Correlation between anti-cyclic citrullinated peptide antibodies and the severity of clinical manifestation, laboratory manifestation, and radiological joint destruction in rheumatoid arthritis patients

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ABSTRACT

Background. The second generation anti-cyclic citrullinated peptide test (CCP2) displays sensitivity comparable to that of rheumatoid factor (RF) (approximately 80%) but with superior specificity (98%) . Several observations have indicated that early rheumatoid arthritis (RA) patients with positive anti-CCP may develop a more erosive disease than those without anti-CCP.

Objective. The purpose of this cross-sectional study was to investigate the correlation between anti-CCP antibodies and clinical and laboratory parameters and radiological joint destruction in RA patients.

Methods. We studied 31 patients with RA fulfilling the 1987 revised criteria of American College of Rheumatology in Rheumatology Clinic of Saiful Anwar General Hospital, Malang, Indonesia. Clinical parameters were collected such as age, sex, visual analog scale, disease duration and diseases activity score (DAS28-3(CRP)). Laboratory parameters were WBC, hemoglobin, platelet count, erythrocyte sedimentation rate, and C-reactive protein. Analyzed autoantibody profiles were RF and anti-CCP (ELISA methode). Radiological joint destruction was evaluated from bilateral postero-anterior manus x ray (Sharp score).

Results. Anti-CCP antibodies were detected in 48.4% of RA patients with mean antibody concentration was 291.24±143.67 (range 16-523.8) units. Anti CCP level was significantly correlated with duration of RA (month) (p=0.04, r=0.371), RF level (p=0.002, r=0.542) and Sharp score (p=0.048, r=0.358), but was not significantly correlated with other clinical and laboratory parameters.

Conclusion. Anti-CCP level was correlated with duration of disease, RF, and Sharp score.

Rheumatoid Arthritis (RA) is a systemic autoimmune disease affecting about 0.5 - 1% of the adult population. The disease is characterized by joint inflammation that can lead to progressive joint damage and affect the quality of life.[1-4]

The course of RA is varied, ranging from mild to progressive forms. Availability of better prognostic markers would make it possible to select predictably severe cases for aggressive therapy at an early stage, while at the same time avoiding unnecessary exposure to the patients with mild disease. To identify the right patient for the right treatment, good predictor is needed.[5-10]

Antibodies against cyclic citrullinated peptide (anti-CCP) are a new and highly specific marker for RA.[2-4] Anti-CCP antibodies are now considered as an important serological marker for the diagnosis of RA and as a possible prognostic marker for the development of erosive disease.[8,9]

We investigated the correlation between anti-CCP antibodies and the severity of clinical manifestation, laboratory manifestation, and radiological joint destruction in RA patients in a cross sectional study.

METHODS

We included 31 patients with RA fulfilling the ACR criteria for diagnosis.[11] All of the patients are the outpatients of Rheumatology Clinic of Dr. Saiful Anwar General Hospital between April 2007 and Desember 2008 who had given their written informed consent.

Clinical evaluation of disease was based on sex, age, duration of disease, duration of DMARD (methotexrate) therapy, BMI, tender joint count, swollen joint count, visual analog scale. Disease activity was assessed by the 28 joint disease activity score (DAS28-3(CRP)).[12]

The patients had venous blood taken for full blood counts, erythrocyte sedimentation rates (ESR), renal and liver function, and C-reactive protein (CRP). Serum antibodies against cyclic citrullinated peptide were analysed using enzyme linked immunoadsorbent assay (ELISA). The result was expressed in units. The samples were considered positive if the antibody titer was greater than 20 U/ml. The Ig-M RF was examined with ELISA and the result greater than 8 IU/ml was regarded as RF positive.

