CHAPTER 4

Three-year clinical outcome following baseline magnetic resonance imaging in anti-citrullinated protein antibody-positive arthralgia patients: an exploratory study

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ABSTRACT

Objective: To investigate whether magnetic resonance imaging (MRI) can visualize subclinical synovitis in arthralgia patients with positive anti-citrullinated protein antibodies (ACPA), and to determine the relationship between MRI and development of clinical arthritis during 3 years of followup.

Methods: MRI scans of both hands/wrists of 28 patients were scored for synovitis and bone marrow edema (BME) according to OMERACT RAMRIS. Cumulative MRI scores (range 0-288) were composed by summing joint scores (synovitis and BME) of wrists, metacarpophalangeal and proximal interphalangeal joints. Development of clinical arthritis was monitored annually during at least 3 consecutive years. MRI scans in healthy volunteers (n=4) were included for comparison.

Results: MRI depicted signs of inflammation in at least 1 hand/wrist joint in 26/28 (93%) patients. The median [IQR] cumulative MRI score was 13.5 [8.3-20.8]. MRI abnormalities were frequent, both in the arthritis (12/28) and no arthritis (16/28) group, as well as in healthy controls. Nevertheless, within the arthritis group, a score 2 synovitis on MRI was associated with a short-term (< 1 year) development of clinical arthritis in at least 1 joint. A higher level of cumulative MRI score was related to aging, both in patients and healthy controls.

Conclusion: (Mild) inflammatory joint signs are frequently present on MRI of hand/wrists in ACPA-positive arthralgia patients without clinical arthritis. Strikingly, only a part of the MRI positive patients developed clinical arthritis during 3 years of followup and MRI abnormalities were also observed in healthy controls. The high frequency of MRI abnormalities may be partly related to aging.

INTRODUCTION

Early therapeutic intervention of rheumatoid arthritis (RA) leads to less joint damage and maintenance of functionality (1). Early treatment requires sensitive diagnostic tests to determine presence of (developing) RA. Previous studies have demonstrated that highly specific antibodies, such as anti-citrullinated protein antibodies (ACPA), can be detected in serum of RA patients years before the disease can be clinically diagnosed (2). Presence of arthralgia may even further enhance the risk of clinical arthritis in ACPA-positive patients (3). Moreover, it is hypothesized that asymptomatic joint synovitis may precede the development of clinical arthritis in RA (4). This all suggests a preclinical phase that could offer a window of opportunity for early detection of RA – even in the preclinical phase – and early treatment with the ultimate aim to prevent further development of RA.

Not all ACPA-positive arthralgia patients will develop RA (40% in the first year) (5), which creates opportunities for additional tests to further select individuals at risk. Advanced imaging may be useful in the detection of subclinical synovitis (i.e., synovitis that cannot be detected by clinical examination) in ACPA-positive arthralgia patients, and it may contribute to timely assessment of which individuals will eventually develop RA (6-8). Magnetic resonance imaging (MRI) in particular may be useful for detection of subclinical synovitis due to its high sensitivity and standardized scoring methods. MRI has been investigated extensively as a method to study residual joint inflammation in RA patients in clinical remission. Studies have shown that MRI abnormalities, in particular bone marrow edema (BME), are associated with progressive joint damage (9;10). One study has reported mainly cross-sectional MRI data in ACPA-positive arthralgia patients, that indicated visualization of subclinical synovitis/BME in these subjects (8). Longitudinal data were, however, only limited to 6 months of followup, and did not show a relationship between MRI at baseline and development of clinical arthritis. Therefore, in this pilot study we investigated whether MRI can visualize subclinical inflammation in the hands and/or wrists of ACPA-positive arthralgia patients, and we determined the relationship between baseline MRI and development of clinical arthritis during 3 years of followup.

