Anti-citrullinated peptide antibodies may occur in patients with psoriatic arthritis


Background: Anti-cyclic citrullinated peptide (anti-CCP) antibodies are considered highly specific markers of rheumatoid arthritis. Despite the high specificity of the test, anti-CCP antibodies have also been observed in psoriatic arthritis.

Objective: To determine the frequency of anti-CCP antibodies in psoriatic arthritis and to describe the clinical characteristics of such patients.

Methods: Serum samples from 192 patients with psoriatic arthritis were analysed for anti-CCP antibodies. A previously defined cut off point was applied at a specificity level of $\geq 98.5\%$ (42 U/ml). Antibodies against pepA and pepB (two synthetic citrullinated peptides) were determined on samples containing anti-CCP antibodies by line immune assay. The swollen joint count and the numbers of affected joints (present or past) were recorded. Clinical features were noted and if available radiographs of hands and feet were scored for erosions. Rheumatoid factor was determined in all samples.

Results: Anti-CCP antibodies were found in 15 patients (7.8%); 13 of 15 anti-CCP2 positive samples were also positive for anti-pepA or pepB antibodies. The prevalence of anti-CCP antibodies was higher than expected in view of the highly specific cut off applied in the test. Detailed analysis of the clinical and radiological features makes it improbable that the high prevalence of anti-CCP antibodies resulted solely from concomitant psoriasis and rheumatoid arthritis or from misclassification.

Conclusions: Anti-CCP antibodies may be present in patients with psoriatic arthritis. Although some of the present cohort could have had psoriasis with concomitant rheumatoid arthritis, a proportion at least had the typical characteristics of psoriatic arthritis as the primary diagnosis.

Psoriatic arthritis is a type of inflammatory joint disease in which axial or peripheral arthritis is associated with psoriasis. The picture of psoriatic arthritis is broad and comprises oligoarticular or polyarticular peripheral arthritis and axial involvement.\textsuperscript{1} Psoriatic arthritis shares features of spondyloarthopathies and rheumatoid arthritis. Evolution from oligoarticular disease to polyarticular disease has been described.\textsuperscript{2, 3} McGonagle et al suggested features of psoriatic arthritis that are helpful in distinguishing it from rheumatoid arthritis.\textsuperscript{4} These comprise the following: asymmetrical oligoarticular disease predominantly of the lower limbs, distal interphalangeal joint (DIP) involvement, enthesitis, dactylitis, typical radiological features (pencil-in-cup phenomenon, ankylosis of small hand or feet joints, arthritis mutilans (fig 1)), radiological sacroilitis, and inflammatory low back pain. The broad spectrum of the disease makes it difficult to develop good criteria for diagnosis and classification. Although different criteria have been suggested, none are widely accepted.\textsuperscript{4, 5, 7} At present an international multicentre validation of diagnostic criteria is under way.\textsuperscript{3}

Anti-cyclic citrullinated peptide (CCP) antibodies are antibodies against synthetic citrullinated peptides and are specific markers of rheumatoid arthritis. They belong to a group of anti-citrullinated protein/peptide antibodies (ACPA). Rheumatoid sera were found to contain antibodies that were detected by indirect immunofluorescence in rat oesophagus (the so called anti-keratin antibodies)\textsuperscript{8} or in human buccal mucosal cells (the so called anti-perinuclear factor), and on western blotting of human epidermis (anti-filaggrin antibodies).\textsuperscript{9} This reactivity was found to be critically dependent on the presence of epitopes containing the amino acid citrulline\textsuperscript{10} Based on this knowledge, other assays were developed using synthetic citrullinated peptides such as CCP,\textsuperscript{11, 12} peptide A (pepA), and peptide B (pepB).\textsuperscript{14, 15} The anti-CCP enzyme linked immunosorbent assay (ELISA) is a more widely available test, based on citrulline containing peptides derived from filaggrin and later improved by screening dedicated peptide libraries.\textsuperscript{13, 15–20}

Despite the described high specificity of the anti-CCP test, we and others\textsuperscript{16} have identified patients with psoriatic arthritis who are positive for anti-CCP antibodies. Based on these observations, we analysed a large group of patients diagnosed by their treating rheumatologist as having psoriatic arthritis, based on the presence of psoriasis with arthritis. We have assessed the prevalence of anti-CCP antibodies in these cases and described in detail their clinical and radiological characteristics in order to determine whether they can be considered genuine cases of psoriatic arthritis.

