The Role of Anti-Cyclic Citrullinated Peptide Antibodies in Predicting Progression of Palindromic Rheumatism to Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine whether the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies at presentation is of prognostic value in patients with palindromic arthritis.

Methods. Stored sera, taken around the time of presentation from patients with palindromic arthritis, where available, were assessed for anti-CCP antibodies, and results were correlated with subsequent clinical outcome.

Results. Twenty-nine of 61 patients had progressed to rheumatoid arthritis after a mean followup of 5.4 years; 83% of these had had anti-CCP antibodies in their baseline sera.

Conclusion. The sensitivity/specificity and likelihood ratios for CCP antibodies were better than rheumatoid factor in predicting outcome. (First Release May 15 2006; J Rheumatol 2006;33:1240–2)

Key Indexing Terms:
PALINDROMIC RHEUMATISM ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES
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Palindromic rheumatism (PR) was first described by Hench and Rosenberg[1] and has been well recognized since. Although common in our region, it is not given much space in standard textbooks. The disorder is defined by sudden short-lived attacks of arthritis (generally one to 3 days) often associated with swelling and redness, which subside spontaneously.

Several studies have shown this to be a syndrome in that a significant proportion of patients will progress to develop another connective tissue disease, but many do not[2]. Some enter remission.

We have previously shown in a retrospective study that 28 (34%) of the group studied at that time had progressed to rheumatoid arthritis (RA) after a mean duration of 6 years[3,4]. This was similar to the report of Guerne and Weisman[2]. We identified positive rheumatoid factor (RF) and hand involvement as risk factors for progression to RA.

Subsequently, we found that the immunogenetic risk profile for palindromic rheumatism resembles that for RA and that a significant gene-dose effect for shared epitope alleles is a risk factor for progression from PR to RA[5].

Salvador, *et al*[6] also recently suggested palindromic was a variant of RA based on their observation that anti-cyclic citrullinated peptide (anti-CCP) antibodies were found in 56% of patients with persistent PR, similar to the 55% found in patients with RA.

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We examined sera taken within one year of presentation to our clinic to determine if the presence of anti-CCP antibodies is predictive for this progression. Many of these patients were described in our previous reports, but many of the patients are not included here as an appropriate serum specimen was not available.

MATERIALS AND METHODS

Patients were selected from our database based on the presence of a stored serum specimen taken generally at the first visit for PR, and always within one year of presentation. Many were having regular followup every year, and those not seen within one year were contacted and reviewed in person. The serum aliquots had been stored at –70°C and not thawed.

The anti-CCP antibody test kit was supplied by Euroimmun (Lubeck, Germany) and the results were expressed as recommended by the manufacturer, semiquantitatively, as negative, positive, or strong positive[7].

The antinuclear antibody test was done in our laboratory as described[8]. RF tests were performed in the hospital laboratory using a commercial latex agglutination test.

For inclusion, patients were required to have had at least 3 attacks of self-limited pain and swelling in or around a joint, with at least one episode observed by a physician, and one episode that, by history, resolved spontaneously (i.e., < 7 days).

The likelihood ratios were calculated according to Sackett, *et al*[9].

This study was approved by the Ethics Review Committee of the Faculty of Medicine and Dentistry, University of Alberta. Prior patient consent had been obtained to store sera.

RESULTS

In total, 61 patients' sera were tested. Twenty-nine had progressed to RA (after a mean of 5.4 yrs, range 1–14 yrs); 3 of the other 32 had progressed, one to Behçet's disease, one to systemic lupus erythematosus, and one to psoriatic arthritis. The remaining 29 had either gone into remission, usually associated with continuing antimalarial drug therapy, or were having infrequent persistent attacks of PR — these patients

had been followed for a mean of 8.9 years (range 4 to 17 yrs). Thirty-one/61 patients had a positive test for RF. Thirty-four/61 patients had a positive test for anti-CCP antibodies and 33/55 tested positive for FANA. Thirty-nine had a positive test for either RF or anti-CCP antibodies.

We found 83% (24) of patients who had developed RA had positive anti-CCP antibodies at presentation. Sixty-six percent (19) had a positive RF test and 70% (20) a positive FANA. In 12 patients the anti-CCP antibodies and RF were discordant. Six of 9 patients with a negative RF and positive CCP developed RA, while 0/3 with a positive RF and negative CCP had progressed. Five of those 27 with a negative CCP antibody had progressed to RA (19%) (after a mean of 5.6 yrs, range 1–11). None of the 3 progressing to other disorders had a positive CCP antibody result. The sensitivity/specificity of positive or negative predictive values of the 3 tests[9] are shown in Table 1 in relation to the subsequent development of RA. None of these sera that were initially negative, but where the patient had developed RA, had become positive on retesting. A strong-positive anti-CCP test was found equally often among the positive tests seen in those patients who progressed to RA (17/24) as in those who did not (7/10).

DISCUSSION

Our results would indicate that a positive anti-CCP test in patients with PR within the first year of presentation suggests these patients should be warned of the markedly increased likelihood of developing RA. Any regimen that appears to maintain remission should therefore be continued. A negative test is more reassuring that continued treatment may not be necessary. While the anti-CCP test seems better than the RF finding, the best likelihood ratios were found using a combination requiring both a positive RF and positive anti-CCP test, rather than either one or the other positive, although this reduced the sensitivity of the tests.

The patients in this group were selected for study because of the availability of stored serum from the initial presentation. This may represent a degree of selection bias, but the progression to RA in 47% of our patients is similar to that described in the report by Salvador, *et al*[6].

The value of anti-CCP antibodies in predicting disease severity in patients with early RA seems established[10,11]; we had too few patients with negative tests who progressed to RA to allow comment on that aspect here.

The study from The Netherlands in particular[12] has shown that, in individuals who later developed RA, anti-CCP antibodies may be present for months or years prior to the disease onset. The sensitivity of the anti-CCP test for prediction of subsequent RA was slightly better than that of the RF test, but was not as good as the combination. Similarly, the 5-year positive predictive value was 96.6% for an anti-CCP test in their study group, from whom blood samples had been drawn before the onset of RA disease symptoms, while it was only 5.3% in the general population. It was consistently higher for anti-CCP than for IgM-RF in all groups. Our results, while consistent with those of Nielen, *et al*[12], are from a different population. Nevertheless, as the sensitivity and specificity of the test should be independent of the specific population studied, so should the likelihood ratios derived from the data. The predictive values are of course very dependent on the pretest probabilities, i.e., the specific case mix used for the study. Our results therefore may not even be generalizable to other groups of patients with PR.

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Table 1. Relative values of laboratory tests in predicting progression of palindromic rheumatism to RA.

	CCP	Rheumatoid Factor	Both Positive	Either Positive	FANA
Sensitivity	83	67	77	83	70
Specificity	68	61	84	53	47
Positive predictive value	71	60	81	62	48
Negative predictive value	81	61	81	77	68
Positive likelihood ratio	2.6	1.7	4.8	1.8	1.30
Negative likelihood ratio	0.12	0.54	0.27	0.32	0.65

CCP: cyclic citrullinated peptide, FANA: fluorescent antinuclear antibody test.

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