (10–15 mg/m^2 per week orally or subcutaneously) in 15 cases. At the last followup visit (median 3 yrs 2 mo after disease onset, range 1 yr 6 mo to 5 yrs 7 mo), the majority of patients (39/59, 66%) were in clinical remission on therapy, still receiving DMARD (85%) or tumor necrosis factor-α blockers (15%), alone or in association with methotrexate; 12/59 (20%) were in remission, free of therapy for at least 1 year, while 8/59 (13%) still had active disease while continuing treatment.

Out of 59 children, 21 reported symptoms of inflammatory low back pain, at a median interval after disease onset of 1 year 3 months (range 0 to 5 yrs 8 mo). Limited anterior and lateral spinal flexion was also present in all these patients, as well as SI tenderness.

Due to these clinical symptoms, radiographs and dynamic MRI of SI joints were immediately obtained. In all cases, radiographs of SI joints were negative, whereas dynamic MRI scans were abnormal in 17. The MRI findings of these subjects are summarized in Table 1. Bone marrow edema, a sign of acute and active sacroiliitis, was present in 17 patients, and bone enhancement, a sign of bone osteitis thus reflecting acute sacroiliitis, was observed in all these 17 positive scans. Bone enhancement was detected in 10/17 in the iliac side of the joint and in 7/17 in the sacral side. The joint destruction score was 1 in all patients; the median total joint score for inflammatory activity was 1 (grade 1 in 12 patients and grade 2 in the remaining 5). The median total overall score, as the sum of joint destruction and inflammatory activity scores, was 1 (grade 1 in 16 patients and grade 2 in 1). An example of active sacroiliitis is shown in Figures 1 and 2.

The interobserver agreement for the evaluation of radiographs reached the best possible qualitative performance assessment between the 2 radiologists, since none out of 21 radiographs performed in all 21 symptomatic children was judged abnormal by each radiologist. Since the 2 radiologists were in disagreement in just one case, the interobserver agreement for MRI evaluation of acute sacroiliitis, judged as kappa value, was 0.82 (95% CI 0.66–0.98, $t = 3.85$, $p < 0.0001$), with a nonsignificant McNemar test, for both bone marrow edema and bone osteitis. In addition, since each radiologist, independently, disagreed between the 2 indicators of acute sacroiliitis in just one case, the result for intraobserver agreement between the 2 variables was again 0.82. The interobserver agreement for the other MR observations ranged between 0.56 and 0.78, with the poorest agreement obtained for the assessment of joint width and sclerosis. However, the McNemar test was nonsignificant.

Table 1. Summary of MRI imaging data in 17 children with ERA-JIA with abnormal MRI findings in the sacroiliac joint. Iliac and sacral sides are considered together. Data indicate numbers of patients.

Finding	Cartilaginous Portion	Ligamentous Portion	Both
Bone marrow edema	14	—	3
Bone enhancement	13	1	3
Enhancement in the joint space	7	—	1
Changes in joint space width (narrowing and/or widening)	6	3	1
Sclerosis	6	—	5
Erosions	2	—	1

As defined, acute sacroiliitis was detected in 17 (80%) cases (bilateral in 12 cases, monolateral in 5 cases). Of these 17 children, 12 were male, 5 female, 9 (52%) were HLA-B27-positive, and a family history for HLA-B27-related diseases was present in 10 subjects (59%). In these children, the median numbers of involved joints and entheses per patient were 3 (range 2–7) and 4 (range 2–6), respectively. Median values of ESR, CRP, and CHAQ were 48 mm/h (range 26–68), 1.7 mg/dl (range 1.1–3.8), and 1.5 (range 0.9–1.8), respectively.

Table 2 summarizes the main features of patients with sacroiliitis compared to children with ERA without sacroiliitis; in Table 3, multivariate analysis shows that early predictors of SI involvement were the number of active joints and the number of active entheses at onset ($p < 0.03$ and $p < 0.001$, respectively; multiple $R = 6.7$, multiple adjusted $R^2 = 4.3$).

DISCUSSION

In our ERA/JIA cohort, up to 30% of children developed signs and symptoms of sacroiliitis. Dynamic MRI showed sacroiliitis within one year from disease onset.