METHODS

Patients and characteristics

We included patients with skin or nail psoriasis who also had spondylitis or peripheral arthritis, and in whom serum samples had been sent to the laboratory of the department of rheumatology for routine work up. Spare serum was available from 192 patients. The study was approved by the local ethics committee. Patient and disease characteristics of all 192 patients included in the study are given in table 1.

Abbreviations: ACPA, anti-citrullinated protein/peptide antibodies; CCP, cyclic citrullinated peptide; DIP, distal interphalangeal joint; ESSG, European Spondyloarthropathy Study Group; pepA, peptide A; pepB, peptide B; RF, rheumatoid factor; RXJC, radiological joint count; SJC, swollen joint count
The clinical and radiological characteristics of the patients were obtained by retrospective analysis of the clinical records and review of the radiographs. A swollen joint count (SJC) was calculated at the sampling date: 74 joints were taken into account and included shoulders, elbows, wrists, metacarpophalangeal joints, temporomandibular joints, acromioclavicular joints, sternoclavicular joints, knees, ankles, tarsus, metatarsophalangeal joints, and all interphalangeal joints, counted as distinct units. Based on radiographs, the number of erosive or destructed hand or foot joints was calculated, taking into account the wrist, all metacarpophalangeal joints, the tarsus, all metatarsophalangeal joints, and all interphalangeal joints as distinct units (radiological joint count (RXJC), maximum 60). Enthesopathy, inflammatory back pain, and radiological sacroiliitis were defined according to the ESSG criteria for spondyloarthritis, briefly summarised as follows:

- **enthesopathy**: past or present spontaneous pain or tenderness on examination of the site of the insertion of the Achilles tendon or plantar fascia;
- **inflammatory back pain**: history of or present symptoms of spinal pain in the back or neck meeting at least four of the following criteria: onset before age 45, insidious onset, improvement with exercise, association with morning stiffness, and of at least three months’ duration;
- **radiological sacroiliitis**: bilateral grade 2 or more or unilateral grade 3 or more.

Dactylitis was defined according to the definitions by Moll and Wright as follows: interphalangeal involvement with flexor tendon sheath effusion; pencil-in-cup phenomenon; arthritis mutilans. Ankylosis of small hand or foot joints was considered a typical radiological feature of psoriatic arthritis.

### Anti-CCP antibodies

Anti-CCP antibodies were detected by a commercially available ELISA containing synthetic peptides (Immunoscan rheumatoid arthritis, mark 2, Eurodiagnostica, Arnhem, Netherlands). The ELISA was carried out according to the manufacturer’s instructions. Briefly, sample sera were diluted 1/50 with dilution buffer and incubated for one hour at 37°C. After removing the liquid and washing three times with rinsing buffer, the conjugate solution (peroxidase conjugated anti-human IgG antibodies) was added into each well and incubated for one hour at 37°C. After three washing steps with rinsing buffer, the substrate solution (tetramethyl benzidine) was added and incubated for 30 minutes at room temperature. The stop solution (sulphuric acid, 0.5 mol/l) was added and the absorbance values were read immediately at 450 nm.

### Rheumatoid factor (RF)

RF was determined by the latex fixation method. A suspension of uniform polystyrene particles sensitised in glycine buffer with heat altered human IgG (BD Diagnostic Systems, Sparks, Maryland, USA) was incubated with progressive dilutions of human sera in microtitre wells. After incubation, the plates were inspected for observable agglutination. The dilution titre present in the last well showing agglutination was recorded.

### Calculation of cut off points

In an independent cohort of patients with inflammatory joint symptoms (containing only four patients with psoriatic arthritis), we previously defined cut off points for anti-CCP antibodies and RF as a function of a preset specificity level.

For anti-CCP antibodies a cut off of ≥42 U/ml corresponded to a specificity of ≥98.5% (98.6%; 95% confidence interval (CI), 95.8 to 99.8). For RF, a cut off of ≥160 corresponded to a specificity of ≥95% (95.5%; 95% CI, 91.7 to 99.3). An RF titre of ≥1280 corresponded to a specificity of ≥98.5% (98.6%; 95% CI, 95.8 to 99.8), comparable with the specificity of the anti-CCP test.

