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Early Diagnosis of Rheumatoid Arthritis Combining the Japan College of Rheumatology Diagnostic Criteria for Detecting Rheumatoid Arthritis and Serum-level Anticyclic Citrullinated Peptide Antibodies

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Summary. Early diagnosis and treatment may prevent irreversible damage arising from rheumatoid arthritis (RA). However, the American College of Rheumatology (ACR) classification criteria has suggested difficulties with early diagnosis. While the Japan College of Rheumatology (JCR) diagnostic criteria for early RA may be useful, their low specificity implies inadequacy. Therefore, the combined use of serum-level of a anticyclic citrullinated peptide (anti-CCP) antibody test with JCR diagnostic criteria was evaluated. Seventy patients with recent-onset undifferentiated arthritis for 1.9 ± 2.7 months who did not meet the ACR 1987 classification criteria were evaluated in a prospective study. The patients were examined to determine whether they met the JCR diagnostic criteria and then tested for serum levels of anti-CCP antibodies. They were re-evaluated at one year after onset for the diagnosis of RA using the ACR classification criteria. All eight patients who met the JCR diagnostic criteria with positive anti-CCP antibodies were diagnosed RA, suggesting that the combination of these two items is highly likely to determine RA. Among nine patients with negative anti-CCP antibodies — but who met the JCR diagnostic criteria; namely three were diagnosed RA; the other hand, among eight patients who did not meet the JCR diagnostic criteria — but with positive anti-CCP antibodies, six were diagnosed RA; and among 45 patients who did not meet the JCR diagnostic criteria and exhibited negative anti-CCP antibodies, five progressed to RA. These findings suggest that a combination of the JCR diagnostic criteria and anti-CCP antibody test can improve the accuracy of early RA diagnosis.

Key words— rheumatoid arthritis, anti-CCP antibody, JCR criteria, diagnosis.

INTRODUCTION

Rheumatoid arthritis (RA), a systemic illness that primarily causes joint destruction, may be prevented by early diagnosis and treatment. Therapeutic strategies for the treatment of RA have changed significantly during the past decade. The pyramid therapy, which was conventionally used to treat RA, was reported to be inferior to early aggressive treatments using early disease modifying antirheumatic drugs (DMARDs).[1] The concept of a "Window of Opportunity," which refers to preventing disability and irreversible damage from RA through early diagnosis and intervention, has increased in

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Abbreviations – ACR, American College of Rheumatology; anti-CCP, anticyclic citrullinated peptide; JCR, Japan College of Rheumatology; RA, rheumatoid arthritis; RF, rheumatoid factor.

acceptance.[2,3] The American College of Rheumatology (ACR) 2002 treatment guidelines also recommend an early diagnosis of RA and the initial administration of antirheumatic drugs within three months from diagnosis.[4] The sensitivity and specificity of the ACR 1987 criteria, which are generally used in RA diagnosis, are 91.2% and 89.3% observed over period of several years, respectively, whether the patient's symptoms can meet four of the seven items that facilitate an RA diagno-sis.[5] However, an early diagnosis of RA remains troublesome. In patients with arthritis of recent onset who did not meet the ACR RA diagnostic criteria, however its sensitivity and specificity increased to 80.9% and 88.2%, respectively, at one year from onset, suggesting difficulties in an early diagnosis.[5]

The Japan College of Rheumatology (JCR) diagnostic criteria for early RA is defined by the presence of at least three out of the following six items: 1) joint pain or motion pain of three or more joints; 2) swelling of two or more joints; 3) morning stiffness; 4) rheumatoid nodules; 5) positive C-reactive protein, or 20 mm/hr or more of erythrocyte sedimentation rate (ESR); and 6) rheumatoid factor. While the JCR diagnostic criteria for early RA may be useful diagnostically, its sensitivity and specificity are 87.0% and 80.3%[6] in patients whose duration was less than two years after onset respectively, and the low specificity implies an inadequacy in an early RA diagnosis.

