

# Magnetic Resonance Imaging of the Hand for the Diagnosis of Rheumatoid Arthritis in the Absence of Anti-Cyclic Citrullinated Peptide Antibodies: A Prospective Study

ELISABETH SOLAU-GERVAIS, JEAN-LOUIS LEGRAND, BERNARD CORTET, BERNARD DUQUESNOY, and RENÉ-MARC FLIPO

**ABSTRACT.** *Objective.* To assess the practical usefulness of magnetic resonance imaging (MRI) in establishing a positive diagnosis of rheumatoid arthritis (RA) in a cohort of patients with early inflammatory polyarthralgia, in the absence of anti-cyclic citrullinated peptide (anti-CCP) antibodies.

*Methods.* We prospectively followed 30 outpatients with inflammatory polyarthralgia and/or synovitis of at least one joint. Patients were disease modifying antirheumatic drug-naïve and received no corticosteroids. At the initial visit a clinical examination, radiographs of hands, wrists and feet, and MRI of hands were performed. Rheumatoid factor and anti-CCP antibodies were assessed. The MRI procedure was T1 fat saturation with gadolinium injection [scores were established on the basis of the axial view of the carpal and metacarpal joints, using the RA MRI scoring system (RAMRIS) defined in the OMERACT study]. In all patients, radiographs at baseline were normal and anti-CCP antibodies were negative.

*Results.* At one-year followup, the final diagnosis was: 16 RA; the non-RA group was composed of 4 cases of spondyloarthropathy, 2 cases of fibromyalgia, 4 cases of undifferentiated arthritis (3 of which were self-limiting), 1 sicca syndrome, 1 hemochromatosis, 1 polymyositis, and 1 paraneoplastic syndrome. No statistical difference was found between patients with and without RA for carpal erosion, synovitis, and tenosynovitis. However, a statistical difference was observed between the RA and non-RA group where metacarpophalangeal (MCP) erosion scores were concerned ( $p = 0.024$ ). This difference persisted when we compared erosions of the second and third MCP in the 2 groups ( $p = 0.044$ ). ROC curve analysis revealed a positive MCP score at 15, with a specificity of 70% and a sensitivity of 64%.

*Conclusion.* In our population of 30 anti-CCP negative patients with normal radiographs, MRI of hands, showing MCP erosions, can be helpful for the diagnosis of RA. (First Release July 1 2006; J Rheumatol 2006;33:1760–5)

## Key Indexing Terms:

MAGNETIC RESONANCE IMAGING  
ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES

RHEUMATOID ARTHRITIS  
DIAGNOSIS

To improve the prognosis of rheumatoid arthritis (RA), treatment has to be prescribed early in the course of the disease within the window of opportunity<sup>1-3</sup>. Therefore early diagnosis is necessary. Clinically, modified American College of Rheumatology (ACR) criteria are not efficient in establishing an early diagnosis<sup>4</sup>. On the other hand, diagnosis of RA is quite easy when immunological markers such as anti-cyclic citrullinated peptide (anti-CCP) antibodies and rheumatoid factor (RF) are present<sup>5</sup>. However, the sensitivity of this test

in the early stage of the disease is only 50% alone<sup>6,7</sup> and 58% if associated with RF<sup>5</sup>. Moreover, radiographs are not helpful in establishing an early diagnosis as only 17% of patients have erosion initially<sup>8</sup>. The diagnosis of RA can be difficult, indeed, in a cohort of patients with early arthritis: 35% to 50% of patients showed undifferentiated polyarthritides and only 55% of these cases evolved into RA<sup>9</sup>. Therefore, there is a need for another tool for diagnosis of RA when anti-CCP antibodies are absent and radiographs are normal.

Magnetic resonance imaging (MRI) has been shown to be a reliable tool for detecting synovitis in RA<sup>10</sup>. In 1988, Gilkeson, *et al* described the presence of erosions revealed with MRI but not visible with radiographs in patients with RA<sup>11</sup>. Since this study, several other studies have highlighted the value of using MRI for the detection of erosions before radiographs<sup>12-20</sup>. Recently, an international Outcome Measures in Rheumatology Clinical Trials MRI working

From the Department of Rheumatology, Lille University Hospital, Lille, France.

