



Anti-Cyclic Citrullinated Peptide Antibody: Diagnostic and Prognostic Biomarker of Rheumatoid Arthritis A Tertiary Care Study

DR JUNAID ANSARI, DR YOGESH LAKKAS
DR SOHEL MOMIN , DR SAQUIB MOMIN, DR ABID SHAIKH
JUNIOR RESIDENT, ASSOCIATE PROFESSOR
DEPARTMENT OF MEDICINE IIMSR JALNA

Abstract-

Foundation

RA that can be detected by serological tests, imaging techniques, or RA biomarkers. Anti-CCP antibody is a marker that can be detected very early in RA. TARGET

Research and test rheumatoid arthritis for anti-CCP antibodies in patients with symmetrical polyarthritis (polyarthropathy)

MATERIALS AND METHODS

Eighty-nine patients in the study were divided into two groups:

In the first group (RA patient), 36 patients met the ACR criteria for RA, and in the second group (non-RA), patients with symmetrical joint pain who did not meet the ACR criteria included 53 Patients.

This 89 patients underwent through clinical examination and disability assessment according to HAQ/disability index and VAS scores. Rheumatoid factor and anti-CCP antibody tests AND other routine laboratory tests were performed. The DAS 28 score was calculated using the DAS calculator and used to monitor drug therapy for treatment improvement.

Settings and design

A cross-sectional case-control study.

Results

A validation comparison showed that autoantibodies directed against citrullinated anti-CCP were better than RF in detecting RA. Anti-CCP antibodies have an independent role in predicting radiological lesions and progression in RA patients

SUMMARY

CRP, bone erosion, HAQ/disability index including VAS score, DAS 28 score parameter are useful in RA treatment and evaluation

Anti-CCP antibodies (APCA) have a high sensitivity and specificity in the diagnosis of RA (especially early RA) compared to rheumatoid factors, the titer does not correlate with disease activity.

Keywords

Anticyclic citrullinated peptide antibody (ACPA), rheumatoid arthritis, rheumatoid arthritis factor, visual analog scale ,C-reactive protein (CRP), 28-point disease activity score (DAS), Health Assessment Questionnaire score

INTRODUCTION

Arthritis is the most common cause. Rheumatoid arthritis is a systemic inflammatory disease that affects nearly 1% of the Indian adult population and is often characterized by circulating autoantibodies. Deformities are numerous and associated with significant morbidity and mortality. Despite this, the etiology of RA remains unknown and there is strong evidence for autoimmunity, as multiple autoantibodies are associated with the disease. Rheumatoid arthritis is mainly diagnosed according to the ACE criteria, which are mostly based on clinical symptoms and serological support. The serological marker included in the criteria is RF. Rheumatoid factor, an antibody directed against the constant region of IgG, is elevated in 75% of RA patients, but its diagnostic specificity for RA is poor because RF is present in many other rheumatic, non-rheumatic diseases and in the healthy elderly. Anticyclic citrullinated peptide autoantibodies called anticyclic citrullinated peptides (APCA) can also be seen in the serum of patients with RA. Anti-CCP antibodies are a better marker for the diagnosis and prognosis of RA because of their specificity. It also shows the development of the disease and can also predict its erosive or non-erosive progression. A serological parameter that meets these requirements is an anti-CCP antibody that binds antigenic determinants containing the unusual amino acid citrulline. Citrulline is a non-standard amino acid because it does not bind to proteins during protein synthesis. Early diagnosis and treatment are key to optimal outcomes in rheumatoid arthritis (RA), according to recent clinical studies. Unfortunately, their mechanical component does not respond to manipulation when deformations occur. Rheumatoid arthritis must be diagnosed early and treated with disease-modifying antirheumatic drugs (DMARDs) to successfully intervene in the disease process and prevent serious damage and injury. Diagnosing RA at an early stage, which can only be achieved with new serological tests, imaging techniques or RA biomarkers. Anti-CCP antibody is such a new serological marker that can be detected in very early RA.

TARGET

To investigate the correlation of rheumatoid arthritis specifically with anti-CCP antibodies I in all patients with symmetrical polyarthropathy.

Objectives

1. Assessment and evaluation of patients with rheumatoid arthritis according to clinical-serological criteria, Symmetrical Polyarthropathy Study Group.
2. To know the positive rate of RA factor and anti-CCP antibodies in patients with clinical RA who meet the ACR criteria or in patients with genetic RA who did not have clinical symptoms at the time of the study
3. Evaluation of the Health Disability Assessment Questionnaire (HAQ) and Visual Analogue Scale (VAS Score) in patients with rheumatoid arthritis
4. Assessment of disease activity in a patient with rheumatoid arthritis based on disease activity scores (DAS scores) using the DAS 28 calculator.

