

CLINICO-SEROLOGICAL EVALUATION OF RHEUMATOID ARTHRITIS WITH SPECIAL REFERENCE TO ANTI-CYCLIC CITRULLINATED PEPTIDE (ANTI-CCP) ANTIBODY - A HOSPITAL BASED STUDY

R.K. Jha¹, Ashis Ranjan²

¹Professor, Department of General Medicine, RIMS, Ranchi.

²Ex. Resident, Department of General Medicine, RIMS, Ranchi.

ABSTRACT

BACKGROUND

The diagnosis of early-stage RA which can be accomplished with novel serological tests, imaging techniques, or RA biomarkers. Anti-CCP antibody is such a novel serological marker, which can be detected in very early RA.

AIM

To study clinicoserological evaluation of rheumatoid arthritis with special reference to Anti-CCP Antibodies in patients presenting with symmetrical polyarthropathy.

MATERIALS AND METHODS

Eighty nine patients included in study were divided into two groups: The first group (RA patient) fulfilled ACR criteria for RA include 36 patients and second group (Non-RA) patients with symmetrical joint pain not fulfilling ACR criteria contained rest 53 patients. All 89 patients underwent thorough clinical examination and disability assessment by HAQ/Disability index and VAS score. All patients were investigated for rheumatoid factor and anti-CCP antibody test (2nd generation) besides other routine baseline laboratory tests. DAS 28 Score was derived by DAS calculator and used to monitor drug therapy for better management of RA cases.

SETTINGS AND DESIGN

Case-control cross-sectional study.

RESULTS

In early RA group, patients with less than 1 year duration of illness. Anti-CCP antibody test was positive in 87% patients compared to 50% RF factor positivity. Similarly, patient with less than 2 year duration of illness, anti-CCP antibody test was positive in 82% patients compared to 72% RF factor positivity, so anti-CCP antibody test is very useful in diagnosis of early RA where ACR criteria may fail due to lack of apparent clinical feature. The mean DAS 28 score in RA group patient was 6.45±0.8647 at the time of presentation, which shows high disease activity according to EULAR response criteria.

CONCLUSION

Anti-CCP antibodies have high sensitivity and specificity for diagnosis of RA (especially early RA) compared to rheumatoid factors, but its titre did not correlate with disease activity. CRP, bony erosion, HAQ/Disability index including VAS score, DAS 28 score is very useful in overall evaluation and management of RA.

KEYWORDS

Anticyclic citrullinated peptide antibody, C-reactive protein, Disease Activity Score of 28 Joints, Health Assessment Questionnaire Score, Rheumatoid Arthritis, Rheumatoid Factor (IgM), Visual Analogue Scale.

HOW TO CITE THIS ARTICLE: R.K. Jha, Ashis Ranjan. "Clinico-serological Evaluation of Rheumatoid Arthritis with Special Reference to Anti-Cyclic Citrullinated Peptide (Anti-CCP) Antibody – A Hospital Based Study." Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 97, December 03; Page: 16245-16249, DOI: 10.14260/jemds/2015/2393

INTRODUCTION

Arthritis is the second leading cause of acute disability (Behind respiratory illness) and is the number one cause of chronic disability in the general population.^[1]

Rheumatoid arthritis (RA) is the commonest inflammatory joint disease affecting nearly 0.8%-1% (range 0.3-2.1%) of population worldwide.

Women are affected nearly three times more often than men.^[2] RA causes joint destruction and thus often leads to considerable morbidity and mortality.

Financial or Other, Competing Interest: None.

Submission 13-11-2015, Peer Review 14-11-2015,

Acceptance 26-11-2015, Published 02-12-2015.

Corresponding Author:

Dr. Ashis Ranjan,

Flat No-1A, Shanti Kamal Enclave,

Ashram Marg, Opposite Bariatu Firing Range,

Bariatu, Ranchi-834009, Jharkhand.

