Discordant Inflammatory Changes in the Apophyseal and Sacroiliac Joints: Serial Observations in Enthesitis-related Arthritis

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ABSTRACT

Objective: To determine the extent to which inflammation of the sacroiliac joints (SIJs) and apophyseal joints (AJs) changes concordantly after treatment in enthesitis-related arthritis (ERA). *Materials and methods:* A retrospective study was performed with Institutional Review Board approval. 31 young people with ERA who had been scanned between March 2009 and November 2014 were included. All patients had post-contrast imaging of the SIJs and lumbar spine and short tau inversion recovery (STIR) images of the SIJs. The severity of sacroiliitis was scored using a modification of an established technique, and inflammation of the apophyseal joints was evaluated using a recently described grading system. The changes in SIJ and AJ scores after treatment were classified as either concordant or discordant, and the proportion of scan-pairs in these groups was recorded. Additionally, the correlation between change in SIJ STIR score and change in AJ score was assessed using Spearman's correlation coefficient. *Results:* Of a total of 43 scan pairs, the changes in inflammation were concordant in 16 scan pairs and discordant in 27 scan pairs. There was no significant correlation between change in SIJ STIR score (ΔSIJ) and change in AJ score (ΔAJ) ($R=0.14$, $p=0.37$). *Conclusions:* Inflammatory changes in the SIJs and AJs are often discordant. This may be a reason why patients experience ongoing back pain despite apparent improvement in one or the other site. *Advances in knowledge:* Inflammation may behave differently at different anatomical sites. The SIJs and AJs should both be imaged in ERA patients with back pain.

INTRODUCTION

Enthesitis related arthritis (ERA) is a juvenile-onset spondyloarthritis and a subtype of juvenile idiopathic arthritis (JIA) as defined by the International League of Associations for Rheumatology (ILAR) classification criteria for childhood arthritis (1). The most commonly affected joints at diagnosis are the sacroiliac joints, knees, ankles, and hips (2). Axial inflammation is a hallmark of ERA and up to 35%–48% of children with ERA have clinical or radiographic evidence of sacroiliitis (3–6). A subset of children with sacroiliitis will progress to spondylitis as adults, which is characterized by back pain, stiffness, and eventual fusion of the vertebra (3). Early treatment in spondyloarthritis may have a disease-modifying effect and consequently improve outcomes (7), but if treatment is inadequate then outcomes are poor in terms of physical health, pain and physical activity (4).

Magnetic resonance imaging (MRI) is commonly used in ERA, and has traditionally focused on the early detection of inflammation at the sacroiliac joints (8,9). However, a recent cross-sectional study described co-existing inflammation of the lumbar apophyseal joints (AJs) and interspinous ligaments on MRI in a significant proportion of patients (10). The extent to which AJ and SIJ inflammation are responsible for lower back pain in ERA patients is unknown. Although it has previously been argued that spinal involvement can be 'inferred' from the presence of sacroiliitis (and that routine imaging of the lumbar spine is therefore unnecessary) this suggestion remains unproven (11). Furthermore, it is unknown whether AJ inflammation causes AJ fusion in ERA patients, although studies in adult spondyloarthritis suggest close relationships between inflammation, excessive bone formation and subsequent fusion (12–14). Fusion is known to contribute to impairment of spinal mobility and increased fracture risk (15,16).

To our knowledge, there are no published data on the relationship between inflammation of the sacroiliac joints (SIJs) and inflammation of the apophyseal joints (AJs) in patients with ERA. In particular, it is unclear whether SIJ and AJ inflammation improve or deteriorate simultaneously, or whether inflammation at these two sites behaves differently. This issue is clinically important because it influences whether imaging of the SIJs alone is sufficient, or whether both the SIJs and lumbar spine should be imaged in ERA patients with lower back pain.

This study aims to determine the extent to which inflammation at the SIJs and AJs changes concordantly over serial MRI scans. We hypothesised that improvements in inflammation in the SIJs would generally be associated with improvements in the AJs, since both joints might be subject to similar fluctuations in immune/inflammatory activity over time (including when patients are treated).

PATIENTS AND METHODS

We performed a retrospective review of patients suspected of having ERA who were attending a specialist outpatient adolescent rheumatology clinic at our institution. The study was performed with Institutional Review Board approval. Informed consent was obtained for review of all clinical investigations.