Due to a higher sensitivity compared to conventional radiography, MRI identified and graded both acute and chronic signs of SI joint involvement earlier than did radiographs. In our cohort, this allowed us to detect acute inflammatory SI changes in 80% of children who developed inflammatory back pain, despite the absence of radiographic signs of sacroiliitis. Of note, the majority of abnormalities were mild (grade 1); however, the strict reading protocol and the high concordance in the blinded assessments render the possibility of false-positive readings unlikely. Previous data for children report a frequency of sacroiliitis, by radiographs, ranging from 9% to 75%[3,7,22,23,24,25]; these variable results can be explained by differences in the followup duration and the classification criteria used. By contrast, using the MRI technique, the rate of SI involvement appears to be more homogenous, ranging from 20% to 32%[9,10]; moreover, as we found in our cohort, the percentage of sacroiliitis

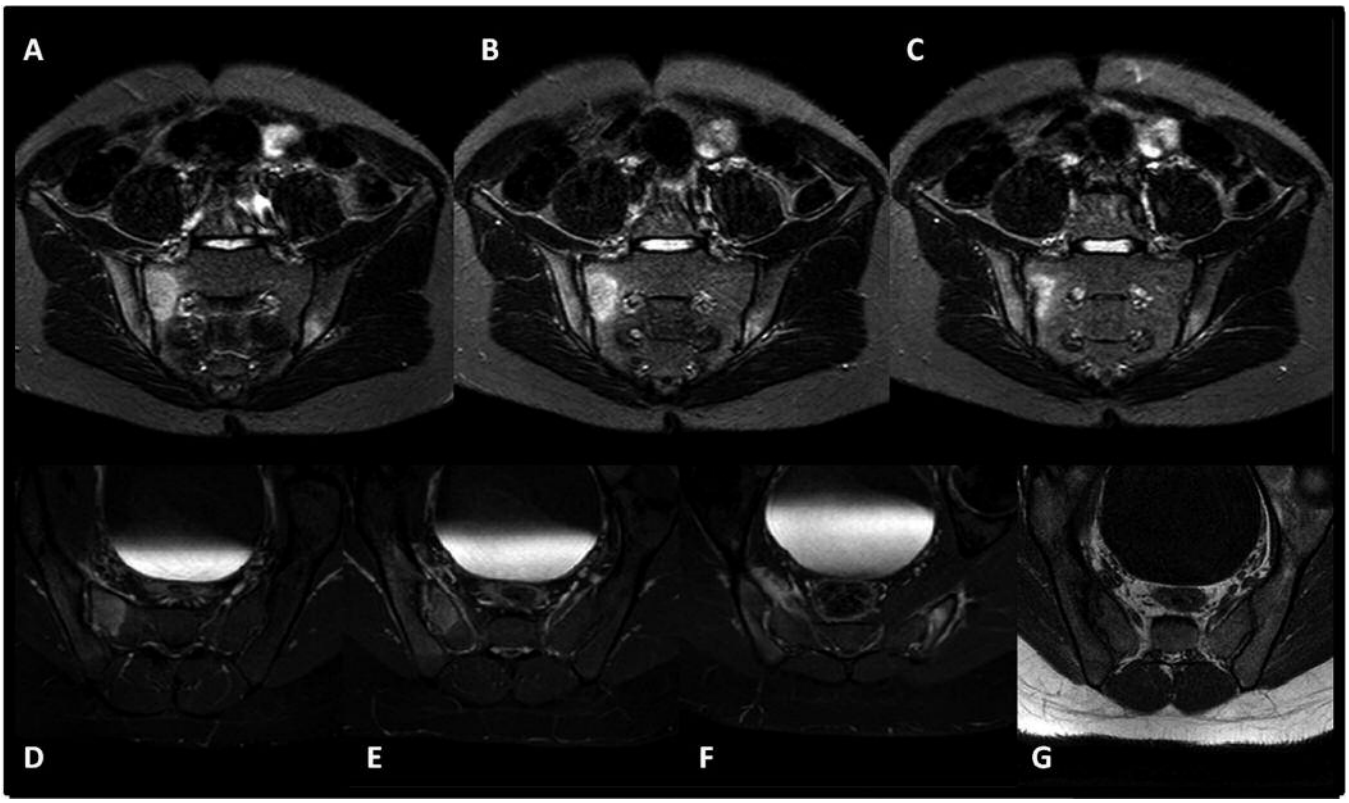

Figure 1. MRI images of a 13-year-old boy with HLA-B27-positive ERA/JIA and inflammatory back pain. A, B, C. Three semicoronal STIR images show bone edema in the sacral cartilaginous portion of the right sacroiliac (SI) joint and in the iliac ligamentous portion of the left joint. D, E, F. Corresponding semiaxial T1 SPIR images after gadolinium injection showing enhancement in the bone marrow and joint space of the sacral cartilaginous portion of the right SI joint and in the bone marrow of the iliac ligamentous portions of the left SI joint. G. Semiaxial T1 spin-echo image showing sclerosis and erosion in the sacral cartilaginous portion of the right SI joint.

detected by MRI was significantly higher than that detected by radiography[9,10].

On the other hand, the excellent agreement (Cohen's kappa value > 0.75) between bone marrow edema and bone osteitis of our data is in accord with the reliable diagnostic ability of STIR sequences, and contrast-enhanced MR sequence, in detecting active sacroiliitis, as recently reported[26] in a large cohort of 105 adults with spondyloarthritides.

