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Original article

MRI-detected synovitis of the small joints predicts rheumatoid arthritis development in large joint undifferentiated inflammatory arthritis

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Abstract

Objectives. New onset undifferentiated large joint inflammatory arthritis can be diagnostically challenging. It is unknown how often these patients progress to RA, and how they can be identified at first presentation. We assessed clinical and serological features associated with RA development in patients with an undifferentiated mono- or oligo-articular large joint arthritis, and with keen interest in whether an MRI of the small joints of the hand and foot would aid diagnosis.

Methods. Leiden Early Arthritis Clinic includes 4018 patients; this prospective study follows 221 consecutively included patients with new onset undifferentiated large joint arthritis. Baseline clinical data and serology were obtained. Forty-five patients had MRIs (hand and foot). MRIs were scored according to the OMERACT RAMRIS. Univariable and multivariable logistic regression were assessed. Test characteristics, predictive values and net re-classification index (NRI) for RA were determined.

Results. Patients mostly presented with knee or ankle mono-arthritis. During the 12 months' follow-up 17% developed RA. Autoantibody positivity (ACPA and/or RF) and MRI-detected synovitis in hands and feet were independently associated with RA development in multivariable analyses [odds ratio 10.29 ($P = 0.014$) and 7.88 ($P = 0.017$), respectively]. Positive predictive value of autoantibodies, MRI-detected synovitis and combination of both features was 63%, 55% and 100%, respectively. The addition of MRI-detected synovitis to autoantibody status improved diagnostic accuracy (NRI 18.1%).

Conclusion. In patients presenting with undifferentiated large joint arthritis, 17% will develop RA. Autoantibody positivity and subclinical synovitis are independent predictors. The data suggest MRI of small joints is beneficial for early identification of RA in large joint arthritis.

Key words: large joint, knee, ankle, elbow, shoulder, undifferentiated arthritis, rheumatoid arthritis, magnetic resonance imaging (MRI), subclinical synovitis

Rheumatology key messages

- Seventeen per cent of patients with undifferentiated arthritis (UA) of only large joints will develop RA within 12 months.
- Autoantibody positivity and MRI-detected subclinical synovitis of small joints predicts RA development.
- Addition of MRI data improves diagnostic accuracy of RA detection in large joint UA patients.

Introduction

Early diagnosis of RA is essential to optimize treatment, decrease joint destruction and improve function [1]. Recognition of RA is challenging in patients who do not present with the classic hallmarks. Large joint involvement in RA is uncharacteristic and uncommon, but does occur. It is essential to identify these patients early, since RA presenting in this manner has a more destructive disease course, higher disease activity score (DAS-28), more functional impairment and lower chance of achieving drug free remission [2–4].

Capturing undifferentiated arthritis (UA) patients in study cohorts depends on the definition of RA applied. Utilizing the 2010 RA criteria, 10–25% of UA patients will progress to RA, compared with 32% who will progress

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using the 1987 RA criteria [5, 6]. This difference is accounted for by the 2010 RA criteria being more sensitive in capturing RA earlier than the 1987 criteria [7]. Limitations of the 2010 RA criteria are that it can overlook autoantibody-negative patients and those with large joint involvement [8, 9]. The frequency of RA development in UA patients presenting with only large joint involvement is, to the best of our knowledge, unknown.

Predictive markers used in UA patients are derived from cohorts consisting of patients with mainly small joint arthritis. These markers include older age, higher morning stiffness scores (on visual analogue scale), elevated CRP and ESR, and autoantibody positivity (ACPA and RF) [10]. The utility of high-resolution imaging [ultrasound (US) and MRI] in early arthritis is being studied, but data on US in predicting inflammatory arthritis are sparse and the current level of evidence is moderate [11]. Several studies on inflammatory markers depicted by MRI in UA have reported that bone marrow oedema, synovitis, tenosynovitis and erosions univariably are associated with RA development; especially flexor tenosynovitis is the strongest predictor that also independently associates with RA development, while lack of MRI-detected synovitis decreased probability of progression to RA [1–6, 12–17].