Subjects

A local database was used to identify young people (aged 11-23) who had MRI scans between March 2009 and November 2014. Patients were recruited for the study if they met the ILAR criteria for ERA (1) and had complete MR imaging of the lumbar spine and SIJs, with post-contrast imaging at both sites (as specified in MRI technique).

MRI technique

MRI of the lumbar spine and SIJs was performed using a 1.5T system (Siemens Avanto). Sequence information is provided in Table 1 [note that the 'STIR' images were acquired using turbo spin echo sequences which are referred to as turbo inversion recovery magnitude (TIRM) in the sequence information]. The contrast agent used was gadoterate meglumine, which was administered as an intravenous bolus at a dose of 0.2 mmol/kg using an infusion pump. Following the contrast bolus, the SIJ images were acquired first (axial then coronal) followed by the lumbar spine images. This regime has been designed such that the majority of images are acquired in the early equilibrium phase.

Image analysis

All images were reviewed by two consultant radiologists with more than 20 and eight years respectively of musculoskeletal MRI experience and with expertise in adolescent spinal imaging. Anonymised images were presented at random to each reader who was blinded to clinical data. Each observer graded the SIJs and apophyseal joints as described below. A reference sheet with examples of the various grades of inflammation was available to each reader to ensure consistency. The reference sheets were produced using a previously-described grading system (10,17). One of the two observers was involved in conceiving the use of the reference sheets, but was not involved in the choice of specific images or preparation of the sheets themselves. The majority of patients had an initial scan compared with a single follow-up scan but in patients with more than one follow-up scan, second scans were compared with a third scan, and third scans compared with a fourth. Comparison was always with respect to the most recent previous scan. The scoring data was recorded on a score sheet and the two readers' scores were averaged.

Apophyseal joint grading

The apophyseal joints were graded using the sagittal STIR, T1-weighted and post-contrast T1-weighted images according to the adapted adult grading method described by Vendhan et al (10). The grades of severity for joint inflammation are: grade 0 = normal, grade 1 = high signal confined to the joint capsule, grade 2 = intra-articular and peri-articular signal abnormality, and grade 3 = features of grade 2 plus bone marrow oedema of articular process. To account for differences in the 'burden' of inflammation associated with each grade of inflammation, we assigned the following weighted scoring system: grade 0 = score 0, grade 1 = score 0.5, grade 2 = score 1, grade 3 = score 2. Levels were scored from T11/12 to L5/S1 (7 vertebral levels). Right and left joints were scored separately and the whole lumbar spine could therefore score a maximum of 28 (i.e. 7 vertebral levels; scored 0.5, 1 or 2; left and right). Each scorer recorded additional observations such as erosions or pars defects separately.

Sacroiliac joint grading

The sacroiliac joints were scored for inflammation according to the method described by the Spondyloarthritis Research Consortium of Canada (17) - an established, validated scoring method for grading sacroiliitis in ankylosing spondyloarthritis in adults. This scoring method takes six coronal slices through the joint from anterior to posterior. For every slice each joint is divided into quadrants and each quadrant is given a point if high signal is present on the STIR images. An extra point is given if any quadrant on the slice demonstrates high signal extending more than 1cm from the articular surface or when the signal is particularly intense. Each slice can therefore score a maximum of 12 points and the whole joint 72 points.

Statistical Analysis

Assessment of concordance

Changes in score were classified as *concordant* if the SIJs and AJs both improved or both worsened and *discordant* if either the SIJ and AJ score changed in opposite directions, or one remained stable while the other changed. We recorded the number of patients in whom inflammatory changes were concordant/discordant and, for each group, determined the median change in inflammatory scores for subjects who improved and for subjects who worsened.

In order to assess for any dependence of concordance on the interval between scans, the interval between scans for each scan pair was compared between concordant and discordant groups using a Mann-Whitney-Wilcoxon test. Spearman correlation was used to assess the correlation between change in SIJ score (ΔSIJ) and change AJ score (ΔAJ) between scans. If patients underwent more than two scans, the change in scores was assessed for each consecutive scan pair (e.g. first to second scan, second to third scan, etc) for both the SIJs and AJs.

Repeatability

Interobserver variation in SIJ and AJ scoring was assessed using Bland-Altman plots (95% limits of agreement) and intraclass correlation coefficient (absolute agreement between measurements).