Schellekens[7] has reported that anticyclic citrullinated peptide (anti-CCP) antibodies are present in 76% of sera from RA patients and have a specificity of 96%. Moreover, the anti-CCP antibody has been studied as an autoantibody specific to RA blood serum. Earlier studies have reported a positive prediction of serum-level anti-CCP antibody in patients who met the ACR 1987 classification criteria.[8-13] Nevertheless the clinical significance of anti-CCP antibody has not resulted in its use as a diagnostic tool, since early treatment may be initiated upon RA diagnosis determined solely by the ACR 1987 criteria. Gaalen[14] has already reported the usefulness of anti-CCP antibodies in patients with undifferentiated arthritis in the Netherlands. The present study examined the usefulness of anti-CCP antibody detection combined with JCR diagnostic criteria for early RA diagnosis among Japanese patients who had joint symptoms at the initial examination and did not meet the ACR 1987 criteria.

PATIENTS AND METHODS

A prospective study was conducted with 70 patients who visited the rheumatology outpatient clinic from April 2005 to March 2006 with major complaints of arthralgia or joint swelling with recent onset, and who did not meet the ACR 1987 classification criteria.[4] The mean duration between onset and initial evaluation was 1.9 months (SD = 2.7 months). Patients included 13 males and 57 females, ranging from 17 to 78 years of age, for an average age of 51.2 years. Patients were registered in order of precedence and also observed the course of their condition.

At the initial examination, patients were tested to determine their serum-levels of anti-CCP antibodies and whether or not they met the JCR diagnostic criteria for early RA.The rheumatoid factor (RF) test was also included in the initial examination. The evaluation was based on whether the patient: 1) met the JCR diagnostic criteria for early RA[6] at the initial examination; 2) tested positive or negative for the anti-CCP antibody; and 3) was determined RA or non-RA in the post-observational final diagnosis (outcome) by the ACR criteria[4] at one year after onset of arthralgia or joint swelling. Sensitivities, specificities, and positive and negative predictabilities of the anti-CCP antibody and JCR criteria, anti-CCP antibody, and RF for RA diagnosis were examined. This study was approved by the Institutional Review Board of the Medical Faculty and informed consent was obtained from all patients.

Anti-CCP antibody levels were determined by the DIASTAT anti-CCP assay (cutoff level: 5 IU/ml), and RF was tested by the immunoturbidimetric assay (cutoff level:10 IU/ml). The occurrence of RA in patients who were tested for anti-CCP antibodies was used to calculate the odds ratio (OR) as well as the sensitivity, specificity, positive predictive value, and negative predictive value.

RESULTS

Seventeen patients met the JCR diagnostic criteria for early RA at the initial examination, of whom eight were anti-CCP antibody positive and nine were anti-CCP antibody negative. Of the remaining 53 patients who did not meet the JCR early diagnostic criteria, eight were anti-CCP antibody positive and 45 were anti-CCP antibody negative (Table 1).

Follow-up examinations revealed that, of those who were anti-CCP antibody positive, all eight patients who met the JCR diagnostic criteria for early RA and six of the eight patients who did not meet the diagnostic criteria met the ACR 1987 criteria for RA. The other two patients who were anti-CCP antibody positive at the initial examination and determined as non-RA at one year after onset included one patient with palindromic rheumatism and another with an undiagnosed ailment whose symptoms disappeared. Moreover, of the nine patients who were anti-CCP antibody negative but had met the JCR diagnostic criteria for early RA, six did not meet the ACR 1987 criteria for RA. These six patients included

Table 1. Positive predicatbility of rheumatoid arthritis (RA) outcome combined with JCR criteria and anti-CCP antibody at initial evaluation

JCR criteria	Anti-CCP Ab	Number at initial evaluation	Number of RA outcomes	RA rate (%)
+	+	8	8	100
+	−	9	3	33.3
−	+	8	6	75.0
−	−	45	5	11.1

Ab, antibody.

