International Journal of Advances in Medicine
Yadav RK et al. Int J Adv Med. 2020 May;7(5):804-808
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20201615

Original Research Article

Anti- cyclic citrullinated peptide antibodies in tuberculosis and human immunodeficiency virus

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Received: 24 February 2020
Accepted: 27 March 2020

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ABSTRACT

Background: Anti-cyclic citrullinated peptide (anti-CCP) antibodies have been considered very specific for rheumatoid arthritis (RA). Some studies have shown that these antibodies can be positive in infectious diseases like tuberculosis, human immunodeficiency virus infection, etc.
Methods: Eighty patients of tuberculosis both pulmonary and extra-pulmonary tuberculosis and thirty patients of human immunodeficiency virus were enrolled in this study from inpatient and outpatient departments from September 2018 to August 2019. Anti-CCP antibody test was done in all the patient by enzyme linked immunosorbent assay.
Results: Fifty-three patients were of pulmonary tuberculosis, 27 patients were extra-pulmonary tuberculosis and 30 patients were human immunodeficiency virus infection. Of the 53 cases of pulmonary tuberculosis, 21 (39.6%) cases were positive for anti-CCP antibodies and 32 (60.4%) cases were negative for the same. Of the 27 cases of extra-pulmonary tuberculosis, 3(11.1%) cases were positive for anti-CCP antibodies and 24 (88.9%) cases were negative. Of the 53 patients of pulmonary tuberculosis, 16 were sputum positive and 37 were sputum negative. Of those with sputum positive 9 (56.2%) cases were positive for anti-CCP antibodies and those with sputum negative, 12 (32.4%) cases were positive for anti-CCP antibodies. Of the 30 cases of human immunodeficiency virus, 5 (16.7%) cases were positive for anti-CCP antibodies and 25 (83.3%) cases were negative.
Conclusions: Anti-CCP can be positive in cases of infectious diseases like tuberculosis and human immunodeficiency virus. Positivity of anti-CCP antibodies for tuberculosis is more for pulmonary (more for sputum-positive than sputum-negative) than extra-pulmonary tuberculosis. Anti-CCP, thus is not very specific for rheumatoid arthritis.

Keywords: Anti cyclic citrullinated peptide antibody, Human Immunodeficiency Virus, Tuberculosis

INTRODUCTION

Anti-cyclic citrullinated peptide (anti-CCP) are a family of antibodies belongs to the IgG class of antibody against amino acid 306-324, where arginine is replaced with citrulline at the position 321.[1] Post translation modification of arginine to citrulline is carried out by the enzyme peptidyl arginine deiminase.[2] Anti-cyclic citrullinated peptide (anti-CCP) antibodies has been used extensively as a new serologic marker of rheumatoid arthritis (RA).[3] Many studies have confirmed that anti-CCP is as sensitive as rheumatoid factor (RF) and much more specific for rheumatoid arthritis (RA). Recently anti-CCP antibodies have been detected in patients suffering from infectious diseases like tuberculosis (TB), human immunodeficiency virus (HIV), leprosy, leishmaniasis and others.[4] There is data reported from Japan, Israel, Brazil, India, South Africa and Europe

about anti-CCP positivity in tuberculosis and human immunodeficiency virus. Its positivity in infectious diseases like tuberculosis and human immunodeficiency virus infection could not be ignored, especially in a country like India where tuberculosis is highly prevalent. Hence, this study was designed to determine the positivity of anti-CCP antibodies in tuberculosis and human immunodeficiency virus.

This study will be conducted to determine the prevalence of anti-CCP antibodies in tuberculosis and Human immunodeficiency virus infection, and to compare pulmonary and extra-pulmonary cases of tuberculosis with their anti-CCP values.

METHODS

This was a cross-sectional observational study done at the Moti Lal Nehru Medical College Prayagraj and associated Swaroop Rani Nehru hospital in Prayagraj, India. The study protocol was approved by the Institutional Ethics Committee of MLN Medical College and Associate Hospitals Prayagraj. 110 patients were enrolled in the study between September 2018 to August 2019.

