CONCISE REPORT

Differences in the symptomatic phase preceding ACPA-positive and ACPA-negative RA: a longitudinal study in arthralgia during progression to clinical arthritis

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ABSTRACT

Objective Although anticitrullinated protein antibody (ACPA)-positive and ACPA-negative rheumatoid arthritis (RA) have different aetiopathology, the clinical presentation at the time of diagnosis is similar. This study evaluated whether there are phenotypic differences in the symptomatic pre-RA phase.

Methods Patients with arthralgia included in the Leiden clinically suspect arthralgia cohort who developed arthritis during follow-up were studied (n=67). Symptoms at symptom onset, symptoms and signs at presentation with arthralgia and time to arthritis development were compared between ACPA-positive and ACPA-negative patients.

Results In ACPA-negative patients (n=37), the location of initial symptoms less often included the lower extremities (22% vs 50%, p=0.014). At presentation with arthralgia, ACPA-positive patients had a longer symptom duration (median 22 vs 14 weeks, p=0.005), less tender joints (mean 5 vs 9, p=0.007) and less difficulty making a fist (11% vs 43%, p=0.004). However, after presentation with arthralgia, ACPA-positive patients developed arthritis more quickly (median 6 vs 18 weeks, p=0.015). A partial least squares regression analysis showed clustering of ACPA-positive and ACPA-negative patients based on the above-mentioned clinical variables.

Conclusion This study is the first showing that ACPA-positive and ACPA-negative patients have clinical differences in the symptomatic phase preceding clinical arthritis. This contributes to the notion that ACPA-positive and ACPA-negative RA develop differently.

INTRODUCTION

Anticitrullinated protein antibodies (ACPA)-positive and ACPA-negative rheumatoid arthritis (RA) are considered as different disease subsets with differences in aetiopathology because there are differences in underlying genetic risk factors and the best-known environmental risk factor, smoking, is confined to ACPA-positive RA.[1–4] Intriguingly, despite the presumed differences in underlying biological processes, the clinical presentation at the time of diagnosis is similar.[5–7]

Autoimmune processes can start months to years before the diagnosis of RA.[8 9] ACPA-positive RA has a phase in which autoantibodies with or without symptoms precede the phase of clinical arthritis, and recent evidence revealed that also ACPA-negative RA has a symptomatic pre-arthritis phase in which subclinical inflammation may be present.[10 11] Currently, it is unknown whether there are phenotypic differences between ACPA-positive and ACPA-negative RA in the symptomatic phase preceding clinical arthritis. Because of the differences in aetiopathology, we hypothesised that differences are present. To investigate this, we longitudinally studied patients who presented with arthralgia and progressed to clinical arthritis. Clinical data at the time of symptom onset, at the time of first presentation with arthralgia to the outpatient clinic and time to arthritis development were compared between ACPA-positive and ACPA-negative patients.

METHODS

Patients

The Leiden clinically suspect arthralgia cohort is a population-based inception cohort that started in April 2012 at the outpatient clinic of the Leiden University Medical Center.[12] Inclusion required the presence of recent onset (<1 year) arthralgia of small joints that was considered suspect to progress to RA according to the clinical expertise of the rheumatologist. Autoantibody status was generally unknown at first presentation as local and national guidelines for general practitioners (GP) discourage autoantibody testing, but instead encourage GPs to refer quickly.[13 14] Hence, inclusion, which generally coincided with the first visit to the outpatient clinic, was based on clinical information. At baseline, patients completed questionnaires; this concerned questions on initial symptoms that were present at symptom onset and questions on current symptoms. Rheumatologists completed a questionnaire on symptoms that they felt to be important for labelling a patient as having clinically suspect arthralgia and performed a physical examination. Laboratory tests were performed after inclusion and included determination of ACPA (EliA CCP, Phadia, Nieuwegein, The Netherlands, positive if ≥7 U/mL), IgM rheumatoid factor (RF) (positive if ≥3.5 IU/mL) and acute-phase reactants. Patients were followed until progression to clinical arthritis with a maximum of 2 years. The cohort has been described elsewhere in detail.[12] At the time of

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Table 1 Clinical characteristics of ACPA-negative and ACPA-positive patients in the symptomatic phase preceding clinical arthritis