Table 2. The relationship between those patients with both JCR diagnostic criteria positive/anti-CCP antibody positive (n = 8), and without (n = 62), and outcome

JCR criteria and anti-CCP Ab at initial evaluation	Outcome	
	RA	Non RA
Both positive	8	0
Not both positive	14	48

Sensitivity, specificity, and positive and negative predictabilities of a combination of JCR diagnostic criteria and anti-CCP antibody for RA outcome were 36.3%, 100%, 100%, and 77.4%. Ab, antibody.

Table 3. The relationship between JCR diagnostic criteria at initial evaluation and ACR criteria at outcome

JCR criteria at initial evaluation	Outcome	
	RA	Non RA
Fulfilled	11	6
Not fulfilled	11	42

Sensitivity, specificity, and positive and negative predictabilities of JCR diagnostic criteria for RA outcome were 50.0%, 87.5%, 64.7%, and 79.2%.

Table 4. The relationship between only anti-CCP antibody reactivity at the initial examination and RA outcome

Anti-CCP Ab at initial evaluation	Outcome	
	RA	Non RA
Positive	14	2
Negative	8	46

Sensitivity, specificity, and positive and negative predictabilities of anti-CCP antibody for RA outcome were 63.6%, 96.0%, 87.5%, and 85.2%. Ab, antibody.

Table 5. Relationship between the results of the RF (rheumatoid factor) test at the initial examination and RA outcome

RF level at initial evaluation	Outcome	
	RA	Non RA
Positive	16	15
Negative	6	33

Sensitivity and specificity of RF test for RA outcome were 72.7% and 68.8%, and positive and negative predictabilities were 51.9% and 84.6%.

Table 6. Each item of JCR diagnostic criteria for early RA and anti-CCP Ab at initial examination, and RA outcome

JCR criteria item	Number at initial examination	Number of anti-CCP Ab Positive/negative	Number of RA outcomes
1) Positive (fulfill)	22	6/16	9 (6/3)*
Negative	48	10/38	13 (8/5)
2) Positive (fulfill)	24	5/19	12 (5/7)
Negative	46	11/35	10 (9/1)
3) Positive (fulfill)	16	4/12	7 (4/3)
Negative	54	12/42	15 (10/5)
4) Positive (fulfill)	0	0/70	0
Negative	70	16/54	22 (14/8)
5) Positive (fulfill)	14	5/9	7 (4/3)
Negative	56	11/45	15 (10/5)
6) Positive (fulfill)	32	14/18	15 (12/3)
Negative	38	2/36	7 (2/5)

Ab, antibody; ( )*, Number of anti-CCP Ab, positive/negative, at initial examination JCR items are as follows: 1) joint pain or motion pain of three or more joints; 2) swelling of two or more joints; 3) morning stiffness; 4) rheumatoid nodules; 5) positive C-reactive protein, or 20 mm/h or more of ESR; 6) RF.

Table 7. Positive predicatbility of RA outcome in the combination with anti-CCP Ab and RF at initial evaluation

Anti-CCP Ab	RF	Number at initial evaluation	Number of RA outcomes	RA rate (%)
+	+	15	13	86.7
+	−	1	1	100
−	+	18	3	16.7
−	−	36	5	14.4

Ab, antibody.

one with polymyalgia rheumatica, one with psoriatic arthritis, one with remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome, one with Still's disease, and two with other ailments.

Of the 45 patients who were anti-CCP antibody negative and had not met the JCR diagnostic criteria for early RA, five met the ACR 1987 criteria for RA. Forty patients who were anti-CCP antibody negative and JCR criteria negative at the initial examination were determined non-RA. These included two patients with palindromic rheumatism, two with polymyalgia rheumatica, three with collagen disorder including systemic lupus erythematosus (SLE), one with gout, three with monoarthritis, and 29 with osteoarthritis or other ailments. Eight patients who were anti-CCP antibody negative at the initial examination were determined RA, including three RF positive and five RF negative patients.