E-mail: ashis.jha98@gmail.com

DOI:10.14260/jemds/2015/2393

According to recent clinical studies, the key to achieving optimal outcomes in Rheumatoid Arthritis (RA) is to diagnose and treat it as early as possible. Unfortunately, once deformities are present, their mechanical component will not respond to medical therapy. The recognition that RA needs to be diagnosed early and treated promptly with Disease-Modifying Antirheumatic Drugs (DMARDs) to most successfully interfere with the disease process and its progression to major damage and disability has become a new paradigm.^[3,4] Therefore, the challenge in this area of medicine lies almost exclusively in the diagnosis of early-stage RA, which can be accomplished only with novel serological tests, imaging techniques or RA biomarkers.

Anti-CCP antibody is such a novel serological marker, which can be detected very early in RA. Although a number of studies have assessed the role of anti-CCP antibodies assay in the diagnosis of RA, the ability of this assay to differentiate an RA patient from another rheumatic disease patient has not been adequately addressed.^[5]

This study is possibly the first cross-sectional case-control study in this region of Jharkhand aimed to evaluate clinical evaluation of rheumatoid arthritis and role of serology, especially rheumatoid factor and newly discovered anti-CCP antibody in diagnosis.

AIM

To study clinicoserological evaluation of rheumatoid arthritis with special reference to anti-CCP antibodies in any patient presenting with symmetrical polyarthropathy.

OBJECTIVE

1. To evaluate rheumatoid arthritis patients by clinicoserological criteria in population studied with symptoms of symmetrical polyarthropathy.
2. Proper disability assessment by Health Assessment Questionnaire (HAQ) and Visual Analogue Scale (VAS Score) of RA patients.
3. In RA patient evaluation of disease activity by Disease Activity Score (DAS score) by DAS 28 calculator.
4. To know rate of rheumatoid factor and anti-CCP antibodies positivity in clinically RA (Fulfilling ACR criteria) patients or patients with genetic history of RA with no clinical features at the time of study.

MATERIALS AND METHODS

SUBJECT SELECTION

All outdoor and indoor patients including males and females in Department of Medicine, RIMS, Ranchi, after having met the inclusion and exclusion criteria were studied. All participants were counseled and an informed consent were obtained.

STUDY DESIGN - This was a single centre, cross-sectional case-control study.

STUDY AREA - Referred patients from Ranchi and peripheral parts of the Jharkhand, Bihar, West Bengal State.

STUDY POPULATION- The patients attending outdoor and indoor of Dept. of Medicine, RIMS, Ranchi.

STUDY PERIOD- 1 year.

SAMPLE SIZE- Eighty nine patients with complaint of polyarthropathy meeting inclusion and exclusion criteria were enrolled in the study.

Inclusion Criteria

1. Patient with some form of symmetrical polyarthropathy meeting 1987 revised ACR criteria for diagnosis of RA (RA patients).
2. Both sex included.
3. Normal patient with no symptom of arthropathy, but history of atopy or hereditary factor of RA.
4. Age group 15-65 years included.

Control Group Includes

5. Patient with some form of symmetrical polyarthropathy not meeting ACR criteria. (Non-RA patients).

Exclusion Criteria

1. Subjects unwilling to participate in the study.
2. Evidence of septic arthropathy (h/o fever, infection).
3. Those in which investigation or follow-up could not be completed.
4. Patient with history of traumatic arthropathy.
5. Patients with prominent asymmetrical arthropathy. We divided the patients of symmetrical arthropathy in two groups.

The first group (RA patient) fulfilled ACR criteria for RA which included besides clinical parameter, laboratory evidence of rheumatoid factor and bony erosion on x-ray. Total 36 patients were included in this group.

Second group (Non-RA) patients with symmetrical joint pain not fulfilling ACR criteria were included in this group. Total 53 patients were included in this group.