Before drawing conclusions from our data, some limitations need to be discussed. We did not perform MRI in a control group of asymptomatic children, but only when clinically indicated in subjects with low back pain. There could therefore be selection bias due to the study population; however, this is an inherent bias of all retrospective study designs, such as ours. Moreover, performing MRI in completely asymptomatic children might be unfeasible, and ethically questionable. In addition, we cannot exclude an overinterpretation of the MRI scans; we attempted to minimize this by reviewing scans blindly, by 2 experienced pediatric radiologists, and choosing the lowest score in cases of disagreement. Another potential limitation from our data could arise from the outcome measurement assessment. Although we are aware of the recent ASAS recommended clinical assessment and outcome measures for spondyloarthritis[27], our study was a retrospective chart review, thus we were not able to retrieve all the required findings, mostly for functional outcome and active/remission criteria. We used instead our routine clinical practice for JIA assessment at that time. Moreover, it must be considered that these criteria have not yet been validated in children.

Notwithstanding these limitations, considering previous reports in adults[8] and children[9,10], our data seem to confirm that contrast-enhanced dynamic MRI is successful in depicting early and acute signs of active sacroiliitis. Our data suggest that in the presence of inflammatory back pain, SI involvement should be suspected in children, even if radiographs are negative. However, despite the consensus in this field among adult rheumatologists[20], additional data from larger pediatric case series are needed in order to assess the real specificity and sensitivity of this technique in the early phase of the disease.

Our study also reports potential clinical predictors of early SI involvement: the number of active joints and the number of active entheses at disease onset seem to herald active SI lesions during followup.

Longterm followup of HLA-B27-positive children with JIA has shown that many develop sufficient clinical and radiographic signs of spondylitis and sacroiliitis that fulfil

