The course of clinically suspect arthralgia and early rheumatoid arthritis : clinical features, imaging and genetics

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Clinical factors, ACPA and MRI-detected subclinical inflammation in relation to progression from Clinically Suspect Arthralgia to arthritis

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ABSTRACT

Introduction

Patients with clinically suspect arthralgia (CSA) have, according to their rheumatologists, an increased risk of rheumatoid arthritis (RA), but their actual outcome is unexplored. This longitudinal study investigated (1) progression from CSA to clinically detectable arthritis and (2) associations of clinical factors, serological factors (among which are anti-citrullinated peptide antibodies (ACPA)) and MRI-detected subclinical inflammation with arthritis development.

Methods

150 patients with CSA were followed for ≥6 months. At baseline, clinical and serological data were collected and unilateral 1.5 T-MRI of metacarpophalangeal (MCP), wrist and metatarsophalangeal (MTP) joints was made. MRI scoring was done according to the RA MRI scoring system. Subclinical MRI inflammation was defined based on MRI results of 193 symptom-free persons.

Results

During follow-up (median=75 weeks, IQR=41-106 weeks), 30 patients developed clinical arthritis; 87% did so <20 weeks after inclusion. In multivariable analyses, age, localisation of initial symptoms in small and large joints (compared with small joints only), C-reactive protein level, ACPA-positivity and subclinical MRI inflammation significantly associated with arthritis development; ACPA and MRI inflammation were most strongly associated (HR (95% CI) respectively, 6.43 (2.57 to 16.05) and 5.07 (1.77 to 14.50)). After 1 year follow-up, 31% of the patients with MRI inflammation and 71% of the ACPA-positive patients with MRI inflammation had progressed to arthritis. Forty-three per cent of the patients that developed arthritis within 1 year were ACPA-negative; 78% of them had subclinical MRI inflammation at baseline. When MRI inflammation was absent arthritis development was infrequent (6% in all patients with CSA and 3% in ACPA-negative patients with CSA).

Conclusions

Subclinical MRI inflammation precedes clinical arthritis with a few months. Subclinical MRI inflammation is, independent of other factors such as ACPA, associated with arthritis development.

INTRODUCTION

There is an upcoming need to identify individuals in the very early phase of rheumatoid arthritis (RA) in which clinically apparent arthritis is not yet present. Although not proven, it is assumed that treatment initiation in this phase enables better disease modification and might contribute towards preventing arthritis becoming chronic. The first possible moment to clinically recognise patients at risk of RA is the phase of symptoms without clinically detectable arthritis [1]. The symptoms that are specific for this phase are not yet identified, but clinical expertise might be an accurate tool to select patients with arthralgia with an increased risk of RA [2]. Patients with arthralgia that, based on their symptoms and signs, have an increased risk of RA according to their rheumatologists, are indicated to have clinically suspect arthralgia (CSA) [3]. The approach to select patients on clinical grounds before ordering additional tests is in line with clinical care and allows identifying autoantibody-positive and autoantibody-negative RA in the phase before clinically detectable arthritis.

Thus far, the long-term outcome of patients with arthralgia that were clinically suspect for progression to RA has not been investigated extensively. Moreover, the value of risk factors or tests in patients with CSA is unexplored. Two previous studies on patients with unspecified arthralgia or aspecific musculoskeletal symptoms who had RA-related autoantibodies revealed that morning stiffness, joint tenderness and (high levels of) anti-citrullinated peptide antibodies (ACPA) were associated with arthritis development [4,5]. However, the prognostic value for arthritis development of clinical and serological factors in patients with CSA is still unknown.

Also the value of advanced imaging in patients with CSA is unexplored. In a previous cross-sectional study, we observed that 44% of the patients with CSA had MRI-detected subclinical inflammation of hand and foot joints and that these patients with subclinical inflammation could not be adequately identified by presence of clinical or serological characteristics, suggesting that MRI-detected inflammation may have some diagnostic value. Though the predictive value of MRI-detected inflammation has still to be determined [3], an advantage of MRI is its sensitivity to detect inflammation [6,7]. MRI depicts synovitis, tenosynovitis and bone marrow oedema (BME), that is also called 'osteitis' in RA [8,9]. Because the specificity of MRI-detected inflammation has been studied scarcely, we recently performed MRI of hands and feet in 193 symptom-free persons [10]. These data served as reference and allowed to define MRI-detected subclinical inflammation for the present study.

In this first longitudinal study on patients with CSA, we aimed to determine (1) progression to clinically detectable arthritis, (2) the association of clinical and serological factors (among which are ACPA) with progression to clinical arthritis, (3) the association of subclinical MRI inflammation with progression to clinical arthritis and (4) whether subclinical MRI inflammation has an additive value compared with the other mentioned risk factors.