Standardized postero-anterior radiograps of right and left hands were performed and radiographic damage was scored by one rheumatologist who had no information about the clinical and laboratory data of each patient using Sharp modified score.[13] In each case, 14 joints were scored for joint erosion and 13 joints were

scored for joint space narrowing. Each joint was scored from 0 to 3 for joint erosion and from 0-4 for joint space narrowing. The evaluated joints for joint erosion were interphalangeal (IP) I, proximal interphalangeal (PIP) II, PIP III, PIP IV, PIP V, metacarpophalangeal (MCP) I, MCP II, MCP III, MCP IV, MCP V, proximal of metacarpal I, distal of radius, distal of ulna, and multangulum, naviculare, lunatum, triquetrum as one joint evaluation. The evaluated joints for joint space narrowing were IP I, PIP II, PIP III, PIP IV, PIP V, MCP I, MCP II, MCP III, MCP IV, MCP V, proximal of metacarpal III/IV/V, multangulum/naviculare, lunatum-triquetrum, capitatum-naviculare-lunatum, and radiocarpal. Sharp score is the total sum of grading from joint erosion and joint space narrowing.

Spearman's correlation coefficient expressed the correlations between the assessed variables. Statistical significant was defined as p value of less than 0.05. All analyses were performed using SPSS program version 17 for windows.

RESULT

Patients characteristic

Rheumatoid arthritis patients in this study as many as 90.32% were female. Female to male ratio was 9:1 and the mean age was 51.2 years. The mean disease activity of RA base on disease activity score (DAS28-3(CRP)) was 3.18. Rheumatoid arthritis patients showing high disease activity was less than ones showing low disease activity (table 1).

Table 1 Patients characteristic

Patients characteristic	n=31
Female (%)	90,32
Age (year) (mean±SD)	51,19±12,03(20-70)
Duration of disease (month) (mean±SD)	56,35±102,64(1-444)
Duration of DMARD therapy (month) (mean±SD)	20,58±16,03(0-60)
BMI (kg/m^2) (mean±SD)	21,99±4,02(14,7-32,9)
Tender joint count (TJC) (mean±SD)	7,84±9,64(0-28)
Swollen joint count (SJC) (mean±SD)	4,87±5,65(0-24)
High disease activity (DAS>3,2) (%)	41,90
Low disease activity (DAS≤3,2) (%)	58,10
Ethnic Java (%)	

Hand joint arthritis, symmetric joint involvement, and morning stiffness were the main signs and symptoms of RA that had made patients looked for treatment (table 2).

Table 2 Clinical signs and symtomps in accordance with the 1987 revised criteria of American College of Rheumatology

Classification criteria	n	Proportion
Morning stiffness	27	87.10%
Hand joint arthritis	29	93.50%
Symmetric joint involvement	28	90.30%
Arthritis ≥ joints simultaneously	13	41.90%
Rheumatoid nodule	0	0%
Rheumatoid factor	18	58.10%
Radiographic changes consistent with rheumatoid arthritis	29	93.50%

Correlation between anti-cyclic citrullinated peptide antibody level and clinical manifestation, laboratory manifestation, and radiological joint destruction in rheumatoid arthritis patients

Using spearman's correlation test, Anti CCP level was significantly correlated with duration of RA (month), RF level, the number of joint erosion, and Sharp score (table 3, figure 1).

Table 3 Correlation between anti-CCP level and clinical, laboratory, and radiological damage

Variables	Correlation*	
	p	r
Age	0.848	0.036
BMI (kg/m^2)	0.582	0.103
Duration of RA (month)	0.04	0.371
Duration of therapy	0.268	0.205
Morning stiffnes	0.871	0.031
VAS (mean)	0.906	0.022
DAS (mean)	0.818	0.043
ESR(mm/1st hour)	0.190	0.242
CRP (mg/L)	0.861	0.033
RF (Unit)	0.002	0.542
JSE (0-78)	0.006	0.481
JSN (0-112)	0.236	0.219
Sharp score(0-190)	0.048	0.358

*Spearman's correlation test; TJC: tender joint count; SJC: swollen joint count; VAS: visual analogue scale; DAS: disease activity score; JE: joint erosion; JSN: joint space narrowing.