METHODOLOGY

All patients undergone thorough clinical examinations with proper disability assessment by Health Assessment Questionnaire (HAQ) and Visual Analogue Questionnaire (VAS score). We then performed basic laboratory, radiological investigations of all patients to come to diagnosis. Sera tested for sero subtype of rheumatoid factor (IgM) and anti-CCP antibodies in one sitting after the recruitment of patients was complete. Anti-CCP antibodies were tested by a commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kit, (Euroimmun, Germany), which is a second-generation anti-CCP assay.

A reading >5 units was considered positive as per manufacturer guidelines. Rheumatoid factor was tested by latex agglutination for the IgM isotype and also by ELISA (Euroimmun, Germany) for IgG isotypes. RA patients positive or negative for RF as tested by latex agglutination are termed as seropositive and seronegative respectively. Radiological assessment was done in radiographs of both hands and feet, using modified Larsen score in patients with RA. Patients were classified as having erosive and non-erosive disease. DAS 28 score was derived by DAS calculator and used to monitor drug therapy for better management of RA cases.

STATISTICAL ANALYSIS

Proper template was generated on MS Excel for data entry. Ten percent of data was randomly rechecked under supervision of my guide. Bivariate statistical analysis was performed using SPSS statistical software. The sensitivity and specificity were calculated for anti-CCP, RF factor. In order to compare the clinical characteristics in subgroups of RA and Non-RA group. Chi-square (χ^2) test was used for categorical variables. Student 't' test was used to compare means. Non-parametric tests (Mann Whitney) were used to compare variables which were not normally distributed and $P < 0.05$ was considered significant. Correlation between quantitative variable was assessed by Pearson correlation coefficient.

RESULT AND ANALYSIS

A total of 89 patients with symmetric polyarthropathy were included in the study, in which there were 36 patients in RA group and 53 patients in non-RA group. We compared characteristic of RA, non-RA group as shown in Table-1. Overall statistical analysis (Chi-square test, t-test and Mann Whitney test) of important parameter are shown in Table-2 and 3.

Main Findings of this Study are as Follows:

6. In RA group female:male ratio was 6:1, whereas in non-RA group female:male ratio was 2:1.
7. Mean age of presentation in RA group was 37.56 ± 10.9 years, whereas mean age of presentation in non-RA group was 41.98 ± 10.9 years. It was found in that 87% of RA patients were in the 25- to 54-year age group.
8. Median duration of illness was 24 months in RA group, whereas it was 6 months in non-RA group. It was found that 75% patients presented in the first 5 years of disease onset, out of which 55% patients came into group of early RA patients.

9. Significant morning stiffness was present in 84% in RA group, whereas in non-RA group morning stiffness was present only in 17% of patients, so morning stiffness is a distinguishing clinical feature of RA.
10. In RA group, bony deformity was present in 44% patients. Most affected joints were wrist, MCP, PIP of hand, knee joint. In non-RA group, bony deformity was present in 10% of patients mostly involving knee and wrist joint.
11. In RA group, most common tender joints involved were wrist (88%), MCP (86%), PIP (86%) joints of hand. DIP joints of hand were spared in all cases.
In non-RA group, most common tender joint involved were knee (84%), wrist (66%), MCP (49%), PIP (45%), DIP joints of hand (13%).
12. In this study, extra-articular feature in rheumatoid arthritis group noted were as follows: Rheumatoid nodule 3(8%), interstitial lung fibrosis 1(2%), ischemic heart disease 2(4%), osteoporosis 3(8%).
13. In RA group 56% patient had marked disability, complaining most of time (HAQ score/disability index=2) during daily activity in comparison to similar grade of disability in only 15% patients in non-RA group.
14. In RA group 58.77% patients were C-Reactive Protein (CRP) positive, whereas in non-RA group only 17% patients were CRP positive.
15. In RA group 47% patients had bone erosion on x-ray, whereas it was present in 11% patients in non-RA group. Among RA group wrist, MCP joint of hand were more involved, whereas in non-RA group knee joint were more involved. Erosion had no correlation with RA factor, anti-CCP antibody or CRP positivity.
16. Rheumatoid factor test in our study was found to have sensitivity=66.7%, specificity=92.5%, positive predictive value=85.71%, negative predictive value=80.32%.
17. Anti-CCP2 antibody test in our study was found to have sensitivity=83%, specificity=100%, positive predictive value=100%, negative predictive value=89%.
18. Among the seronegative RA (RF factor negative) group, antibodies to anti-CCP antibody could be demonstrated in 50% of patients. Thus, anti-CCP antibodies may serve as a better diagnostic marker than RF in Indian population.
19. In early RA group patients with less than 1 year duration of illness, anti-CCP antibody test was positive in 87% patients compared to 50% RF factor positivity. Similarly, patient with less than 2 year duration of illness, anti-CCP antibody test was positive in 82% patients compared to 72% RF factor positivity, so anti-CCP antibody test is very useful in diagnosis of early RA where ACR criteria may fail due to lack of apparent clinical feature. (Bar Diagram1).
20. Median titre of anti-CCP antibody test was 26 in RA group, whereas it was 3.86 in non-RA group. There was no correlation between anti-CCP titre and disease activity.
21. The mean DAS 28 score in RA group, patient was 6.45 ± 0.8647 at the time of presentation which shows high disease activity according to EULAR Response criteria.