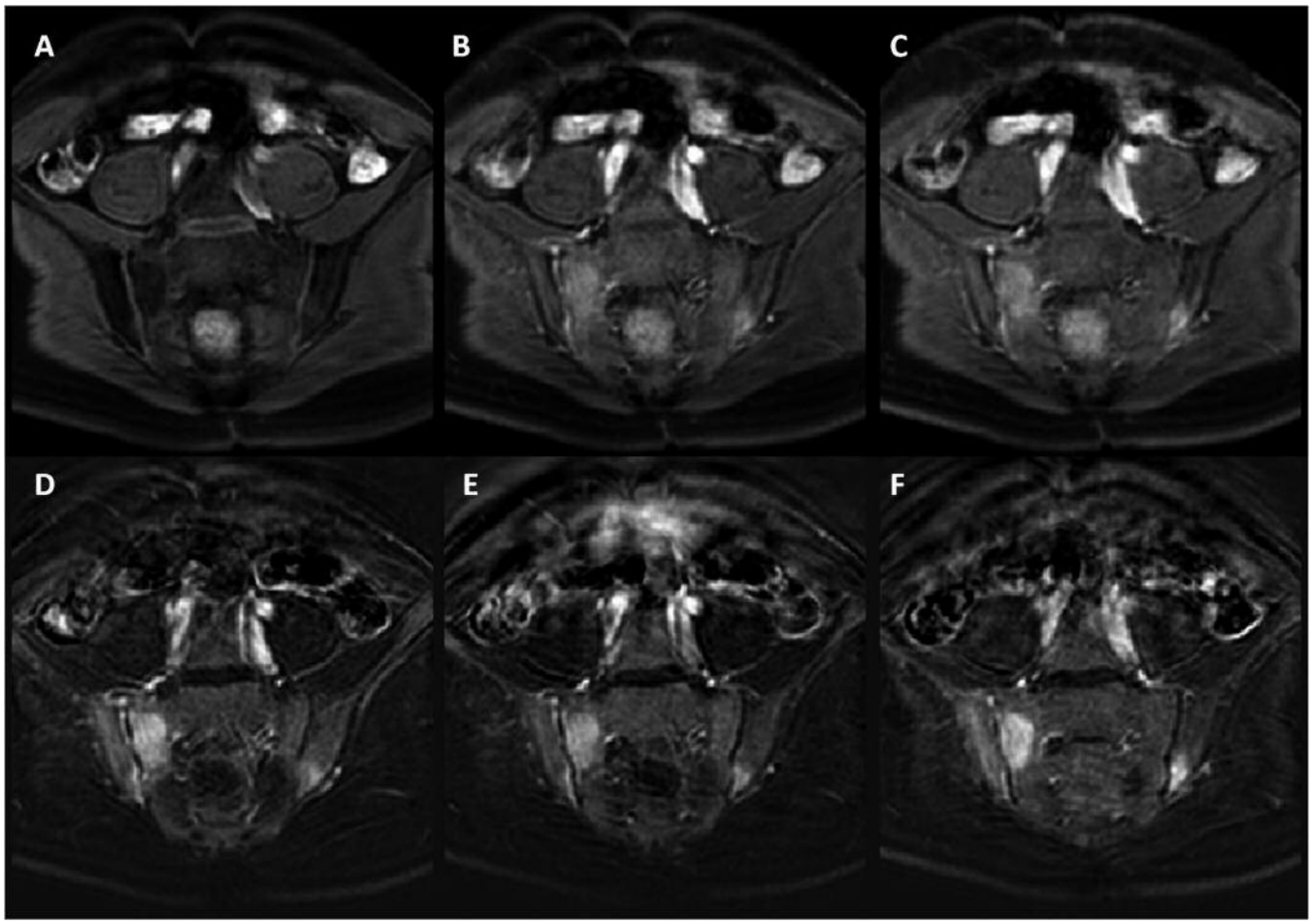

Figure 2. Three semicoronal T1 fat saturated images from the same patient as in Figure 1, (A) before and (B, C) after gadolinium injection, with 3 subtracted images (D, E, F) showing grade 2 enhancement in the bone marrow and joint space of the sacral cartilaginous portion of the right SI joint, and grade 2 enhancement in the bone marrow and joint space of the iliac ligamentous portions of the left SI joint.

the diagnostic criteria for ankylosing spondylitis. Similarly, 70%–90% of children with ERA/JIA fulfil the same criteria 5–10 years after onset[2]. Increased spinal or SI pain and stiffness and limited anterior spinal flexion or chest expansion may become apparent at 2.5 years and are maximal at 5–10 years from disease onset, while early onset of axial symptoms occurs in less than 15% of patients[28]. A recent retrospective study of a 15-year followup of 55 children with ERA/JIA observed sacroiliitis on radiographs in 35% of the subjects; persistently elevated ESR, hip arthritis, ankle arthritis, and high numbers of affected joints within the first 6 months were identified as risk factors for sacroiliitis[3].

A recent retrospective report comparing data from adult-onset and juvenile-onset AS describes SI pain in 33.8% of 84 children; one-quarter of these 84 children started with an exclusively peripheral disease and eventually developed radiographic sacroiliac signs[29]. Our study showed a similar percentage of sacroiliitis: 28.8% of all 59 children with ERA and roughly 80% of the 21 children with inflammatory back pain, but in a shorter followup time due to the capability of MRI.