MATERIALS AND METHODS

Outpatients and inpatients, including male and female patients, who fully met the inclusion and exclusion criteria of the Department of Medicine, IIMSR, JALNA, MAHARASHTRA were studied. All participants were counseled and informed consent was obtained.

Study Design

Cross sectional study

Study population

Outpatients and inpatients at Department of Medicine , IIMSR Noor Hospital, Jalna.

Study period

1 year from June 2022 to June 2023

Sample size

Eighty-nine patients who met the inclusion and exclusion criteria were included in the study. Who complained of polyarthropathy

Inclusion criteria

1. Patient with any symmetric polyarthropathy meets ACR criteria for the diagnosis of RA (RA patients).
2. Includes males and females.
3. Including age group 15-65 years
4. A normal patient without symptoms of arthropathy but with a history of atopy or hereditary rheumatoid factor

Exclusion criteria

1. Patients who did not receive consent to participate in the study.
2. Patient with traumatic arthropathy.
3. Signs of septic arthropathy (h/o fever, infection).
4. Those where the investigation or follow-up could not be completed.

METHODOLOGY

All patients underwent laboratory and radiological examinations to obtain a diagnosis. Sera were tested for rheumatoid factor serotype (IgM) and anti-CCP antibodies. All patients underwent thorough clinical examinations and appropriate disability was assessed using the Health Assessment Questionnaire (HAQ) and Visual Analogue Questionnaire (VAS score).

Anti-CCP antibodies were tested by available enzyme-linked immunosorbent assay (ELISA) kit, whose reading >5 units considered positive according to the manufacturer's instructions. Radiographs of both hands and feet were performed using the modified Larsen score in patients with rheumatoid arthritis. Patients were classified into erosive and non-erosive disease. Rheumatoid factor was tested by latex agglutination for IgM and also by ELISA (Euroimmun, Germany) for IgG isotypes. The DAS 28 score was obtained with the DAS calculator and used to monitor drug therapy to ensure better control of RA cases.

Significance of the study:

1. The mean age of presentation in the RA group was 37.56 ± 10.9 years, compared with 41.98 ± 10.9 years in the non-RA group. It found that 87% of patients with rheumatoid arthritis were between 21 and 59 years old.
2. Bone deformities occurred in 48% of patients in the RA group. The most affected joints were wrist, MCP, hand PIP, knee joint.
3. 75% of patients presented within the first 5 years of the disease, of which 55% of patients belonged to the group of early RA patients.
4. 82% of the RA group there was significant morning stiffness present , while only 18% of patients in the non-RA group had morning stiffness indicates morning stiffness is a characteristic clinical feature of RA

5. RA group patients had most common painful joints as wrist (88%), MCP (86%) and PIP (86%) joints. DIP joints of the hands were spared in almost all the cases. In the non-RA group, the most common painful joints were the knee (84%), wrist (66%), MCP (49%), PIP (45%), and hand DIP joints (13%).
6. Extra-articular features observed in the RA group were: coronary heart disease 2 (4%), osteoporosis 3 (8%) rheumatoid nodule 3 (8%), interstitial pulmonary fibrosis 1 (2%),
7. Radiologically bone erosion was present in 49% of patients in the RA group compared with 14% of patients in the non-RA group. In the wrist of the RA group, the MCP joint of the hand was more involved, compared to the knee joint in the non-RA group. Erosion was not correlated with RA factor, anti-CCP antibody or CRP positivity
8. In the RA group, 59.17% of the patients were C-reactive protein (CRP) positive, while in the non-RA group, only 17% of the patients were CRP-positive.
9. RA group, 54% of patients had a significant disability complaining most of the time (HAQ score / disability index = 2) during daily activities, compared to only 15% of patients in the non-RA group with a similar disability.
10. In our study, the sensitivity of rheumatoid factor test = 66.7%, specificity = 91.5%, positive predictive value = 88.61%, negative predictive value = 78.22%.
11. Group of early RA patients in which disease duration less than 1 year, anti-CCP antibody test was positive in 87% of patients, compared to RF factor positivity in 50%. Similarly, in patients with less than 2 years of disease, the anti-CCP antibody test was positive in 82% of patients compared to 72% positive for RF factor, so the anti-CCP antibody test is very useful in the diagnosis of early RA. ACR criteria sometimes fails due to patients sometimes have lack of clinical signs.
12. In our study 52% of patients could detect antibodies against CCP antibodies in Seronegative RA (RF factor negative) group. Hence, anti-CCP antibodies serve as a better diagnostic marker than RF in the Indian population.
13. Our study found that the sensitivity of the anti-CCP2 antibody test was 83%, specificity = 100%, positive predictive value = 100%, negative predictive value = 87%.

