THE RELATIONSHIP BETWEEN THE CLINICAL MANIFESTATIONS AND THE PRESENCE OF ANTI CYCLIC CITRULLINATED PEPTIDE ANTIBODIES IN VERY EARLY RHEUMATOID ARTHRITIS

Ibrar Ahmed[1], Zafar Ali[2], Amjad Taqweem[3], Intekhab Alam[4], Amjad Mehboob[5]

ABSTRACT

Objective: *To establish whether the clinical presentation of anti-cyclic citrullinated peptide (Anti-CCP) antibodies and negative disease are distinct at the earliest clinically apparent phase of disease.*

Methodology: *Patients were seen in outpatient department of Lady Reading Hospital Peshawar from February 2009 to February 2011. Participants were included in the current study if they presented within 3 months of symptom onset and fulfilled 1987 ACR criteria for Rheumatoid Arthritis (RA) in the beginning or at some point during an 18 month follow-up. Data were collected on demographic variables and joint symptoms (tender and swollen joint counts). C- reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor and Anti-CCP antibodies status were measured.*

Results: *110 patients were included (57 were Anti-CCP antibodies positive). The Anti-CCP antibodies positive and negative groups were comparable in terms of demographic variables, inflammatory markers,tender and swollen joint counts and 1987 ACR classification criteria. Rheumatoid arthritis factor was detected more in Anti-CCP antibodies positive patients as compared with Anti-CCP antibodies negative patients.(83.3% vs. 35.8%). There was no significant difference in the pattern of joint involvement, except for an increased prevalence of knee joint swelling in Anti-CCP antibodies positive patients (56.1% vs.17.5%).*

Conclusions: *Patients with and without Anti-CCP antibodies present in a similar way, even within three months of clinically apparent disease that eventually develops into Rheumatoid arthritis.*

Keywords: *Anti-cyclic citrullinated peptide (Anti-CCP) antibodies, Rheumatoid arthritis (RA), American college of Rheumatology (ACR), C- reactive protein(CRP),erythrocyte sedimentation rate(ESR).*

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INTRODUCTION

Rheumatoid arthritis is a common systemic autoimmune disease affecting 0.5-1% of population[1,2]. It typically manifest as symmetrical polyarthritis.It is characterized by chronic inflammation of synovial joints which leads to progressive joint destruction and consequent disability and reduction in quality of life[3].

In the previous decades different auto antibodies were found in relation to RA. These auto antibodies were also present in other autoimmune diseases. These antibodies are RA factor, antiRA33[4-6], anti calpastin[7,8], anti nuclear cytoplasmic antibodies (ANCA)[9,10] etc. In the last decades some RA specific antibodies were found e.g. anti cyclic citrullinated antibodies.

These are established as important etiological and predictive factors in early RA[11-13]. Citrullination is a post translational modification[14] which may induce antibody formation in susceptible individuals[15]. It predates clinical arthritis by several years[16].

Anti cyclic citrullinated peptide antibodies are highly specific for RA but are not detectable in

[1-5] Department of Medicine, Lady Reading Hospital Peshawar- Pakistan

Address for Correspondence:
Dr. Ibrar Ahamed
Medical Officer,
Department of Medicine,
Lady Reading Hospital Peshawar- Pakistan
Email: ibrar2127@hotmail.com

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all patients[17]. So there may be distinct mechanism involved in the pathogenesis of synovitis in Anti CCP positive and negative patients such as smoking is a well recognized risk factor for Anti CCP antibodies positive patients[18]. These patients also shows more radiological destructions[19].

A recent study of RA patients presenting within 2 years of symptoms shows no clinical phenotypic differences according to anti CCP status[20]. It may be possible that as the RA evolves, regardless of anti CCP status it develop a common pattern of joint involvement. It is possible that the pathogenesis in the first few months may differ from those with longer duration disease and this phase is responsive to therapy[21,22]. So we attempted to elucidate whether the clinical presentation of anti ccp antibodies positive and negative disease were distinct at the earliest clinical phase of disease, within 3 months of symptoms onset.

METHODOLOGY

The study was performed in outpatient department of medicine department at lady reading hospital Peshawar from February 2009 to February 2011. Patients who were included were having symptoms of joint involvement like tenderness, swelling etc in the three months of their onset. These patients were then assessed according to the ACR criteria 1987 for RA[23] at the baseline.

Patients having established RA according to ACR criteria, on DMARDs, deforming arthritis and having side effects of DMARDs were excluded from the study. Data was collected from patients about clinical manifestations, fulfillment of ACR criteria, duration of symptoms and whether the onset was acute or insidious. Tender and swollen joint counts were performed. CRP, ESR, rheumatoid factor and anti CCP antibodies status were measured at baseline. Anti-CCP antibodies were detected with commercial enzyme-linked immunosorbent assay kits in accordance with the manufacturer's instructions. In brief, microtitre plates were incubated for 60 min at 22°C with serum samples diluted 1:100 in phosphate-buffered saline. Pre-diluted anti-CCP standards and positive and negative controls were added to each plate. All assays were performed in duplicate. After three washes, plates were incubated for 30 min at 22°C with alkaline phosphatase-labelled murine monoclonal antibody against human IgG. After three washes, the enzyme reaction was developed for 30 min and stopped with sodium hydroxide–EDTA–carbonate buffer, and plates were read (SPECTRA II; SLT Lab instruments, Grödig, Austria) at 550 nm. Anti-CCP antibodies were considered to be positive when the absorbance was higher than the cut-off of the kit (5 U/ml). The concentration of anti-CCP antibodies was estimated by interpolation from a dose-response curve based on standards.