PATIENTS AND METHODS

Patients and healthy controls

The study was embedded in a cohort study that recruited seropositive arthralgia patients at the rheumatology outpatient clinics of the VU University Medical Center and Jan van Breemen Research Institute | Reade (5). During 26 months, all arthralgia patients with a positive ACPA status

(independent of IgM-rheumatoid factor status) were consecutively asked to participate in the present MRI substudy. Inclusion and exclusion criteria have been reported previously (5,7). Baseline MRI was performed on 28 included patients and 4 healthy volunteers without a history of joint disorders or clinical arthritis. Development of clinical arthritis was monitored according to the schedule of the cohort study during at least 3 consecutive years. The study protocol was approved by the local medical ethics committee and informed consent was given by participants of the study prior to inclusion.

MRI protocol and analysis

MRI sequences (Siemens Sonata 1.5T MR scanner) were chosen according to Outcome Measures in Rheumatology (OMERACT) guidelines (11). STIR images and 3-dimensional T1-weighted magnetization-prepared rapid gradient-echo images before and after intravenous gadolinium administration were obtained. Synovitis and BME in individual hand and wrist joints were scored by 2 independent observers (NA, CD) according to the OMERACT RA MRI Scoring (RAMRIS) system (11). The MRI protocol included scanning of all proximal interphalangeal (PIP) joints (PIP joints 1-5), metacarpophalangeal (MCP) joints (MCP joints 1-5), and wrist joints of both hands. At the patient level, MRI positivity was defined as the presence of synovitis and/or BME in at least 1 joint/bone. Individual cumulative MRI scores (range 0-288) were calculated by summing synovitis and BME scores of each hand/wrist joint. In addition, presence of subclinical synovitis in flexor and/or extensor tendons of hands and wrists was scored as being absent or present.

Initially, 13 MRI scans derived from different cohorts of RA patients were used to determine intraclass correlation (ICC) between 2 observers (CD, and CvdL) (ICC = 0.98). This set included MRIs of 6 patients of the preclinical RA cohort described in this current article, resulting in an ICC of 0.96. As the ICCs were quite high, eventually all remaining MRIs from this cohort were scored by 1 observer (CD). If this observer had concerns or doubts on the MRI scores, observer 2 and 3 (CvdL and NA) scored the scans additionally to reach consensus. The consensus score was applied for analysis.

Statistical analysis

Data are presented as mean values ± standard deviation (SD) or as median (interquartile range (IQR)) in case of skewed distribution. Linear regression analyses was used to analyze differences in MRI scores for age and gender (α = 5 %). Time to development of arthritis was assessed with Kaplan Meier curve (survival curve). All analyses were performed using IBM SPSS statistics 20 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

At baseline, the median age of the 28 patients was 44 years (IQR 37-53 years). Twenty-three patients (82%) were women. The median duration of arthralgia was 15 months (IQR 11-35 months). In 14 patients, arthralgia was located in hands and/or wrists. Twelve patients (43%) were positive for RF. The median age of the 4 healthy controls (1 man, 3 women) was 31 years (IQR 26-56 years).

Baseline MRI of ACPA-positive arthralgia patients and healthy controls

At baseline, MRI abnormalities were frequently found. In 26 of 28 patients (93%), MRI synovitis (i.e. score ≥1) was present in ≥1 joint of both hands/wrists (Figure 1A and B). Ten of 26 patients had a synovitis score of 2 in ≥1 joint. A synovitis score of 3 was not observed. BME was present in only 3 of 28 patients (11%): 2 patients had a score 1 in 1 joint and 1 patient had a score 2 in 1 joint. The median (IQR) cumulative MRI score (composed of summed synovitis and BME scores) was 13.5 (8.3-20.8). MRI signs of tenosynovitis were observed in 15 of 28 (54%) patients.

Focusing on the distribution of MRI abnormalities, it was found that the cumulative MRI scores of left and right hands differed ≥4 points in 11 of 28 patients. In 5 patients, 1 hand was MRI negative in all joints while the other hand showed inflammation with a cumulative score up to 5. The location of the highest score varied between left and right hand and did not show a particular pattern (data not shown).