DISCUSSION

Rheumatoid arthritis is a systemic autoimmune disease which is characterized by progressive joint damage seen on x-rays as bone erosion and joint narrowing. Post-translational modification of proteins been important in the development of autoimmune diseases such as rheumatoid arthritis.

Citrullination – Conversion of peptidyl arginine to peptidyl citrulline by peptidyl arginine deaminase this triggers formation of a newly discovered autoantibody system which can be effectively measured by cyclic citrullinated peptides (ccp) as antigens. This structural damage to the joints is irreversible, early recognition of stress and treatment aimed at halting the progression of the disease are now essential

The high specificity of anti-CCP antibodies in rheumatoid arthritis supports the importance of a modification process such as citrullination during RA early development. The main challenge in this field of medicine lies almost exclusively in the diagnosis of early phase RA, which can be overcome by serological tests, imaging methods or RA biomarkers. Anti-CCP antibodies can be detected very early in RA, although the sensitivity is slightly lower (40-60%), with a high specificity of approximately 96-98%. Anti-CCP shows promise as a good prognostic marker and can differentiate between erosive and non-erosive RA. Anti-CCP-positive RA patients develop significantly more radiological lesions than anti-CCP-negative patients, although anti-CCP with RF appears to be an even better prognostic marker]

Anti-CCP antibodies are associated with extra-articular diseases, especially nodules such as RF. This study compared the diagnostic specificity of anti-CCP antibodies in RA with patients with rheumatic diseases other than RA.

Similar study conducted by Bizzaro et al. found that anti-CCP antibodies are 41% sensitive and 97% specific for the diagnosis of RA compared to patients with other rheumatic diseases. The diagnostic specificity of anti-RA CCP antibodies found in our study is 98%, which is similar to previous studies. Anti-CCP antibodies tends to be less likely in non-RA group, suggesting that

a patient with joint pain who is positive for anti-CCP antibodies is more likely to have RA than some other rheumatic disease. Of the seronegative patients, 6 of 12 patients were also positive for anti-CCP antibodies. It follows that a positive anti-CCP antibody supports the diagnosis of RA when RF is negative in the appropriate clinical setting. Thus, anti-CCP antibody may be a better diagnostic marker for the diagnosis of RA, especially to identify the seronegative group. In the early RA population in our study group with disease duration less than 1 year, anti-CCP antibody test was positive in 87% of patients compared to 50% RF factor positivity. Compared to patients with less than 2 years of RA disease, 82% of patients were positive for anti-CCP antibodies compared to 72% positive for RF factor. Therefore, the anti-CCP antibody test is very useful in the diagnosis of early RA, where the ACR criteria may fail due to the lack of an obvious clinical feature. DAS 28 can help inform treatment decisions that can be made based on current DAS 28 values or changes in DAS 28 compared to pretreatment values.

The Health Assessment Questionnaire / HAQ score is a self-report measure of functional status (disability) and is a very useful tool in the study of arthritis. These new tools used to assess disease activity in RA are the Health Assessment Questionnaire (HAQ)/Disease Index, DAS 28, Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI). This helps doctors achieve an early diagnosis and continue follow-up

SUMMARY

The key to good outcomes for rheumatoid arthritis (RA) is early diagnosis and treatment.

The study also suggests an association of anti-CCP with radiological joint damage and progression. Anti-CCP antibody seems to be more sensitive and specific marker than RF in the diagnosis of RA .

Anti-CCP improves the ability of clinicians to make early and informed treatment decisions in clinical practice. Positive anti-CCP antibody and seronegative RA patients strongly support the diagnosis of RA, even if not all clinical features were present at the time of diagnosis. In this study, CCP antibodies were not useful for predicting severity in RA patients, although they may be a better diagnostic marker than RF in patients with severe arthritis. CRP, bone erosion, HAQ/disability index including VAS score, DAS 28 score are some other tools that can help in faster evaluation and treatment of patients with RA.