E. Solau-Gervais, MD; J-L. Legrand, MD; B. Cortet, PhD; B. Duquesnoy, MD; R-M. Flipo, MD. Dr. Solau-Gervais and Dr. Legrand contribute equally to this report.

Address reprint requests to Dr. E. Solau-Gervais, Department of Rheumatology, Hôpital Roger Salengro, 59035 Lille, France.  
E-mail: e-solau@chru-lille.fr

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group developed an RA MRI scoring system (OMERACT RAMRIS) and published an atlas<sup>22</sup>. However, the significance of these erosions is not known. Indeed, some of them did not evolve into radiographic erosions (59% of erosions initially detected with MRI were not detected with radiographs 7 years later)<sup>23-25</sup> and some of them (18% to 25% at one year) simply disappeared<sup>20</sup>.

Most studies on MRI in RA have focused on early RA<sup>11,23-35</sup>. However, no study has taken into account the presence or absence of anti-CCP in early arthritis. We assessed the usefulness of MRI of hands in the diagnosis of RA in a prospective cohort of 30 patients with polyarthralgia and/or early polyarthritis, without anti-CCP antibodies and without erosions as established by radiographs.

## MATERIALS AND METHODS

**Patient recruitment and selection criteria.** Between 2000 and 2002, 30 patients with polyarthritis or polyarthralgia suggestive of early inflammatory rheumatism [involving wrists and metacarpophalangeal (MCP) joints symmetrically and with morning stiffness  $\geq$  45 min] were recruited consecutively from among outpatients of a rheumatology department.

Inclusion criteria were as follows: age > 18 years; polyarthralgia with or without synovitis but with morning stiffness  $\geq$  45 min; symptom onset < 2 years. Exclusion criteria were as follows: oral corticotherapy more than one month; established diagnosis with disease modifying antirheumatic drugs (DMARD); anti-CCP antibody positivity; erosions as established by radiographs of hands, wrists, and feet.

**Clinical and radiographic assessment.** Baseline data were collected by the same rheumatologist and included: date of birth, sex, duration of symptoms, morning stiffness, tender joint count on 28 joints, swollen joint count on 28 joints, squeeze test, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), IgM RF (assessed by ELISA), anti-CCP antibodies (assessed by ELISA), antinuclear antibody, and HLA-DR or B27 if necessary.

The patients had radiographs taken of hands, wrists, and feet. Results were interpreted by an experienced radiologist blinded to the clinical diagnosis. No patient in this cohort had radiographic erosive lesions at the onset of the study.

**MRI assessment.** MRI was performed after informed consent with a 1.5 Tesla superconducting magnet (Vision; Siemens, Erlangen, Germany), equipped with a transmit-receive, 20 cm diameter circular surface coil. Both hands and wrists were imaged first. Patients underwent imaging in prone or supine position, with the arms semiflexed above the head and the hands positioned in the center of the coil. Straps kept the palms facing each other in the "prayer position" and the fingers were extended. An intravenous bolus injection of gadolinium-DTPA (0.1 mmol/kg body weight; Dotarem, Guerbet, Roissy, France) was administered after completion of the initial coronal scout view. In all patients, the imaging protocol consisted of fat suppressed gadolinium enhanced T1-weighted spin-echo axial images and gadolinium enhanced 3-dimensional (3D) fast low angle shot (FLASH) axial images. The FLASH sequence employed frequency-selective water excitation. A 45 mm slab was partitioned into 30 axial sections, resulting in a slice thickness of 1.5 mm. Other imaging variables were TR 36 ms, TE 9 ms, flip angle 505, field of view 20  $\times$  20 cm, one signal acquired, matrix 300  $\times$  512, and time of acquisition 5 min 25 s. Axial slices consisted of 2 simultaneous series (2  $\times$  8 and 2  $\times$  30 sections with spin-echo and FLASH sequences, respectively). The first series covered the wrists from the distal radioulnar joints to the metacarpal bases and the second one the MCP joints.

