MRI Detection of Active Sacroiliitis in First Degree Relatives of Ankylosing Spondylitis Patients with Clinical and Laboratory Correlations

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Abstract

Background. Detection of ankylosing spondylitis (AS) in the preclinical stage could help prevent long term morbidity in this patients' population. The aim of this study was to examine the prevalence of active sacroiliitis in first-degree relatives of AS patients using MRI with clinical and laboratory correlations as these patients may benefit from MRI screening and early treatment.

Methods. Seventeen first-degree relatives of AS patients were recruited prospectively. AS screening questionnaires (Ankylosing Spondylitis Disease Activity Score, Bath Ankylosing Spondylitis Disease Activity Index & Visual Analogue Scale), blood tests (C-Reactive Protein, HLA-B27), and an MRI of the SIJs were taken. Two musculoskeletal radiologists interpreted the MRI scans, and two physiotherapists applied four symptom provocation tests (Gaenslen's test, posterior pelvic pain provocation test, Patrick's Faber (PF) test and palpation of the long dorsal SIJ ligament test), and two functional movement tests (active straight leg raise and Stork test).

Results. Seven (41%) of the 17 participants demonstrated MRI evidence of active sacroiliitis. Of the 7 participants with active sacroiliitis, two (29%) had no history of recent low back pain (LBP), two (29%) had negative HLA-B27, and one (14%) participant had neither back pain nor positive HLA-B27. The Cohen's Kappa score for the interobserver agreement between the radiologists was 1.00 (*p-value <0.0001*). Despite fair to strong between therapist agreement for the physical test outcomes (Kappa 0.26 to 1.00), the physical test results *per se* did not have any predictive association with a positive MRI.

Conclusions. MRI detected active sacroiliitis in 41% of first-degree relatives of AS patients. The lack of a history of prior LBP or positive HLA-B27 in active sacroiliitis participants might suggest that MRI screening for this high-risk population is warranted; however, further larger studies are needed to help elucidate its cost-effectiveness and long-term benefits.

Introduction

Ankylosing spondylitis (AS) is the prototypic form of spondyloarthritis (SpA) with a predominantly axial presentation and bilateral symmetric sacroiliitis.[1] Earlier identification of spondyloarthritis using diverse imaging, clinical and proteomic measures offer potential to initiate early therapy, reduce future disability and diagnostic costs.[2] In particular, utilization of anti-tumor necrosis factor (TNF) alpha biologic therapies has been shown to be effective in treating AS symptoms and associated with limitation in radiographic progression of the disease.[3] The Assessment of SpondyloArthritis International Society (ASAS) recently developed widely endorsed criteria for identifying and classifying axial spondyloarthritis (axSpA) that includes magnetic resonance imaging (MRI) to detect active inflammation in the sacroiliac joints.[4] Validated self-report symptom tools [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), and spinal pain Visual Analogue Scale (VAS)] have been utilized in assessing disease activity in AS patients.[5] It has been well documented that

biomarkers such as Human Leukocyte Antigen B27 (HLA-B27) status and C-reactive protein (CRP) have diagnostic, prognostic, and predictive value.[6,7]

A 2017 longitudinal study by Costantino et al. detected radiographic evidence of sacroiliitis in 68.5% of surveyed first-degree relatives of SpA patients over a period of 15 years.[8] The prevalence of MRI confirmed active sacroiliitis in first-degree relatives was previously estimated at 25.5%; observations were made from a single radiologist's interpretation of a single coronal oblique STIR sequence, a significant limitation.[9] This current study examines the prevalence of MRI confirmed active sacroiliitis in first degree relative of AS patients using 4 MRI sequences (axial T2FS and T1 and coronal oblique T1 and STIR), which are independently interpreted by two musculoskeletal radiologists and correlated with clinical and laboratory tests.