RESULTS

Subjects

There were a total of 31 ERA patients who had at least two MR scans between March 2009 and November 2014, with 74 scans available for analysis. The subjects' mean age at the time of the first scan was 16.1 years (range 11.5 – 23 years). This included 24 males with a mean age of 16.7 years years (range 12.7 – 23 years) and seven females with a mean age of 14.2

years (range 11.5 – 17.3 years). All patients had at least two scans, eight patients had three scans and two patients had four scans. This allowed for direct comparison between 43 pairs of scans. The mean interval between the first and the last scan was 1.7 years (range 0.3 – 5.7 years). The mean interval between successive follow-up scans was 1.3 years (range 0.3 – 3 years).

The number of patients receiving treatment at each scan is provided in Table 2. Between the initial scans and the first follow-up scan the medication regime was reduced in one patient, fourteen patients remained on the same therapy and fifteen patients required an escalation in therapy. In those patients who had a third scan, five patients remained on the same therapy and four patients required an escalation; in the one patient who had a fourth scan their medication did not change between the third and fourth scans.

SIJ and AJ scores

On the initial scan, 28 patients (93%) had sacroiliitis and 23 patients (74%) had apophyseal joint inflammation. In 21 patients (68%) there was coexisting sacroiliitis and apophyseal joint inflammation. Two patients (6%) had apophyseal joint inflammation on the initial scan but no sacroiliitis. The most severe sacroiliitis scored 64 points (out of a maximum 72 points) and the most severe apophyseal joint inflammation in the spine scored 24 points (out of a maximum of 28 points). Twenty-six patients (90%) had SIJ erosions on their initial scan.

SIJ inflammation improved in 23 scan pairs (21 patients), with a median score reduction of 10 (range 1 – 33). SIJ inflammation progressed in 17 scan pairs (15 patients), with a median score increase of 5 (range 1 – 37). In three scan pairs there was no change in SIJ inflammation.

AJ inflammation improved in 17 scan pairs (16 patients), with a median score reduction of 3 (range 1 to 6). AJ inflammation progressed in 14 scan pairs (14 patients), with a median score increase of 3 (range 1 - 8). In 12 scan pairs (12 patients) there was no change in AJ inflammation.

Assessment of Concordance

Inflammatory changes were **concordant** (i.e. the inflammation either got worse, remained stable or improved at both sites) in 16/43 scan pairs (37%). An example of a subject's scans showing concordant improvement is shown in Figure 2. Of the concordant scan pairs, inflammation became more severe at both the SIJs and the AJs in six pairs (median increase in inflammation score: SIJ +8, AJ+ 2), remained stable at both joints in two pairs and improved at both sites in eight scan pairs (median decrease in inflammation score: SIJ -16, AJ -3).

Inflammatory changes were **discordant** (i.e. changes in inflammation at either the sacroiliac joints or the apophyseal joints did not correspond with the same change at the other joint) in 27/43 scan pairs (63%). An example of a subject's scans showing discordance is shown in Figure 3. Of the discordant scan pairs, inflammation worsened at the SIJs and improved/remained stable at the AJs in 11 pairs (median increase in inflammation score: SIJ +5, AJ -1). Inflammation improved at the SIJs and worsened/remained stable at the AJs in 15 pairs (median increase in inflammation score: SIJ -5, AJ +2). In one scan pair, inflammation remained stable at the SIJs but increased at the AJs (AJ +1).

The mean interval between scans for each scan pair was 1.23 years for concordant scan pairs and 1.20 years of discordant scan pairs; there was no significant difference between these groups (p=0.80).

Details of inflammatory changes in discordant cases are given in Table 3. Concordant and discordant cases are also highlighted in Figure 1, which shows a scatterplot demonstrating the relationship between change in SIJ score (ΔSIJ) and change in AJ score (ΔAJ). There was no significant correlation between ΔSIJ and ΔAJ (R=0.14, p=0.37).

Repeatability

For the SIJ scores, the Bland Altman 95% limits of agreement for the two observers were ± 13 across a range of values from 0 to 66. The intraclass correlation coefficient was 0.90.

For the AJ scores, the Bland Altman 95% limits of agreement for the two observers were ± 8.5 across a range of values from 0 to 25. The intraclass correlation coefficient was 0.57.

DISCUSSION

Inflammation of the lumbar apophyseal joints is a recently-described phenomenon which has been proposed as a potential cause for back pain in patients with enthesitis-related arthritis (10). However, to our knowledge there is no existing literature describing the relationship between AJ and SIJ inflammation over successive scans. The results of this study indicate a surprising degree of discordance between AJ and SIJ inflammation. This suggests that imaging of the sacroiliac joints alone may be insufficient for diagnosis in ERA patients with ongoing back pain, since an absence of SIJ inflammation does not necessarily imply an absence of AJ inflammation. Our data also indicates that apophyseal joint

inflammation can sometimes precede sacroiliitis, which is consistent with previous studies (18).