	All patients		
	ACPA negative (n=37)	ACPA positive (n=30)	p Value
Symptoms at symptom onset			
Symptom onset			
Acute (<1 week)	8 (22)	8 (27)	0.53
Gradual	26 (70)	16 (55)	
Intermittent	3 (8)	5 (17)	
Symptoms started with*			
Pain	34 (92)	29 (97)	0.41
Stiffness	26 (70)	17 (57)	0.25
Loss of function	16 (43)	10 (33)	0.41
Localisation affected joints			
Small joints hand/feet	27 (73)	21 (70)	0.18
Large joints	5 (14)	1 (3)	
Both	5 (14)	8 (27)	
Localisation affected joints			
Upper extremities	29 (78)	15 (50)	0.014
Lower extremities	5 (14)	4 (13)	
Both	3 (8)	11 (37)	
Localisation affected joints			
Symmetric	22 (60)	22 (73)	0.23
Presentation with arthralgia			
Family history of RA	13 (35)	11 (37)	0.90
Symptoms determining inclusion in the cohort			
Inflammatory type of symptoms	14 (39)	18 (60)	0.089
Morning stiffness ≥60 min	9 (25)	2 (7)	
Both	13 (36)	10 (33)	
Physical examination			
68 TJC, mean±SD	9±8	5±3	0.007†
Difficulties making a fist	16 (43)	3 (11)	0.004†
Squeeze test			
Positive for both MTP and MCP joints	8 (22)	4 (14)	0.48
Positive for MCP joints only	11 (31)	7 (24)	
Positive for MTP joints only	4 (11)	2 (7)	
Negative for both	13 (36)	16 (55)	
HAQ score, mean±SD	0.8±0.6	0.7±0.6	0.57

All values are indicated as n (%), unless indicated otherwise.
Missings were as follows: symptom onset (1), symptoms determining inclusion in the cohort (1), difficulties making a fist (1), squeeze test (2), HAQ score (2).
*Multiple answers could be given, so the percentages can add up to >100%.
†Significant after correction for multiple testing.
ACPA, anticitrullinated protein antibodies; HAQ, health assessment questionnaire; MCP, metacarpophalangeal; MTP, metatarsophalangeal; RA, rheumatoid arthritis; TJC, tender joint count.

analysis (1 November 2016), 441 patients were included, of whom 74 had developed clinical arthritis. Seven of these patients participated in a placebo-controlled trial (NTR4853) and received either methotrexate or placebo; these patients were not studied here. Disease modifying antirheumatic drugs (DMARDs) (including steroids) were not prescribed in the phase of arthralgia outside this trial. Hence, 67 DMARD-naive arthralgia patients that progressed to arthritis were studied. The study was approved by the local medical ethical committee. All patients provided written informed consent.

Sensitivity analyses

Sensitivity analyses were performed in patients with RA, defined as fulfilling the 2010 criteria and/or DMARD initiation at the time of arthritis development. The latter criterion reflects the expert opinion on RA and was added because patients with seronegative arthritis require >10 involved joints to fulfil the 2010 criteria, which may have been hampered by the early initiation of DMARDs.[15 16]

Statistics

Student's t-test, χ^2 test and log-rank test were used when appropriate. The Benjamini-Hochberg method was used to correct for multiple testing.[17] A partial least squares (PLS) regression analysis was used to study whether certain clinical characteristics frequently occurred together in ACPA-positive or ACPA-negative patients. PLS clusters variables into latent factors. Individual patient scores on these factors were then plotted against each other to look for clustering. SPSS V.23.0 was used for all analyses.

RESULTS

Of the patients with arthralgia who developed clinical arthritis, 37 (55%) were ACPA negative and 30 (45%) were ACPA positive. The mean age in both groups was 45 years and the majority was female (73% and 77%, respectively).

Symptoms at symptom onset

Eighty-six per cent of ACPA-negative patients initially experienced symptoms at the upper extremities, while only 22% reported initial involvement of the lower extremities. In contrast, 50% of ACPA-positive patients reported initial involvement of the lower extremities (p=0.014, table 1).

Symptoms and signs at first presentation with arthralgia

At the time of first presentation with arthralgia, ACPA-positive patients had less tender joints (mean 5 vs 9, p=0.007, table 1), less difficulties making a fist (11% vs 43%, p=0.004, table 1) and a longer symptom duration than ACPA-negative patients (median of 22 compared with 14 weeks, p=0.005, figure 1). When splitting symptom duration in patient delay (symptom onset—first visit to the GP) and in GP delay (first visit to the GP—first visit to the rheumatologist), both patient delay (median 10 vs 7 weeks) and GP delay (median 6 vs 3 weeks) were longer in ACPA-positive patients.