Methods

Ethical considerations and recruitment

Ethical approval was provided by the University of Saskatchewan Biomedical Research Ethics Board (15–218) with operational approval granted by Saskatchewan Health Authority, Canada. Potential participants were invited to take part in this study using a variety of recruitment strategies, including recruitment posters and flyers advertised in 3 local hospitals, private practice rheumatology clinics, paid advertisement through local newspapers, in-person invitations during out-patient rheumatology clinic visits within the university-affiliated hospital, electronic mails to patients diagnosed with AS and several other media outlets. Informed consent was obtained from all individual participants included in the study.

Inclusion and Exclusion Criteria

Inclusion criteria were first-degree relatives of clinically diagnosed AS patients, aged between 18 and 45 years, with no history of any previous diagnosis of SpA, spinal surgery, recent infection, or recent trauma and no contraindication for using MRI. All test participants were required to be capable of giving informed consent before inclusion in the study. Potential participants who advised they were receiving anti-TNF α biologic medications were excluded from the study.

MRI Imaging

All participants underwent a dedicated unenhanced spondyloarthropathy MRI scan protocol of the sacroiliac joints, which included coronal oblique T1 and STIR and axial T1 and T2FS sequences (Table 1). All scans were performed on a Siemens 3 Tesla scanner (Siemens, Skyra Healthcare, Erlangen, Germany) using a spine coil. All images were independently read by two fellowship-trained musculoskeletal radiologists (with 18 years of experience each) on Philips PACS workstations and Barco monitors. Each scan was scored according to the ASAS criteria.[10] The sacroiliac joints were assessed for acute enthesitis, periarticular osteitis (bone edema), articular erosions, and joint effusions (Fig. 1). The

two radiologists were blinded to each other's results, and an inter-observer agreement analysis was performed for reliability of results.

Table 1
MRI sequences of the sacroiliac using a 3 Tesla Siemens Skyra MRI scanner.

Sequence	TR† (ms)	TE‡ (ms)	Slice Thickness (mm)	Matrix (mm)	Field of View (mm)
Axial T2 FS§	7580	77	3.0	0.8x0.8x3	300
Axial T1 Oblique	750	11	3.0	0.9x0.9x3	300
Coronal Oblique T1	750	9.4	3.0	0.9x0.9x3	300
Coronal Oblique STIR¶	3000	32	3.0	1.2x1.2x3	300
Abbreviations: †TR: Time to Repeat, ‡TE: Time to Echo, §FS: Fat Saturated, ¶STIR: Short Tau Inversion Recovery.					

Measurement Tools

Three disease activity measurement tools were employed:

1. Ankylosing Spondylitis Disease Activity Score (ASDAS)

The ASDAS is a composite index used to assess disease activity in AS patients. The score can be calculated with the erythrocyte sedimentation rate (ESR) or CRP values.[5] Scores are categorized in four groups as: 'inactive disease activity' when < 1.3, 'moderate disease activity' from 1.3 to < 2.1, 'high disease activity' from 2.1 to 3.5, and 'very high disease activity' when > 3.5.[5] For this study, we used the ASDAS-CRP score as recommended by ASAS.[11]

2. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score consists of 10 cm visual analogue scales used to answer six questions pertaining to the five major symptoms of AS [5]. Scores are categorized as: 'mild disease activity' for values 1–3, 'moderate disease activity' for values 4–7, 'severe disease activity' for values 8-10.[12]

3. Visual Analogue Scale (VAS) for spinal pain

The VAS is a continuous scale comprised of a vertical line measuring 100 mm in length and anchored by two verbal descriptors (best and worst) describing extremes of pain.[13,14]

Research timeframe per participant

For each participant, data collection was carried out within a seven-day period, in two stages.

3.1 Stage 1

Blood work and MRI scan

On the day of recruitment, participants first met with a research assistant to gather demographic data and complete the BASDAI, ASDAS, and VAS disease activity measurement tools. A phlebotomist then drew blood samples for CRP, ESR, and HLA-B27 serum analysis. Participants then underwent an MRI scan of the sacroiliac joints with a 3.0 Tesla MRI using a dedicated non-contrast spondyloarthropathy protocol.