Importantly, several authors have recently questioned the need for gadolinium-enhanced scans when imaging young people with lower back pain, arguing that imaging the sacroiliac joints alone is sufficient (19–21). This study reinforces previous suggestions that imaging of the lumbar spine (in addition to the sacroiliac joints) is necessary for complete assessment of young people with lower back pain.

There is an ongoing debate about the pathological mechanisms underlying inflammatory enthesitis, but it is possible that the discordance between AJ and SIJ scores may arise because the pathological processes underlying inflammation at these sites are different (12). Interestingly, a recent inception cohort study has suggested that enthesitis often persists after treatment in ERA, even in patients who have no active joints (as determined by clinical assessment) (22).

Previous studies (10) have suggested that contrast-enhanced images are more sensitive than STIR images for the detection of synovitis. For this reason, we based our scoring on the T1 sagittal contrast-enhanced images. We employed a weighted scoring system of 0.5, 1 and 2 for the three grades of inflammation, thereby giving greater importance to the presence of bone marrow oedema, which is known to be strongly associated with symptoms (23). Grade 1 inflammation is, by definition, confined to the joint capsule and therefore arguably reflects only a small inflammatory burden. However, there is clearly scope for further research to determine the clinical significance of different grades of AJ inflammation.

In general, the medication requirements of the patients in our cohort increased over the duration of our study. This is consistent with existing data describing the natural history of ERA and disease progression (24). Compared to other sub-groups of JIA, ERA is associated with worse function, quality of life, and pain (25) as well as a smaller likelihood of attaining inactive disease 1 year after treatment initiation (26).

We found that erosions of the SIJs were common in our patients and were present in 81% (25/31) of cases on the initial scan. Other authors studying ankylosing spondylitis suggest that erosions should be given more attention in quantitative MRI assessment scores of SI joints (27). They conclude that erosions, not bone marrow oedema or contrast enhancement, are the most disease-specific measurable imaging finding in sacroiliac joints.

There are some limitations in our study. Although the mean scan interval was 12 months, there was considerable variation. This is an inherent problem when studying an adolescent population. Routinely, these patients are scanned at 6-12 month intervals as part of their normal follow-up. However, appointments were invariably missed, cancelled or rescheduled to allow for events such as school examinations. Specialist nurses maintained contact with patients between outpatient appointments and if symptoms progressed patients were scanned earlier than the standard interval time. The patient numbers in this study are modest, although ERA is an uncommon subtype affecting 2-10% of all children with JIA [which has an overall prevalence in the UK of 1-2 per 1,000 children (28,29)]. Therefore, this study does represent a sizable population and is comparable to other studies. It would also be of interest to correlate measures of inflammatory back pain and function to MRI changes within the SIJ and AJ to ascertain which of these sites is most associated to pain and functional compromise.

A further limitation of this work is that there is there is scope for improvement in terms of interobserver variation, particularly when scoring AJ inflammation. Descriptions of AJ inflammation have emerged relatively recently, and more work is required to increase the repeatability of this score. It is possible that scoring only 'definite' inflamed joints may improve this.

In this study we have shown that in patients with ERA, sacroiliitis and apophyseal joint inflammation can change independently and consequently back pain could be due to the persistence of one site of inflammation even though the other is responding to therapy. Full assessment of back pain in ERA should include imaging of both the sacroiliac joints and the spine with post-contrast imaging of the apophyseal joints.

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Tables

Table 1: Scan parameters.