METHODS

Patients

All patients were included in the CSA cohort which is described previously in detail elsewhere [3]. This inception cohort was set up in 2012 in the Leiden University Medical Centre (Netherlands), which is the only referral centre in a healthcare population of >400000 inhabitants to study the symptomatic phase of RA without clinically detectable arthritis. Inclusion criteria were having arthralgia of the small joints for <1 year that was, according to the clinical expertise of the rheumatologist, suspected to progress to RA over time. No further criteria were made with regards to the type of symptoms and thus inclusion was essentially based on the expert opinion of the rheumatologist. Importantly, CSA was not present if clinical arthritis was observed at physical examination or another explanation for the arthralgia was more likely (eg, osteoarthritis and fibromyalgia).

At baseline, questionnaires (among others on work ability, the Health Assessment Questionnaire and Short-Form health survey-36) were completed, physical examination performed, blood obtained (among others for determination of ACPA (anti-cyclic citrullinated peptide 2 (anti-CCP2), positive if >7 U/mL, Eurodiagnostica, Netherlands) and IgM rheumatoid factor (RF) (positive if >3.5 IU/mL) and an MRI performed [3].

Patients were prospectively followed with scheduled visits at 4 months, 12 months and 24 months. If necessary (for instance when the patient experienced more symptoms or noticed a swollen joint) patients were seen in between the scheduled visits by their rheumatologist. Follow-up ended earlier when clinical arthritis had developed.

For the present study, the patients with a follow-up duration of ≥6 months were selected; these patients (n=150) were included between April 2012 and July 2014. None of the patients with CSA were treated with disease-modifying antirheumatic drugs (DMARDs) or (systemic and local) glucocorticoids prior to inclusion and during follow-up.

MRI scanning and scoring

MRI of the metacarpophalangeal (MCP)2–5, wrist and metatarsophalangeal (MTP)1–5 joints of the most painful side, or the dominant side in case of equally severe symptoms at both sides, was performed ≤2 weeks after clinical assessment. Patients were asked not to use nonsteroidal anti-inflammatory drugs (NSAIDs) during 24 h before MRI. The joints were scanned with a musculoskeletal (MSK)-extremity 1.5T-MRI scanner (GE, Wisconsin, USA) using contrast-enhancement and according to the RA MRI scoring system (RAMRIS) protocol. See online Supplementary File 1 for a detailed scan protocol.

Synovitis and BME in the MCP, wrist and MTP joints were scored according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) RAMRIS [8], the carpometacarpal (CMC)-1 joint (trapezium and base metacarpal-1) was excluded. Tenosynovitis in the wrist and MCP joints was assessed as described by Haavardsholm et al

[9]. The sum of the synovitis, BME and tenosynovitis scores was the total MRI inflammation score. Scoring was performed by two independent trained readers (HWvS, LM) blinded to clinical data. The within-reader intraclass correlation coefficients for the total MRI inflammation score were 0.99 and 0.98; the between-reader interclass correlation coefficient was 0.96. Mean scores of the two readers were studied.

At the time of analyses, MRIs were also categorised into positive or negative for subclinical MRI-detected inflammation. Frequencies of MRI-detected synovitis, tenosynovitis and BME that were observed at the same anatomical location in symptom-free persons recruited from the general population of the same age category were used as reference (see additional file in this chapter) [10]. In these symptom-free persons it was observed that MRI-detected inflammation was prevalent, especially at higher age and at preferential locations. Subclinical MRI inflammation was considered present if (1) both readers scored that joint (or bone in case of BME) positive for MRI inflammation and (2) the score obtained at a joint/bone was present in <5% of age-matched symptom-free persons. For example, subclinical MRI inflammation was present when both readers scored grade ≥1 for synovitis at MCP3 in a 30-year old patient. The MRI was considered negative if only one reader scored grade 1 and the other reader grade 0. If the patient was aged 50 years and both readers scored grade 1, the MRI was also negative as ≥5% of symptom-free persons of the same age category had also synovitis grade 1 at MCP3 [10]. The MRI results were not reported to the treating rheumatologist.

Outcome

The main outcome was development of arthritis detected at physical examination (66 joints were assessed) by the rheumatologist. If arthritis was achieved, follow-up in the CSA cohort ended. In sensitivity analyses another outcome, initiation of DMARD therapy (including steroids), was studied. Medical files of all patients were studied on these outcomes until 24 December 2014.

Statistical analyses

Cox proportional hazards regression analyses were used. Time to clinical arthritis was the time from inclusion to the date of first detection of clinical arthritis. Patients who did not develop arthritis were censored at the date of the 2 years' follow-up visit or at the date that all medical files were studied on arthritis development. Additionally, the diagnostic performance of ACPA-positivity and presence of subclinical MRI inflammation were evaluated for arthritis development at 1 year follow-up. Details on the statistical methods are presented in online Supplementary File 2).

RESULTS

Baseline clinical characteristics

One hundred and fifty patients with CSA were studied. Table 1 presents the baseline characteristics. Mean age of the studied patients was 43.2 years (SD 12.9) and 72.7% were female. The median symptom duration was 18 weeks (IQR 9-30) and 16.0% were ACPA-positive (Table 1).