3.2 Stage 2

Physical tests

Two to seven days following blood draw and MRI, test participants were physically evaluated by two experienced musculoskeletal physiotherapists for independent and blinded physical evaluation. Prior to data collection, the two physiotherapists met with the research team to familiarise with the physical test protocol and questions to ask participants regarding LBP history within the past three months.

The six recommended clinical tests described in the European Guidelines for the physical diagnosis and treatment of pelvic girdle pain[15] were independently applied by each physiotherapist. The results were recorded for comparison. This physical assessment was composed of four pain provocation tests [Gaenslen's test, posterior pelvic pain provocation test (PPPT), Patrick's Faber test (PFT), and palpation of the long dorsal sacroiliac joint ligament] and two functional or movement tests [active straight leg raise (ASLR) and the Stork test on the support side] that also tested for symptom response.[16–19]

Both diagnostic imaging specialists and both physiotherapists were blinded to the outcome of the laboratory and BASDAI/ASDAS/VAS assessments and to each other's assessments. To minimize for naturally occurring fluctuations in AS symptoms over time, surveys, MRI, and physical evaluation were completed for each participant within a 7-day window.

Data Analysis

Descriptive analysis was completed for BASDAI/ASDAS/VAS, demographic and clinical data, physical test, and MRI results. Radiologist and physiotherapist inter-examiner reliability of MRI evaluation and individual physical tests, respectively, were assessed using Cohen's Kappa. We chose the following Kappa benchmarks for evaluating the inter-examiner strength of agreement: ≤ 0 = poor, 0.01 to 0.20 = slight, 0.21 to 0.40 = fair, 0.41 to 0.60 = moderate, 0.61 to 0.80 = substantial and 0.81 to 1.00 = almost perfect.[20] All data analyses were carried out using the Statistical Package for Social Sciences (SPSS Statistics version 24, IBM Corporation, Armonk, NY).

Results

Study Participants

Nineteen first-degree relatives of known AS-diagnosed individuals, aged 18 to 45 years, with no history of clinically diagnosed spondyloarthritis, met eligibility criteria and were recruited into the study. All participants were males. Two participants dropped out due to scheduling conflicts and travel limitations, leaving 17 participants.

Descriptive analysis

A descriptive overview of the demographic and clinical variables of the 17 male participants is presented in Table 2. Mean values and standard deviation are summarized for age, ASDAS-CRP, BASDAI, and VAS scores. Frequencies and percentages are also described for participants who tested positive for HLA-B27, CRP, and MRI; as well as participants reporting 'yes' for having had at least one episode of LBP in the last three months. Eight of 17 participants (47%) tested positive for HLA-B27 antigen; 2 (12%) tested positive for elevated CRP; while seven (41%) were positive for an MRI diagnosis of active sacroiliitis (Fig. 1). A descriptive overview of clinical participants (with LBP or HLA-B27), with MRI positive versus MRI negative results, is presented in Table 3. Two of the 7 (29%) participants who had an MRI confirmed active sacroiliitis had no history of LBP in the past three months. HLA-B27 was negative in 2 of the 7 (29%) participants who demonstrated active sacroiliitis on MRI. One participant who had no history of LBP and negative HLA-B27 demonstrated active sacroiliitis on MRI.

