Publisher
MEDRESEARCH
www.medresearch.in

Tropical Journal of Pathology and Microbiology
2019 Volume 5 Number 7 July

E-ISSN:2456-1487
P-ISSN:2456-9887
RNI:MPENG/2017/70771

Research Article
Diagnostic

A retrospective case-control hospital based study on the diagnostic utility of anti-cyclic citrullinated peptide antibodies in comparison with rheumatoid factor, C-reactive protein and erythrocyte sedimentation rate as a diagnostic inflammatory biomarker of rheumatoid arthritis

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DOI: https://doi.org/10.17511/jopm.2019.i07.04

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Introduction: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease, characterised by persistent joint inflammation resulting in joint damage and disability. Diagnosis of RA is primarily on clinical manifestations and radiological findings due to lack of reliable diagnostic tests. As substantial joint damage occurs before patient presents clinically, a validated biomarker is required forits early detection. **Objectives:** To compare diagnostic utility of laboratory variables like anti–cyclic citrullinated peptide(Anti-CCP) antibodies, Rheumatoid factor (RF), C-reactive protein (CRP)and Erythrocyte sedimentation rate(ESR)in patients with Rheumatoid arthritis(RA). **Materials and Methods:** Blood from 80 clinically suspected RA patients and 80 age and sex matched healthy controls were tested for Anti-CCP antibodies, RF, CRP and ESR. Diagnostic properties of Anti-CCP in comparison with RF, CRP and ESR were statistically analysed and p value<0.05 was considered significant. **Results:** Anti-CCP was 100% positive in test group and 100% negative in control group with p value <0.001. Correlation between Anti-CCP and RF and Anti CCP and CRP showed significant titres with p value <0.001. Anti-CCP was 100% sensitive and 80% specific compared to RF. **Conclusion:** Anti-CCP is more sensitive and specific than other tests available for diagnosis of RA. Combined detection of all four parameters is valuable in confirming diagnosis of RA. Recognition of utility of such biomarkers is essential to gain insight into activity of this disease, which is vital for early management to limit consequential morbidity and to improve quality of life.

Keywords: Anti-CCP antibodies, Rheumatoid arthritis, Rheumatoid factor

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How to Cite this Article

Shamanna P, Arundhathi S, Kumar RP, Vanishree. A retrospective case-control hospital based study on the diagnostic utility of anti-cyclic citrullinated peptide antibodies in comparison with rheumatoid factor, C-reactive protein and erythrocyte sedimentation rate as a diagnostic inflammatory biomarker of rheumatoid arthritis. Trop J Pathol Microbiol. 2019;5(7):437-442.
Available From https://pathology.medresearch.in/index.php/jopm/article/view/285

To Browse

Manuscript Received	Review Round 1	Review Round 2	Review Round 3	Accepted
2019-06-12	2019-06-22	2019-06-20		2019-07-03

Conflict of Interest	Funding	Ethical Approval	Plagiarism X-checker	Note
No	Nil	Yes	6%	

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease, characterised by persistent symmetric poly-arthritis that results in joint destruction, deformity and decline in functional status. RA is the most common inflammatory joint disease, affecting 1-2% of world population, with female to male ratio of 2.5:1. The exact aetiology of RA remains a mystery, in spite of many years of intensive research. Besides environmental influences, like infectious agents, smoking and oral contraceptives, genetic factors are believed to play a pivotal role in pathogenesis of RA in approximately 60% of the patient population [1].

Appropriate intervention with effective treatment modalities alter the course of the disease, reduce functional impairment and can improve the quality of life. Thus, efficient biomarkers are needed for early diagnosis and to monitor the prognosis of the disease to determine better outcome [2].

Majority of chronic diseases have a gold standard test for diagnosis. There is no such similar standard reliable laboratory test for diagnosis of RA. The criteria to define RA used internationally was defined by American College of Rheumatology (ACR) in 1987 [3]. New criteria for RA classification (or diagnosis) were introduced in 2010 [4]. Anti CCP was included in the ACR/EULAR (European League against Rheumatism) RA classification criteria in 2010. Rheumatoid factor (RF) is another serological test along with acute phase reactant tests like Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) which are included in RA classification criteria [4].