In a subgroup of patients (n=14) with baseline arthralgia located in hands and/or wrists (derived from anamnesis), we investigated at the level of the joints whether the location of baseline arthralgia corresponded to that of local MRI abnormalities. For this analysis, the wrist was considered as 1 joint, resulting in assessment of 22 joints per patient. Arthralgia was reported in 58 of 308 (19%) hand/wrist joints. MRI synovitis and/or BME were present in 156 of a total of 308 (51%) hand/wrist joints. Thirty-four of 58 (59%) joints with arthralgia and 122 of 250 (49%) joints without arthralgia were positive for synovitis and/or BME.

MRI scans in all healthy controls showed signs of mild synovitis (score of 1) in ≥1 joint (range 3-23). A score of 2 for synovitis was found in 1 joint of 1 healthy control. BME was not observed on MRI scans in healthy controls. The median (IQR) cumulative MRI (including score 1) score of all 4 healthy controls was 9.5 (3.3-22.5), with a range from 3 to 25.

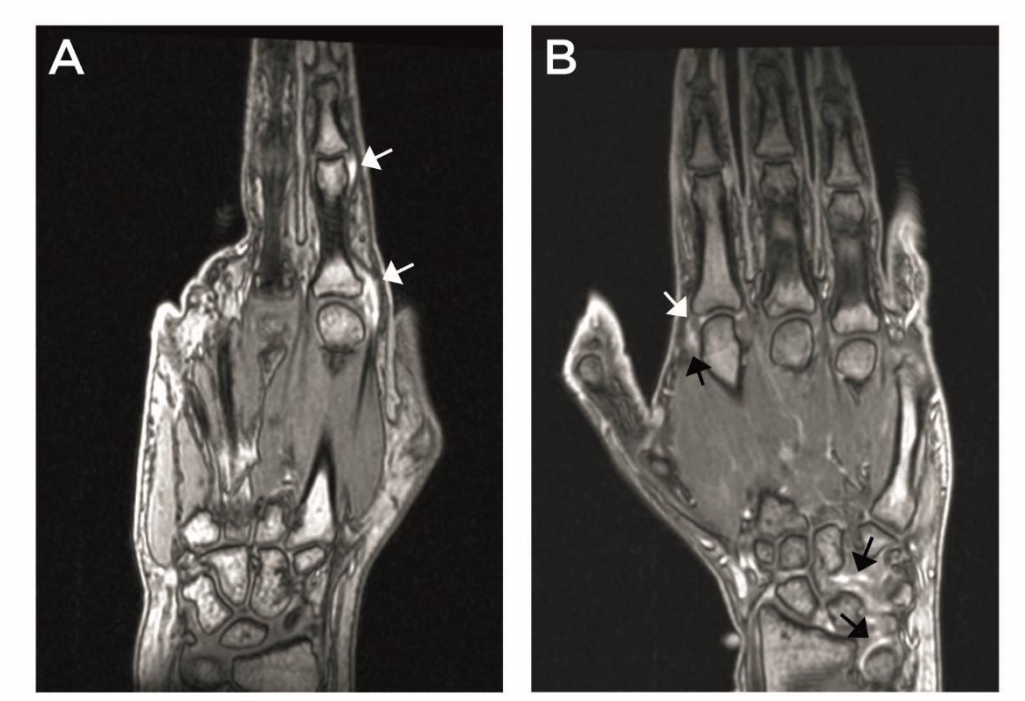

Figure 1. Baseline T1-weighted contrast-enhanced magnetic resonance imaging (MRI) scan of the hand/wrist joints of (A) an anti-citrullinated (ACPA)-positive arthralgia patient who developed arthritis in hand/wrist joints during 3-year followup. (B). an ACPA-positive arthralgia patient who dit not develop arthritis in hand/wrist joints during 3-year followup. White arrows (panel A and B) and black arrows (panel B) indicate MRI signs of synovitis.