A written informed consent was taken from each patient. Patients suffering from pulmonary or extra-pulmonary tuberculosis and human immunodeficiency virus infection were selected from inpatient wards and outpatient department of Swaroop Rani Nehru hospital. The diagnosis of tuberculosis was made on the basis of clinical features, radiology, sputum smear examination for acid fast bacilli by Ziehl Neelson staining and culture, pleural fluid staining and culture, pleural fluid, cerebrospinal fluid reports and fine needle aspiration cytology of lymph-nodes demonstrating the histopathology of tuberculosis. Diagnosis of HIV was made by enzyme linked immunosorbent assay for human immunodeficiency virus.

Patients with inflammatory arthritis were excluded. Complete blood counts, liver and renal function tests, serum electrolytes were done on each patient. Chest X-rays, pleural fluid analysis, ultrasound thorax and abdomen, CT scan of brain, thorax or abdomen, MRI brain, sputum for acid fast bacilli, cerebrospinal fluid analysis and culture of Mycobacterium tuberculosis were done as per individual patient's requirement for the diagnosis of tuberculosis.

Anti-CCP antibody was tested by ELISA on each patient and results were obtained with specific titres. The titres of >5 U/ml were considered positive as specified by the laboratory (<5.0 U/ml negative as per the laboratory range).

Statistical analysis with Chi Square test was applied using SPSS software version 19 to compare the correlation between pulmonary and extra-pulmonary cases of tuberculosis and their anti-CCP values. There was a statistical significance while comparing the pulmonary and extra-pulmonary tuberculosis cases as regards to anti-CCP antibodies ($p < 0.05$).

RESULTS

Eighty patients of tuberculosis and thirty patients of human immunodeficiency virus infection were enrolled in the study. In tuberculosis, 53 were diagnosed to have pulmonary tuberculosis and 27 were extra-pulmonary tuberculosis. The distribution of the total cases with their anti-CCP is shown in Table 1.

Table 1: Anti-CCP antibody and total cases.

Diagnosis	Anti-CCP antibody					
	Positive		Negative		Total	
	N	%	N	%	N	%
Pulmonary tuberculosis	21	39.6%	32	60.4%	53	100.0%
Extra-pulmonary tuberculosis	3	11.1%	24	88.9%	27	100.0%
HIV	5	16.7%	25	83.3%	30	100.0%
Total	29	26.4%	81	73.6%	110	100.0%

Pulmonary tuberculosis was subdivided based on sputum positivity for acid fast bacillus. Table 2 shows the distribution of pulmonary tuberculosis cases as regards anti-CCP antibodies. Of the 53 patients of pulmonary tuberculosis, 16 were sputum positive and 37 were sputum negative. Of the sixteen sputum positive, nine (56.2%) were positive for anti-CCP antibodies and seven were negative. Out of 37 sputum negative, 12 (32.4%) were positive for anti CCP antibodies.

Thus anti-CCP positivity was more in sputum-positive than sputum-negative tuberculosis in this study. In total anti-CCP antibodies were positive in 21 (39.6%) cases of pulmonary tuberculosis and negative in 32 (60.4%) cases.

Table 2: Anti-CCP positivity in pulmonary tuberculosis.

Pulmonary tuberculosis: sputum status	Anti-CCP antibody					
	Positive		Negative		Total	
	N	%	N	%	N	%
Positive	9	56.2%	7	43.8%	16	100.0%
Negative	12	32.4%	25	67.6%	37	100.0%
Total	21	39.6%	32	60.4%	53	100.0%

Table 3 shows the distribution of extra-pulmonary tuberculosis cases as regards anti-CCP antibodies. Due to a smaller sample size of individual extra-pulmonary tuberculosis cases, no concrete conclusions can be drawn. However, this is an eye-opener to conduct further research in this field.

Table 3: Anti-CCP positivity in extra-pulmonary tuberculosis.