Table 2
Demographic and clinical characteristics of first-degree relatives

Variable	Frequency (%)	Mean (SD)	Range
Age (years)	-	30.2 (7.3)	21–43
ASDAS† (CRP)	-	1.04 (0.50)	0.15–1.89
VAS‡ (100mm)	-	23.2 (16.8)	3–70
BASDAI§	-	2.00 (1.65)	0.2–6.2
HLA-B27¶ positive	8 (47%)	-	-
HLA-B27 negative	9 (53%)	-	-
CRP□ ≥ 4.1	2 (12%)		
CRP < 4.1	15 (88%)		
MRI positive for active Sacroiliitis	7 (41%)		
MRI negative for active Sacroiliitis	10 (59%)	-	-
LBP ∞ in past 3 months	9 (53%)	-	-
Abbreviations: †ASDAS: Ankylosing Spondylitis Disease Activity Score, ‡VAS: Visual Analog Scale, §BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ¶HLA-B27: Human Leukocyte Antigen B27, □CRP: C-reactive protein, ∞LBP: Low Back Pain,			

Table 3

Descriptive results showing MRI result cross-tabulations for HLA-B27 positive, LBP and HLA-B27 positive + LBP combinations

Variables	MRI negative	MRI positive
	Frequency (%)	Frequency (%)
Participants (n = 17)	10/17 (59%)	7/17 (41%)
LBP† positive (n = 9)	4/10 (40%)	5/7 (71%)
HLA-B27‡ positive (n = 8)	3/10 (30%)	5/7 (71%)
HLA-B27 positive + LBP positive (n = 5)	1/10 (10%)	4/7 (57%)
Abbreviations: †LBP: Low Back Pain, ‡HLA-B27: Human Leukocyte Antigen B27		

Reliability assessments

The Cohen's Kappa score for the interobserver agreement between the two radiologists was 1.00 (*p-value < 0.0001*). While interobserver physiotherapist agreement for the six physical tests ranged from fair to perfect agreement (Kappa 0.26 to 1.00) for symptom provocation or movement analysis, no physical test, either singularly or in combination with others, demonstrated any significant predictive association with a positive MRI.

Discussion

First degree relatives of AS are considered high-risk population for developing SpA[21]; however, these individuals may remain in the preclinical phase of the disease for a number of years before presenting with clinical and imaging features of SpA.[8,9,22] Imaging plays a key role in the detection and monitoring of SpA, and MRI is considered the gold standard for identifying active sacroiliitis.[4,23]

The results of this study showed that eight of 17 participants (47%) tested positive for the presence of HLA-B27 antigen, while 7 (41%) were positive for an MRI diagnosis of active sacroiliitis. Despite the small sample size, the proportion of HLA-B27 positive participants in this study (47%) is consistent with previously published proportional results of relatives of known patients with diagnosed spondyloarthritides.[7,23–25] MRI demonstrated active sacroiliitis in 2 (29%) participants with negative HLA-B27, illustrating the role of MRI, which requires one or more SpA features with sacroiliitis on imaging to meet the ASAS classification criteria for axial SpA compared to having two or more SpA features to meet the criteria in individuals with HLA-B27 positive test.[10] Furthermore, MRI detected sacroiliitis in 2 (29%) participants who have had no history of LBP in the three months prior to the MRI, highlighting the potential role of MRI screening for preclinical high-risk individuals.

The 41% prevalence of MRI confirmed sacroiliitis in this study is higher than previously reported prevalence rate of 25.5% by Turina et al.[9] This maybe related to the fact that, in their study, the authors imaged the sacroiliac joints with a single coronal oblique STIR sequence, while in this current study, the MRI protocol included four sequences (axial T2FS and T1 and coronal oblique T1 and STIR), adding more anatomical and pathological details to the imaging data. In addition, the interpretation of the MRI scans in this current study was carried out by two fellowship-trained musculoskeletal radiologists compared to a single radiologist's read in the previous study.[9]

There was perfect interobserver agreement between the two radiologists in detecting active sacroiliitis on MRI in this study. The physiotherapist inter-rater reliability results demonstrate fair to substantial agreement for both positive and negative responses to all physical test procedures[20]; however, it is possible that these clinical tests were not sufficiently sensitive for discriminating low back symptom reproduction in a small non-clinical sample where only 9 out of 17 participants described the presence of at least one episode of LBP in the past three months. This argument is supported by the BASDAI, ASDAS, and VAS scores observed in Table 1, which do not approach threshold values that would be clinically indicative of any active disease process.[11,12,26] It is therefore unclear whether these therapist evaluations

would relate any more strongly to MRI findings in a clinically recruited sample of patients with inflammatory LBP related to AS. It was noted that participants with negative MRI for active disease, were negative responses for pain provocation tests (Gaenslen's, PPPT, PFT, and ASLR) as well as detection of pelvic movement asymmetry on the Stork test.

