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CASE REPORT

CORRELATION BETWEEN SERUM LEVELS ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODY AND RHEUMATOID FACTOR IN PATIENTS WITH ARTHRALGIA

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ABSTRACT

Introduction: Rheumatoid arthritis (RA), which has an estimated worldwide prevalence in adults of 0.8% and more frequently affects females, is characterized by joint inflammation and destruction and gives rise to functional limitations, working disability, and a poor quality of life. The etiology of this disease is unknown; however interaction between both genetic and environmental factors is thought to contribute to its occurrence. Consequently, the purpose of this study was to examinate correlation between RF, CRP, Uric acid and Anti CCP in patients with join pain. **Materials and Methods:** This study was carried at the Department of medical biochemistry and Department of reumatologu of Public Health Organization Clinical hospital d-r Trifun Panovski in Bitola. Written informed consent was taken from all the subjects before undergoing any investigation. The research protocol was conducted in accordance with the Helsinki Declaration. **Results:** A total of 50 patients were available for this study and were included in the analysis. From 50 patients, 33 patients (66%) were female and 17 males (34%). The mean age of the cohort was 54 years old ranging from 28 to 84 years old. Serum concentration of anti CCP in all participants was in range <0,5 U/ml to 641 U/ml, mean 23,9 U/ml. Males serum concentration of Anti CCP was in range <0.5 U/ml to 189 U/ml, mean 14,78 U/ml. Females serum concentration of Anti CCP was in range <0.5 U/ml to 641 U/ml, mean 28.7 U/ml. A significant association of RF and anti-CCP antibody co-occurrence was observed: Positive for both RF and anti-CCP antibody were 7 patients (5 female and 2 males). RF-positive/anti-CCP antibody-negative were 12 patients (9 female and 2 males). RF-negative/anti-CCP antibody-positive were 2 female patients. **Discussion:** We found a significant association of RF and Anti CCP in 36 of 50 patients with arthralgia, which is in a correlation with previous studies. We found that female patients safer frequent from arthralgia compare to males which is in a correlation with previous studies. **Conclusion:** The usage of anti-CCP antibody is useful in the detection of early disease as evidenced by significant association between anti-CCP antibody and RF.

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INTRODUCTION

Rheumatoid arthritis (RA), which has an estimated worldwide prevalence in adults of 0.8% and more frequently affects females, is characterized by joint inflammation and destruction and gives rise to functional limitations, working disability, and a poor quality of life (Smolen et al.). The etiology of this disease is unknown; however interaction between both genetic and environmental factors is thought to contribute to its occurrence (Sulaiman et al., 2019). Formerly, the presence of rheumatoid factor (RF) in the patient's serum was the most important biomarker for the diagnosis of RA.

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However, RF can also be detected in the sera from patients with other rheumatic diseases, such as: primary Sjögren's syndrome (pSjS), systemic lupus erythematosus (SLE), dermatomyositis, polymyositis, progressive systemic sclerosis, chronic hepatitis B infection, and hepatitis C infection (YU et al., 2019). The principal sites of pathology in RA are joint tissues affected by chronic synovial inflammation, synovial hyperplasia and joint cartilage, and bone destruction. The unquestioned success of the last years in an aspect of RA diagnosis was characterisation of Anti CCP (Kurowska et al. 2017). The presence of Anti CCP in the serum is now the most specific biomarker for the diagnosis of RA. The presence of Anti CCP can predict the development of RA in patients with early, undifferentiated arthritis.

Anti CCP are also present in RA sera several years before a definite diagnosis of RA. In RA patients, the presence of Anti CCP has been associated with active inflammation and subsequent destruction and deformity of the joints (YU et al., 2019). Anti CCP are autoantibodies against citrullinated peptide and proteins. During inflammation arginine residues present in some protein get converted into citrulline residue, a process called citrullination. This leads to drastic change in their shape because of which these proteins are recognised as antigen by immune system thus leading to antibody formation. Anti CCP is an autoantibody produced when the patient's immune system attacks its own body. Till date Anti CCP is used as a diagnostic marker for rheumatoid arthritis but now studies are going on to establish its role in other autoimmune diseases, with and without arthritis (Bandana et al., 2017).

Thus, Anti CCP alone appear to have enough predictive power to effectively distinguish high-risk individuals from the background population. Importantly, adding Anti CCP results to the 1987 criteria increased sensitivity for early RA (≥ 6 months' disease duration) diagnosis from 25 to 44% and have excellent discriminative ability to assess progression from UA to RA (van der Helm-van Mil et al.,2008). Some studies revealed that Anti CCP appear significantly earlier than RF and their presence has the highest predictive value for development of RA (Rantapää-Dahlqvist et al., 2003). Thus, it seems that generation of Anti CCP precedes the signs of subclinical inflammation in RA. Biological activities of Anti CCP include the stimulation of proinflammatory cytokines production, induction of osteoclastogenesis and promotion of autoantigens release from neutrophils. All these Anti CCP - mediated processes can be involved in the development and/or perpetuation of RA (Kurowska et al. 2017). In 2010, 12 years after the identification of Anti CCP, the American College of Rheumatology/European League Against Rheumatism revised their classification criteria to include the presence of Anti CCP in the diagnosis of RA. On the basis of current understandings of RA etiopathogenesis, the EULAR study group for risk factors for RA has defined several phases of RA development. These phases comprise of: genetic and environmental risk factors for RA, autoimmunity associated with RA, symptoms such as joint pain but without clinical arthritis (arthralgia) and clinical arthritis (which can be either unclassified arthritis or RA). Such observations have encouraged a call for 'preventive trials': trials that assess treatment initiation in pre-arthritis phases with the ultimate aim of preventing the onset of RA (van Steenbergen et al., 2018). Consequently, the purpose of this study was to examinate correlation between RF, CRP, Uric acid and Anti CCP in patients with join pain.