Relationship between baseline MRI and development of clinical arthritis

Twelve of 28 patients (43%) developed clinical arthritis and were subsequently diagnosed as having RA according to the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria (12). In 10 of those 12 patients, arthritis was observed in hand and/or wrist joints. At the patient level, 11 of 12 patients who developed clinical arthritis and all 16 patients who did not develop clinical arthritis, had a positive baseline MRI (Figure 2, left panel). The median (IQR) cumulative MRI score of patients with arthritis was even significantly lower than that of patients without arthritis (9.0 [6.3-13.8] versus 20.0 [10.8-21.8]) (odds ratio 0.87 [95% confidence interval 0.76-0.99], *P* = 0.03). In addition, when only MRI scores of 2 for synovitis/BME were taken into account, no significant differences were found (Figure 2, right panel).

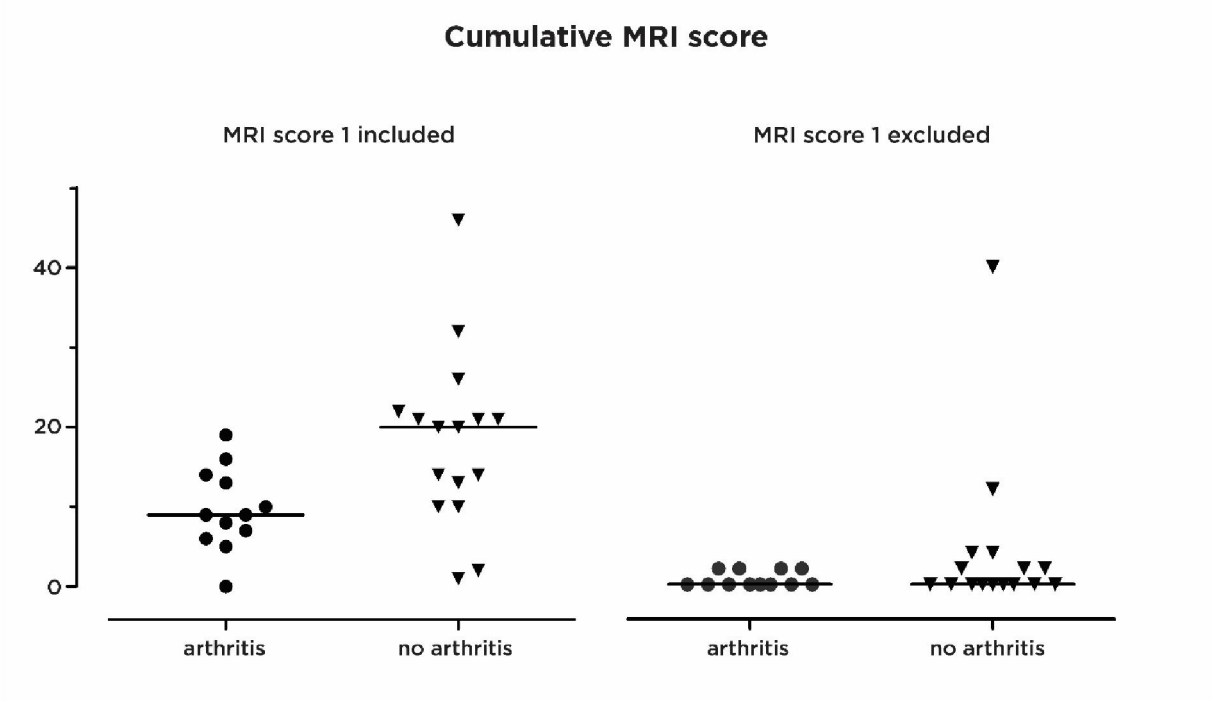

Figure 2. Cumulative magnetic resonance imaging (MRI) scores of patients with and those without development of arthritis during 3-year followup. Left panel: cumulative MRI scores including score 1 for synovitis and bone marrow edema (BME). Right panel: cumulative MRI scores excluding score 1 for synovitis and BME. Symbols represent individual patients; horizontal bars show the median.

