MR imaging in early rheumatoid arthritis : techniques and applications

Stomp, W.

Chapter 7

MRI of hand and foot joints of patients with anticitrullinated peptide antibody positive arthralgia without clinical arthritis

A Krabben, W Stomp, D van der Heijde, JA van Nies, JL Bloem, TWJ Huizinga, M Reijnierse, AHM van der Helm-van Mil

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Abstract

Background

Anticitrullinated peptide antibodies (ACPA) and acute phase reactants may be increased before arthritis becomes clinically detectable, suggesting that the processes underlying rheumatoid arthritis (RA) start preclinically. Whether local inflammation occurs in the preclinical phase is unknown. Therefore, we studied the small joints of ACPA positive arthralgia patients for local subclinical inflammation.

Methods

Imaging was performed using 1.5 T extremity MRI. Painful hand or foot joints of 21 ACPA positive arthralgia patients without clinical arthritis were imaged. For comparison, hand and foot joints of 22 ACPA positive RA patients and 19 symptom free controls were studied. Within ACPA positive arthralgia patients, painful and symptom free joint regions were imaged. Scoring was performed according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) method. Analyses were performed on joint region level and focused on inflammation (synovitis plus bone marrow oedema).

Results

The mean combined inflammation scores of the metacarpophalangeal/proximal interphalangeal joints of controls, painful joints of ACPA positive arthralgia patients and ACPA positive RA patients were 0.1, 0.7 and 3.7, respectively ($p<0.001$). Likewise, the mean combined inflammation scores of the wrist were 0.9, 2.3 and 10.3, respectively ($p<0.001$) and that of the metatarsophalangeal joints 0.5, 0.9 and 3.8, respectively ($p=0.10$). At the MCP joints, the combined inflammation score was significantly correlated with C reactive protein and erythrocyte sedimentation rate levels ($rs=0.83$ and $rs=0.78$, respectively)

Conclusions

The present data suggest that local subclinical inflammation occurs in ACPA positive arthralgia patients.

Introduction

Recent studies have shown that anticitrullinated peptide antibodies (ACPA) can be detected in the serum of ACPA positive rheumatoid arthritis (RA) patients years before arthritis becomes clinically detectable.[1] C reactive protein (CRP), cytokines and bone degradation markers have also been found to be elevated in this phase,[2] suggesting that the processes underlying the development of RA may start long before clinical arthritis occurs. Therefore, detailed studies on inflammation in the preclinical phase may enhance our understanding of the development of ACPA positive RA.[3]

It is not yet known whether local inflammation occurs in small joints in the preclinical phase. A recent MRI study on knee joints of 13 ACPA positive arthralgia patients showed no subclinical inflammation.[4] However, ACPA positive RA probably does not start in the knee joints, leaving unanswered the question of whether local inflammation is present in the preclinical phase of ACPA positive RA.

This study aimed to investigate whether there is subclinical inflammation in painful metacarpophalangeal (MCP) joints, the wrist or metatarsophalangeal (MTP) joints in ACPA positive arthralgia patients. To this end, MRI scans of painful small joints of ACPA positive arthralgia patients were compared with scans of small joints of ACPA positive RA patients and of symptom free controls. Then, the results of the MRI scans of painful and symptom free joints were compared within ACPA positive arthralgia patients.

Methods

Subjects

Three groups were studied. The first group comprised ACPA positive (anti-CCP2, Immunoscan RA Mark 2; Euro-Diagnostica, Arnhem, The Netherlands) patients with painful hand or foot joints but without clinical arthritis, who were recruited from the rheumatological outpatient clinic in Leiden University Medical Center between May 2011 and July 2012. In total, 25 ACPA positive arthralgia patients were recruited; three patients were excluded as clinically detectable arthritis was observed by a rheumatologist on the day of the MRI and one patient had an MRI artefact due to a metal fragment in his hand, leaving 21 patients for evaluation. Per patient, the region of the (most) painful joints (proximal interphalangeal (PIP) 2–5, MCP 2–5, wrist or MTP 1–5) was imaged. To allow comparisons within patients, the symptom free contralateral side was also scanned. When both sides were painful, another non-painful region was scanned (e.g., in case of arthralgia of MCP joints at both sides, symptom free MTP joints were scanned). The regions that were scanned in ACPA positive arthralgia patients were not fixed in order to allow the flexibility to scan painful joints as well as symptom free joints in every patient. The second group of subjects were 22, 1987 American College of Rheumatology criteria positive ACPA positive early RA patients. These patients were included in the early arthritis cohort (EAC) Leiden between

August 2010 and July 2012. In these RA patients, MRI of the MCP, wrist and MTP joints at the most painful side was performed. The third group comprised 19 healthy subjects without joint complaints, who underwent MRI of the MCP, wrist and MTP joints at the dominant side. Written informed consent was obtained from all participants. The study was approved by the local medical ethics committee.