MATERIALS AND METHODS

This study was carried at the Department of medical biochemistry and Department of reumatologu of Public Health Organization Clinical hospital d-r Trifun Panovski in Bitola. Written informed consent was taken from all the subjects before undergoing any investigation. The research protocol was conducted in accordance with the Helsinki Declaration. The blood samples were taken after overnight fast (12 hours). The serum was separated and Anri CCP, RF, CRP, uric acid were measured using Abbot Architect CI 4100 analyzer. The data are presented as mean± standard deviation (SD) and $p \leq 0.05$ is considered statistically significant. The results were done with the SPSS version 16.

RESULTS

A total of 50 patients were available for this study and were included in the analysis. From 50 patients, 33 patients (66%) were female and 17 males (34%). The mean age of the cohort was 54 years old ranging from 28 to 84 years old. We can conclude that female patients safer frequent from arthralgia compare to males. Serum concentration of anti CCP in all participants was in range <0,5 U/ml to 641 U/ml, mean 23,9 U/ml.. Males serum concentration of Anti CCP was in range <0.5 U/ml to 189 U/ml, mean 14,78 U/ml. Females serum concentration of Anti CCP was in range <0.5 U/ml to 641 U/ml, mean 28.7 U/ml. We can see that female had higher values of Anti CCP compared to males. A total of 19 patients had positive RF (14 females, 5 males); while 9 were positive for anti-CCP antibody (7 females, 2males).

A significant association of RF and anti-CCP antibody co-occurrence was observed: Positive for both RF and anti-CCP antibody were 7 patients (5 female and 2 males). RF-positive/anti-CCP antibody-negative were 12 patients (9 female and 2 males). RF-negative/anti-CCP antibody-positive were 2 female patients. Positive for RF, anti-CCP antibody and CRP were 5 patients (4 female, 1 male). Positive for both RF and CRP were 9 patients (3 female, 1 male). Positive for both RF and uric acid were 5 patients (3 female and 2 males). As we can see females had more frequent positive values of RF and Anti CCP compared to males. Negativity for both RF and anti-CCP antibody were 29 patients (16 female and 13 males).

DISCUSSION

During inflammation of joints secondary to any immune mediated disease, there is release of enzyme called Peptidylarginase Deiminase (PADs) which catalyses the conversion of proteins (fibrin, fibrinogen, vimentin found in synovium of inflamed joint) arginine residue to citrulline in the presence of calcium. This process is called citrullination or deimination (Wang et al., 2013). It is referred to as deimination because the enzyme PADs replace the primary ketimine group (=NH) by a ketone group (=O). Arginine being positively charged at neutral pH is replaced by citrulline that has no net charge. This leads to increased hydrophobicity of protein that causes defective protein folding affecting its structure and function. Due to change in shape, these proteins are recognised by immune system as antigen, thus leading to antibody formation (Coenen et al., 2007).

We found a significant association of RF and Anti CCP in 36 of 50 patients with arthralgia, which is in a correlation with previous studies of Sulaiman 2019, Sockalingman 2009 and Abdul 2013 (Sulaiman et al., 2019, Sockalingam et al., 2009, Abdul Wahab et al., 2013). We found that female patients safer frequent from arthralgia compare to males which is in a correlation with previous studies (Forslind et al., 2007, Tengstrand et al., 2004, Symmons 2002, Kuiper et al., 2001, Da Silva et al., 1992). We discover that female had higher values of Anti CCP compared to males, what is comparable to the scarce data reported by other scientist (Mackey et al, 2015). We found that females had more frequent positive values of RF and Anti CCP compared to males. At early stages of disease, RA is often difficult to differentiate from other inflammatory arthritis conditions and RF alone has low sensitivity in diagnosing early RA (Niewold et al., 2007).

Table 1. Association of anti-CCP antibody with RF, CRP and uric acid in patients with arthralgia

	Total number	Total %	Female number	Female %	Male number	Male %
Positive RF	19	28	14	74	5	26
Positive Anti CCP	9	15	7	78	2	22
Positive for both RF and anti-CCP antibody	7	12	5	71	2	29
RF-positive/anti-CCP antibody-negative	12	19	9	82	2	18
RF-negative/anti-CCP antibody-positive	2	4	2	100	0	0
Positive for RF, anti-CCP antibody and CRP	5	10	4	80	1	20
Positive for both RF and CRP	9	15	3	75	1	25
Positive for both RF and uric acid	5	10	3	60	2	40
Negativity for both RF and anti-CCP	29	37	16	55	13	45

Combination of both RF and anti-CCP antibody has been shown to improve the sensitivity of early RA diagnosis (Vencovsky et al., 2003) and might help in predicting poor prognosis in terms of disease activity (Bas et al., 2003).

Conclusion

RA is common disease with widespread focal joint destruction and complications secondary to systemic inflammation. Recent treatment options based on better understanding of disease pathology have led to immense changes in the management of this disease. The usage of anti-CCP antibody is useful in the detection of early disease as evidenced by significant association between anti-CCP antibody and RF.

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