Median (IQR) time from inclusion into this study to development of clinical arthritis was 11 (4-22) months. There appeared to be a temporal relationship between the presence of a synovitis score of 2 on MRI and the first appearance of clinical arthritis. The survival plot in Figure 3 shows that those with a synovitis score of 2 in 1 joint all developed clinical arthritis within 1 year, whereas those with a synovitis score of only 1 in at least 1 joint developed clinical arthritis more gradually up to 3 years of followup. Finally, presence of BME (n=3) or tenosynovitis (n=15) on MRI were not significantly associated with development of arthritis (data not shown).

Results at the level of the joints were investigated in the group of patients that developed arthritis in hand/ wrist joints (n=10, 22 joints per patient). Arthritis occurred in 12 of 64 (19%) MRI positive joints (of which only 1 joint (wrist) was positive for both BME and synovitis; in all other joints only signs of synovitis were found). In 4 of 65 MRI positive joints, a score 2 for synovitis was found. However, arthritis developed only in 1 of these joints. Furthermore, arthritis also developed in 21 of 156 (13%) MRI negative joints.

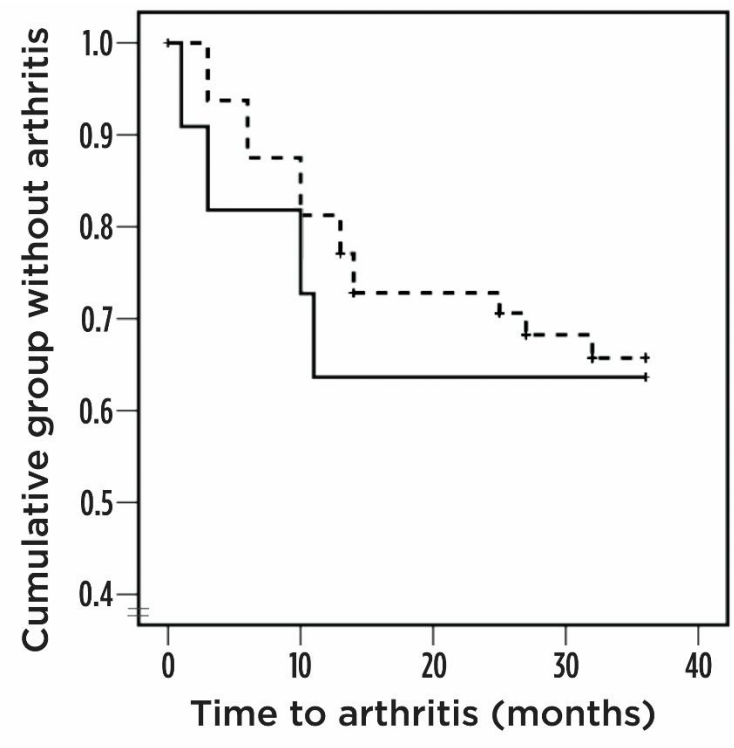

Figure 3. Survival curve. Survival curves for all included patients, comparing the group with an magnetic resonance imaging (MRI) synovitis score of 2 in at least 1 joint (solid line) and the group with an MRI synovitis score of 1 in at least 1 joint (dashed line). Patients with a synovitis score of 2 developed arthritis faster than those with a synovitis score of 1. Plus sign indicates a censored patient.

Relationship between age and cumulative MRI score

To identify possible factors that influenced MRI positivity, the relationship between age and cumulative MRI scores was investigated. ACPA-positive arthralgia patients with a higher age tended to have higher cumulative MRI scores, which was also confirmed in healthy controls (Figure 4). Furthermore, when ACPA-positive arthralgia patients were categorized into 2 groups with median age as the cutoff (i.e., 44 years), linear regression analysis showed that cumulative MRI scores of patients age ≤ 44 years differed significantly from those of patients with age > 44 years (β=0.39, *P*=0.038) (Figure 5). Sex was not significantly associated with developing arthritis (results not shown).