**Analysis of MRI images.** This view set was analyzed by 2 rheumatologists who were blinded to the diagnosis. Scores were obtained by consensus. Analyses were based on the OMERACT scoring system<sup>36</sup>. The articular sites were examined for synovitis (radioulnar joint, radiocarpal joint, intercarpal-

carpometa-carpal joints, and the second to fifth MCP joints), for erosions within the carpus (distal ulna, distal radius, lunate, scaphoid, triquetrum, pisiform, hamate, capitate, trapezoid, trapezium) and the head of the metacarpal bone from the second to fifth MCP joints; for tenosynovitis (digital flexor, flexor radial carpi, ulnar carpi extensor, and digital extensor).

Synovitis and tenosynovitis were scored as follows: 0 = normal aspect, 1 = enhancement of synovium, 2 = moderate enhancement and enlargement of synovium, 3 = major enhancement and enlargement of synovium. For the purpose of our analyses, we separated scores for each region of the hand: carpal synovitis (18) and erosion (160) score, MCP synovitis (24) and erosion (80) score, carpal (48) score, digital (48) tenosynovitis score, second, third MCP erosion (20) and synovitis (6) score.

To determine interobserver reliability, MR images of 10 patients, presented in a randomized fashion, were independently interpreted by the 2 reviewers, with an interval of 7–20 months (mean: 15 months) between the 2 interpretations.

**Followup.** The 30 patients were followed up at least one year (mean: 30.6 months). Diagnoses were performed by an expert rheumatologist; patients had radiographs taken of hands, wrists, and feet, and RF and anti-CCP antibodies were assessed. Eight of the 16 patients with RA were followed up at 2 years with radiographs, RF, and anti-CCP antibodies.

**Statistics of analysis.** The Mann-Whitney U-test (2 sample rank sum test) and the chi-square were used for inter-group comparisons. The threshold value for the detection of erosions was determined using a receiver-operating characteristic (ROC) curve. To assess interobserver reliability,  $\kappa$  statistics were employed on all variables;  $\kappa$  values can be interpreted as follows: 0.0–0.20, poor; 0.20–0.40, fair; 0.40–0.60, moderate; 0.60–0.80, good; 0.80–1.00, excellent.

## RESULTS

**Demographic data.** The demographic and clinical characteristics of the 30 patients at baseline are shown in Table 1. The mean age was 46.8 years and the mean duration of symptoms was 7.8 months.

**Two groups of patients.** At the one-year followup, diagnoses were as follows: 16 patients had RA. The non-RA group was composed of 4 patients with spondyloarthropathy (peripheral involvement), 2 with fibromyalgia, 4 with undifferentiated arthritis (3 of which were self-limiting), 1 patient with sicca syndrome, 1 with hemochromatosis, 1 with polymyositis, and 1 with paraneoplastic syndrome.

**Clinical and biological characteristics of the 2 groups at baseline.** At the initial visit, 12 patients fulfilled ACR criteria:

Table 1. Clinical and biological characteristics of the 30 patients at baseline.

Characteristic	Mean (SD)
Age, yrs	46.8 (11.18)
Symptom onset, mo	7.8 (6.21)
Morning stiffness, min	60.5 (56.59)
Tender joint count/28	7.1 (5.7)
Swollen joint count/28	2.03 (0–7)
DAS28, 3 criteria	3.42 (1.3)
ESR, mm	18.3 (14.81)
CRP, mg/l	22.3 (41.97)

DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

9 patients with RA and 3 patients with other diseases (hemochromatosis, polymyositis, and self-limiting arthritis). Where clinical and biological characteristic were concerned, the RA group was only statistically different as regards swollen joint count (Table 2).