Type of extra-pulmonary tuberculosis	Anti-CCP antibody					
	Positive		Negative		Total	
	N	%	N	%	N	%
Pleural effusion	0	0.0%	10	100.0%	10	100.0%
Abdominal tuberculosis	2	40.0%	3	60.0%	5	100.0%
Tubercular meningitis	0	0.0%	4	100.0%	4	100.0%
Pott's spine	0	0.0%	4	100.0%	4	100.0%
CNS-tuberculoma	1	50.0%	1	50.0%	2	100.0%
Disseminated tuberculosis	0	0.0%	2	100.0%	2	100.0%
Total	3	11.1%	24	88.9%	27	100.0%

Table 4: Anti-CCP positivity in Human immunodeficiency virus.

Diagnosis	Anti-CCP antibody					
	Positive		Negative		Total	
	N	%	N	%	N	%
HIV	5	16.7%	25	83.3%	30	100.0%
Total	5	16.7%	25	83.3%	30	100.0%

Table 4 shows the distribution of human immunodeficiency virus cases as regards anti-CCP antibodies. In human immunodeficiency virus infection, 5 (16.7%) cases were positive and 25 (88.3%) cases were negative for anti-CCP antibodies.

DISCUSSION

The present cross-sectional observational study was conducted in Moti Lal Nehru Medical College, Prayagraj and Associated hospital Swaroop Rani Nehru Hospital with aim to know prevalence of anti-CCP antibodies in tuberculosis and human immunodeficiency virus (HIV) infection, and to compare cases of pulmonary and extra-pulmonary tuberculosis with their anti-CCP values. This study included total 110 cases including 80 cases of tuberculosis and 30 cases of human immunodeficiency virus infection over a period of one year.

In this study, 48.2% of the total cases had pulmonary tuberculosis, 24.5% cases had extra-pulmonary tuberculosis and 27.3% cases had human immunodeficiency virus infection.

In this study, 39.6% cases of pulmonary tuberculosis were positive for anti-CCP antibodies and 60.4% cases were negative for anti-CCP antibodies. In extra-pulmonary tuberculosis, 11.1% cases had anti-CCP antibodies positive and 88.9% cases had anti-CCP antibody negative. In human immunodeficiency virus infection, 16.7% cases were positive and 88.3% cases were negative for anti-CCP antibodies. This is similar with the Elkayam et al study, that showed, 32% cases with anti-CCP antibody positive in pulmonary tuberculosis. Vikram et al, study showed 38.70% cases with anti-CCP antibody positive in pulmonary tuberculosis and 10.52% cases of extra-pulmonary tuberculosis had anti-CCP antibodies positive.[5,6] Kakumanu et al, study showed 37% cases with anti-CCP antibody positive in pulmonary tuberculosis.[7] He observed that there was a transitory increase in positivity of anti-CCP in the first 2 months of treatment, showed that anti-CCP is frequently present in patients with active pulmonary tuberculosis. Lima et al, study showed 4% cases with anti-CCP antibody positive in pulmonary tuberculosis, which does not coincides with above studies.[8] Riette du Toitet et al, studies showed 19% cases of human immunodeficiency virus infection had anti-CCP antibody positive. Zeljiko Romic et al, observed higher positivity of anti-CCP antibody (median value 5.5 IU/ml) in human immunodeficiency virus infection. Which support positivity of anti-CCP in human immunodeficiency virus infection.[9,10]

In this study, 30.2% cases of total pulmonary tuberculosis were sputum positive and 69.8% cases were sputum negative. Vikram et al, also had similar observation, their study had 29.0% sputum positive and 70.9% sputum negative cases of pulmonary tuberculosis.[6]

In this study of sputum positive pulmonary tuberculosis, 56.2% cases had anti-CCP antibody positive and 43.8% cases were negative for anti-CCP antibodies. In sputum negative pulmonary tuberculosis, 32.4% cases were positive for anti-CCP antibodies and 67.6% cases were negative for anti-CCP antibodies. There was no significant difference between the various groups in terms of distribution of anti-CCP antibody ($X^2 = 2.649$, $p = 0.104$). In the study by Vikram et al, had observed 55.56% cases of sputum positive pulmonary tuberculosis had anti-CCP antibody positive and in sputum negative pulmonary tuberculosis 31.81% cases had anti-CCP antibody positive.[6]