Development of clinical arthritis

During follow-up one patient developed gout. This patient was excluded from further analyses as the patient did not belong to the non-arthritis group and the diagnosis was outside the spectrum of chronic arthritis/RA. The remaining 149 patients with CSA had a median follow-up duration of 75 weeks (IQR 41-106). Within this follow-up period 30 patients developed clinically detectable arthritis. At arthritis development, 23 patients were diagnosed with RA (according to the 2010 ACR/EULAR criteria), 6 with undifferentiated arthritis and 1 with psoriatic arthritis.

The median time period between inclusion and arthritis development was 7 weeks.

Table 1. Baseline clinical and MRI characteristics of all patients and separately for the patients that have and have not developed clinical arthritis during follow-up

	All patients n=150*	No arthritis during follow-up (n=119)	Arthritis during follow-up (n=30)
Clinical characteristics			
Age in years, mean (SD)	43.2 (12.9)	43.1 (12.8)	43.9 (13.7)
Female, n (%)	109 (72.7)	87 (73.1)	22 (73.3)
Family history positive for RA, n (%)	51 (34.0)	38 (31.9)	12 (40.0)
Symptom duration# in weeks, med (IQR) (n=141)	18 (9-30)	18 (10-31)	17 (8-30)
Gradual symptom onset (>1 week) (n=149)	31 (20.8)	95 (80.5)	22 (73.3)
Localisation of initial symptoms (n=149)			
Small joints, n (%)	127 (85.2)	107 (90.7)	19 (63.3)
Small and large joints, n (%)	15 (10.1)	6 (5.1)	9 (30.0)
Large joints, n (%)	7 (4.7)	5 (4.2)	2 (6.7)
Localisation of initial symptoms			
Upper extremities, n (%)	108 (72.0)	88 (73.9)	20 (66.7)
Upper and lower extremities, n (%)	28 (18.7)	21 (17.6)	7 (23.3)
Lower extremities, n (%)	14 (9.3)	10 (8.4)	3 (10.0)
Symmetrical localisation of initial symptoms, n (%) (n=149)	110 (73.8)	91 (77.1)	19 (63.3)
Morning stiffness ≥60 min at inclusion, n (%) (n=144)	53 (36.8)	38 (33.6)	15 (50.0)
68-TJC, med (IQR) (n=146)	5 (3-10)	6 (3-10)	5 (3-7.5)
BMI in kg/m2, mean (SD) (n=149)	26.6 (5.2)	26.5 (5.0)	26.7 (6.1)
Present smoker, n (%)	38 (25.3)	29 (24.4)	9 (30.0)

CRP-level in mg/L, med (IQR)	0 (0-4.6)	0 (0-4)	1.5 (0-14.5)
CRP-level >5 mg/L, n (%)	31 (20.7)	21 (17.6)	10 (33.3)
RF-positive (>3.5 IU/mL), n (%)	33 (22.0)	15 (12.6)	18 (60.0)
ACPA-positive (>7 U/mL), n (%)	24 (16.0)	8 (6.7)	16 (53.3)
MRI characteristics			
MRI categorised into positive or negative for any subclinical inflammation and for specific inflammatory features			
	All patients n=144*	No arthritis during follow-up (n=116)	Arthritis during follow-up (n=27)
Presence of any MRI-detected inflammation, n (%)	66 (45.8)	44 (37.9)	22 (81.5)
Only synovitis, n (%)	9 (6.3)	9 (7.8)	0 (0)
Only BME, n (%)	12 (8.3)	10 (8.6)	2 (7.4)
Only tenosynovitis, n (%)	15 (10.4)	7 (6.0)	8 (29.6)
Synovitis and BME, n (%)	3 (2.1)	2 (1.7)	1 (3.7)
Synovitis and tenosynovitis, n (%)	18 (12.5)	12 (10.3)	6 (22.2)
BME and tenosynovitis, n (%)	2 (1.4)	1 (0.9)	1 (3.7)
Synovitis, BME and tenosynovitis, n (%)	7 (4.9)	3 (2.6)	4 (14.8)
Presence of MRI-detected synovitis, n (%)	37 (25.7)	26 (22.4)	11 (40.7)
Presence of MRI-detected BME, n (%)	24 (16.7)	16 (13.8)	8 (29.6)
Presence of MRI-detected tenosynovitis, n (%)	42 (29.2)	23 (19.8)	19 (70.4)

38 patients (25.3%) were positive for ACPA and/or RF.
The median total RAMRIS inflammation score was 2 (IQR 1-5); the total RAMRIS scores for synovitis, BME and tenosynovitis were 1 (IQR 0-2.5), 0.5 (IQR 0-1.5) and 0 (IQR 0-1.5), respectively. Characteristics were not compared between the groups of patients that have and have not developed clinical arthritis during follow-up because the patients have different follow-up durations.
* One patient that developed gout during follow-up was excluded from further analyses as the patient did not belong to the non-arthritis group and the diagnosis was outside the spectrum of chronic arthritis/RA.
# Duration since the start of symptoms

Of all patients that progressed to arthritis, 87% had done so within 20 weeks after inclusion (Figure 1).