### Anti-pepA and anti-pepB antibodies

To confirm ACPA reactivity, anti-pepA and pepB antibodies were determined on all samples showing anti-CCP reactivity by a line immune assay (prototype of INNO-LIA™ rheumatoid arthritis, Innogenetics, Gent, Belgium), as described previously. This test detects antibodies against two synthetic citrullinated peptides, pepA and pepB. Previous studies indicated that the sensitivity and specificity of anti-pepA antibodies were, respectively, 63.4% and >98.5% (100; 95% CI, 98.0 to 100), and the sensitivity and specificity of anti-pepB antibodies were 54% and >98.5% (99.3; 95% CI, 96.8 to 100). Briefly, serum samples were diluted 1/100 and incubated with the strip for one hour at room temperature.

<table>
<thead>
<tr>
<th>Table 1 Patients and disease characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic features</strong></td>
</tr>
<tr>
<td>Sex (male/female ratio)</td>
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<tr>
<td>Mean age (years) (range)</td>
</tr>
<tr>
<td>Mean disease duration (years) (range)</td>
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<tr>
<td>Familial psoriasis</td>
</tr>
<tr>
<td>Familial IBD, PsA, or AS</td>
</tr>
<tr>
<td>Actual use of DMARDs</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
</tr>
<tr>
<td>Skin involvement</td>
</tr>
<tr>
<td>Nail involvement</td>
</tr>
<tr>
<td>Inflammatory low back pain</td>
</tr>
<tr>
<td>DIP involvement</td>
</tr>
<tr>
<td>Enthesitis</td>
</tr>
<tr>
<td>Dactylitis</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
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<tr>
<td>Persistent asymmetrical mono- or oligoarticular disease, predominantly of the lower limbs</td>
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<tr>
<td><strong>Radiological features</strong></td>
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<tr>
<td>Erosive disease</td>
</tr>
<tr>
<td>Typical radiographic features</td>
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<tr>
<td>Sacroiliitis</td>
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<tr>
<td>Number of patients with at least one feature helpful in discriminating psoriatic arthritis from rheumatoid arthritis</td>
</tr>
</tbody>
</table>

AS, ankylosing spondylitis; DIP, distal interphalangeal joint; DMARD, disease modifying anti-rheumatic drug; IBD, inflammatory bowel disease; PsA, psoriatic arthritis.

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**Figure 1** Radiographs of the hands of a patient with positive anti-cyclic citrullinated peptide antibodies (male, aged 68 years), showing ankylosis of different finger interphalangeal joints.
Table 2  Clinical features of patients with anti-CCP antibodies