Our study has several limitations. Despite a variety of advertising and recruitment strategies over a 2-year period, we were unable to identify more than 19 participants. A number of potential participants were unable to attend due to travel restrictions and personal factors, and a number of contacted patients with AS did not have first-degree relatives who met the inclusion and exclusion criteria. Thus, at the completion of the study, we were only able to recruit 17 participants. A limitation of our sampling approach was all first-degree relatives who entered the study were male subjects. While all 17 participants were asked for a recollection of occurrences of LBP in the past three months, none were undergoing any process of clinical investigation or clinical management. Thus, screening procedures were applied to participants who had not yet chosen to enter a clinical pathway. Since the physical tests applied in this study are clearly described as recommended clinical tests for the physical diagnosis and treatment of pelvic girdle pain, it is possible the procedures may not have been sufficiently sensitive for use as a screening procedure in a non-clinical population. A further limitation is that recruitment in this study relied on volunteer participation by first-degree relatives. This procedure to select study participants raises the possibility of selection bias, as individuals with greater concerns regarding a family history of back pain and spondyloarthritis may have been more likely to inquire and agree to participate in the study but may not be fully representative of the population with latent axial SpA.

Conclusion

MRI remains the gold standard for the diagnosis of active sacroiliitis. The study has identified active sacroiliitis in 41% (n = 7/17) of the first-degree relatives of patients with ankylosing spondylitis. MRI detected active sacroiliitis in 2 participants who had no history of LBP, 2 participants with negative HLA-B27, and one participant with neither a history of back pain nor positive HLA-B27. The findings of this study provide some support for MRI screening of this high-risk population for active sacroiliitis in order to help guide informed patient management, minimize long-term disease burden, reduce disability, and improve patients' quality of life; however, further studies are needed to explore the cost effectiveness and long-term benefits of this imaging strategy moving forward.

Abbreviations

ASDAS: Ankylosing Spondylitis Disease Activity Score

CRP: C-Reactive Protein

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

VAS scores: Visual Analogue Scale

HLA-B27: Human Leukocyte Antigen B27

ASAS: Assessment of SpondyloArthritis International Society

LBP: Low Back Pain

AS: Ankylosing Spondylitis

Declarations

1. Ethics approval was obtained from our institutional ethics board and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.
2. Consent for publication- Not Applicable.
3. The authors declare that they have no competing interests,
4. Funding: This research project was funded by the Spondyloarthritis Research Consortium of Canada (SPARCC) with the number 344892.
5. Author's contributions:

Haron Obaid has contributed to the (1) conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be published, and (4) agree to be accountable for all aspects of the work if questions arise related to its accuracy or integrity.

Stephan Milosavljevic has contributed to the (1) conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be published, and (4) agree to be accountable for all aspects of the work if questions arise related to its accuracy or integrity.

Udoka Okpalauwaekwe has contributed to the (1) conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be published, and (4) agree to be accountable for all aspects of the work if questions arise related to its accuracy or integrity.

Brenna Bath has contributed to the (1) conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be published, and (4) agree to be accountable for all aspects of the work if questions arise related to its accuracy or integrity.

Catherine Trask has contributed to the (1) conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be published, and (4) agree to be accountable for all aspects of the work if questions arise related to its accuracy or integrity.