Clinical factors and ACPA in relation to arthritis development

In order to investigate whether baseline clinical factors and ACPA were associated with progression from CSA to clinical arthritis, univariable Cox regression analyses were performed (Table 2). An increased hazard on developing arthritis was observed for patients that presented with initial symptoms located in the small and large joints (HR=5.28 compared with small joints only (95% CI 2.38 to 11.73, p<0.001), patients with higher C reactive protein (CRP) levels (HR=1.06/mg/L, 95% CI 1.03 to 1.09, p<0.001), RF-positive patients (HR=6.94, 95% CI 3.34 to 14.43, p<0.001) and ACPA-positive patients (HR=10.07, 95% CI 4.87 to 20.82, p<0.001)). Age, presence of morning stiffness and number of tender joints were not significantly associated.

Subclinical MRI inflammation in relation to arthritis development

Table 2. Results of univariable Cox regression analyses of baseline clinical and serological factors in relation to arthritis development

	HR (95% CI)	p-value
Age, per year	1.004 (0.98 to 1.03)	0.78
Female	1.02 (0.45 to 2.29)	0.96
Family history positive for RA	1.37 (0.66 to 2.85)	0.39
Symptom duration per week (n=141)	0.99 (0.98 to 1.01)	0.32
Gradual symptom onset (n=148)	0.68 (0.30 to 1.53)	0.35
Localisation of initial symptoms (n=148)		
Small joints only	Ref	Ref
Large joints only	1.89 (0.44 to 8.14)	0.39
Small and large joints	5.28 (2.38 to 11.73)	<0.001
Localisation of initial symptoms		
Upper extremities	Ref	Ref
Lower extremities	1.36 (0.40 to 4.58)	0.62
Upper and lower extremities	1.47 (0.62 to 3.47)	0.38
Symmetrical localisation of initial symptoms (n=148)	0.59 (0.28 to 1.23)	0.16
Morning stiffness ≥60 min (n=143)	1.89 (0.92 to 3.87)	0.081
68-TJC (n=145)	0.98 (0.93 to 1.04)	0.47
BMI, per kg/m2 (n=147)	1.01 (0.94 to 1.08)	0.80
Present smoker	1.28 (0.59 to 2.79)	0.54
CRP-level, per mg/L	1.06 (1.03 to 1.09)	<0.001
RF-positive	6.94 (3.34 to 14.43)	<0.001
ACPA-positive	10.07 (4.87 to 20.82)	<0.001

Presented are the HRs of univariable analyses including 149 patients with CSA of which 30 developed clinical arthritis. When data on clinical characteristics were missing, the number of patients with available data is presented in the first column.

In six patients MRI was not performed, because of (suspected) pregnancy (n=2), metallic foreign body in biceps tendon (n=1), logistical reasons (n=2) or development of clinical arthritis ≤2 weeks after inclusion (n=1).

Table 1 presents baseline MRI characteristics. Median continuous RAMRIS scores were low (online Supplementary Table S1 presents continuous RAMRIS scores for individual joints/bones). Univariable analyses showed that higher MRI inflammation scores were associated with arthritis development (Table 3).

Then the continuous MRI inflammation scores were dichotomised. Since it was recently observed that MRI-detected inflammation is also present in the general population and depends on age, anatomical location and type of inflammation [10], these were considered when defining an 'abnormal MRI'. A joint (or bone in case of BME) was categorised as

positive for inflammation when <5% of the general population of the same age category had inflammation at this location (online Supplementary Table S2 presents frequencies of positive joints/bones for MRI-detected inflammation). Sixty-six patients with CSA (45.8%) had a positive MRI for any subclinical inflammation, indicating that at least 1 joint/bone had synovitis, BME or tenosynovitis (Table 1): 20.1% of the patients had 1 positive joint/bone, 18.8% 2-5 positive joints/bones and 6.9% ≥6 positive joints/bones (the maximum number of positive joints/bones was 24). When evaluating the individual MRI features, 25.7% of the patients had MRI-detected synovitis, 16.7% BME and 29.2% tenosynovitis (Table 1).

Univariable Cox regression analyses with arthritis development as outcome revealed that presence of any MRI-detected subclinical inflammation at baseline was associated with a six times increased hazard on arthritis (HR=6.12, 95% CI 2.32 to 16.19, p<0.001, Figure 1). In addition, the hazard on clinical arthritis increased when more joints/bones were scored positive for MRI inflammation (HR=1.23 per additional positive joint/bone, 95% CI 1.13 to 1.33, p<0.001). Evaluating the three MRI features separately showed the strongest association for MRI-detected tenosynovitis (HR=7.56), though MRI-detected synovitis and BME were also significantly associated with arthritis development (HR=2.22 and 2.39 respectively, all p<0.05, Table 3). Because synovitis, BME and tenosynovitis were frequently present in the same patient (Table 1), multivariable Cox regression analyses were done to determine which type(s) of MRI-detected inflammation were independently associated with arthritis development (Table 3). We observed that MRI-detected tenosynovitis was independently associated (HR=8.39, 95% CI 3.38 to 20.81, p<0.001) with arthritis development.