Rheumatoid factor (RF) is an antibody specific for the FC portion of human immunoglobulin (IgG) which is considered as a marker for RA. It is one of the diagnostic criteria for RA established by the American College of Rheumatology (ACR) [5]. It is present in 75% of RA patients, but this antibody can also be detected in other autoimmune diseases, infectious diseases, in 3-5% of healthy population which increases to 10-30% in elderly illustrating that these antibodies are not very specific for RA [6].

Anti CCP antibodies represent a novel group of auto antibodies, currently under study, which has the highest specificity for diagnosis of RA [7]. The anti CCP antibodies are produced locally in inflamed synovium of RA patients [8, 9] and can be Detected very early in the course of RA and can therefore be helpful in early diagnosis and in limiting irreversible joint damage. But, its sensitivity is low and thus a negative test result does not exclude the disease. These antibodies are not detected in other diseases unlike RF and hence are more specific than RF in RA diagnosis and its confirmation [10]. Although C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) correlate with degree of joint inflammation and development of erosions, they are indicators of inflammation in general that may be influenced by other stimuli as an acute phase response [1].

The objective of this study was to analyse and compare the diagnostic utility of various modalities, including Anti CCP, RF, CRP and ESR in 80 blood samples collected from patients with RA and to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of anti-CCP in RA patients at Sanjay Gandhi Institute of Trauma and Orthopaedics (SGITO) Bangalore, Karnataka over a period of one year.

Materials and Methods

Setting: Department of Pathology and Microbiology, Sanjay Gandhi institute of trauma and orthopaedics, Bengaluru.

Type of study: A prospective case- control study conducted on 80 patients with rheumatoid arthritis and 80 healthy controls.

Sampling method: A prospective study was conducted from May 2017 to October 2018 on eighty patients with Rheumatoid arthritis fulfilling the revised criteria of the American College of Rheumatology and eighty age and sex matched healthy controls without history of inflammatory disease.

Sample collection: Blood samples obtained from such patients attending out- patient department at SGITO were tested for RA, CRP, ESR and Anti CCP in the department of Microbiology and Pathology.

Anti-CCP antibody titres was detected using a commercial Quanta Lite CCP ELISA, Anti CCP 2 kit (INOVA Diagnostics, San Diego, CA, USA). The normal cut off value for Anti CCP ELISA was 20IU/ml. A value >20 IU/ ml was considered positive. RF and CRP were measured by turbidometric immunoassay by Coral Clinical systems (Division of Tulip Diagnostics (P) Ltd).

The normal cut off value for RF was <20mg/dl and CRP was <0.6mg/dl. The quality controls were run regularly according to standard operating protocol. ESR was measured by Westergren's method and normal values for male and females were 0 to 10 mm and 0 to 20 mm respectively at the end of one hour.

Inclusion criteria: Cases: Subjects fulfilling revised criteria of American College of Rheumatology Controls: Healthy individuals without evidence of inflammatory disease

Exclusion criteria: Cases: Subjects not fulfilling revised criteria of American College of Rheumatology

Controls: Subjects with clinical and laboratory evidence of inflammation

Ethical clearance: Obtained

Statistical methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in numbers and percentages. Significance is assessed at 5% level of significance. The following assumptions on data were made, **assumptions: 1.** Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, and cases of the samples should be independent.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven`s test for homogeneity of variance has been performed to assess the homogeneity of variance.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups and non-parametric setting for qualitative data analysis. Fisher exact testis used when cell samples are very small.

Sensitivity, Specificity, PPV, NPV, Accuracy are computed to find the diagnostic properties of Anti-CCP with CRP RA factor and ESR

Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)

* Moderately significant (P value: 0.01<P £ 0.05)

** Strongly significant (P value: P£0.01)

Statistical software: The Statistical software namely SPSS 18.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Results

In the present study, 30 (37.5%) among cases and 25 (31.3%) among controls were in the age group of 41- 50 years followed by 21 (26.3%) among cases and 19 (23.8%) among controls were between 31 and 40 years. A small number constituted extremes of age in both groups (Table. 1). It was observed that there was female preponderance in both cases and control groups. Among cases 64 (80%) were females and 16 (20%) were males with female to male ratio being 4:1. Among controls 53 (66.3%) were females and 27 (33.8%) were males.