DISCUSSION

Early and aggressive treatment of RA has become the most promising of the mentioned therapeutic strategies, as damage can be prevented and then sustained low disease activity or remission is achieved. Although, all efforts have currently been made to fortify the evidence around this concept, the

degree to which it is transposed and indeed established in daily practice remains uncertain.^[6]

Regarding the fact that exactly how much early is early rheumatoid, we have taken duration of 2 years as the cutoff. But there are several studies that have used 6 months or 1 year or even 3 months as the cutoff. The basis being that diagnosis as early as possible will lead to early therapeutic decisions and reduced joint related morbidity. Hence, some researchers are now using the term very early RA. Joint erosions start appearing by 2 years.

The challenge in this area of medicine lies almost exclusively in the diagnosis of early stage RA, which can be accomplished only with novel serological tests, imaging techniques, or RA biomarkers.

Anti-CCP antibodies can be detected very early in RA, although with a somewhat lower sensitivity (40–60%), but high specificity of about 96%–98%. Anti-CCP appears to be a good prognostic marker and has a high discriminating power between erosive and non-erosive RA. RA patients positive for anti-CCP develop significantly more radiological damage than anti-CCP-negative patients, although anti-CCP combined with RF appears to be an even better prognostic marker.^[7,8] However, anti-CCP antibodies are less strongly associated with extra-articular disease, in particular nodules than RF.

In this study, we compared the diagnostic specificity of anti-CCP antibodies in RA with respect to patients who have rheumatic diseases other than RA. Bizzaro et al. found anti-CCP antibodies to be 41% sensitive and 97% specific in diagnosing RA compared to patients with other rheumatic diseases.^[7] The diagnostic specificity of anti-CCP antibodies in RA found in our study is 100%, which is comparable to figures from previous studies. The low frequency of anti-CCP antibodies in the non-RA group, leads us to conclude that a patient with joint pain with anti-CCP antibodies positivity is most likely to have RA rather than a different rheumatic disease.

Six of the 12 seronegative patients were also positive for anti-CCP antibodies. Therefore, a positive anti-CCP antibody supports the diagnosis of RA when RF is negative in the appropriate clinical setting. Thus, anti-CCP antibody serves as a better diagnostic marker in the diagnosis of RA, especially to detect the seronegative group.

In early RA group in our study, patients with less than 1 year duration of illness, anti-CCP antibody test was positive in 87% patients compared to 50% RF factor positivity. Similarly, patient with less than 2-year duration of illness, anti-CCP antibody test was positive in 82% patients compared to 72% RF factor positivity. So anti-CCP antibody test is very useful in diagnosis of early RA, where ACR criteria may fail due to lack of apparent clinical feature.