In addition, our study shows that the number of affected joints and entheses at onset was the best predictor for sacroiliitis. A previous study also reported a high number of affected joints at onset as the predictor of an unfavorable functional outcome and radiographic changes[3]. Similar results were reported in a smaller prospective study in 12 children with juvenile spondyloarthropathy: Selvaag, *et al* found that a high number of active joints at baseline predicted persistent disease after 3 years[30].

ERA/JIA and sacroiliitis in children might closely resemble adult AS, but they represent a clearly different phenotype from other types of JIA. O'Shea, *et al* suggest a distinctively different clinical course between adult and juvenile AS, even if children who then develop radiographic sacroiliitis "constitute an important part of juvenile onset ankylosing spondylitis spectrum"[29]. Although the exact percentage remains to be determined, the group of ERA/JIA children with SI involvement could be the juvenile, earlier-onset variant of adult AS; whereas, as suggested[29], children with ERA/JIA without sacroiliitis might represent a different clinical entity with its own distinctive peripheral pattern of disease course.

Table 2. Comparison of main features of children with ERA/JIA with and without sacroiliitis. Continuous variables are expressed as median (range).

Feature	42 Children without Sacroiliitis	17 Children with Sacroiliitis	p
Male/female %	28/14 (66.7)	12/5 (70.6)	NS
HLA-B27 %	30 (71.4)	9 (52.9)	NS
Positive family history for HLA-B27-associated disease (%)	11 (26.2)	10 (58.8)	0.03
No. affected joints at disease onset	2 (1–3)	3 (1–6)	0.01
No. affected entheses at disease onset	1 (0–2)	2 (1–5)	0.001
ESR, mm/h	40 (8–68)	48 (26–68)	NS
CRP, mg/dl	1.1 (0.7–3.8)	1.7 (1.1–3.8)	NS
Childhood Health Assessment Questionnaire score	1.4 (0.8–1.8)	1.5 (0.9–1.8)	NS

NS: nonsignificant

Table 3. Predictors for development of sacroiliitis in 59 children with ERA/JIA.

Factor	Univariate Analysis OR (95% CI)	p	Multivariate Analysis OR (95% CI)	p
Positive family history	3.1 (2.3–8.4)	0.01		
No. affected joints at onset	4.9 (1.2–19.5)	0.001	2.4 (0.8–20.7)	0.03
No. affected entheses at onset	6.1 (1.9–26.2)	0.001	4.7 (1.6–31.9)	0.001

In our cohort of children with ERA/JIA, sacroiliitis was documented by MRI in the majority of subjects who reported inflammatory back pain, within a median time of 1 year and 3 months from disease onset. Dynamic MRI for SI joints seems to be a sensitive technique for early detection of sacroiliitis. A high number of active joints and entheses at onset might be predictors of sacroiliitis.