This study revealed a relationship between the JCR criteria and anti-CCP antibody results at the initial examination and RA outcome. The positive predictability of the combination of JCR diagnostic criteria and anti-CCP antibody results was 100% for positive JCR diagnostic criteria/positive anti-CCP antibody (n = 8), 33.3% for positive JCR diagnostic criteria/negative anti-CCP antibody (n = 9), 75% for negative JCR diagnostic criteria/positive anti-CCP antibody (n = 8), and the false negative rate was 11.1% for negative JCR diagnostic criteria/negative anti-CCP antibody (n = 45)(Table 1).

Table 2 shows the relationship between positive JCR diagnostic criteria/positive anti-CCP antibody (n = 8) and RA outcome as well as the relationship between all other combinations (n = 62) and RA outcome. The sensitivity, specificity, and positive and negative predictabilities of the combination of JCR diagnostic criteria for RA and anti-CCP antibody results were 36.3%, 100%, 100%, and 77.4%, respectively. All patients who were positive for both JCR diagnostic criteria and anti-CCP antibody progressed to RA.

Table 3 shows the relationship between JCR diagnostic criteria at initial examination and ACR criteria at outcome. The sensitivity, specificity, and positive and negative predictabilities of JCR diagnostic criteria for RA outcome were 50%, 87.5%, 64.7%, and 79.2%, respectively.

Table 4 shows the relationship between the reactivity of the anti-CCP antibody alone at the initial examination and RA outcome. The sensitivity, specificity, positive and negative predictabilities of anti-CCP antibody for RA outcome were 63.6%, 96%, 87.5%, and 85.2%, respectively. As expected from these data, the presence of anti-CCP antibodies was a significant risk factor for RA, with an OR of 40.3 (95% CI:19.9–81.4).

Table 5 shows the relationship between RF test results at the initial examination and outcome. Among the 22 RA patients, 16 were RF positive and six were RF negative. Moreover, of the 48 non-RA patients, 15 were RF positive and 33 were RF negative. As a result, the sensitivity and specificity were 72.7% and 68.8%, respectively, and the positive and negative predictabilities were 51.9% and 84.6%, respectively. IgM-RF positivity had an OR of 5.9 (95% CI 4.3–8.1).

Table 6 shows the relationship between each item of the JCR diagnostic criteria and anti-CCP antibody results at initial examination, and RA outcome. None of the patients had a rheumatoid nodule at initial examination. It is interesting to note that, of the 24 patients who had swelling of two or more joints and of the five patients who were anti-CCP antibody positive, 12 patients met the ACR 1987 criteria for RA outcome.

The positive predictability of the combination of anti-CCP antibody and RF for RA outcome was 86.7% for anti-CCP antibody positive/RF positive (n = 15), 100% for anti-CCP antibody positive/RF negative (n = 1), and 16.7% for anti-CCP antibody negative/RF positive (n = 18), and the false negative rate was 14.4% for anti-CCP antibody negative/RF negative (n = 36) (Table 7).

DISCUSSION

Early diagnosis and treatment for RA are essential in order to prevent joint destruction and subsequent dysfunction. The JCR diagnostic criteria have been used for early RA diagnosis in patients who are difficult to diagnose using the ACR 1987 criteria. The results of this study showed that, among 17 patients who received early diagnosis, 11 patients met the ACR criteria at one year after onset. Furthermore, 11 patients who did not receive early diagnosis met the ACR criteria at one year after onset. These findings suggest that the prediction of RA diagnosis is difficult when using only the JCR diagnostic criteria for recent onset RA. While the JCR diagnostic criteria for early RA may be useful diagnostically, its sensitivity and specificity are 87% and 80.3%,[6] respectively, compared to 50% and 87.5%, respectively, for the JCR criteria in this present study. One of the reasons for the low sensitivity in this study may be due to the difference in duration after onset. In this study, the mean duration was 1.9 months, while the JCR diagnostic criteria for early RA was reported based on patients whose duration was less than two years after onset. In our study, patients diagnosed with RA at one year after onset met the JCR criteria. Our study showed a higher specificity than the JCR diagnostic criteria reports. One of the reasons for the higher specificity in this study may be due to the small number of patients.