The frequency of RA development in UA patients presenting with large joint arthritis is unknown. We aim to determine the prevalence of RA development and identify clinical and/or serological predictors in patients with only large joint UA. In addition, the added value of MRI of the small joints, based on the hypothesis that patients progressing to RA will have subclinical inflammatory changes in the small joints, will be investigated.

Methods

Patients

The Leiden Early Arthritis Clinic (EAC) is a longitudinal inception cohort comprising consecutively included DMARD-naïve patients with clinically confirmed arthritis and symptom duration <2 years, recruited from the Leiden rheumatological outpatient clinic. The cohort was initiated in 1993 and MRI was added to the study protocol in 2010. At baseline, demographic information, clinical assessments including tender and swollen joint counts, blood samples (including CRP, ESR, ACPA and RF) and MRI imaging were undertaken. Patients were prospectively followed at baseline, 4 months, 12 months and then yearly.

A total of 4018 patients are included in the Leiden EAC between 1993 and 2018; 160 patients had missing joint-count data and were excluded (Supplementary Fig. S1, available at *Rheumatology* online). Of the remaining 3858 patients, 3317 with clinically detected synovitis of small joints [distal interphalangeal joints 1–5, proximal interphalangeal joints 2–5, metacarpophalangeal joints (MCPs) 2–5, wrist and metatarsophalangeal joints (MTPs) 1–5)] at physical examination were excluded. In total, 541 patients presenting with inflammatory large joint arthritis (one or more joints) were prospectively followed. Patients with baseline diagnosis of RA (according to 1987 or 2010 RA classification criteria [7, 18]) ($n=29$) or baseline diagnosis of another rheumatological condition ($n=291$) were excluded. In total, 221 UA patients were studied of which 45 patients underwent a routine baseline MRI scan. There were no clinically relevant differences between patients with or without an MRI scan (Supplementary Table S1, available at *Rheumatology* online).

MRI and scoring

Patients underwent a 1.5 T musculoskeletal extremity MRI (GE, Wisconsin, USA) with gadolinium chelate contrast of the most symptomatic or dominant hand, wrist and foot within 2 weeks of inclusion into the EAC. Patients were asked to withhold NSAIDs (if they were taking them) 24 h prior to scanning.

MCPs 2–5, wrist and MTPs 1–5 joints were scored for erosion, bone marrow oedema (BME) and synovitis according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA MRI score (RAMRIS) system [19]. Tenosynovitis was scored as described by Haavaardsholm *et al.* [20]. Two trained and experienced readers scored the MRI data blinded to patient details, with a between-reader intraclass correlation coefficient of >0.90. Detailed MRI scanning and scoring protocols are included in the Supplementary Data S1, available at *Rheumatology* online.

MRI evaluation

The mean score for both readers was used. MRI-detected inflammation can be present in the general healthy population, and therefore adjustment for symptom-free controls was performed by dichotomizing MRI scores into positive and negative, as described previously [21, 22]. Individual RAMRIS parameters (erosion, BME, synovitis, tenosynovitis) were considered positive only in the circumstance of being present at the same location in $<5\%$ of the healthy age-matched controls. Subclinical inflammation was present if any features of BME, synovitis or tenosynovitis was positive. Total RAMRIS score was positive if subclinical inflammation or erosion score was positive.

Outcome

The primary outcome was development of RA within 12 months according to 2010 RA criteria, 1987 RA criteria or clinical diagnosis of RA with appropriate DMARD treatment by the rheumatologist. We chose not to restrict the outcome to criteria-based RA only, as early initiation of DMARDs could have prevented the fulfilment of classification criteria. Furthermore, exclusively using the 2010 RA classification criteria would limit identification of RA patients in our study, as they are heavily weighted on ACPA and RF positivity, and do not capture autoantibody-negative disease adequately [8]. However,

a 1987 and 2010 classification criteria-based RA sub-analysis was completed.

Statistical analysis

The Mann–Whitney *U*-test and the χ^2 test were used to compare clinical, serological and MRI characteristics between patients with RA and those without RA (UA or other arthritis). Univariable and multivariable logistic regression analysis was used to assess the association between clinical, serological and MRI features and the development of RA in patients presenting with large joint UA. Test characteristics were determined, and the diagnostic accuracy of MRI, in addition to autoantibody status, was ascertained using the C-statistic. The net reclassification index (NRI) was determined to assess the value of MRI data added to presence of autoantibodies. *P* values <0.05 were considered statistically significant. All analyses were conducted in IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA). The study was approved by the local Medical Ethical Committee 'Commissie Medische Ethiek Leiden University Medical Centre'. All participants signed informed consent.