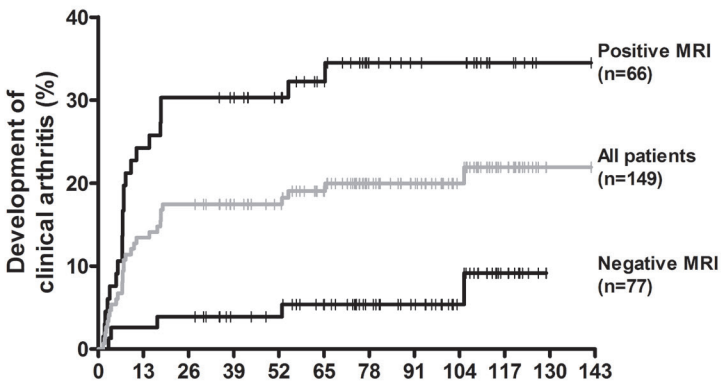

Figure 1. Development of clinical arthritis over time for all patients and for the patients with and without MRI-detected inflammation separately. Presented are the curves for development of clinical arthritis over time in all 149 patients with CSA and for the patients with a positive and a negative MRI separately (six patients did not undergo an MRI). The HR of developing arthritis with a positive MRI was 6.12 (95% CI 2.32 to 16.19, p<0.001). All patients were followed for ≥6 months (median follow-up duration 75 weeks). The vertical lines indicate that a patient is censored.

Table 3. Results of Cox regression analyses of MRI-detected subclinical inflammation at baseline in relation to arthritis development

	HR (95% CI)	p-value
Continuous RAMRIS scores		
Univariable		
Total inflammation score, per unit	1.14 (1.08 to 1.20)	<0.001
Total synovitis score, per unit	1.29 (1.14 to 1.47)	<0.001
Total BME score, per unit	1.28 (1.13 to 1.46)	<0.001
Total tenosynovitis score, per unit	1.25 (1.11 to 1.39)	<0.001
Multivariable		
Total synovitis score, per unit	1.09 (0.86 to 1.38)	0.47
Total BME score, per unit	1.20 (1.03 to 1.38)	0.016
Total tenosynovitis score, per unit	1.15 (0.94 to 1.41)	0.17
MRI dichotomised for the presence of any subclinical inflammation and for specific inflammatory features		
Univariable		
Presence of any MRI-detected inflammation	6.12 (2.32 to 16.19)	<0.001
Presence of MRI-detected synovitis	2.22 (1.03 to 4.78)	0.042
Presence of MRI-detected BME	2.39 (1.04 to 5.46)	0.039
Presence of MRI-detected tenosynovitis	7.56 (3.30 to 17.32)	<0.001
Multivariable		
Presence of MRI-detected synovitis	0.72 (0.31 to 1.69)	0.45
Presence of MRI-detected BME	2.09 (0.91 to 4.81)	0.084
Presence of MRI-detected tenosynovitis	8.39 (3.38 to 20.81)	<0.001

Presented are the HRs of analyses including 143 patients with CSA that underwent MRI of which 27 developed clinical arthritis. The HR of 1.14 for the total inflammation score indicates that when the total MRI inflammation score increased with 1 unit the hazard on arthritis development increased with a factor 1.14.

Combination of clinical factors, ACPA and subclinical MRI inflammation in relation to arthritis development

Then, we questioned if the association of subclinical MRI inflammation with arthritis development was independent of the associations of other factors (age, initial localisation of the symptoms, CRP-level, ACPA-positivity). Multivariable Cox regression analyses (Table 4) revealed an increased hazard for younger patients (HR=0.96 per year older, 95% CI 0.93 to 0.996, p=0.028), patients with initial localisation of symptoms in small and large joints (HR=4.30 compared with small joints only, 95% CI 1.70 to 10.86, p=0.002), patients with higher CRP-levels (HR=1.05/mg/L, 95% CI 1.01 to 1.09, p=0.021), ACPA-positive patients (HR=6.43, 95% CI 2.57 to 16.05, p<0.001) and patients with presence of any MRI-detected subclinical inflammation (HR=5.07, 95% CI 1.77 to 14.50, p=0.002). Similar results were obtained when including continuous total MRI inflammation scores instead of MRI positivity

Table 4. Results of multivariable Cox regression analysis of clinical and serological factors and MRI-detected subclinical inflammation at baseline in relation to arthritis development

	HR (95% CI)	p-value
Age, per year	0.96 (0.93 to 0.996)	0.028
Localisation of initial symptoms		
Small joints only	Ref	Ref
Large joints only	2.35 (0.41 to 13.61)	0.34
Small and large joints	4.30 (1.70 to 10.86)	0.002
CRP-level, per mg/L	1.05 (1.01 to 1.09)	0.021
ACPA-positive	6.43 (2.57 to 16.05)	<0.001
Presence of any MRI-detected inflammation	5.07 (1.77 to 14.50)	0.002

Presented are the HRs of multivariable analyses including 142 patients with CSA that underwent MRI of which 27 developed the outcome clinical arthritis. One patient that underwent MRI had missing data on localisation of initial symptoms and was not included in present analysis.