In the RA group, 7 were RF-positive (40%). Three patients were RF-positive (21.43%) in the non-RA group (one case each of ankylosing spondylitis, polymyositis, and undifferentiated arthritis). As regards inclusion criteria, none of the patients were anti-CCP antibody-positive.

**MRI results at baseline.** Regarding the quality of MRI, some analyses were performed on fewer patients than the initial number.

**Global analysis.** Of the 15 patients with RA whose carpus could be evaluated, 10 (66%) had erosions. Moreover, of the 11 patients without RA, 8 (72%) had erosions. No differences were found in terms of carpus erosions between the RA and non-RA group.

Of the 15 RA patients whose MCP could be evaluated, 12 (80%) had erosions and of the 13 non-RA patients, 6 (46%) had erosions. But this result is not significant (chi-square  $p = 0.062$ ).

**OMERACT score.** When results are expressed in terms of the OMERACT scoring system, synovitis was observed to be more frequent in the RA group compared to the non-RA group. However, this difference was not significant. No difference was observed as regards tenosynovitis (Table 3).

Where erosions were concerned, no difference between the 2 groups was observed in the carpus. However, erosion scores in the MCP joints and in the second and third MCP joints (Figure 1) were significantly higher in the RA group. ROC curve analysis revealed a positive level at 15 for MCP erosions, with a specificity of 70% and a sensitivity of 64%, and an area under the curve at 0.75 (Figure 2).

**Interobserver reliability.** Interobserver reliability values showed good and excellent agreement ( $\kappa = 0.715$  for synovitis,  $\kappa = 0.9$  for erosions).

Table 2. Comparison of clinical and biological characteristics at baseline between the two groups (patients with and without RA).

Characteristic	RA (n = 16) mean (SD)	Non-RA (n = 14) mean (SD)	p
Age, yrs	48 (12.44)	45.2 (9.78)	0.47
Morning stiffness, min	47.5 (44.77)	75.3 (65.32)	0.33
Symptom onset, mos	7.9 (6.55)	7.8 (6.04)	0.97
Tender joint count/28	7.9 (4.86)	6.2 (6.5)	0.21
Swollen joint count/28	2.75 (2.05)	1.2 (1.8)	0.04
DAS28, 3 criteria	3.88 (1.11)	2.86 (1.35)	0.05
ESR, mm	22.8 (16.48)	12.7 (10.52)	0.09
CRP, mg/l	28.7 (51.25)	14.4 (28.55)	0.24
RF: n (%)	7 (43.75)	3 (21.43)	0.15

RF: rheumatoid factor.

Table 3. MRI-of-the-hand scores in RA and non-RA groups. MCP: metacarpophalangeal.

	RA (n = 16) mean (SD)	Non-RA (n = 14) mean (SD)	p
Total erosion score	38.6 (35.6)	30.9 (31.1)	0.21
Total synovitis score	13.38 (5.77)	11.71 (6.42)	0.19
Carpal erosion score	21 (29)	24 (28)	0.86
MCP erosion score	19.3 (13.2)	7.7 (9.2)	0.024
2nd and 3rd MCP erosion score	16.4 (13.9)	5.7 (6.4)	0.044
Carpal synovitis score	4.54 (2.18)	3.43 (1.81)	0.25
MCP synovitis score	9.29 (3.38)	7.69 (3.86)	0.18
2nd and 3rd MCP synovitis score	5.93 (1.9)	4.64 (2.31)	0.13
Carpal tenosynovitis score	5.18 (4.75)	6.33 (4.92)	0.57
MCP tenosynovitis score	6 (5.96)	7.69 (7.3)	0.91

RA: rheumatoid arthritis; MCP: metacarpophalangeal.