Although this study focused on clinical characteristics, acute-phase reactants were routinely measured and were not different between ACPA-positive and ACPA-negative patients (C-reactive protein mean of 9 vs 8 mg/L and erythrocyte sedimentation rate mean of 16 vs 15 mm/h).

Time to arthritis development

Although ACPA-positive patients had a longer symptom duration when first presenting with arthralgia, they developed arthritis more quickly (median 6 weeks vs 18 weeks, p=0.015, figure 1).

Clustering of patients

A PLS regression analysis was performed to look for clustering of ACPA-positive and ACPA-negativepatients. All clinical variables included in table 1, age, gender, symptom duration and time to arthritis development, were entered. Two latent factors were identified that together explained 51.3% of the variance between ACPA-positive and ACPA-negative patients. Individual patient scores on these factors were plotted against each other

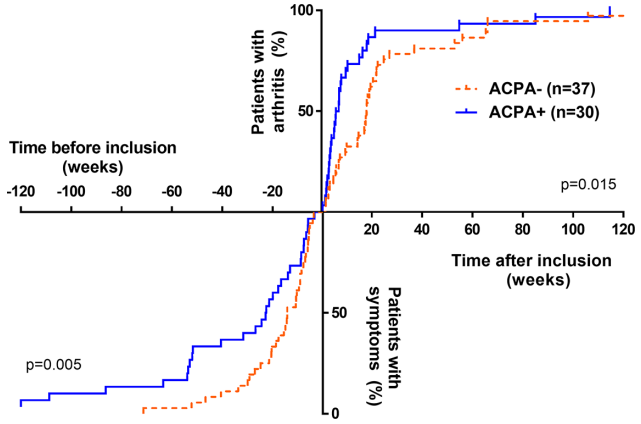

Figure 1 Time from symptom onset to presentation with arthralgia (left part) and from presentation with arthralgia to arthritis development (right part) in ACPA-positive and ACPA-negative patients. This graph shows that ACPA-negative patients have a shorter symptom duration at the time of first presentation with arthralgia, but that ACPA-positive patients progress to arthritis more quickly thereafter. Three data points were not shown (but were included in the analyses): two ACPA-positive patients had a symptom duration of ≥120 weeks and one ACPA-negative patient developed arthritis ≥120 weeks after inclusion in the cohort. Symptom duration was unknown in one patient. ACPA, anticitrullinated protein antibodies.

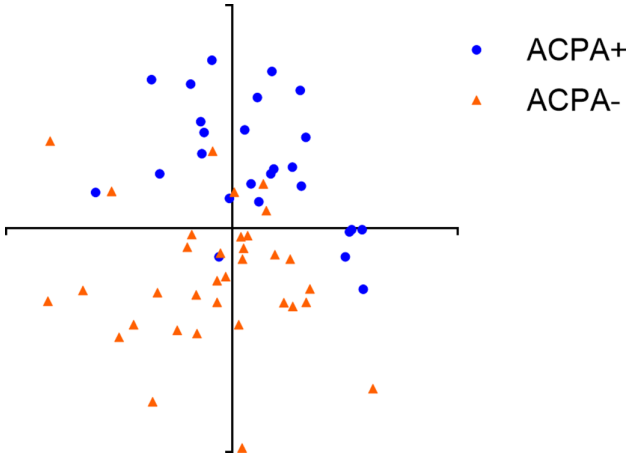

Figure 2 Clustering of anticitrullinated protein antibody (ACPA)-positive and ACPA-negative patients based on a partial least squares regression analysis that included only clinical information. Scores on latent factor 1 are plotted on the Y-axis, scores on latent factor 2 are plotted on the X-axis. Together these factors explain 51.3% of the variance in ACPA-positive and ACPA-negative patients. Importantly, results of laboratory tests were not included. This figure shows that especially the first latent factor partially clusters ACPA-positive and ACPA-negative patients. Important variables contributing to a higher score on factor 1 were initial symptoms in both upper and lower extremities, initial symptoms in both large and small joints and inflammatory type of symptoms. Variables contributing to a lower score on factor 1 were initial symptoms in the upper extremities only, morning stiffness ≥60 minutes as a reason for inclusion in the cohort, a shorter symptom duration, a higher TJC, problems making a fist and a positive squeeze test of the MTP joints. ACPA, anticitrullinated protein antibodies; MTP, metatarsophalangeal; PLS, partial least squares; TJC, tender joint count.

and showed clustering (figure 2). Variables contributing to this clustering included the same variables that were observed to be different between ACPA-positive and ACPA-negative patients in table 1 and figure 1 (identified by a variable importance projection >1, see online supplementary table 1). These findings indicate that there are indeed clinical differences between ACPA-positive and ACPA-negative patients in the phase preceding clinical arthritis.