RF is one of the items used for RA diagnosis in both the ACR and JCR criteria. The reported sensitivity and specificity of RF are 80.4% and 87.0%,[5] respectively. Jacoby RK et al.[15] reported that conversion from RF

negative to positive was noted in 18% of early RA patients. Fifty percent of the RF negative patients became RF positive within the first year of the disease, 22% became positive during the second year, and the remaining 28% became positive at a later time. The sensitivity and specificity of RF in this study were 72.7 % and 68.8%, respectively.

Many studies have tried to achieve a more accurate diagnosis for early RA using metalloproteinase (MMP)-3, anti-agalactosyl IgG antibody, and anti-CCP antibody tests as well as magnetic resonance imaging (MRI) of the metacarpal phalangeal (MCP) joints.[8-12,16,17,18] In particular, the anti-CCP antibody test is believed to be one of the most prominent factors for early and accurate RA diagnosis.[13] Schellekens[7] reported that anti-CCP antibodies are present in 76% of RA patients, with a specificity of 96%. Earlier studies have indicated a higher specificity of anti-CCP antibodies (around or more than 90%) as compared to RF.[8,9,11] The sensitivity of the anti-CCP antibody test varies depending on the study, ranging from 33%[9] to 87.6%.[11] In this study, the sensitivity and specificity of the anti-CCP antibody test for RA outcome were respectively 63.6% and 96% values.

Gaalen et al.[14] reported the predictive value of the anti-CCP antibody test in patients with recent-onset undifferentiated arthritis. Their study showed that RA developed in 46 out of 249 patients (18%) with negative anti-CCP antibodies and in 57 of 69 patients (83%) with positive anti-CCP antibodies, after one year follow-up. At three years follow-up, 63 out of 249 patients (25%) with negative anti-CCP antibodies and 64 out of 69 patients (93%) with positive anti-CCP antibodies progressed to RA. They concluded that the presence of anti-CCP antibodies was a significant risk factor for RA, with an OR of 37.8 (95% CI: 13.8–111.9), which is similar to the OR of 40.3 (95% CI 19.9-81.4) found in this present study. Our data also showed that RA developed in eight out of 54 patients (15%) with negative anti-CCP antibodies and in 14 out of 16 patients (88%) with positive anti-CCP antibodies after one year follow-up. Gaalen et al.[14] also reported that multivariate analysis of the presence of anti-CCP antibodies and parameters from the ACR criteria identified polyarthritis, symmetric arthritis, erosion on radiographs, and anti-CCP antibodies as significant predictors of RA. In this present study, 12 out of 24 patients who had polyarthritis at initial examination developed RA, although only five patients were anti-CCP antibody positive at initial examination. X-rays of the feet were also reported to be good predictors for early RA diagnosis.[19, 20] Symmetric arthritis and erosion on radiographs, which were not included in the JCR criteria, should be carefully assessed. Anti-CCP antibody tests are effective for early RA diagnosis, though 15% (our data) to 25% (Gaalen) of anti-CCP antibody negative patients progressed to RA. In addition, the evaluation of arthritis or joint swelling was also important for RA diagnosis.

The present study showed that all eight patients who had positive JCR diagnostic criteria for early RA at the initial examination and who were anti-CCP antibody positive progressed to RA. The specificity and positive predictabilities of the combination of positive JCR diagnostic criteria/positive anti-CCP antibody were 100%. These patients should be treated with DMARDs upon initial examination. It should be noted that this study was conducted only one year after onset and a longer follow-up is needed to evaluate RA patients who progress in condition, as reported in previous studies.

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