MRI

Imaging was performed on an ONI-MSK-Extreme 1.5 T extremity MRI (GE, Wisconsin, USA). Acquired sequences were T1 weighted fast spin echo sequences, T2 weighted fast spin echo sequences with fat saturation (both coronal plane), and after intravenous gadolinium contrast (0.1 mmol/kg), T1 weighted fast spin echo sequences with fat saturation in the coronal and axial planes. The field of view was 100 mm for all sequences. For ethical reasons, contrast was not administered in healthy controls. MRI scoring was performed by two trained readers according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis MRI Scoring (RAMRIS) method, evaluating erosions, bone marrow oedema and synovitis.[5, 6] The mean scores of the two readers were analysed (within reader intraclass correlation coefficient total RAMRIS score 0.98 and 0.83, and between reader intraclass correlation coefficient 0.82).

Analyses

Analyses were performed per different joint regions. The 'combined inflammation score' (synovitis plus bone marrow oedema) was analysed using Kruskal–Wallis tests or Mann–Whitney U tests because of non-normally distributed data. The correlation between the painful and symptom free joints in ACPA positive arthralgia patients was tested with Spearman's correlation. SPSS V.20.0 was used. A p value<0.05 was considered significant.

Results

Baseline characteristics of the ACPA positive arthralgia patients, ACPA positive RA patients and symptom free controls are presented in table 1. The arthralgic joint regions in the ACPA positive arthralgia patients were: MCP joints (n=4), PIP joints (n=4), wrist (n=3) and MTP joints (n=10) (see table 2 for an overview of the scanned regions).

Given the study question, we specifically studied the inflammatory markers bone marrow oedema and synovitis (summed in the combined inflammation score) without the erosion score. In the wrist joints, the combined inflammation scores of the symptom free controls, ACPA positive arthralgia and ACPA positive RA patients were 0.9, 2.3 and 10.3, respectively ($p<0.001$). The combined inflammation scores of the MCP/PIP joints were 0.1, 0.7 and 3.7, respectively ($p<0.001$), and the combined inflammation score of the MTP joints 0.5, 0.9 and 3.8, respectively ($p=0.10$). When comparing ACPA positive arthralgia patients and symptom free controls, the combined inflammation scores were significantly higher in the wrist joints of ACPA positive arthralgia patients ($p=0.02$), but not in the MCP/PIP and MTP joints ($p=0.06$ and $p=0.32$, respectively) (figure 1A–C).

Table 1. Patient characteristics

	Symptom free controls (n=19)	ACPA positive arthralgia (n=21)	ACPA positive RA (n=22)
Age (years) (mean±SD)	46.2±11.8	47.9±7.9	53.7±15.9
Female sex (n (%))	15 (78.9)	17 (81.0)	12 (54.5)
Symptom duration at MRI (weeks) (median (IQR))	n/a	34.5 (15.3–114.5)	20 (11–37)
Onset of symptoms (n (%))			
• (Sub) acute	n/a	6 (28.6)	7 (31.8)
• Gradual	n/a	15 (71.4)	15 (68.2)
Morning stiffness (min) (median (IQR))	n/a	30 (5–60)	60 (45–120)
Swollen joint count (median (IQR))	0	0	5 (3–12)
Tender joint count (median (IQR))	0	2 (1–3)	6 (5–11)
ACPA level (median (IQR))	n/a	326 (94–340)	182 (87–324.3)
RF positivity (n (%))	n/a	15 (71.4)	19 (86.4)
RF level (median (IQR))	n/a	22 (10.5–120)	20 (11.5–91)

Sixty-eight tender joint count and 66 swollen joint count were performed. Symptom duration refers to the period between the first symptom onset of any joint and the MRI date. ACPA, anticitrullinated peptide antibodies; n/a, not applicable; RA, rheumatoid arthritis; RF, rheumatoid factor.

Subsequently, we evaluated all MRI features separately. In the wrist, MCP/PIP and MTP joints, a gradual increase was observed in all three features when comparing symptom free controls, ACPA positive arthralgia patients and ACPA positive RA patients (figure 1D–F).