Drawback

1. Study sample size was conducted with a small group of patients with RA. Larger patient population is needed to determine their utility, effectiveness as diagnostic and prognostic markers
2. Challenges in patient monitoring for rheumatoid arthritis treatment. This reduces the effectiveness of DAS 28 scores and HAQ scores in future treatment strategy and management.

ACKNOWLEDGEMENTS

We express our word of mouth of thanks to Dr Azhar Siddique Dean, IIMSR ,Badnapur,Jalna and Management Of JIIU Specially Dr Ilyas Sir (CEO IIMSR) Dr Ishrat (Medical Superintendent IIMSR Noor Hospital).We are also thankful to Dr Sanjay Patne , Professor and Head Department of Medicine ,IIMSR ,Jalna for their guidance and support.

DECLARATIONS :

Funding : No funding sources

Conflict of interest : None

FEATURES	RA GROUP	NON-RA GROUP
NO. OF PATIENTS	38	58
RF-POSITIVE (%)	66.7%	7.5%
DISEASE DURATION IN MONTH (MEDIAN)	22	8
FEMALE (%)	84%	62%
AGE IN YEARS (MEAN±SD)	37.56±12.148	41.98±63.338
ANTI-CCP POSITIVE (%)	87%	0%
DAS 28 SCORE (MEAN±SD)	6.45±0.8647	NA
C-REACTIVE PROTEIN POSITIVE (%)	59.17%	17%
EROSIVE DISEASE, n (%)	18, (49%)	14%
EARLY RA	54.97%	NA
Anti-CCP titre (Median)	26.00	3.86
ESR mm1st hr (Median)	59.00	28 .00
EARLY RA	52.77%	NA
MORNING STIFFNESS (%)	82%	18%

Table 1 : Summary of Study Group findings

References

1. Silveira IG, Burlingame RW, von Muhlen CA, Bender AL, Staub HL. Anti-CCP antibodies have more diagnostic impact than rheumatoid factor (RF) in a population tested for RF. Clin Rheumatol 2007;26(11):1883–9
2. Stenger AA, van Leeuwen MA, Houtman PM, Bruyn GA, Speerstra F, Barendsen BC, et al. Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. Br J Rheumatol 1998;37:1157–63.
3. Bizzaro N, Bartoloni E, Morozzi G, Manganelli S, Riccieri V, Sabatini P, et al. Anti-cyclic citrullinated peptide antibody titer predicts time to Rheumatoid Arthritis Onset In Patients With Undifferentiated Arthritis: Results from a 2-year prospective study. Arthritis Res Ther 2013;15(1):R16. Available from: <http://arthritis-research.com/content/15/1/R16>
4. Usefulness of anti -CCP antibodies in rheumatic diseases in Indian patients, Rajiv Gupta, Molly M Thabah, Ritu Aneja, Ashok Kumar, Titus Varghese, PJ Chandrasenan Department of Medicine, All India Institute of Medical Sciences, New Delhi -110029, India, Indian journal of medical science
5. Serdaroglu, Kurbay, Deger, Cengiz, Kul. The association of Anti-CCP antibodies with disease activity in rheumatoid arthritis. Rheumatol Int 2008;28:965-70.
6. Shankar, Grover Handa. Role of Anti-Cyclic citrullinated peptide antibodies in erosive disease in patients with rheumatoid arthritis. Indian J Med Res. December 2006 689-96.
7. Eric-Jan JA, Kroot EJ, De Jong BA, van Leeuwen MA, Swinkels H, Van Den Hoogen FH, et al. The prognostic value of anti-cyclic citrullinated peptide antibody in patients with recent-onset rheumatoid arthritis. Arthritis Rheum. 2000 Aug;43

8. 1831-35. [6] Arnett, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988 Mar;31(3):315-24.
9. Mikuls TR, ODell JR, Stoner JA, Parrish LA, Arend WP, Norris JM, et al. Association of rheumatoid arthritis treatment response and disease duration with declines in serum levels of IgM rheumatoid factor and anti-cyclic citrullinated peptide antibody. *Arthritis Rheum.* 2004 Dec;50(12):3776-82
10. Khosla, Shankar, Duggal. Anti CCP antibodies in rheumatoid arthritis *J Indian Rheumatol Assoc* 2004;12:143-46
11. Subramanian M, Parthasarathy A. Analysis of rheumatoid factor and anti-cyclic citrullinated peptide in individuals with rheumatological disorders attending a tertiary care hospital. *Indian J Microbiol Res* 2019;6(2):123-5.