<table>
<thead>
<tr>
<th>Sex, age (y)</th>
<th>Dis dur</th>
<th>Anti-CCP (U/ml)</th>
<th>Anti-pepA or pepB reactivity</th>
<th>RF titre</th>
<th>SJC</th>
<th>RXJC</th>
<th>Features helpful in distinguishing PsA from RA</th>
<th>Family history</th>
<th>DMARD*</th>
<th>Psoriasis subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>M, 39</td>
<td>15</td>
<td>54</td>
<td>PepA+PepB</td>
<td>160</td>
<td>6</td>
<td>19</td>
<td>Enthesitis, dactylitis, inflammatory low back pain, DIP involvement.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M, 24</td>
<td>5</td>
<td>54</td>
<td>Neg</td>
<td>320</td>
<td>10</td>
<td>17</td>
<td>DIP involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M, 60</td>
<td>5</td>
<td>72</td>
<td>PepA+PepB</td>
<td>1280</td>
<td>4</td>
<td>3</td>
<td>DIP involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M, 68</td>
<td>17</td>
<td>95</td>
<td>Neg</td>
<td>640</td>
<td>10</td>
<td>34</td>
<td>DIP involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M, 67</td>
<td>20</td>
<td>353</td>
<td>PepA</td>
<td>2560</td>
<td>2</td>
<td>38</td>
<td>DIP involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F, 50</td>
<td>5</td>
<td>500</td>
<td>PepA</td>
<td>80</td>
<td>0</td>
<td>NA</td>
<td>DIP involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M, 37</td>
<td>6</td>
<td>1100</td>
<td>PepA+PepB</td>
<td>160</td>
<td>6</td>
<td>1</td>
<td>DIP involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M, 54</td>
<td>11</td>
<td>1113</td>
<td>PepA+PepB</td>
<td>80</td>
<td>0</td>
<td>1</td>
<td>DIP involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M, 68</td>
<td>6</td>
<td>1375</td>
<td>PepA+PepB</td>
<td>160</td>
<td>4</td>
<td>0</td>
<td>DIP involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F, 48</td>
<td>9</td>
<td>1456</td>
<td>PepB</td>
<td>320</td>
<td>2</td>
<td>14</td>
<td>Ankylosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F, 31</td>
<td>1</td>
<td>&gt;1600</td>
<td>PepA+PepB</td>
<td>640</td>
<td>5</td>
<td>0</td>
<td>Enthesitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F, 51</td>
<td>8</td>
<td>&gt;1600</td>
<td>PepA+PepB</td>
<td>1280</td>
<td>1</td>
<td>0</td>
<td>Dactylitis, enthesitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M, 46</td>
<td>1</td>
<td>&gt;1600</td>
<td>PepA+PepB</td>
<td>320</td>
<td>0</td>
<td>0</td>
<td>Enthesitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M, 63</td>
<td>5</td>
<td>&gt;1600</td>
<td>PepA+PepB</td>
<td>1280</td>
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<td>7</td>
<td>DIP involvement</td>
<td></td>
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<tr>
<td>M, 69</td>
<td>6</td>
<td>&gt;1600</td>
<td>PepA+PepB</td>
<td>160</td>
<td>0</td>
<td>NA</td>
<td>DIP involvement</td>
<td></td>
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</tr>
</tbody>
</table>

*Current treatment in bold.

asym oligo dis, asymmetrical oligoarticular disease (No(1), polyarticular disease; No(2), symmetrical oligoarticular disease); CCP, cyclic citrullinated peptide; CS, corticosteroids; CyA, ciclosporine; DIP, distal interphalangeal joint; Dis dur, disease duration; Dpen, D-penicillamine; IBD, inflammatory bowel disease; MTX, methotrexate; NA, no radiographs available; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; RXJC, radiological erosive or destructive joint count; SASP, salazopyrine; SJC, number of swollen joints; y, years.

The clinical features of the patients with anti-CCP antibodies are summarised in table 2. Differences between groups are summarised in table 3. The Mann–Whitney U test was used to evaluate differences between groups. Exact tests were used for differences in categorical data. We computed 95% confidence intervals (CI) for differences in proportions using the Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA).

RESULTS

The Mann–Whitney U test was used to evaluate differences between groups. Exact tests were used for differences in categorical data. We computed 95% confidence intervals (CI) for differences in proportions using the Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA).

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Observed number of patients with anti-CCP antibodies vs expected number given the specificity of the test

In a separate study, we calculated cut off points at a preset specificity level of at least 98.5% (a cut off of 42 U/ml for anti-CCP antibodies). The corresponding specificity and 95% CI were 98.6% (95.8% to 99.8%).

In this cohort of 192 patients with psoriatic arthritis, we found 15 (7.8%) with anti-CCP antibodies. This is more than would be expected in view of the high specificity of the test. PepA or pepB reactivity was confirmed in 13 of these 15 patients, pointing to specific anti-citrullinated peptide reactivity. Although patients with anti-CCP antibodies had a similar disease duration and similar treatment, they tended to have a higher radiological joint count than patients without anti-CCP antibodies. Some also had rheumatoid factor. These data point to specific anti-citrullinated peptide reactivity.

DISCUSSION

In this study, we found that 15 of 192 patients (7.8%) with psoriasis (skin or nail or both) and peripheral or axial arthritis had anti-CCP antibodies. This is more than would be expected in view of the high specificity of the test. PepA or pepB reactivity was confirmed in 13 of these 15 patients, pointing to specific anti-citrullinated peptide reactivity. Although patients with anti-CCP antibodies had a similar disease duration and similar treatment, they tended to have a higher radiological joint count than patients without anti-CCP antibodies. Some also had rheumatoid factor. These data raise the question of whether positivity for anti-CCP antibodies in such patients is caused by the co-occurrence of rheumatoid arthritis and psoriasis. When we excluded the patients who did not have at least one feature helpful in discriminating psoriatic arthritis from rheumatoid arthritis, there were still more patients with anti-CCP antibodies than expected (10 of 187; 5.3%).