(see online Supplementary Table S3). Hence, MRI-detected inflammation was associated with progression to clinical arthritis, independent of other clinical and serological factors.

Sensitivity analyses on initiation of DMARD treatment

Sensitivity analyses were performed with initiation of DMARD therapy as outcome. Twenty-five out of the 30 patients that developed clinical arthritis were started with DMARD treatment. Repeating the latter multivariable Cox regression analysis (including clinical and serological factors and presence of any MRI-detected inflammation) with DMARD initiation as outcome revealed similar results (data not shown).

Diagnostic value of ACPA and subclinical MRI inflammation

The previous analyses showed that the presence of subclinical MRI inflammation and ACPA were the two strongest and independent factors associated with arthritis development. We continued with determining test characteristics of both factors with arthritis development within the first year as outcome (Table 5). To this end, analyses were restricted to the patients with CSA with 1 year follow-up who had data on ACPA and MRI (n=122). Of these, 21 (17.2%) had developed clinical arthritis within this year. Two patients developed arthritis after the first year had passed; these patients are now categorised in the non-arthritis group.

Test characteristics of ACPA

The sensitivity of ACPA for arthritis development was 57%, indicating that 57% of the patients with CSA that developed arthritis were ACPA-positive and 43% ACPA-negative. Of the patients that developed arthritis 24% were negative for ACPA and RF. The specificity of ACPA was 93%. The positive predictive value (PPV) of ACPA was 63%, indicating that 63% of ACPA-positive patients with CSA have developed clinical arthritis within 1 year (Table 5).

Test characteristics of subclinical MRI inflammation

Subclinical MRI inflammation was present in 81% of the patients that have developed arthritis

Table 5. Test characteristics of ACPA and subclinical MRI-inflammation for arthritis development within 1 year

	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)	AUC (95% CI)
ACPA in all patients with CSA	57% (48% to 66%)	93% (89% to 98%)	63% (55% to 72%)	91% (86% to 96%)	8.24 (3.69 to 18.44)	0.46 (0.28 to 0.76)	0.75 (0.62 to 0.89)
MRI in all patients with CSA	81% (74% to 88%)	63% (55% to 72%)	31% (23% to 40%)	94% (90% to 98%)	2.21 (1.59 to 3.07)	0.30 (0.12 to 0.74)	0.72 (0.61 to 0.84)
MRI in ACPA-positive patients with CSA	83% (67% to 100%)	43% (21% to 65%)	71% (51% to 92%)	60% (38% to 82%)	1.46 (0.73 to 2.91)	0.39 (0.08 to 1.79)	0.63 (0.36 to 0.90)
MRI in ACPA-negative patients with CSA	78% (70% to 86%)	65% (56% to 74%)	18% (10% to 25%)	97% (93% to 100%)	2.22 (1.42 to 3.46)	0.34 (0.10 to 1.17)	0.71 (0.54 to 0.88)

Presented are the test characteristics for arthritis development within the first year in 122 patients with CSA who had completed 1 year follow-up and had data on ACPA and MRI.

within 1 year (sensitivity=81%). The specificity was 63%. In case of a positive MRI, 31% of the patients progressed to arthritis (PPV) within 1 year and of all persons with a negative MRI at baseline only 6% developed arthritis (100% minus negative predictive value (NPV)) (Table 5). These 6% concerned four patients; three of them developed initial clinical arthritis in a joint that was not depicted on MRI and one developed arthritis 17 weeks after inclusion in joints that were depicted on MRI.

Test characteristics of subclinical MRI inflammation within ACPA-negative and ACPA-positive patients with CSA

Test characteristics for subclinical MRI inflammation were determined within the ACPA-negative and ACPA-positive patients separately to evaluate the diagnostic value in the different sub-groups (Table 5). Although patient numbers became small, especially in the ACPA-positive subgroup, these stratified analyses indicate the value of subclinical MRI inflammation if ACPA results are known. Within the ACPA-positive patients 71% with a positive MRI progressed towards arthritis within 1 year (PPV=71%). Hence, whereas the chance on arthritis in case of ACPA-positivity in the total CSA population was 63%, within the ACPA-positive patients with a positive MRI it was 71%. Of the ACPA-positive patients with a negative MRI 60% did not develop arthritis within 1 year (NPV). Within the ACPA-negative patients with CSA, a negative MRI made the chance on arthritis development very low (3%, 100% minus NPV). Furthermore, the sensitivity of a positive MRI in ACPA-negative patients was 78%. Thus, whereas 43% of the patients that developed arthritis had a negative ACPA test, 78% of these patients were identified by a positive MRI at baseline. Similar results were obtained in ACPA-negative and RF-negative patients (data not shown).