Next the correlation between local and systemic inflammation in ACPA positive arthralgia patients was determined, revealing an association between both CRP and erythrocyte sedimentation rate (ESR) and the combined inflammation score of the MCP joints (rs=0.83, p=0.01 and rs=0.78, p=0.02, respectively). ACPA or rheumatoid factor levels were not correlated with MRI combined inflammation scores in the present study.

Thus far we studied the painful joints of ACPA positive arthralgia patients. Within the ACPA positive arthralgia patients, the mean combined inflammation score in the painful joints was 1.0 and in the symptom free joints 1.2. In the 21 patients studied, we did not observe a significant correlation between these two joint regions (rs=0.32 and p=0.16).

In the follow-up period (mean 9 months (range 1–15 months)), 12 arthralgia patients developed RA according to the 2010 American College of Rheumatology/European League Against Rheumatism RA criteria. The combined inflammation scores between the arthralgia patients that did and did not develop RA were not different, although the number of subjects was too low to allow within group comparisons.

Table 2. Overview of scanned joint regions

	Scanned joint region		
	wrist	PIP/MCP	MTP
Symptom-free controls	19	19	19
ACPA+ arthralgia patients, symptom-free joint region	3	11	6
ACPA+ artralgia patients, painful joint region	3	8	10
ACPA+ RA patients	22	22	22

In ACPA-positive arthralgia-patients the most painful joint region was scanned. For comparison within patients; in these patients the symptom-free contralateral side was scanned as well. When both sides were painful, another non-painful region was scanned. In seven patients this resulted in another joint region scanned as symptom-free joint region. Two of them had painful MCP region and symptom-free MTP scanned joint region. In five patients the MTP joint region was scanned whereas MCP joint region was scanned as symptom-free joint region.

Discussion

This study has explored whether subclinical inflammation occurs in painful small joints of ACPA positive arthralgia patients without clinical synovitis, using MRI to measure inflammation sensitively.[7] We observed differences between ACPA positive arthralgia patients, ACPA positive RA patients and symptom free controls. Furthermore, a correlation between local inflammation, as measured using MRI, and systemic inflammation, measured using CRP and ESR, was found in ACPA positive arthralgia patients. These data are in line with a study in monkeys showing that subclinical inflammation precedes clinical arthritis.[8] They are also in line with a recent ultrasound study and a study reporting an increased signal on macrophage position emission tomography in ACPA positive arthralgia patients that developed clinical arthritis.[9, 10] The present data are intriguing as they suggest that there is subclinical inflammation in ACPA positive patients in the preclinical phase. An example of synovitis and bone marrow oedema, as observed in ACPA positive arthralgia patients, is presented in figure 2.

Importantly, the present study used both positive and negative controls (RA patients and symptom free controls, respectively). In particular, the latter is crucial, as several studies have observed MRI abnormalities to a certain degree in healthy persons.[11–13]

This study has several limitations. First and most importantly, the numbers of subjects studied was small and the RAMRIS scores were quite low. The former is due to the low prevalence of ACPA positive arthralgia patients in outpatient clinics and the latter is due to measuring in very early disease stages. Consequently, the power to find statistically significant differences was limited. The power to perform within patient comparisons in particular was low. This was done when comparing within the group of ACPA positive arthralgia patients: MRI inflammation between painful and symptom free joints, level of local inflammation with systemic markers of inflammation (ESR and CRP) and MRI inflammation scores of patients that developed RA and those who did not develop RA. Larger studies are required to address these questions more extensively.

Figure 1A Combined inflammation score wrist joints in; controls, ACPA+ arthralgia patients and ACPA+ 1987-RA patients

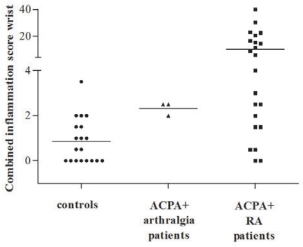

Figure 1B Combined inflammation score MCP/PIP joints in; controls, ACPA+ arthralgia patients and ACPA+ 1987-RA patients

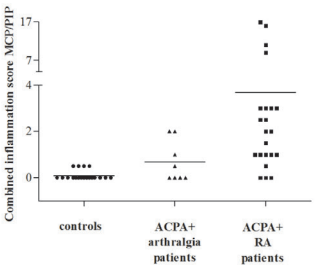

Figure 1C Combined inflammation score MTP joints in; controls, ACPA+ arthralgia patients and ACPA+ 1987-RA patients