REFERENCES

1. 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.
2. Burgos-Vargas R. The juvenile-onset spondyloarthritides: rationale for clinical evaluation. Best Pract Res Clin Rheumatol 2002;16:551-72.
3. Flato B, Hoffmann-Vold AM, Reiff A, Førre Ø, Lien G, Vinje O. Long-term outcome and prognostic factors in enthesitis-related arthritis. Arthritis Rheum 2006;54:3573-82.
4. Burgos-Vargas R, Vazquez-Mellado J, Cassis N, Duarte C, Casarin J, Cifuentes M, et al. Genuine ankylosing spondylitis in children: a case-control study of patients with early definite disease according to adult onset criteria. J Rheumatol 1996;23:2140-7.
5. Burgos-Vargas R. The juvenile-onset spondyloarthritides. In: Weisman MH, van der Heijde DMFM, Reveille JD, editors. Ankylosing spondylitis and the spondyloarthropathies. Philadelphia: Mosby; 2006:94-106.
6. Cabral DA, Oen KG, Petty RE. SEA syndrome revisited: a longterm follow-up of children with a syndrome of seronegative enthesopathy and arthropathy. J Rheumatol 1992;19:1282-5.
7. 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.
8. Bollow M, Braun J, Hamm B, Eggens U, Schilling A, Konig H, et al. Early sacroiliitis in patients with spondyloarthropathy: evaluation with dynamic gadolinium-enhanced MR imaging. Radiology 1995;194:529-36.
9. 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.
10. Bollow M, Braun J, Biedermann T, Mutze S, Paris S, Schauer-Petrowskaja C, et al. Use of contrast-enhanced MR imaging to detect sacroiliitis in children. Skeletal Radiol 1998;27:606-16.
11. Rosenberg AM, Petty RE. A syndrome of seronegative enthesopathy and arthropathy in children. Arthritis Rheum 1982;25:1041-7.
12. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewe R, van der Tempel, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis 2003;62:127-32.
13. Sieper J, van der Heijde DMFM, Landewe R, Brandt J, Burgos-Vargas R, Collantes-Estevez E, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of Spondyloarthritis international Society (ASAS). Ann Rheum Dis 2009;68:784-8.
14. Akkoc N, Khan MA. Epidemiology of ankylosing spondylitis and related spondyloarthropathies. In: Weisman MH, van der Heijde DMFM, Reveille JD, editors. Ankylosing spondylitis and the spondyloarthropathies. Philadelphia: Mosby; 2006:117-31.
15. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202-9.
16. Wallace C, Ruperto N, Giannini EH. Preliminary criteria for clinical remission for selected categories for juvenile idiopathic arthritis. J Rheumatol 2004;31:2290-4.
17. Ruperto N, Ravelli A, Pistorio A, Malattia C, Viola S, Cavuto S, et al. The Italian version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) [abstract]. Clin Exp Rheumatol 2001;19 Suppl:S91-5.
18. van der Linden SJ, 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.
19. Puhakka KB, Jurik AG, Schiottz-Christensen B, Stengaard-Pedersen K, van Overeem Hansen G, Vallo Christiansen J. Imaging of sacroiliitis in early seronegative spondylarthropathy. Acta Radiol 2003;44:218-29.
20. Rudwaleit M, Jurik AG, Herman KG, Landewe R, van der Heijde DM, 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.
21. Van der Heijde DMFM, Landewe RBM, Hermann KG, Jurik AG, Maksymowych WP, Rudwaleit M, et al. Application of the OMERACT filter to scoring methods for MRI of the sacroiliac joints and the spine. Recommendations for a research agenda at OMERACT 7. J Rheumatol 2005;32:2042-7.
22. Flato B, Aasland A, Vinje O, Førre O. Outcome and predictive factors in juvenile rheumatoid arthritis and juvenile spondyloarthropathy. J Rheumatol 1998;25:366-75.
23. Sheerin KA, Giannini EH, Brewer EJ, Barrons K. HLA B-27 associated arthropathy in childhood: long term clinical and diagnostic outcome. Arthritis Rheum 1988;31:1165-70.
24. Minden K, Niewerth M, Listing J, Biedermann T, Bollow M, Schontube M, et al. Long-term outcome in patients with juvenile idiopathic arthritis. Arthritis Rheum 2002;46:2392-401.
25. Stone M, Warren RW, Bruckel J, Cooper D, Cortinovis D, Inman RD. Juvenile-onset ankylosing spondylitis is associated with worse functional outcomes than adult-onset ankylosing spondylitis. Arthritis Rheum 2005;53:445-51.
26. Althoff CE, Feist E, Burova E, Eshed I, Bollow M, Hamm B, et al. Magnetic resonance imaging of active sacroiliitis: do we really need gadolinium? Eur J Radiol 2009;71:232-6.
27. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis international Society handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009;68 Suppl II:ii1-44.
28. 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.
29. O'Shea FD, Boyle E, Riarh R, Tse SM, Laxer RM, Inman RD. Comparison of clinical and radiographic severity of juvenile-onset versus adult-onset ankylosing spondylitis. Ann Rheum Dis 2009;68:1407-12.
30. Selvaag AM, Flatø B, Dale K, Lien G, Vinje O, Smerdel-Ramoya A, et al. Radiographic and clinical outcome in early juvenile rheumatoid arthritis and juvenile spondyloarthropathy: A 3-year prospective study. J Rheumatol 2006;33:1382-91.