DISCUSSION

This longitudinal study of patients with CSA, with a median follow-up duration of 75 weeks observed that part of the patients with CSA progressed to arthritis. The majority already had subclinical MRI inflammation when presenting with CSA and progressed to arthritis within 4-5 months. These data indicate that the period of CSA and subclinical inflammation is relatively short and encompasses several months.

MRI-detected inflammation is one of the risk factors for arthritis development explored in this study. Thirty-one per cent of patients with CSA with a positive MRI progressed to arthritis within 1 year. Arthritis development within the 1st year was rare (6%) if the baseline MRI was negative.

The association of subclinical MRI inflammation with arthritis development was independent of other factors such as ACPA. Interestingly, the effect sizes in the multivariable analyses of both variables were in the same range. In clinical practice serological results are generally available before imaging tests are ordered. To get a better impression of the additional value of MRI, the analyses on the diagnostic value of MRI were performed in the ACPA-

positive and ACPA-negative subgroups. This revealed that the risk of arthritis development within 1 year was 71% if ACPA-positive patients had a positive MRI. Additionally, 60% of the ACPA-positive patients with a negative MRI did not develop arthritis within 1 year. MRI was valuable in ACPA-negative patients with CSA as the majority (78%) of the ACPA-negative patients that developed arthritis had a positive MRI at baseline.

A strength of this study is that a positive MRI was defined using the prevalence of MRI features in the general population as reference, lowering the risk of false-positive MRI findings. Of the different types of MRI-detected inflammation (synovitis, BME, tenosynovitis), tenosynovitis was most predictive for arthritis development. Previous studies showed that MRI-detected tenosynovitis is frequently present in RA [11] and rarely present in the general population [10].

A limitation is that in the first 77 patients MRI of the feet was made without contrast-enhancement. This may have affected the RAMRIS scores for synovitis on the feet. In this study, we scored MRIs without contrast conservatively, which may have resulted in an underestimation of inflammation on MRIs without contrast enhancement [12]. Another limitation is the median follow-up duration of 75 weeks. It is unsure whether longer follow-up will change our results; nonetheless, we observed that the majority of patients had already progressed in the first months after inclusion.

Further replication studies are needed in other CSA populations before it can be decided if MRI is a useful tool in CSA in daily practice. In this study, MRI was used because an accepted validated scanning and scoring protocol exists [8], it is a minimal operator-dependent procedure and the prevalence of MRI-detected inflammation in the general population is known 10. These issues are not yet solved for ultrasound and further studies are needed to determine whether ultrasound might also be useful in CSA.

Previous studies on patients with symptoms without clinical arthritis evaluated patients with unspecified arthralgia [4,5,13,14]. These studies identified morning stiffness and joint tenderness as predictors for progression to arthritis [4,5]. These clinical factors were not associated with arthritis development in patients with CSA. This is presumably caused by the fact that patients with CSA were selected on the basis of their symptoms and signs. Indeed, the frequency of morning stiffness in CSA was higher than that in unspecified arthralgia [4,5].

The reported risk of developing arthritis within 1 year in autoantibody-positive patients with unspecified arthralgia was 20-34% and up to 41-43% if other risk factors were present [4,5]. Of patients with CSA that were ACPA-positive 63% progressed to arthritis within 1 year, suggesting that the predictive value of ACPA is higher in CSA than in unspecified arthralgia.

The present study is the first exploring the outcome of patients with CSA. We did not aim to derive a prediction rule because the current data set is too small to use part of the data for identification and the other part for validation. In addition, we anticipated that

for accurate prediction more predictors are needed than those entered in our multivariable analysis. Further work is needed to this end.

In conclusion, the phase of CSA without clinically apparent arthritis but with subclinical inflammation encompasses several months. Present data suggest that MRI is diagnostically relevant in this disease phase. With regards to the role of MRI in identifying patients with an increased risk of arthritis, the absolute value of MRI may be higher in ACPA-negative then in ACPA-positive patients with CSA, as ACPA-positive patients with CSA already have a higher prior risk of arthritis development. Importantly, MRI is also useful to rule out imminent arthritis; patients with a clinical suspicion to progress to RA but a negative MRI had a low risk of developing arthritis. Further studies are needed to identify the set of variables that optimally identifies patients with RA in the phase of arthralgia without clinical arthritis and to examine if treatment in this phase is more effective than initiating treatment when clinical arthritis has developed.

SUPPLEMENTARY DATA

Supplementary data are published on the website of the *Annals of the Rheumatic Diseases*.