Sensitivity analyses

At the visit at which clinical arthritis was identified, 59/67 (88%) started on DMARD therapy and/or fulfilled the 2010 criteria (2010 RA+/DMARD initiation− (n=3), 2010-RA-/DMARD-initiation+ (n=17), 2010 RA+/DMARD initiation+ (n=39)). Analyses were repeated in these patients and showed similar results (online supplementary table 2; supplementary figure 1). None of the patients classified with RA had a spontaneous resolution of arthritis.

Finally, as ACPA-negative patients can be RF positive, analyses were further stratified for RF. Although subgroups became small, this did not change the results (online supplementary table 3).

DISCUSSION

This study identified phenotypic differences between ACPA-positive and ACPA-negative patients in the symptomatic phase preceding arthritis development. Initial symptoms in ACPA-negative patients were less often located in the lower extremities. At first presentation with arthralgia, ACPA-positive patients had less tender joints, less difficulty making a fist and longer symptom duration compared with ACPA-negative patients. However, ACPA-positive patients progressed to arthritis more rapidly. This study is the first showing that, in addition to the differences in underlying risk factors, there are also clinical differences in very early symptomatic disease phases. This suggests that ACPA-positive and ACPA-negative RA are intrinsically different.

Previous studies among patients with RA (classified with the 1987 criteria) revealed no clinical differences between ACPA-positive and ACPA-negative patients.[5 7] This may be due to circularity as fulfilment of classification criteria requires certain clinical characteristics to be present, or to the disease stage, as a final common phenotype can have developed over time. A study on the symptomatic pre-arthritis phase does not have this drawback. Furthermore, whereas recall bias may be an issue when information on the earliest disease phases is collected at the time of diagnosis, most data in this study were collected prospectively. Only data on first symptoms were collected in retrospect, but symptom onset was recent.

In ACPA-negative patients, symptoms often started in the upper extremities only. A previous study that compared ACPA-negative and ACPA-positive RA at the time of diagnosis (hence studying different individuals) revealed the same.[5] Although it was then unclear if this finding was due to multiple testing, the present data on patients in a different disease phase support the validity of this finding. The observation that ACPA-negative patients had more difficulties making a fist prior to developing clinical arthritis is in line with these findings as well.

Both patient and GP delay were longer in ACPA-positive patients. This is in line with previous studies showing a longer delay in ACPA-positive RA.[6 18] This may be explained by a difference in symptom onset. It has been reported that autoantibody-positive RA has a more gradual onset and that initial symptoms more often 'come and go'.[6 19] This tendency was also present in the current data, although not statistically

significant. Interestingly, after presentation, ACPA-positive patients progressed to arthritis quicker and the total time period between symptom onset and arthritis development was not different. Together, these results suggest that ACPA-positive patients present in a later part of the symptomatic pre-arthritis phase.

This study only evaluated arthralgia patients who developed arthritis. A previous study compared patients with clinically suspect arthralgia who developed arthritis with those who did not develop arthritis to identify predictors,[20] which is a different study question than addressed here.

The sample size (n=67) may be considered as a limitation and may lead to false-negative results. In addition, we cannot exclude false-positive results as replication in independent datasets was not available. However, this is the first time that ACPA-positive and ACPA-negative patients were identified in a symptomatic pre-arthritis phase and were followed to arthritis development. Comparison of these disease phases reveals novel insights in the pathophysiology of RA development.

In conclusion, ACPA-positive and ACPA-negative patients have clinical differences in the symptomatic phase preceding arthritis development. This contributes to the notion that ACPA-positive and ACPA-negative RA are disease subsets that develop differently.

Contributors All authors contributed to the design of the study, the interpretation of the results and gave feedback on the manuscript. All authors approved the final version and agreed to be accountable for all aspects of the work. HWvS, RMtB and LEB contributed to the acquistion of data. LEB analysed the data. LEB and AvdH-vM drafted the manuscript.

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Notes