The determination of anti-CCP antibodies is important for prognosis. Previous studies have found that anti-CCP antibody positivity is associated with higher probability of erosive disease in long-term follow-up studies.^[9] In our study, we found that anti-CCP antibody positive patients did not have any significant erosion on plain radiograph when compared with the anti-CCP antibodies seronegative group. This is probably because our study is cross-sectional and the sample size is small. Patients need to be followed up to see how they behave in the long run.

The DAS 28 can be very helpful in daily clinical practice. Treatment decisions can be based on current DAS 28 values or on changes in DAS 28 compared to values before the start of the treatment.^[10]

Health Assessment Questionnaire/HAQ Score was one of the first self-report functional status (disability) measures and has become the dominant instrument in many disease areas including arthritis. It is widely used throughout the world and has become a mandated outcome measure for

clinical trials in rheumatoid arthritis and some other diseases.^[11]

The Health Assessment Questionnaire (HAQ)/Disability Index, DAS 28 and other disease activity measuring methods like Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) are new tools for the evaluation of disease activity in RA. The comparative construct, content and discriminate validity of all three indices--the DAS 28, the SDAI and the CDAI--allow physicians to base their choice of instrument on their infrastructure and their needs and all of them can also be used in clinical trials.^[12,13]

CONCLUSION

The diagnosis of RA is a clinical one requiring a collection of historical and physical features as well as an alert and informed clinician. Unfortunately, there is no one single finding on physical examination or laboratory testing that is diagnostic of RA. According to recent clinical studies, the key to achieving optimal outcomes in rheumatoid arthritis (RA) is to diagnose and treat it as early as possible. Therefore, the challenge in this area of medicine lies almost exclusively in the diagnosis of early-stage RA, which can be accomplished only with novel serological tests, imaging techniques or RA biomarkers. Anti-CCP antibody is such a novel serological marker, which can be detected very early in RA.

A positive anti-CCP antibody is highly specific and moderately sensitive for RA patients. A positive anti-CCP antibody in seronegative RA patients strongly supports the diagnosis of RA serologically, even if all clinical features are not present at time of diagnosis. Anti-CCP antibodies were not useful in predicting the severity in RA patients in this study. Anti-CCP antibodies may serve as a better diagnostic marker than RF in Indian population, especially in patients with significant synovitis. It may also help in diagnosis of early RA or patients with undifferentiated arthritis. CRP, bony erosion, HAQ/Disability Index including VAS score, DAS 28 score is very useful in overall evaluation and management of RA.

LACUNAE

Among the many shortcoming of this study, a small size of the sample and absence of follow-up of patients on treatment to check efficacy of DAS 28 score, HAQ score on future treatment strategy demand particular mention.

REFERENCES

1. John B Imboden, David B Hellmann, John H Stone, MD, MPH, approach to arthritis: current diagnosis and treatment of rheumatology:2nd ed.
2. Wolfe AM: The epidemiology of rheumatoid arthritis: a review. I. Surveys. Bull RheumDis 1968;19:518-523.
3. Harrison BJ, Symmons DP. Early inflammatory polyarthritis: results from the Norfolk Arthritis Register with a review of the literature. II. Outcome at three years. Rheumatology (Oxford) 2000;39:939-49.
4. Wolfe F, Ross K, Hawley DJ, Roberts FK, Cathey MA. The prognosis of rheumatoid arthritis and undifferentiated polyarthritis syndrome in the clinic: a study of 1141 Patients. J Rheumatol. 1993;20:2005-9.
5. Kroot EJ, de Jong BA, van Leeuwen MA, Swinkels H, van den Hoogen FH, van't Hof M, et al. The prognostic value of anti-cyclic citrullinated peptide antibody in patients with recent-onset rheumatoid arthritis. Arthritis Rheum 2000;43:1831-5.
6. 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.