Out of 80 patients who were clinically suspected cases of RA only 75 had positive RF while all the 80 had positive Anti CCP. None of the controls were positive for RF/Anti CCP. Results were variable with respect to CRP and ESR. When a comparative evaluation of Anti-CCP vs RA factor and Anti CCP vs CRP and Anti CCP vs ESR was made, a positive correlation was seen in Anti CCP vs RA factor with P value <0.001 which was statistically significant. Also sensitivity and specificity were high 100% and 80% respectively.

Table-1: Age distribution among case and control groups

Age in years	Cases	Controls	Total
10-20	0 (0%)	4 (5%)	4 (2.5%)
21-30	10 (12.5%)	8 (10%)	18 (11.3%)
31-40	21 (26.3%)	19 (23.8%)	40 (25%)
41-50	30 (37.5%)	25 (31.3%)	55 (34.4%)
51-60	12 (15%)	16 (20%)	28 (17.5%)
61-70	6 (7.5%)	7 (8.8%)	13 (8.1%)
>70	1 (1.3%)	1 (1.3%)	2 (1.3%)
Total	80 (100%)	80 (100%)	160 (100%)
Mean ± SD	44.55±11.66	43.88±12.63	44.21±12.12

Samples are age matched P=0.726, student t test

Table-2: Gender distribution of subjects studied

Gender	Cases	Controls	Total
Female	64 (80%)	53 (66.3%)	117 (73.1%)
Male	16 (20%)	27 (33.8%)	43 (26.9%)

Total	80 (100%)	80 (100%)	160 (100%)

P=0.050*, Significant, Chi-square test

Table-3: Anti CCP, RA factor, CRP and ESR values in cases and control groups

	Test Group (n=80)	Control Group (n=80)	Total (n=160)	P value
Anti CCP				
· <20IU/ml	0 (0%)	80 (100%)	80 (50%)	<0.001**
· >20IU/ML	80 (100%)	0 (0%)	80 (50%)	
RA Factor				
· <20IU/ML	20 (25.0%)	80 (100.0%)	100 (62.5%)	<0.001**
· >20IU/ML	55 (68.8%)	0	55 (34.4%)	
· NA	5 (6.3%)	0	5 (3.1%)	
CRP				
· <0.6mg/dl	35 (43.8%)	65 (81.3%)	100 (62.5%)	<0.001**
· >0.6mg/dl	30 (37.5%)	13 (16.3%)	43 (26.9%)	
· NA	15 (18.75%)	02 (2.5%)	17 (10.63%)	
ESR				
· <10 for Male; <20 for female	10 (12.5%)	15 (18.8%)	25 (15.6%)	0.420
· >10 for Male; >20 for Female	62 (77.5%)	65 (81.3%)	127 (79.4%)	
· NA	08 (10%)	0	08 (05%)	

NA* – test results not available
Discrepancy in total numbers in the cases and control groups in CRP and ESR is due to non-availability of test results.

Table-4: Correlation of findings of Anti-CCP with RA factor, CRP and ESR

	Observation					Correlation					
	TP	FP	FN	TN	Total	Se	Sp	PPV	NPV	Accuracy	P value
Anti CCP vs RA factor	55	20	0	80	155	100.0	80.0	73.3	100.0	87.2	<0.001**
Anti CCP vs CRP	30	35	0	80	145	100.0	69.5	46.2	100.0	75.9	<0.001**
AntiCCP vs ESR	62	10	65	15	152	48.8	60.0	86.1	18.8	50.7	0.420

Discussion

Earlier, the diagnosis of RA had been primarily based on manifestations due to lack of reliable alternative tests. Approximately one third of the RA patients do not fulfil the ACR classification criteria, which makes the diagnosis of this disease difficult in the early stages [10]. Though RF test has been widely used routinely in the diagnosis of RA, the enhanced sensitivity and specificity and early prediction of joint damage have made the assay for Anti-CCP antibodies an attractive option. This study was performed in order to analyse the correlation of anti-CCP with other markers like RF factor, CRP and ESR and to evaluate their role in inflammation.