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Additional File. RAMRIS-based frequencies of synovitis, BME and tenosynovitis per joint/bone, age category and grade of severity; presented are percentages present in symptom-free persons (derived from reference 10)

	MCPs								
	Grade 1			Grade 2			Grade 3		
	<40 years	40-59 years	≥60 years	<40 years	40-59 years	≥60 years	<40 years	40-59 years	≥60 years
Synovitis									
MCP-2	0	8	19	0	0	0	0	0	0
MCP-3	0	14	17	0	0	0	0	0	0
MCP-4	0	2	4	0	0	0	0	0	0
MCP-5	0	1	6	0	0	0	0	0	0
BME*									
MCP-2	2	2	4	0	0	0	0	0	0
MCP-3	2	3	6	0	0	0	0	0	0
MCP-4	0	0	0	0	0	0	0	0	0
MCP-5	0	2	0	0	0	0	0	0	0
Tenosynovitis									
Extensor MCP-2	0	0	0	0	0	0	0	0	0
Extensor MCP-3	0	1	0	0	0	0	0	0	0
Extensor MCP-4	0	0	0	0	0	0	0	0	0
Extensor MCP-5	0	0	0	0	0	0	0	0	0
Flexor MCP-2	0	1	6	0	0	0	0	0	0
Flexor MCP-3	0	3	12	0	0	0	0	0	0
Flexor MCP-4	0	3	6	0	0	0	0	0	0
Flexor MCP-5	0	1	2	0	0	0	0	0	0

Wrist									
	Grade 1			Grade 2			Grade 3		
	<40 years	40-59 years	≥60 years	<40 years	40-59 years	≥60 years	<40 years	40-59 years	≥60 years
Synovitis									
Intercarpal-CMC joint	4	16	27	0	0	0	0	0	0
Radio-carpal joint	0	17	35	0	0	0	0	0	0
Distal radio-ulnar joint	0	8	17	0	0	0	0	0	0
BME									
Metacarpal-1 basis	0	3	8	0	0	2	0	0	4
Metacarpal-2 basis	4	1	2	0	0	0	0	0	0
Metacarpal-3 basis	0	0	2	0	0	0	0	0	0
Metacarpal-4 basis	0	0	2	0	0	0	0	0	0
Metacarpal-5 basis	0	0	0	0	0	0	0	0	0
Trapezium	0	0	4	0	0	4	0	0	4
Trapezoid	2	1	6	0	0	0	0	0	0
Capitate	6	3	4	2	0	0	0	0	0
Hamate	0	3	8	0	0	0	0	0	0
Scaphoid	2	7	19	0	0	0	0	0	0
Lunate	6	19	27	0	1	4	0	0	0
Triquetrum	2	6	2	0	0	0	0	0	0
Pisiform	0	0	0	0	0	0	0	0	0
Distal radius	0	0	0	0	0	0	0	0	0
Distal ulna	0	7	8	0	0	0	0	0	0
Tenosynovitis									
I extensor	0	0	0	0	0	2	0	0	0
II extensor	0	0	0	0	0	0	0	0	0
III extensor	0	0	0	0	0	0	0	0	0
IV extensor	0	0	2	0	0	0	0	0	0
V extensor	0	0	0	0	0	0	0	0	0
VI extensor	0	9	12	0	0	0	0	0	0
1 flexor	0	0	0	0	0	0	0	0	0
2 flexor	0	0	0	0	0	0	0	0	0
3 flexor	0	0	0	0	0	0	0	0	0
4 flexor	2	0	2	0	0	0	0	0	0

MTPs									
	Grade 1			Grade 2			Grade 3		
	<40 years	40-59 years	≥60 years	<40 years	40-59 years	≥60 years	<40 years	40-59 years	≥60 years
Synovitis									
MTP-1	4	11	13	0	0	2	0	0	0
MTP-2	0	1	0	0	0	0	0	0	0
MTP-3	0	1	0	0	0	0	0	0	0
MTP-4	0	0	0	0	0	0	0	0	0
MTP-5	0	0	4	0	0	0	0	0	0
BME*									
MTP-1	10	12	23	0	1	8	0	0	0
MTP-2	2	0	0	0	1	0	0	0	0
MTP-3	0	1	0	0	0	0	0	1	0
MTP-4	0	1	0	0	0	0	0	0	0
MTP-5	0	1	4	0	0	0	0	0	0

Presented are the percentages out of the total number of persons in each age category: 51 symptom-free persons were included in the category <40 years, 90 persons in the category from 40-59 years and 52 persons in the category ≥60 years. These tables are used for present study of patients with CSA to derive age, MRI-feature and location specific reference values for a 'positive MRI'. The locations that were inflamed in ≥5% of individuals are highlighted in dark. Joints/bones in the CSA-patients with scores as presented in in the light areas are categorized as positive for MRI-detected inflammation and the joints/bones with scores as presented the dark areas as negative.

* BME is scored in the proximal and distal MCP and MTP bones separately. The scores of the 2 bones are summed into a 1 score, therefore the range is 0-6 in the MCP and MTP joints. Five bones scored a grade 2 in MTP-1 this consists of 4 persons with a grade 1 in both the proximal and the distal bone and 1 person had a score of 2 in the proximal bone of MTP-1