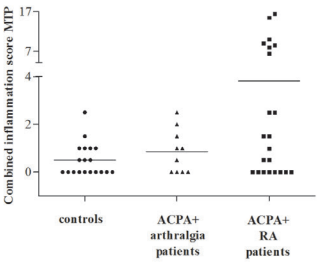

Figure 1D Mean RAMRIS subscores in wrist joints in; controls, ACPA+ arthralgia patients and ACPA+ 1987-RA patients

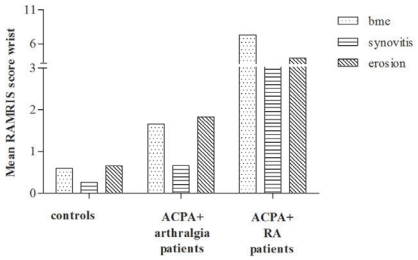

Figure 1E Mean RAMRIS subscores in MCP/PIP joints in; controls, ACPA+ arthralgia patients and ACPA+ 1987-RA patients

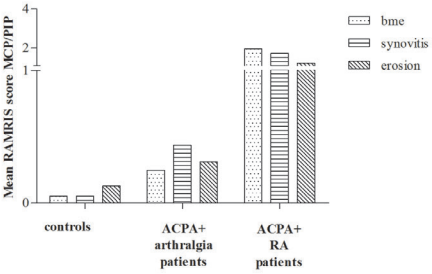

Figure 1F Mean RAMRIS subscores in MTP joints in; controls, ACPA+ arthralgia patients and ACPA+ 1987-RA patients

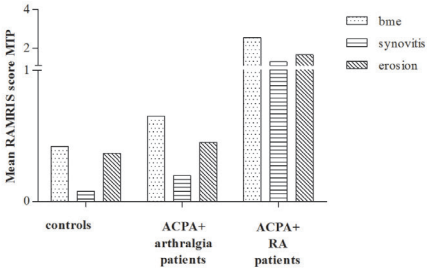

Figure 1. Combined inflammation scores (bone marrow oedema (bme) plus synovitis) (A–C) and separate scores for bone marrow oedema, synovitis and erosion (D–F) in symptom free healthy controls, anticitrullinated peptide antibody (ACPA) positive arthralgia patients and ACPA positive rheumatoid arthritis (RA) patients per joint region. All scores are mean scores of two readers. Horizontal lines represent mean scores. The y axes were split as RA patients had higher scores than ACPA positive arthralgia patients and healthy controls. The mean combined inflammation scores of the wrist joints of the controls, painful joints of ACPA positive arthralgia patients and ACPA positive RA patients were 0.9, 2.3 and 10.3, respectively ($p<0.001$).The mean combined inflammation scores of the metacarpophalangeal (MCP)/proximal interphalangeal (PIP) joints were 0.1, 0.7 and 3.7, respectively ($p<0.001$) and that of the metatarsophalangeal (MTP) joints 0.5, 0.9 and 3.8, respectively ($p=0.10$). Similarly, for these three groups, the mean erosion scores were 0.7, 1.8 and 3.8 in the wrist, 0.1, 0.3 and 1.2 in the MCP/PIP and 0.4, 0.5 and 1.7 and in the MTP joints, respectively. RAMRIS, Rheumatoid Arthritis MRI Score.

