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Diagnostic Performance of Anti-Cyclic Citrullinated Peptide Antibodies in Rheumatoid Arthritis and Other Rheumatological Disorders

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A B S T R A C T

Anticyclic citrullinated peptide antibodies (anti-CCP) are considered specific markers of rheumatoid arthritis and have been included in the revised classification criteria for RA diagnosis. However, these antibodies have also been detected in patients with other rheumatological disorders is to identify the prevalence of positive anti-CCP patients in RA and non-RA rhematological diseases, to determine the diagnostic value of anti-CCP for the diagnosis of RA. An observational study was carried out in department of Microbiology at Dr. Ram Manohar Lohia Hospital, New Delhi over a period of 1 year. In 343 RA and 52 other rheumatological disease patients anti-CCP antibodies were determined. Anti-CCP antibodies were detected in 277 of the 395 patients. The prevalence of anti-CCP was 274/373 in RA, 1/4in patients with spondyloarthritis, 1/4 in patients with juvenile rheumatoid arthritis and 1/15 in patients with systemic lupus erythematosus. Anti-CCP are a hallmark of RA, but may be observed in other inflammatory, systemic, or rheumatological diseases.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease, characterized by chronic and erosive polyarthritis with abnormal growth of synovial tissue or pannus that eventually causes irreversible joint disability (Mimori *et al.,* 2005). Early diagnosis and treatment are needed to avoid unwanted complications of the disease.

However, patients with rheumatoid arthritis do not always show typical symptoms and signs early in their disease course, making diagnosis difficult at early stage (Mimori *et al.,* 2005). The serology test which is routinely used in RA is the determination of serum rheumatoid factor (RF) which has high and acceptable sensitivity, but has modest specificity due to presence in many other autoimmune disorders, non-rheumatic conditions, and in even healthy individuals (Miriovsky *et al.,* 2010 and Smolen *et al.,* 1996).

The more recent serological test for the diagnosis of RA is anti-cyclic citrullinated peptide antibodies which has been shown to be more specific than RF (Bizzaro *et al.,* 2001, Khan *et al.,* 2012 and Ioannis *et al.,* 2007). Anti-CCP antibodies are autoantibodies that are appear to be produced

in the inflamed synovium by local plasma cells (Alghuweri *et al.*, 2012). The sensitivity of anti-CCP antibodies for the diagnosis of rheumatoid arthritis varies from 50 to 75%, while the specificity is relatively high, usually more than 90% (Alghuweri *et al.*, 2012 and Nishimura *et al.*, 2007). Increased anti-CCP antibody levels are associated with disease progression, more severe disease and more radiological damage (Lee *et al.*, 2003, Egerer *et al.*, 2009 and Fathi *et al.*, 2008). Owing to diagnostic accuracy of anti-CCP antibodies, this serological parameter has been included in the new 2010 ACR/EULAR (American college of rheumatology/European league against rheumatism collaborative initiative) classification criteria for the diagnosis of rheumatoid arthritis (Longo *et al.*, 2012).

The objective of our study was to assess diagnostic performance of anti-CCP antibodies in patients with RA and other rheumatological disorders.

Materials and Methods

Our study group consisted of 343 RA patients (M/F: 1:3) fulfilling the ACR revised criteria and 52 patients with other rheumatological disorders like SLE, progressive systemic sclerosis, psoriatic arthritis, ankylosing spondylitis, reactive arthritis were also included in the study. All the patients were referred from the Department of Medicine, Dr. R.M.L. hospital during the period Sept 2015- Sept 2016. Blood samples of all study participants were collected in plain vacutainer vial after obtaining informed consent. Anti-CCP antibodies were detected by using a second generation commercial enzyme linked immunsorbent (ELISA) assay from Hycor biomedicals. The levels ≥5 U/mL were taken as positive. The assay was reliable up to concentrations of 300 U/ml; all values above that were analyzed as 300 U/ml. The samples were not diluted.