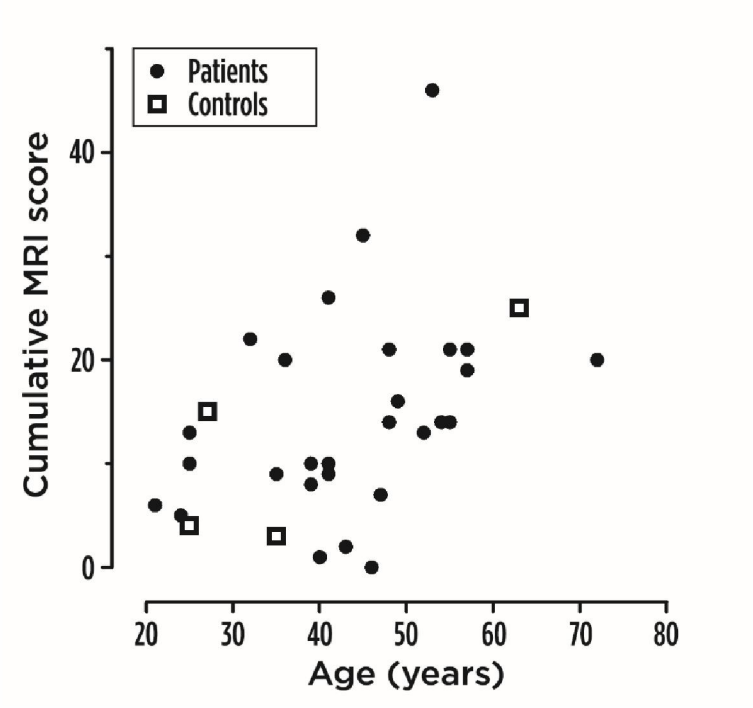

Figure 4. Cumulative magnetic resonance imaging (MRI) scores (including score of 1 for synovitis and bone marrow edema) in relation to age, in individual anti-citrullinated protein antibodies-positive arthralgia patients and individual healthy controls.

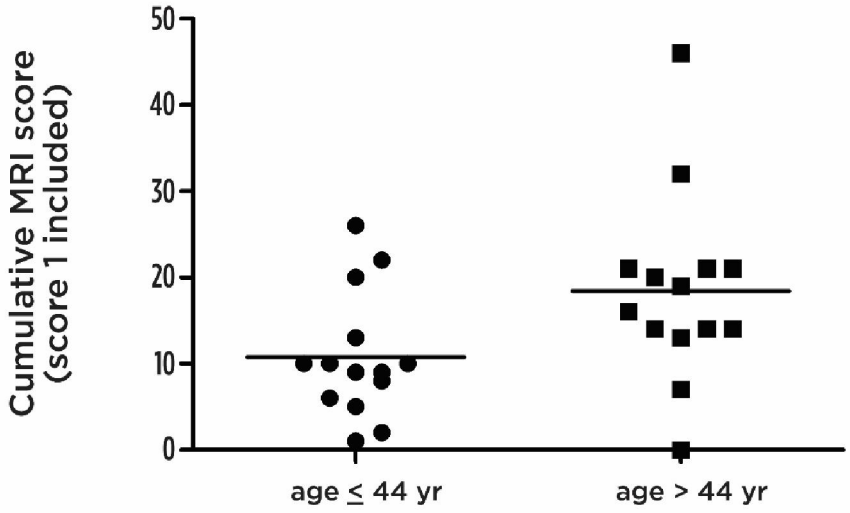

Figure 5. Cumulative magnetic resonance imaging (MRI) scores of individual anti-citrullinated protein antibodies-positive arthralgia patients grouped according the median age of 44 years. Cumulative MRI scores including score 1 for synovitis and bone marrow edema of patients that are 44 years of age and below versus patients that are over 44 years of age. Symbols represent individual patients, horizontal bars show the mean. Yr = years.