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References

1. Claudepierre P, Wendling D, Breban M, Goupillle P, Dougados M. Ankylosing spondylitis, spondyloarthropathy, spondyloarthritis, or spondylarthritis: what's in a name? Joint Bone Spine 2012;79(6), 534-535.
2. Yi, E, Ahuja A, Rajput T, George AT, Park Y. Clinical, Economic, and Humanistic Burden Associated With Delayed Diagnosis of Axial Spondyloarthritis: A Systematic Review. Rheumatol Ther 2020;7(1), 65-87.
3. Haroon N, Inman RD, Learch T. et al. The impact of tumor necrosis factor alpha inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum 2013;65(10), 2645-2654.
4. Rudwaleit M, Jurik AG, Hermann KG. 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(10), 1520-1527.
5. Pedersen SJ, Sorensen IJ, Garnero P. et al. ASDAS, BASDAI and different treatment responses and their relation to biomarkers of inflammation, cartilage and bone turnover in patients with axial spondyloarthritis treated with TNFalpha inhibitors. Ann Rheum Dis 2011;70(8), 1375-1381.
6. Maksymowych WP. Biomarkers for Diagnosis of Axial Spondyloarthritis, Disease Activity, Prognosis, and Prediction of Response to Therapy. Front Immunol 2019;10, 305.
7. Sheehan NJ. The ramifications of HLA-B27. J R Soc Med 2004;97(1), 10-14.
8. Costantino F, Zeboulon N, Said-Nahal R, Breban M. Radiographic sacroiliitis develops predictably over time in a cohort of familial spondyloarthritis followed longitudinally. Rheumatology (Oxford) 2017;1;56(5):811-817.
9. Turina MC, de Winter JJ, Paramarta JE et al Clinical and Imaging Signs of Spondyloarthritis in First-Degree Relatives of HLA-B27-Positive Ankylosing Spondylitis Patients: The Pre-Spondyloarthritis (Pre-SpA) Cohort Study. Arthritis Rheumatol. 2016;68(10):2444-55.
10. Rudwaleit M, van der Heijde D, Landewe R, 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(6), 777-783.
11. van der Heijde D, Lie E, Kvien T. et al. Assessment of SpondyloArthritis international, S. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68(12), 1811-1818.

12. Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21(12), 2286-2291.
13. Delgado DA, Lambert BS, Boutris N, et al. Validation of Digital Visual Analog Scale Pain Scoring With a Traditional Paper-based Visual Analog Scale in Adults. J Am Acad Orthop Surg Glob Res Rev 2018;2(3), e088.
14. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63 Suppl 11, S240-252.
15. Vleeming A, Albert HB, Ostgaard HC, Sturesson B, Stuge B. European guidelines for the diagnosis and treatment of pelvic girdle pain. Eur Spine J 2008;17(6), 794-819.
16. Castro MP, Stebbings SM, Milosavljevic S, Bussey MD. Criterion-concurrent validity of spinal mobility tests in ankylosing spondylitis: a systematic review of the literature. J Rheumatol 2015;42(2), 243-251.
17. Castro MP, Stebbings SM, Milosavljevic S, Bussey MD. Construct validity of clinical spinal mobility tests in ankylosing spondylitis: a systematic review and meta-analysis. Clin Rheumatol 2016;35(7), 1777-1787.
18. Castro MP, Stebbings SM, Milosavljevic S, Pedersen SJ, Bussey MD. Assessing the construct validity of clinical tests to identify sacroiliac joint inflammation in patients with non-radiographic axial spondyloarthritis. Int J Rheum Dis 2019;22(8), 1521-1528.
19. Arnbak B, Jurik AG, Jensen RK, et al. The diagnostic value of three sacroiliac joint pain provocation tests for sacroiliitis identified by magnetic resonance imaging. Scand J Rheumatol 2017;46(2), 130-137.
20. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33(1), 159-174.
21. Geirsson AJ, Kristjansson K, Gudbjornsson B. A strong familiality of ankylosing spondylitis through several generations. Ann Rheum Dis 2010;69(7), 1346-1348.
22. Wang R, Gabriel SE, Ward MM. Progression of Nonradiographic Axial Spondyloarthritis to Ankylosing Spondylitis: A Population-Based Cohort Study. Arthritis Rheumatol 2016;68(6), 1415-1421.
23. Weber U, Zhao Z, Rufibach K, et al. Diagnostic utility of candidate definitions for demonstrating axial spondyloarthritis on magnetic resonance imaging of the spine. Arthritis Rheumatol 2015;67(4), 924-933.
24. Braun J, Bollow M, Remlinger, G. et al. Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. Arthritis Rheum 1998;41(1), 58-67.
25. Khan MA. Epidemiology of HLA-B27 and Arthritis. Clin Rheumatol 1996;15 Suppl 1, 10-12.
26. Reveille JD. Epidemiology of spondyloarthritis in North America. Am J Med Sci 2011;341(4), 284-286.