7. Bizzaro N, Mazzanti G, Tonutti E, Villalta D, Tozzoli R: Diagnostic accuracy of the anti-citrulline antibody assay for rheumatoid arthritis. Clin Chem 2001;47:1089-1093.
8. Usefulness of anti -CCP antibodies in rheumatic diseases in Indian patients, Rajiv Gupta, Molly M Thabab, 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, Year : 2009; Volume : 63, Issue : 3, Page : 92-100.
9. Vencovský J, Machacek S, Sedova L, Kafkova J, Gatterova J, Pesackova V, et al. Autoantibodies can be prognostic markers of an erosive disease in early rheumatoid arthritis. Ann Rheum Dis 2003;62:427-30.
10. The use of the disease activity score in the analysis of clinical trials in rheumatoid arthritis. Fuchs HA. J Rheumatol 1993 Nov;20(11):1863.
11. Pincus T, Callahan LF, Brooks RH, et al: Self-report questionnaire scores in rheumatoid arthritis compared with traditional physical, radiographic, and laboratory measures. Ann Intern Med 1989;110:259.
12. Health Assessment Questionnaire (HAQ) Stanford University School of Medicine Division of Immunology & Rheumatology.
13. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. clinexp rheumatol 2005 Sep-Oct;23(5 Suppl 39):S100-8.

FEATURES	RA GROUP	NON-RA GROUP
NO. OF PATIENTS	36	53
AGE IN YEARS (MEAN±SD)	37.19±11.148	42.06±13.428
DISEASE DURATION IN MONTH (MEDIAN)	24	6
FEMALE (%)	84%	62%
RF-POSITIVE (%)	66.7%	7.5%
ANTI-CCP POSITIVE (%)	83%	0%
Anti-CCP titre (Median)	26.00	3.86
ESR mm1st hr (Median)	60.00	24.00
VAS SCORE (MEAN±SD)	73.16±8.54	56.79±14.247
DAS 28 SCORE (MEAN±SD)	6.45±0.8647	NA
C-REACTIVE PROTEIN POSITIVE (%)	58.77%	17%
EROSIVE DISEASE, n (%)	17, (47%)	11%
EARLY RA (duration <2y)n,(%)	52.77%	NA
MORNING STIFFNESS (%)	84%	17%

Table 1: Summary of Observation for Study Groups

PARAMETER	T-value	df	P value
AGE	-1.792	87	0.713
DURATION	4.001	87	0.000*
VAS Score	6.186	87	0.000*
ESR	4.049	87	0.810
Anti-CCP Titre	4.158	87	0.000*

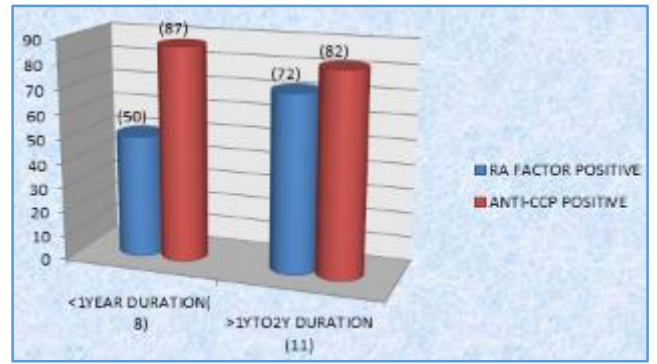
Table 2: T-Test in Study Group

*= statistically significant

PARAMETER	Chi-square value	P value
MORNING STIFFNESS	38.339	0.000*
HAQ SCORE	16.276	0.000*
CRP	16.604	0.000*
RA FACTOR	34.749	0.000*
Anti-CCP Test	66.664	0.000*

Table 3: Chi-Square Test in Study Group

*= statistically significant



Bar Diagram 1: RF Factor and Anti-CCP AB Positivity in Early RA