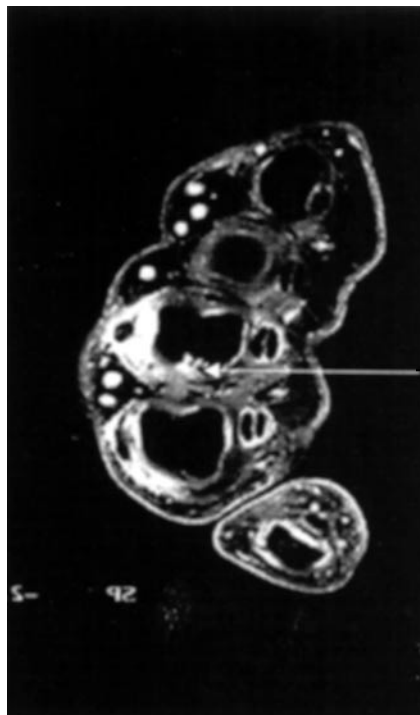
**Characteristics of RA patients at one year.** At one year, all patients had DMARD except one who refused treatment. The activity of the disease was controlled with treatment with a Disease Activity Score (DAS28) at 3.55 on average (SD 0.97). One of the 16 patients had positive anti-CCP antibodies at one year.

Of 16 patients with RA, only 3 had radiographic erosions at 2 years. One had radiographic erosions on MCP with an OMERACT score at 30; the second had no erosions on MCP at baseline with MRI but developed radiographic erosions in the shoulder; the third had radiographic erosions on MCP with an OMERACT score at 20 at baseline and, 2 years later, developed radiographic erosions on the fifth metatarsophalangeal joint.

## DISCUSSION

Although diagnosis of RA is quite easy when anti-CCP antibodies and RF are present<sup>5</sup>, and/or when radiographs highlight erosions, in the case of non-erosive symptoms and in the absence of anti-CCP antibodies, early RA diagnosis can be difficult. We assessed the usefulness of MRI of hands in patients in whom the diagnosis could not be confirmed using conventional tools. So our population comprised patients with mild symptoms, such as polyarthralgia or polyarthritis with a moderate activity score, without anti-CCP antibodies and with normal radiographs. Such patients could be defined as having "benign" RA.

We investigated the presence of erosions on MCP with MRI and found more erosion in patients with RA compared to patients without RA. Our study confirmed that MRI of hands may be useful in the diagnosis of RA when the MCP joint is examined, even in this RA population without anti-CCP antibodies. It is of interest to have another diagnosis tool such as MRI when immunological markers and radiographs fail. Indeed, we showed that MCP erosion scores are useful for distinguishing the RA disease with a sensitivity of 64% and a specificity of 70%. Similarly to our findings, Backhaus, *et al* showed that, in early arthritis, erosions on MRI localized more



Erosion on 3rd metacarpophalangeal with MRI of hands.

Figure 1. Axial T1 weighted spin-echo and gadolinium enhanced MRI of metacarpophalangeal (MCP) joints of a study patient at baseline showing one erosion on 3rd MCP (arrow).

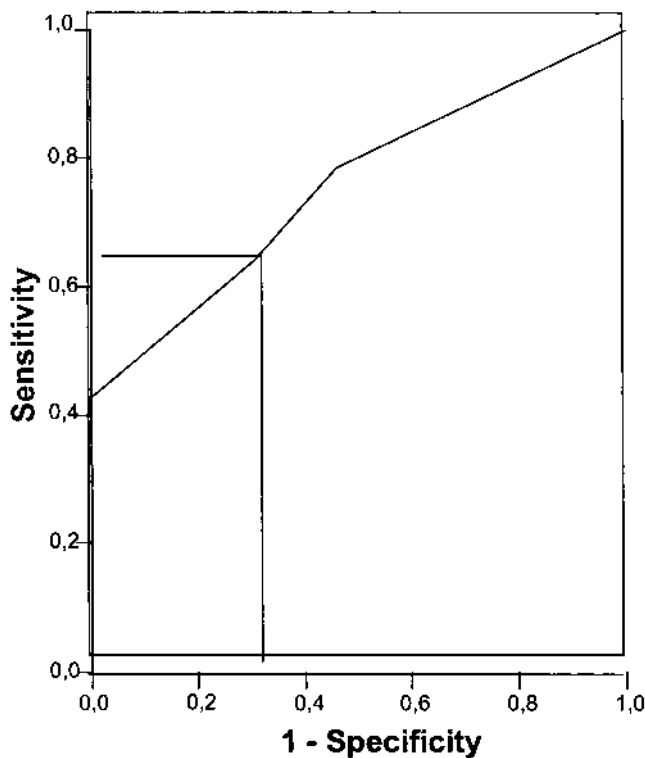


Figure 2. Receiver-operating characteristic curve for the diagnosis of RA by baseline MCP MRI erosions score.