Results and Discussion

In total, anti-CCP determinations were performed for 395 patients, and positive results were obtained for 277 patients (70.13%).

Among the study population of 395 patients, 343 had RA, 6 PsA (psoariatic arthritis), 5 spondyloarthritis (SpA), 5 reactive arthritis, 10 ankylosing spondylitis (AS), 5 juvenile arthritis, 16 SLE (systemic lupus erythematosus), 2 SS (Sjogren's syndrome) and 3 unclassified connective tissue disorders (Table 1).

Anti-CCP antibodies were present in 274 patients with RA and 3 patients with other diseases. Anti-CCP tests were negative in 69 patients with RA and in 49 patients with other diseases. The sensitivity of anti-CCP antibodies for the diagnosis of RA in this population was thus 79.9%, specificity was 94.2%, positive predictive value was 98.9%, and negative predictive value was 41.5%.

In the patients positive for anti-CCP, mean anti-CCP level was 161.5 U/ml in patients with RA and 34.9 U/ml in patients with other rheumatological disorders (Table 2). Significant correlation was found in anti-CCP positivity between patients with RA and patients with other rheumatological disorders (p value < 0.01).

There is growing evidence that therapeutic intervention early in the course of RA can lead to a better prognosis. However, the diagnosis of RA is often difficult due to atypical presentation of patients. Moreover, many other rheumatic or immune diseases can also mimic the clinical presentation of RA. Clinicians have been particularly interested in the new serological test of anti-CCP antibodies, which appear to improve early diagnostic capacities as well as accuracy.

Our study helped us analyse the presence and levels of anti- CCP in 343 RA patients and 52 patients of other rheumatological disorders and thus assess the diagnostic performance of anti-CCP test in RA patients.

Table.1 Anti-CCP positivity in RA and other rheumatological disorders

DISEASE	POSITIVE	NEGATIVE
RHEUMATOID ARTHRITIS	274	69
SLE	1	15
AS	0	10
JIA	1	4
PSA	0	6
REACTIVE ARTHRITIS	0	5
SPA	1	4
MIXED CONNECTIVE TISSUE DISORDERS	0	3
SJOGREN'S SYNDROME	0	2

Table.2 Mean levels of anti-CCP in RA and other rheumatological disorders

SUBJECTS	ANTI-CCP LEVELS (MEAN)	NUMBER OF PATIENTS
Rheumatoid arthritis	161.5	343
Other rheumatological disorders	34.9	52

In our study population, anti-CCP antibodies were present in 79.9% of the patients with RA and 5.8% of the patients with other rheumatological disorders.

The three patients with other rheumatological disorders who were anti-CCP antibodies positive, had ankylosing spondylitis, SLE and juvenile arthritis. Previous studies have shown that anti-CCP antibodies can also be detected in a small percentage of patients with immune diseases other than RA like SLE, psoariatic arthritis, ankylosing spondylitis, systemic sclerosis and Sjogren's syndrome (Alenius *et al.,* 2006, Takasaki *et al.,* 2004 and Zhao *et al.,* 2009). The specificity and sensitivity of test was 79.9% and 94.2% respectively and the PPV was 98.9% and NPV was 41.5%.

The high specificity and moderate sensitivity of our study were consistent with the results of previous studies (Bizzaro *et al.,* 2001, Ioannis *et al.,* 2007; Quinn *et al.,* 2005 and Sakineh *et al.,* 2007). However, the low prevalence and levels of anti-CCP antibodies in other rheumatological disorders as compared to RA suggests that anti-CCP antibodies are a reliable marker for diagnosing RA and for distinguishing RA from other rheumatological disorders.

In conclusion, the anti-CCP antibody assay is a very valuable tool for the diagnosis of RA. Its low sensitivity does not allow its use as a screening test, but because of its high specificity, especially when high antibody concentrations are present, it becomes one of the most useful serologic tests for the diagnosis of RA.

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