Table 3  Comparison between CCP negative and CCP positive patients

<table>
<thead>
<tr>
<th></th>
<th>CCP negative</th>
<th>CCP positive</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median disease duration (range)</td>
<td>7 years (0 to 47)</td>
<td>6 years (1 to 20)</td>
<td>NS</td>
</tr>
<tr>
<td>Use of DMARD or biological agent</td>
<td>149/177</td>
<td>14/15</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SJC</td>
<td>2 (0 to 21)</td>
<td>4 (0 to 10)</td>
<td>NS</td>
</tr>
<tr>
<td>RXJC</td>
<td>0 (0 to 44)</td>
<td>3 (0 to 38)</td>
<td>p = 0.044</td>
</tr>
<tr>
<td>Typical radiographic features*</td>
<td>20/126 (16%)</td>
<td>3/13 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>40/136 (29%)</td>
<td>2/13 (15%)</td>
<td>NS</td>
</tr>
<tr>
<td>RF positive at 98.5% specific level</td>
<td>0/177</td>
<td>4/15 (27%)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Persistent oligoarticular disease predominantly of the lower limbs</td>
<td>42/177 (24%)</td>
<td>1/15 (7%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean (range) or n (%) unless stated otherwise.

*Pencil-in-cup phenomenon, arthritis mutilans, ankylosis of small hand or foot joints.

CCP, cyclic citrullinated peptide; DMARD, disease modifying antirheumatic drug; RXJC, radiological joint count (number of erosive or destructive joints); SJC, swollen joint count.
findings raise other questions. Thus it could be hypothesised that reactivity for CCP could be a false positive, caused by reactivities to non-specific epitopes in the citrullinated peptide substrate. This phenomenon has been observed in animal models. However, we confirmed real ACPA reactivity with two independent synthetic citrullinated substrates (pepA and pepB), showing the presence of anti-pepA or pepB antibodies in 13 of the 15 psoriatic arthritis patients with anti-CCP antibodies. This supports the view that the observed CCP positivity was caused by genuine anti-citrullinated peptide antibodies.

Another hypothesis could be that those patients with anti-CCP antibodies suffer from an overlap with a preclinical form of rheumatoid arthritis. Indeed, anti-CCP antibodies may be present years before the clinical manifestation of rheumatoid arthritis. Additionally, current DMARD treatment in those patients might prevent the full expression of rheumatoid arthritis. Thus, as suggested before, patients with anti-CCP antibodies require a cautious clinical and radiographic follow up to confirm the absence of future evolution to rheumatoid arthritis.

Conclusions

Our data suggest that anti-CCP antibodies may be present in patients with psoriatic arthritis although it is possible that some of these patients have rheumatoid arthritis with concomitant psoriasis, in a proportion of them at least there are typical characteristics of psoriatic arthritis. The number of patients with psoriatic arthritis who have anti-CCP antibodies is greater than would be expected in view of the high specificity of the test.

ACKNOWLEDGEMENTS

Bert Vander Cruysen is supported by a research grant of the ‘Bijzonder Onderzoeksfonds’; Ghent University. The work of Leon De Rycke is supported by the ‘Vlaams instituut voor de bevordering van het wetenschappelijk–technologisch onderzoek in de industrie’ (IWTS/111277). Dominique Baeten is a senior clinical investigator for the Fund for Scientific Research-Vlaanderen (FWO-Vlaanderen).

Authors’ affiliations

B V Cruysen, I E A Hoffman, H Zmierczak, M Van den Berge, E Krutihof, I De Rycke, H Mielants, E M Veys, D Baeten, F De Keyser, Department of Rheumatology, Ghent University Hospital, 9000 Gent, Belgium

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Anti-citrullinated peptide antibodies may occur in patients with psoriatic arthritis


Ann Rheum Dis 2005 64: 1145-1149 originally published online February 4, 2005
doi: 10.1136/ard.2004.032177

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