In this study of extra-pulmonary tuberculosis, 37% cases had pleural effusion, 18.5% cases had abdominal tuberculosis, 14.8% cases had tubercular meningitis, 14.8% cases had Pott's spine, 7.4% cases had CNS

tuberculoma and 7.4% cases had disseminated tuberculosis. Vikram et al, had similar observation, with 36.8% cases had pleural effusion, 15.7% cases had abdominal tuberculosis, 15.7%cases had tubercular meningitis, 15.7% cases had bone involvement and 10.5% cases had disseminated tuberculosis.[6]

In this study of extra-pulmonary tuberculosis, none cases of pleural effusion had anti-CCP antibody positive and 100% cases had anti-CCP antibodies negative. In abdominal tuberculosis, 40% cases were positive for anti-CCP antibodies and 60.0% cases were negative for anti-CCP antibodies. All cases (100%) of tubercular meningitis had anti-CCP antibodies negative and all cases (100%) of Potts spine were negative for anti-CCP antibody, 50% cases of CNS tuberculoma had anti-CCP antibody positive and 50% cases were negative for anti-CCP antibody. In disseminated tuberculosis, all (100%) cases had anti-CCP antibody negative which coincides with the following study. Vikram et al, found in their study of extra-pulmonary tuberculosis that all cases of pleural effusion, all cases of tubercular meningitis, all cases of Potts spine and all cases of disseminated tuberculosis had anti-CCP antibody negative.[6] In abdominal tuberculosis 33.3% cases were positive for anti-CCP antibodies.

The various studies done on other infectious diseases are as follows, Riccio et al, in their study on hepatitis C virus related arthritis found that 33.3% cases had anti-CCP antibody positive.[11] Bassyouni et al, found that anti-CCP antibodies were positive in 8.5% of the cases of hepatitis C virus.[12] Which support the finding of anti-CCP antibody in infectious diseases. Koga et al, studies found anti-CCP antibody positive in 10.9% cases of autoimmune hepatitis, and 2.7% cases of primary biliary cirrhosis.[13] Barbosa et al, In their studies of anti-CCP antibodies in Hansen's disease found that 3.1% cases were positive for anti-CCP antibodies.[14] Ribeiro et al, find in their study, anti-CCP antibodies were positive in 2.5% cases of Hansen's disease.[15] Atta et al, studied anti-CCP antibodies in patients with untreated visceral leishmaniasis.[16] They found 30% cases had anti-CCP antibody positive. Anti-CCP was not observed in patients cured of leishmaniasis.

Studies searched anti-CCP antibodies in infectious diseases, and the finding of positivity, ranging from 0% to 39%, being the figures of tuberculosis the highest one, putting in doubt the specificity anti-CCP antibody test for the diagnosis of rheumatoid arthritis. Furthermore, the infectious diseases may run their course with osteoarticular symptoms, and if added to this, there is anti-CCP positivity; one may establish a wrong diagnosis and an inadequate treatment.

CONCLUSION

From the present study, we concluded that anti-CCP antibodies were found in infectious diseases like tuberculosis and human immunodeficiency virus infection in addition to autoimmune diseases like rheumatoid arthritis. Anti-CCP antibodies prevalence was higher in pulmonary tuberculosis as compared to extra-pulmonary tuberculosis. We also concluded that anti-CCP antibodies were also found in patients with human immunodeficiency virus infection, although its prevalence was less as compared to tuberculosis.

Thus anti-CCP antibodies can be positive in cases of infectious diseases. The low prevalence of anti-CCP positivity in extra-pulmonary tuberculosis could be due to decreased ability of patients to mount an inflammatory response in cases of disseminated tuberculosis, tubercular meningitis, Potts spine. Thus Anti-CCP is not very specific for rheumatoid arthritis. Its positivity in other infectious diseases like tuberculosis and human immunodeficiency virus infection could not be ignored, especially in a country like India where tuberculosis is highly prevalent.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Yadav RK, Raj K, Kachnar V, Mathur MK, Shukla AD. Anti- cyclic citrullinated peptide antibodies in tuberculosis and human immunodeficiency virus. Int J Adv Med 2020;7:804-8.