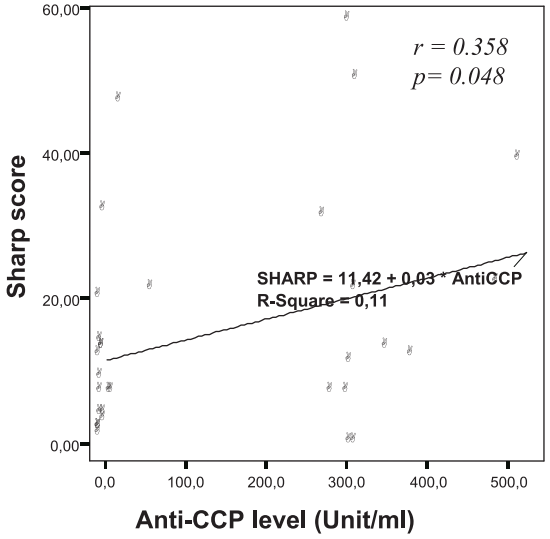

Figure 1 Correlation between serum anti-CCP level and Sharp score in rheumatoid arthritis patient

DISCUSSION

Female to male ratio in this study is higher than the known sex ratio (3:1).[14] Studies in Indonesia (6:1),[15] Malaysia (8:1),[16] Japan (12:1)[17] showed a similar sex ratio. The studies in population of established RA patients may involved in the hight sex ratio as showed in these study.

The mean age of patients in this study was 51.2 years with the mean age of onset was 46.6 years. This is consistent that the most RA often occurs in the fourth and fifth decade, 80% of patients got RA at the age of 35-50 years.[14]

In this study, anti-CCP antibodies and inflammation (CRP) were correlated with the degree of joint damage assessed by Sharp score, but anti-CCP antibodies were not correlated with the degree of inflammation and clinical manifestations. These finding led to assumption that anti-CCP causes joint damage not through the mechanism of inflammation. A prospective study by Lindqvist et al in 183 early-stage of RA patients, showed the role of anti-CCP, IgA, RF, anti-IL1, ESR, CRP, and cartilage oligomeric matrix protein in predicting damage to the hand and foot joints.[9] However, Serdaroglu et al showed that there was no significant difference or correlation in DAS, VAS, ESR, CRP, duration of disease, radiological damage of hands between the anti-CCP positive and anti-CCP negative RA groups.[18]

The important strategy to prevent joint damage in RA is to start therapy early in the disease course.[19-21] However, disease severity varies widely, and it is difficult to predict the course of the disease in each RA patient. Rheumatoid arthritis can be stable for a long time in some patients. The ability for early diagnosis and to predict a severe disease outcomes in patients with RA becomes very important. Therefore, sensitive and specific serological tests are needed to predict the development of erosive damage.[22-24]

Most of the study proved that a positive RF is an important predictor for joint damage over the years of disease. For the long term, RF positivity is associated with an unfavourable prognosis.[20] It appears that anti-CCP antibodies have prognostic relevance similar to RF.[2,8,25-30] Vencovsky et al found that anti-CCP positivity was better than RF at predicting progression of Larsen score over two years.[31] Also, in a prospective cohort study of 242 patients with early RA followed up for three years, the anti-CCP antibody results correlated with RF, but were better than RF as predictor of a more aggressive disease course. Kroot et al in a study of patients with early rheumatoid arthritis, found that anti-CCP positive patients at follow up had developed more significant radiological damage than patients without this antibody.[32]

We found in this study, the duration of DMARD therapy was not correlated with levels of anti-CCP antibodies. Some studies evaluate the correlation of anti-CCP positivity and anti-CCP levels with therapeutic response. They were generally performed on patients who have been diagnosed with RA who received DMARD therapy, particularly methotrexate and anti-TNF drugs, and showed a low correlation between the therapies and anti-CCP level and some indicators of disease activity as well.[33,34] In the largest study of this type, Ronnelid and colleagues followed 379 patients with RA under treatment for a total of 5 years. Anti-CCP positivity was reversed in only 3.9% of patients. There was a small but significant decrease in the mean anti-CCP level during the first year of treatment, and this decrease correlated with sulfasalazine treatment but not with other treatment agents. During the subsequent years of follow-up there was no significant change in anti-CCP levels, and no correlation between treatment response, disease activity, and anti-CCP levels.[35]

Our study limitation were using cross sectional study, uncontrolled duration of disease as confounding variable and less number of samples. Further investigations using cohort study, controlling duration of disease as confounding variable and involving more number of samples are necessary to show the prognostic value of anti-CCP.

CONCLUSION

Anti-CCP level was correlated with duration of disease, RF and Sharp score.

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