Results

Population characteristics

The clinical characteristics of the 221 patients with UA included in the study are summarized in Supplementary Table S2, available at *Rheumatology* online. Seventy-three per cent of the patients presented with a mono-arthritis; knee (69%) and ankle (29%) were the most frequently involved joints.

During the 12-month follow-up, 38 patients (17%) were diagnosed with RA (18 classification criteria based—7 via 2010 criteria, 7 via 1987 criteria, 4 via both 1987 and 2010 criteria and 20 based on clinical diagnosis and DMARD commencement), 117 (53%) remained undifferentiated and 66 (30%) developed another rheumatological diagnosis. Within the three outcome subgroups, mono-arthritis of the knee remained the most frequent presentation (66–70%). Patients who progressed to RA were significantly older, had a higher tender joint count (TJC), were more likely to be ACPA or RF positive and had a higher ESR (Supplementary Table S2, available at *Rheumatology* online).

Autoantibody positivity and MRI-detected synovitis were associated with RA development

To investigate whether baseline clinical, serological and MRI features were associated with RA development, univariable logistic regression was performed. ACPA positivity [odds ratio (OR) 7.50; 95% CI: 2.63, 21.37] and RF positivity (OR 6.97; 95% CI: 2.70, 17.97) were associated with RA development (Table 1).

Forty-five patients received a baseline MRI scan. Subclinical synovitis (OR 5.60; 95% CI: 1.28, 24.56) was associated with RA development, while other MRI features were not associated (Table 1).

An enter approach multivariable model, derived from significant univariable logistic regression results, was constructed in the 45 patients with complete data (clinical, serological and MRI). To prevent over-fitting we combined the presence of autoantibodies (ACPA and/or RF) and studied this in relation to MRI-detected subclinical synovitis, as all three factors were deemed important in the univariable model. Both the presence of

Table 1 Results of univariable logistic regression analyses of baseline clinical (221 patients) and MRI (45 patients) characteristics and association with RA development

	Univariable analysis OR (95% CI)	*P*-value
Clinical characteristic		
Gender (female)	1.52 (0.74, 3.09)	0.25
Age	1.04 (1.02, 1.07)	<0.01
Symptom duration	1.00 (1.00, 1.00)	0.78
Tender joint count	1.15 (1.02, 1.30)	0.02
Swollen joint count	1.04 (0.65, 1.67)	0.86
ESR	1.01 (1.00, 1.03)	0.01
RF	6.97 (2.70, 17.97)	<0.001
ACPA	7.50 (2.63, 21.37)	<0.001
ACPA and/or RF	3.95 (1.68, 9.32)	<0.01
MRI characteristic		
RAMRIS total	3.08 (0.77, 12.34)	0.11
Inflammation	3.50 (0.87, 14.11)	0.08
Erosions	1.45 (0.23, 9.16)	0.69
Synovitis	5.60 (1.28, 24.56)	0.02
Tenosynovitis	3.63 (0.74, 17.81)	0.11
BME	0.89 (0.20, 4.04)	0.88

MRI-features are presented dichotomized (negative/positive) according to the presence of features in healthy controls. BME: bone marrow oedema; OR: odds ratio.

autoantibodies (OR 10.29; 95% CI: 1.59, 66.41; $P = 0.014$) and subclinical synovitis (OR 7.88; 95% CI: 1.45, 42.64; $P = 0.017$) remained independently associated with RA development (Table 2).

Positive autoantibodies and MRI-detected synovitis improve diagnostic accuracy of RA

Autoantibody positivity and subclinical synovitis were the strongest predictors of RA development; hence we studied the test characteristics of these features. The sensitivity of autoantibodies for RA development in patients with undifferentiated large joint arthritis was 42% with a positive predictive value (PPV) of 63% (Table 3). Comparatively, subclinical synovitis had a sensitivity of 50% with a PPV of 55%. Although the combination of autoantibodies and subclinical synovitis was uncommon and resultant sensitivity was 17%, the PPV was 100%. The combination of positive autoantibodies and subclinical synovitis is strongly predictive of RA development.