DISCUSSION

This explorative study showed that MRI abnormalities (mainly synovitis) were nearly always present in hand and wrist joints of ACPA-positive arthralgia patients without signs of clinical arthritis, regardless whether clinical arthritis developed during 3-year followup. High cumulative MRI scores were mainly driven by a high prevalence of a synovitis score of 1. The presence of a synovitis score of 2 on MRI seemed to be related with short-term (< 1 year) development of clinical arthritis. Finally, our data indicated that aging contributes, at least in part, to the high frequency of inflammatory signals on MRI.

Our results confirmed the presence of subclinical synovitis in ACPA-positive arthralgia patients as was shown before (4;6;8). Krabben *et al.* previously reported significant differences between the level of baseline MRI inflammatory signs of ACPA-positive patients and healthy controls, but conclusions were based on small subgroup numbers and no relationship was found with clinical findings during 6 months of followup (8). The latter was corroborated by our 3-year longitudinal data. In our experience, a followup period of 3 years is sufficient, because thereafter new cases are infrequent. In fact, in a cohort of individuals at risk of RA, the incidence of clinical arthritis was highest during the first year of clinical followup (5).

Our study raises some interesting questions concerning the sensitivity and specificity of MRI for detection of preclinical synovitis. The sensitivity appears to be high which can be exploited for the detection of subtle, subclinical arthritis (10;13;14). However, signs on MRI, in particular a synovitis score of 1, may not always be associated with subsequent development of clinically evident signs or symptoms, and can be found in healthy controls as well (15-17). This issue was also addressed in an ultrasound (US) study of a large cohort of healthy controls (18). Therefore, the meaning of a synovitis score of 1 on MRI remains unclear and high sensitivity may thus lead to poor specificity and a low positive predictive power for the development of clinical arthritis. Finally, our data indicated that aging contributes, at least in part, to the high frequency of inflammatory signals on MRI, which are likely to be related to the presence of degenerative changes in joints (19). Osteoarthritis imaging with MRI has indeed revealed both synovitis and bone marrow lesions (20;21). Our study, indicates that age may be a confounder in the relationship between MRI score and the development of arthritis. Therefore, age of patients should be considered in the interpretation of MRI data and in the selection of health controls.

Despite the high prevalence of primarily mild MRI synovitis in ACPA-positive arthralgia patients, a higher score of synovitis at the level of the joints on MRI may have predictive significance. Our results demonstrated that patients with a score 2 synovitis, developed arthritis faster than those with a score 1 synovitis. The presence of a score 2 synovitis on MRI seemed to be related with short-

term (< 1 year) development of clinical arthritis. This is line with previous MRI findings in established RA showing that a higher grade of synovial thickness on MRI is related to a higher chance of erosion development in the joint as reflection of clinical relevant synovitis (22).

Limitations of this explorative study are the small numbers of included patients and healthy controls. In particular, no definite conclusions could be drawn on the relationship between BME on MRI and the development of clinical arthritis due to the low prevalence of BME in our cohort. Nevertheless, our observation of a high prevalence of synovitis in the non-arthritis group is of clinical relevance for the assessment of MRI as a predictive tool for the development of RA. Also due to the limited number of patients, the statistical significance of the relationship between aging and cumulative MRI scores (as shown in Figure 4) was highly dependent on the age definition according to which patients were grouped; however, the trend of our observation remained consistent independent of the age cutoff point. Furthermore, only baseline MRI scans of hands and wrists were performed, while MRI outcome may vary in time for both ACPA-positive arthralgia patients and healthy controls. The potential benefit of consecutive scanning should be addressed in future studies.

In conclusion, this study shows that inflammatory signs on MRI are frequently present in hand and wrist joints of ACPA-positive arthralgia patients, but with substantial overlap between those with and without development of clinical arthritis and with healthy controls. Defining MRI values that have predictive power for development of RA is highly needed. An important factor of influence on MRI inflammatory signals may be aging. Other possible factors of influence on MRI outcome should also be investigated. Therefore, further exploration of MRI as a diagnostic test to select individuals at risk for development of RA should include extensive investigation of MRI profiles in healthy controls.

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