RF was assayed with a quantitative immunonephelometry test . RF was considered to be positive when the concentration was higher than the cut-off value of the kit (15 IU/ml). Radio-graphs of the involved joints were performed.

Different categorical variables between the antiP antibodies positive and negative groups were compared using the chi square test and continuous variables were compared using the t-test. Data was analyzed using Statistical Package for Social Sciences version 17. P values of $<.05$ was considered significant.

RESULTS

A total number of 310 patients with initial symptom duration of less than 3 months were included in this study. Of them a total of 110 patients who fulfilled 1987 ACR criteria for RA at baseline or at some point during follow up were included in the study. The mean age of the patients included in the study was 41.77±8.68. 57 patients were anti CCP antibodies positive while 53 patients were anti CCP antibodies negative. Forty three of the patients were treated with DMARDs because of the severity of disease. Rest of patients were stable with NSAIDs.

Both of the patients groups were comparable in gender, age and disease severity status. Patients had similar duration of symptoms and mode of onset. There was no significant difference in the presence of duration of morning stiffness between the two groups of patients as shown in Table 1.

In anti CCP antibodies patients' presence of RA factor was more likely present as compared to patients with anti CCP antibodies negative patients (84.2% vs 60.4%). The patients who were anti CCP positive met more than 4 criteria for the diagnosis of RA in about 73.7% as compared to 52.8% of patients of anti CCP negative patients. There was no significant difference in the total number of tender and swollen joint count. Inflammatory markers were comparable in both groups of patients. Among different joint groups involvement the involvement of knee joint involvement was more in anti CCP antibodies positive patients as compared to anti CCP negative patients.

DISCUSSION

This study shows that RA patients with and without anti CCP antibodies presents similarly even within three months of onset of clinical presentation. It was believed that anti CCP positive

Table 1: Clinical manifestations of patients with anti CCP positive and Negative patients

	Anti CCP Positive (n=57)	Anti CCP Negative (n=53)	p-value
Female	63.2%(36)	50.9%(27)	0.196
Smoking status	71.9%	66%	0.504
Symptom Duration(days)	68.98±12.71	67.23±12.46	0.84
Mode of onset			
Acute	59.6%	45.3%	
Insidious	28.1%	41.5%	0.282
Unspecified	12.3%	13.2%	
Morning Stiffness duration(min)	85.72±16.36	67.23±16.78	0.760
Symmetry	71.9%	64.2%	0.381
Hand Joints involvement	78.9%	60.4%	0.034
≥ 3 Joints involvement	80.7%	73.6%	0.373
Rheumatoid factor	84.2%	35.8%	0.005
Fullfilling = 4 cieteria	73.7%	52.8%	0.023
Tender joint count	11.58±4.37	11.09±4.161	0.64
Swollen joint count	6.07±3.32	5.48±2.8	0.397
ESR	58.68±14.173	57.96±15.4	0.391
CRP	35.26±9.54	36.3%±1.183%	0.622

and negative states had different clinical presentations. They have different molecular mechanisms as well as different genetic and environmental predisposition and clinical progression.

Similar to other previous studies of patients presenting with 2 years regardless of the above pathological differences our data also shows similar clinical manifestations of RA regardless of anti CCP antibodies status. These patients had similar distribution of joint diseases as well as comparable age of onset and levels of inflammation. The group of patients having positive anti CCP antibodies fulfills the ACR criteria more as compared to the other group. This is due to the fact that anti CCP antibodies more often express RA factor[24].

This study may have limitations. As there is evidence that anti CCP antibodies and rheumatoid factor are associated with delayed presentation in patients with RA[25,26]. This observation may raise the possibility, that patients were not seen early for inclusion in the study, so this study may have selection bias.

This study showed an increased likelihood of Knee involvement in patients with anti CCP antibodies. This finding is consistent with results of previous studies which shows anti CC antibodies patients had increased radiological destruction[27]. Our data supports previously reported data which shows involvement of knee joints in patients who are anti CCP antibodies positive.

CONCLUSION

In summary anti CCP antibodies positive and negative patients have similar baseline presentation. It does not negate the fact that anti CCP had a role in pathogenesis of RA.

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CONTRIBUTORS

IA conceived the Idea, collected & analyzed data & wrote the first draft. ZA helped in formulating questionnaire and data collection. AT helped in basic concept of the study, data collection and revision of the article. IA and AM helped in data collection and writing the article.

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None Declared