To ascertain the accuracy and additional value provided by an MRI, we studied patients who had positive autoantibodies or subclinical synovitis. Presence of autoantibody positivity and/or subclinical synovitis improved the area under the curve (AUC; 0.75) compared with autoantibodies alone (AUC = 0.66) for predicting RA. Positive autoantibody status or subclinical synovitis resulted in a net increase for correct classification of RA by 33% and net increase in incorrect classification by 15%. The addition of MRI-detected synovitis data to autoantibody status therefore resulted in an NRI of 18% (Table 4). Thus, signifying subclinical synovitis in small joints at baseline helps predict and correctly reclassify RA in large joint UA patients.

Sensitivity analyses

When the 1987 or 2010 RA classification criteria-based outcome were applied as a sensitivity analyses, similar results were obtained. Positive ACPA and/or RF, as well as MRI-detected synovitis were associated with criteria-based RA development. (Supplementary Tables S3 and S4, available at *Rheumatology* online).

Discussion

Undifferentiated inflammatory arthritis encompasses a heterogeneous patient population, with large joint mono- or oligo-articular disease being an easily identifiable phenotype. To our knowledge this is the first study to show that 17% of patients with a large joint arthritis will develop RA. Further we demonstrated that ACPA and MRI-detected subclinical synovitis predict RA development and therefore are relevant diagnostic tests. Clinicians feel comfortable ordering ACPA for risk stratification, but may express hesitation about the use of MRI in the same situation. The EULAR task force has highlighted the importance of MRI as a sensitive tool for RA detection in doubtful clinical scenarios and to improve the certainty of a diagnosis of RA [23].

Cost and accessibility remain the main barriers to the application of MRI in clinical practice. Low field extremity MRI may provide a potential solution; being a smaller machine it can be placed in an adjacent clinic room. However, potential pitfalls include reduced image clarity

Table 2 Results of multivariable logistic regression if presence of RF and/or ACPA and MRI-detected synovitis at baseline in relation to RA development

	Multivariable analysis OR (95% CI)	Multivariable analysis *P*-value
ACPA and/or RF positivity	10.29 (1.59, 66.41)	0.014
MRI-detected synovitis	7.88 (1.45, 42.64)	0.017

In order not to overfit the model, only ACPA/RF and subclinical synovitis were included in the multivariable model. OR: odds ratio.

Table 3 Test characteristics of presence if ACPA and/or RF and MRI synovitis for RA development at 12 months

Test	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %	LR+ (95% CI)	LR– (95% CI)
ACPA and/or RF	42 (19, 68)	91 (76, 97)	63 (31, 86)	81 (66, 91)	4.58 (1.29, 16.32)	0.64 (0.39, 1.05)
MRI-detected synovitis	50 (25, 75)	85 (69, 93)	55 (28, 79)	82 (66, 92)	3.3 (1.23, 8.84)	0.59 (0.33, 1.06)
ACPA and/or RF MRI-detected synovitis	17 (5, 45)	100 (90, 100)	100 (34, 100)	77 (62, 87)	NA	0.83 (0.65, 1.07)

Test characteristics for RA development within 12 months. Forty-five patients with both autoantibody and MRI data. LR+: positive likelihood ratio; LR–: negative likelihood ratio; NPV: negative predictive value; NA: Not Applicable; PPV: positive predictive value.

TABLE 4 The net reclassification index of autoantibody status (ACPA and/or RF) and/or MRI-detected synovitis in relation to accurately classifying RA

Net reclassification index			
	Not RA	RA	Total
ACPA and/or RF			
Autoantibody-negative	30	7	37
Autoantibody-positive	**3**	**5**	8
ACPA and/or RF and/or MRI synovitis			
Autoantibody-negative and MRI-negative	25	3	28
Autoantibody-positive or MRI-positive	**8**	**9**	17
Total	33	12	45

Twenty per cent ($n = 9$) of patients were reclassified. Net increase for correct classification was 33.3% and net increase for incorrect classification was 15.2%. NRI = 18.1%. NRI: net reclassification index. Bold text is the number of patients with a positive test.

and limited availability of imaging sequences [24]. Ultrasonography has been proposed as an alternative to MRI due to its ease of availability, lower cost and physician convenience. However, it is less validated and less sensitive than MRI in the early inflammatory arthritis space and issues of reliability and standardization have hampered its use in clinical trials [11, 25, 26].