frequently in MCP joints and particularly the second and third joints<sup>37</sup>. Similarly, Klarlund, *et al* showed that erosions on MRI in MCP joints did not occur in undifferentiated arthritis as opposed to RA<sup>29</sup>. Moreover, Tan, *et al* observed 5 times fewer MCP erosions on MRI in their control group when compared to their early RA group, with a higher frequency of bone erosions in the radial site<sup>38</sup>. Compared to our previous study, the number of patients with RA having MCP erosions was almost identical (80% in this study compared to 77% in previous study)<sup>39</sup>. In our previous study, we compared MRI of hands and feet and when MRI of hands did not show any erosion, MRI of feet could be positive. We proposed that in patients of uncertain diagnosis the investigation should be completed with a MRI of feet when MRI of hands was negative.

However, in our present study, no coronal sequences were performed, as was advised in OMERACT. This might have influenced the number of erosions found. With coronal sequences the number of erosions should be lower, but probably in both groups.

In our study, carpal erosion could not differentiate our 2 groups. McQueen, *et al* found that baseline wrist MRI erosion scores were predictive of radiographic erosion scores at 2 years, but their analysis was prognostic rather than diagnostic<sup>24</sup>. Savnik, *et al* also showed that wrist bone edema observed with MRI was predictive of erosions<sup>20</sup>. We did not assess bone edema but only erosions in 2 different groups, and our aim was to distinguish an RA group from a non-RA group in a cohort of patients for whom the diagnosis proved difficult.

Regarding tenosynovitis and synovitis in the carpal and



MCP joints, no differences were observed between the RA and the non-RA group. This is not surprising, as patients in the non-RA group had diseases in which synovitis and tenosynovitis may occur. Savnik, *et al* found the same results in a study comparing RA and other arthritis<sup>19</sup>. Sugimoto, *et al* found a higher occurrence of synovitis in wrist and MCP joints in early RA, but this study did not involve any other forms of arthritis<sup>10</sup>.

In our study, only 3 of the 16 patients with RA had erosions detectable on radiograph at one year. This confirmed the mild status of our population with normal radiographs at baseline and no anti-CCP antibodies. Two of the 3 patients had erosions with MRI, but most RA with erosions does not develop radiograph-detectable erosions at one year. Savnik, *et al*, who compared MRI of hands at one-year intervals, showed that bone erosions were not reconfirmed in patients who had RA for less than 3 years and patients with arthralgia at baseline<sup>20</sup>. Moreover, when Backhaus, *et al* followed early arthritis for 2 years, of 20 erosions detected with MRI of hands, only 2 erosions were detected by radiographs in the group of patients with no erosions at baseline. Recently, Scheel, *et al* showed that only 41% of erosions detected with MRI at baseline lead to radiograph-detectable erosions 7 years later<sup>25</sup>. So, even if erosions detected with MRI of hands might differentiate populations of patients with RA, these patients could not develop erosions as established by radiographs.

Our study shows that MRI of hands may be useful in the diagnosis of mild RA, when MCP erosions are considered. Recent publications have shown the possibility of using low-field dedicated MRI to analyze erosions and synovitis in MCP joints with a lower cost than using high-field MRI<sup>40</sup>. And recently, based on a previously developed RA MRI scoring system, a new classification with a reference atlas has been published<sup>41,42</sup>. This will certainly lead to the specific development of MRI of hands for diagnosis and prognosis in RA.

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