Figures

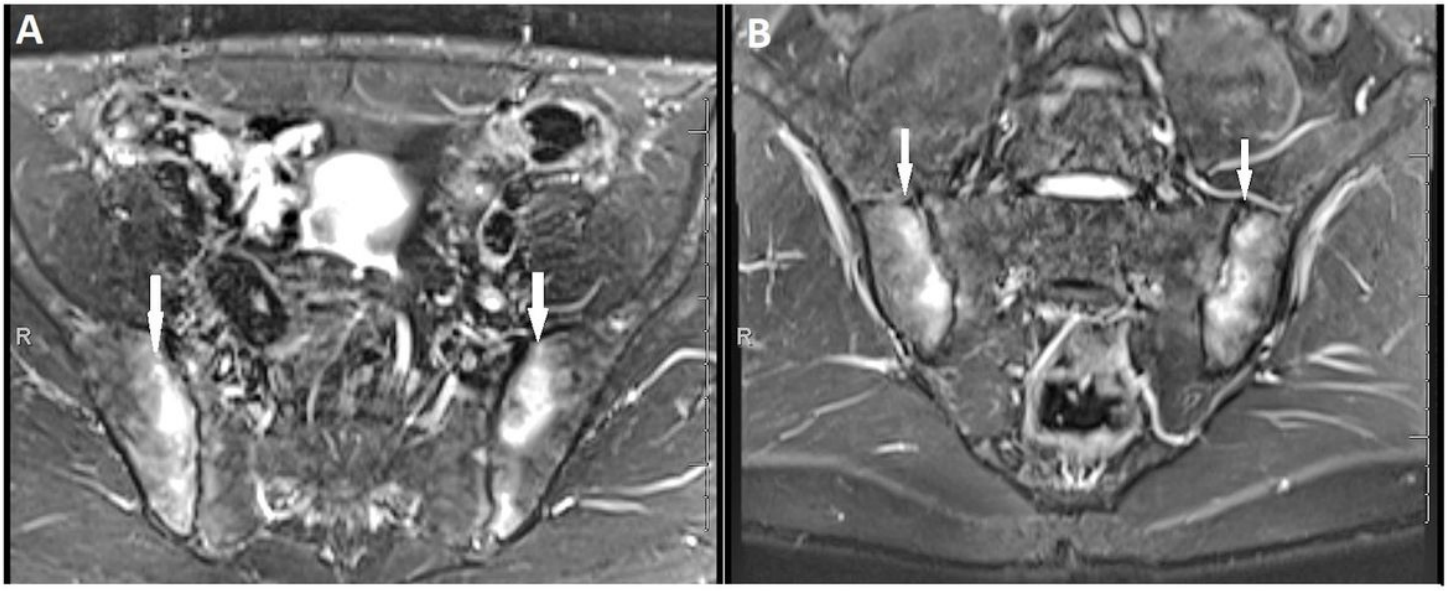

Figure 1

A 29-year-old male first-degree relative of ankylosing spondylitis patient. Axial STIR (a) and coronal oblique STIR (b) MRI sequences demonstrating bilateral periarticular osseous oedema (arrows) in keeping with active bilateral sacroiliitis.