RA has a substantial impact on work disability and job loss, and hence poses an economic burden [27]. The optimal role of MRI in clinical practice should allow a clinical benefit at an acceptable cost. Limited studies have evaluated the role of MRI in early RA and suspected RA patients and did not find MRI to be cost effective [28, 29]. There are no studies that have examined the cost-benefit ratio of early RA detection in UA patients using MRI, and hence the cost effectiveness of MRI in this setting remains undetermined. There are multiple concerns that arise with cost effective analysis from disease simulation models; the data are only as meaningful as the input values, the time analysis may extend beyond the data that are available and generally it is not possible to measure everything necessary for a comprehensive analysis [30]. The most appropriate test may not be the most cost-effective one; aside from fiscal considerations, patient and societal needs also need to be understood and valued.

Preceding studies with combined small and large joint UA patients have demonstrated subclinical MRI inflammation is predictive of progression to RA and some studies found a predictive value for MRI-detected erosions, whereas other studies did not [12, 14, 31–33]. Perhaps, the heterogeneity of RA development accounts for the multitude of subclinical MRI changes [34]. Our study focused on large joint UA patients and demonstrated the crucial role of subclinical small joint synovitis in RA development.

Accurately defining RA as an outcome is challenging due to its heterogeneous nature. Our study defined RA according to the 2010 and 1987 classification criteria and clinical expertise of the rheumatologist (e.g. early treatment initiation). The 2010 criteria focus on early disease identification, while the 1987 RA criteria have low sensitivity for early RA [7]. Clinically, the standard of care expected from a rheumatologist is early DMARD treatment of RA; this may prevent fulfilment of classification criteria. A major strength of our study is inclusion of a clinically based diagnosis of RA and/or fulfilment of RA classification criteria; our study is representative of real-world practice, in which classification criteria and diagnosis are not mutually exclusive.

Another strength of our study is that MRI features were defined as positive and negative based on the prevalence of each individual feature in the healthy age-matched population [22]. Although data dichotomization probably led to loss of information, using the healthy population as a reference lowered the risk of false-positive MRIs.

A limitation of this study was the sample size. Although a large group of patients were studied (221 large joint UA patients), only 38 patients developed RA within 12 months. This was further compounded by only 20% of patients having a baseline MRI scan. Indeed, the number of patients with both autoantibody positivity and MRI changes were small. However, we did not anticipate any selection bias, as the baseline characteristics of patients with or without an MRI were similar. Furthermore, we limited the number of variables in the multivariable analysis to prevent overfitting of the data and making the results too optimistic. Another limitation of the analysis was the number of criteria-based classification patients was small (18/38); however, a sensitivity analysis in this subgroup still supported the conclusion that positive ACPA and/or RF and MRI-detected synovitis were associated with RA development. A replication of our results in an independent set of consecutive patients presenting with large joint UA would be beneficial.

To conclude, ACPA and/or RF positivity and MRI-detected subclinical synovitis of the small joints of the hand and foot predicts progression to RA in patients presenting with large joint UA. These findings demonstrate the increasing utility and importance of MRI in research and clinical practice. Further work is required to design clinical algorithms in which there will be a cost–benefit ratio of using high resolution imaging.

N.S., F.W. and A.H.M.vdH.vM. contributed to the conception and study design. N.S. and F.W. analysed the data. N.S., F.W., E.N. and A.H.M.vdH.vM. contributed to interpretation of the data. N.S. and A.H.M.vdH.vM. wrote the first version of the manuscript and F.W. and E.N. revised it critically. All authors read and approved the final version of the document.

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Data availability statement

The dataset can be provided from Leiden University Medical Centre Rheumatology Department, upon request from any interested parties.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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