RA is the most common inflammatory arthritis affecting 0.5-1% of the general population worldwide with a male to female ratio of 1:2.5, may appear at any age, but commonly seen among those aged from 40-70 years [11].

In the present study, 37.5% of clinically suspected RA patients belonged to age group of 41-50 years with maximum patients in the age group of 31-50 years (63.8%) and male to female ratio being 1:4. Out of 80 patients who were clinically suspected to be suffering from RA, 75 had positive RF while all the 80 had positive Anti-CCP. None of the controls were positive for RF or Anti-CCP. The results were variable with respect to CRP and ESR.

When a comparative evaluation of Anti- CCP v/s RA factor, Anti- CCP v/s CRP and Anti -CCP v/s ESR was carried out, a positive correlation between Anti- CCP and RA factor with p value being <0.001, which was statistically significant strongly was noticed. In addition, sensitivity, specificity, PPV and accuracy were also high being 100%, 80%, 73.3%, 87.2% respectively. The results show that the diagnostic sensitivity of Anti- CCP antibodies in patients with recent onset RA is the same as that of RF and that seropositivity for the two tests correlate significantly.

Rongchun et.al., observed significant differences in concentration and positive rate of RF, anti CCP antibody, CRP and ESR between the RA and healthy control groups($p<0.01$). The specificity, sensitivity, and accuracy of RF and anti CCP antibody for the diagnosis of RA were74.4% vs 91%,87% vs 90.4%, and 88% vs 88.1% respectively. Their results showed that the specificity of RF was lower than that of anti CCP antibody ($p<0.01$) whereas there was no significant difference in sensitivity and accuracy between them [12]. The results were similar to Kim et al [13] and the percentages were greater than those detected by Al-Shukaili et al [14]. However, Garcia-Berrocal et al [15] and van Schaardenburg et al [16] reported lower sensitivities and specificities for Anti CCP-2 (43% vs 85% and 57.8% vs 94.2%, respectively). Such differences can be explained by the use of various ELISA kits with different cut off values. Lin et al in their study showed the sensitivity, specificity, PPV and NPV for anti CCP antibodies in diagnosing RA were 82.1%, 88.0%, 93.0% and 71.7% respectively and those for RF were 80.0%, 62.7%, 81.1% and 61.0% respectively [17].

There was strongly significant correlation between anti-CCP and CRP with p value being < 0.001. This shows that acute phase reactant protein like CRP was elevated in RA patients as compared to controls with a significant correlation observed with disease activity. Patients with RA show considerable variability in disease activity that can be difficult to predict at the onset of disease. The characterisation of acute phase reactants responses in RA is essential to gain insight into the activity of this disease and to assess the degree of inflammation. A study on the association between acute phase reactant response and the disease activity score concluded that CRP was elevated in RA patients as compared to controls with a significant correlation observed with the disease activity score [18]. In another study CRP was significantly higher in the anti CCP positive patients than in the anti-CCP negative group and the differences in disease activity measures between IgMRF positive and negative patients showed same tendency as with anti CCP [19].

Aotsuka et al, measured anti-CCP antibody in RA patients during the period 1982-2004 and found that anti CCP levels tended to fluctuate in parallel with ESR or CRP level [20]. A significant statistical correlation of Anti CCP with another inflammatory marker (ESR) was not observed.

Though RA is a disease defined by well accepted criteria, the clinical presentation and pathogenesis of this disease are varied and complex due to which prioritising diagnostic tests or predicting treatment responsiveness is not easy.

Conclusion

In conclusion, it can be stated that performing anti-CCP test in the diagnosis of RA could be beneficial since it has high specificity and PPV. If this test is performed together with RF, it may be more beneficial. From the present study it can be concluded that RF and Anti CCP antibody both are sensitive markers for diagnosis of rheumatoid arthritis. Although CRP and ESR are nonspecific for the diagnosis of RA, they are important auxiliary markers for the diagnosis of RA. Simultaneous detection of all the four markers is helpful for the confirmed diagnosis of RA.

Contribution from authors

Pratibha Shamanna: Data collection, data compiling, literature review, manuscript preparation, final approval. **Arundhathi. S**: literature review, manuscript preparation, manuscript editing, final approval. **Praveen Kumar R:** Data collection. **Vanishree:** Performing test

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