JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

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

DR.NITHIN(JUNIOR RESIDENT)
DR.SHRINIVAS KULKARNI (PROFESSOR)
DEPARTMENTOF MEDICINE
(DR BALASABHEB VIKHE PATIL MEDICAL COLLEGE LONI)

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 Researchandtestrheumatoidarthritisforanti-CCPantibodiesinpatients withsymmetrical polyarthritis (polyarthropathy)

I. 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,asmultipleautoantibodies are associatedwith 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 thecriteria is RF. Rheumatoidfactor, anantibody directed against theconstant regionof IgG,is elevatedin 75% ofRA 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

3.1Population and Sample

StudyDesign Crosssectional study
Study population Outpatients and inpatientsat Department of Medicine,Dr balasaheb Vikhe patil Loni Studyperiod 1yearfrom June2022 toJune2023

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

Inclusioncriteria
1. Patientwith any symmetricpolyarthropathy meetsACR criteriafor the diagnosisofRA (RApatients).
2. Includes males andfemales.
3. Including age group15-65years
4. Anormalpatientwithout symptomsofarthropathybutwith ahistoryof atopyor hereditaryrheumatoidfactor

Exclusion criteria

1. Patients who didnot receive consent toparticipate inthe study.
2. Patient with traumatic arthropathy.
3. Signs of septic arthropathy (h/o fever, infection).
4. Thosewhere theinvestigation or follow-upcouldnotbe completed.

METHODOLOGY

All patients underwentlaboratory andradiological examinationsto obtaina diagnosis. Serawere testedfor rheumatoidfactor 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 DAS28score was obtained with the DAS calculator and used to monitor drug therapy to ensure better control of RA cases.

Significance of the study:

1. Themeanageofpresentation 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%oftheRAgroup there wassignificant 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 grouppatienst 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. GroupofearlyRA patientsinwichdiseasedurationlessthan1year,anti-CCPantibody testwaspositivein87%ofpatients, compared to RFfactor 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 coulddetect 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 thatthe sensitivity of the anti-CCP2 antibody test was 83%, specificity = 100%, positive predictive value =100%,negativepredictive 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– Coversion 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 medicinelies 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. Simialr 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%RFfactor positivity. Compared to patients with less than 2 years of RA disease, 82%of patients were positivefor anti-CCP antibodies compared to72%positivefor RFfactor. Therefore, the anti-CCP antibody test is very useful in thediagnosis 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 scoreis a self-report measure of functional status (disability) and is avery 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

Thekey togoodoutcomesforrheumatoidarthritis(RA)isearlydiagnosisandtreatment. 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 samplesize wasconducted with asmall groupofpatients withRA. Larger patient populationis 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 HAQscores in future treatment strategy and management..

ACKNOWLEDGEMENTS

We express our word of mouth of thanks to Dr Azhar Siddique Dean,IIMSR,Badnapur,Jalnaand 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 source

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

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