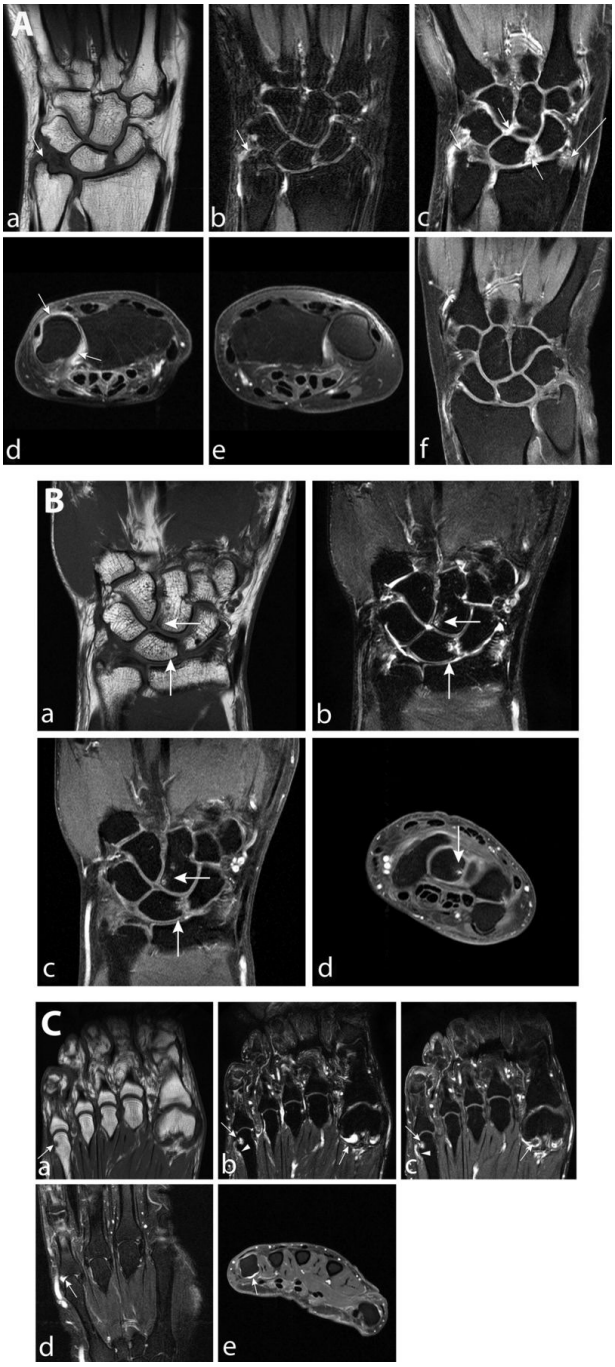

Figure 2. MR images of anticitrullinated peptide antibody positive arthralgia patients without clinically detectable arthritis. (A) MR images of the left hand; the right hand is shown for comparison. Coronal T1 TSE, T2 TSE fatsat and T1 fatsat after gadolinium (A (a–c)). Axial image at the level of the distal radioulnar joint (A (d)). The right hand is shown for comparison: T1 fatsat after gadolinium axial (A(e)) and coronal (A (f)) without enhancement. In the left hand, increased volume of soft tissues is evident around the distal ulna, intermediate of signal intensity on T1 (A (a)), high on T2 (A (b)) (arrow). After gadolinium, abundant enhancement of thickened synovium is evident around the distal ulna and among the carpal joints (arrows A (c), (d)). According to the Rheumatoid Arthritis MRI Scoring (RAMRIS) method, synovitis was scored. Partial volume is seen at the processus styloideus radii (long arrow). (B) MR images of the left wrist. At the proximal end of the hamate and at the lunate, regions of low intensity on T1 (B (a)) and high intensity on T2 (B (b)) and high intensity on T1 after gadolinium (B (c), (d)) are appreciated, which represents bone marrow oedema. Furthermore, no enhancement of the synovium is seen (B (c), (d)). Therefore, no synovitis was scored. (C) MR images of the left foot (C (a–c)) and left hand (C (d), (e)). The head of metatarsal 5 showed a small lesion (arrows), low on T1 (C (a)), high on T2 (C (b)), enhancing after gadolinium (C (c)), which could be an erosion or synovial cyst. Subtle enhancement of synovium is seen laterally (arrowhead). A small amount of fluid with rim enhancement of synovium of metatarsophalangeal 1 (arrow) is present. No bone marrow oedema is appreciated. The left hand shows a subtle amount of high signal intensity in metacarpophalangeal 5, enhancing after gadolinium (C (d), (e)), consistent with subtle synovitis.

Another limitation is that the duration of follow-up was too short to definitely conclude which arthralgia patients progressed to RA. Also, in this respect, further studies with a longer follow-up of ACPA positive arthralgia patients are required.

A third limitation is that, for ethical reasons, the symptom free control group did not receive intravenous contrast, which may have underestimated synovitis scores in these people. However, differences were also observed in erosion and bone marrow oedema scores, evaluations which do not require contrast administration. Furthermore, the scanned joint regions were fixed in RA (MCP, wrist and MTP joints at the most painful side) and in the controls (MCP, wrist and MTP joints at the dominant site), but not in the ACPA positive arthralgia patients. This was done in order to ensure that within ACPA positive arthralgia patients both joint regions with and without symptoms were evaluated. The number of painful joint regions in the arthralgia patients was low and a preset scanning protocol might have resulted in imaging of only symptom free joints.

In conclusion, the present study provides suggestive evidence that there is subclinical inflammation in ACPA positive arthralgia patients. Large longitudinal studies are needed to define the diagnostic or prognostic value of MRI in this preclinical phase.

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