Sacroiliac joints		
Sequence	**Plane**	**Parameters**
T1-weighted TSE	Coronal	TR/TE 610/11ms, slices 15, slice thickness 4mm, FOV 200mm, matrix size 256 x 256, ETL 7, series time 3 minutes.
T1-weighted TSE	Axial	TR/TE 475/11ms, slices 15, slice thickness 5mm, FOV 200mm, matrix size 256 x 256, ETL 7, series time 5 minutes.
TIRM	Axial	TR/TE 6070/83ms, inversion time 150ms, flip angle 150°, slices 15, slice thickness 5mm, FOV 200mm, matrix sixe 256 x 256, ETL 13, series time 5 minutes.
TIRM	Coronal	TR/TE 4340/83ms, inversion time 150ms, flip angle 150°, slices 15, slice thickness 4mm, FOV 200mm, matrix size 256 x 256, ETL 13, series time 8 minutes.
Post-contrast T1-weighted TSE with fat saturation	Axial	TR/TE 619/11ms, slices 15, slice thickness 5mm, FOV 200mm, matrix size 256 x 256 ETL 7, series time 5 minutes.
Post-contrast T1-weighted TSE with fat saturation	Coronal	T1 TSE fat sat coronal - TR/TE 795/11ms, slices 15, slice thickness 4mm, FOV 200mm, matrix size 256 x 256, ETL 7, series time 3 minutes.
Lumbar spine		
Sequence	**Plane**	**Parameters**
T1-weighted TSE	Sagittal	TR/TE 400/10ms, slice thickness 4mm, slices 15, FOV 300mm, matrix size 512 x 512, ETL 7, series time 4 minutes.
TIRM	Sagittal	TR/TE 4000/74ms, inversion time 150ms, slice thickness 4mm, slices 15, flip angle 150°, FOV 300mm, matrix size 256 x 256, ETL 13, series time 4 minutes.
Post-contrast T1-weighted TSE with fat saturation	Sagittal	TR/TE 510/10ms, slice thickness 4mm, slices 15, matrix size 512 x 512, ETL 7, series time 4 minutes.
TIRM, turbo inversion recovery magnitude; TR, repetition time; TE, echo time; FOV, field of view; TSE, turbo spin echo; ETL, echo train length. Series times represent the total interval between each series being acquired inclusive of imaging reconstruction time and time for contrast administration.		

Table 2: Medication information. The number of patients receiving disease-modifying anti rheumatic drugs (DMARDs), tumour necrosis factor inhibitors (TNFi), non-steroidal anti-inflammatory (NSAIDs) and oral steroids are recorded for each successive scan.

	Scan 1	**Scan 2**	**Scan 3**	**Scan 4**
DMARD	12	20	4	2
TNFi	4	9	6	2
NSAID	9	2	0	0
Oral steroid	1	0	0	0
Patients on medication	**26**	**26**	**8**	**2**
No medication	**5**	**5**	**0**	**0**

Table 3: Discordant Cases

a) SIJ inflammatory scores improving vs. apophyseal joint scores worsening

Scans are 1st scan vs. 2nd scan unless otherwise stated

Patient Number	**Sacroiliac Joint Mean Scores**	**Δ SIJ**	**Apophyseal Joints Mean Scores**	**Δ AJ**
6	14 to 12	-2	6 to 13	+7
7	41 to 27	-14	0 to 3	+3
13	4 to 2	-2	1 to 4	+2
15	52 to 25	-27	0 to 1	+1
18	50 to 17	-33	16 to 24	+8
25	27 to 25	-2	0 to 4	+4
29	5 to 0	-5	1 to 4	+3

b) SIJ inflammatory scores worsening vs. apophyseal joint scores improving

Patient Number	**Sacroiliac Joint Mean Scores**	**Δ SIJ**	**Apophyseal Joints Mean Scores**	**Δ AJ**
3	0 to 1	+1	8 to 4	-4
4	27 to 64	+37	2 to 1	-1
5	25 to 41	+16	1 to 0	-1
6[2]	12 to 27	+13	13 to 10	-3
6[3]	27 to 32	+5	10 to 6	-4

14	27 to 31	+4	4 to 3	-1
26[3]	10 to 11	+1	3 to 2	-1
29[2]	0 to 1	+1	4 to 3	-1
31[2]	4 to 14	+10	12 to 11	-1
[2] 2nd vs. 3rd scan, [3] 3rd vs.4th scan				

Figure Legends

Figure 1 Scatterplot showing change in inflammation in the SIJs and AJs. Each point represents the change between one pair of scans. There was no significant correlation between SIJ change and AJ change (R=0.14, p=0.37).

Figure 2: Concordant improvement in both SIJs and AJs (ΔSIJ -23, ΔAJ -6). The AJ images are T1-weighted post gadolinium and the SIJs are shown on STIR images.

Figure 3: Discordance. In this case, the AJ inflammation has worsened on the follow-up scan (ΔAJ +9)., while the SIJ inflammation has improved (ΔSIJ -33). The AJ images are T1-weighted post gadolinium and the SIJs are shown on STIR images.