COMPARATIVE CLINICAL STUDY OF C-REACTIVE PROTEIN AND RHEUMATOID FACTOR IN RHEUMATOID AND REACTIVE ARTHRITIS

Nihad Selimović and Maja Omerović

Faculty of Education, Travnik, Bosnia & Herzegovina

Abstract

The purpose of this study is to allow insight into rheumatoid and reactive arthritis, the two diseases which still puzzle many scientists, and are an interesting field of research. Retrospective study incorporated 74 patients suffering from these diseases, out of which 46 were patients with rheumatoid, and 28 with reactive arthritis. The patients were treated at Clinic for Heart Diseases and Rheumatism; at Clinical centre University in Sarajevo during the period of two years (2007/2008). Out of 46 patients with rheumatoid arthritis, 67% were women. Most of the patients (59%) were over 50 years old. There was no significant difference in male to female ratio in patients with reactive arthritis, and the age groups were evenly matched, too. Male to female ratio was 57% to 43%, and the overall percentage of patients up to 30 years old is 35%, identical to the percentage of patients who are over 50 years old. The study demonstrates positive CRP values in 65% of the patients with rheumatoid arthritis. 93% of the patients with reactive arthritis show high CRP value. The average values are 40,5 mg/l (max 147 mg/l) for patients with rheumatoid arthritis, and 41,2 mg/l (max 232 mg/l) for patients with reactive arthritis. It has been proven that the RF test is much more sensitive in diagnosing rheumatoid arthritis. The test was positive in 91,3% of the subjects with rheumatoid arthritis. In the case of reactive arthritis, 29% of the subjects were positive when put to RF test. This is a proof of particular specificity of this test. Anti CCP test is a standard method for diagnosing rheumatoid arthritis worldwide, and in our country, too. The test identified rheumatoid arthritis 91,3% of the cases. Anti CCP was negative in all the patients with reactive arthritis, which is a proof of great specificity of this test.

Key words: arthritis, rheumatoid, reactive, clinical, CR protein

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the binding tissue, with unknown aetiology, which attacks locomotive system. In the case of RA, the immune system attacks cartilage, bones, and sometimes internal organs. The characteristic pathological result of this disease is a permanent inflammation of the synovial membrane of the peripheral joints, usually symmetrically dispersed. With the disease striking 0,5% to 1% of the general population, it is the most common systematic autoimmune disease. Seen that the recent studies showed that irreversible joint damage occurs in the first two years of the occurrence of the symptoms, the modern approach to the treatment of the RA implicates utilisation of the aggressive anti-rheumatic therapy within the first months of the occurrence of the disease. Due to potentially toxic medication which might cause serious side effects, a highly specific marker is needed in order to identify RA patients before damage to the joints occur. Today we are able to use a large spectrum of methods for early diagnosis, monitoring, and treatment of RA. C-reactive protein (CRP) is in lab diagnostics recognized as most frequently tested plasmatic protein, serving as an inflammatory marker. A marker makes it an important indicator of inflammation, tissue necrosis or trauma to the tissue. It has high sensitivity, and low specificity. Taking into consideration many cases of two diseases overlapping, CRP analysis becomes a problem in defining a n exact diagnosis and aetiology. Along with CRP, the standard procedure involves measuring the values of the erythrocyte sedimentation, rheumatoid factor and anti-cyclic citrullinated peptide antibody (anti-CCP), which were in this study correlated with the same values in patients with reactive arthritis. Reactive arthritis is a non-purulent arthritis that occurs as an immunologically conditioned inflammatory response to the infection that occurred in another part of the body in a certain time period. It is an acute, non-secretion, sterile inflammation (without the presence of microorganisms) of one or more joints, which occurs after an inflammatory process usually in the distant part of the body. The patients are usually young adults, up to 35 years old. There is no specific test for diagnosing reactive arthritis. The early diagnosis of RA is possible with the above mentioned serological tests. Anti-CCP is positive in 87% of the patients with RA, and it has a high specificity of ap. 95%.
Anti-CCP is currently the leading serological test used to confirm the clinical diagnosis, and for early diagnosis of RA in general. Only one biomarker found in the blood, Anti-CCP autoantibody, first identified by the group of Dutch scientists, is proven to be more reliable than the rheumatoid factor. It is considered better than the rheumatoid factor, and considered a marker of choice in diagnosing RA.

**Methodology**

**Primary hypotheses**
- The values of CRP are significantly different in RA and reactive arthritis patients
- The values of RF are significantly different in RA and reactive arthritis patients
- The values of Anti-CCP test show higher specificity compared to the RF test

**Zero hypotheses**
- There are no significant differences in quantitative CRP values in RA and reactive arthritis
- There are no significant differences in quantitative RF values in RA and reactive arthritis
- The values of Anti-CCP test do not show higher specificity compared to the RF test

**Objectives**

Basic objectives of this study are:
- Establishing quantitative CRP value levels in RA and reactive arthritis, and comparing of the results
- Establishing quantitative RF value levels in RA and reactive arthritis, and comparing of the results
- Establishing quantitative Anti-CCP test value levels in RA and reactive arthritis, and comparing of the results

**Material and methods**

Clinical retrospective comparative study had been performed at the Clinic for Heart Diseases and Rheumatism, at Clinical centre University of Sarajevo. The overall number of patients included was 72 (43 females, 31 male). Their lab results and medical history were processed. Two groups of patients were formed:
I) patients suffering from reactive arthritis (28 patients)
II) patients suffering from rheumatoid arthritis (46 patients)

The diagnosis of rheumatoid arthritis is based on clinical tests, medical history of the patient, x-rays and blood tests. Standards for diagnosing the disease were set by American Rheumatoid Association (1987) and New York Criteria.

In diagnosing reactive arthritis, microbiologic methods to determine the focus in the body are needed along together with the clinical features and lab tests.

<table>
<thead>
<tr>
<th>No</th>
<th>Laboratory research</th>
<th>Referent values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Erythrocyte sedimentation</td>
<td>0 – 15 mm/h</td>
</tr>
<tr>
<td>2</td>
<td>C reactive protein</td>
<td>0 – 6 mg/l</td>
</tr>
<tr>
<td>3</td>
<td>Rheumatoid factor</td>
<td>0 – 8 U/ml</td>
</tr>
<tr>
<td>4</td>
<td>Anti-cyclic citrullinated peptide antibody</td>
<td>&gt; 17 U/ml</td>
</tr>
</tbody>
</table>

**Results and discussion**

Intention of this paper was to offer an insight into rheumatoid and reactive arthritis - two diseases that intrigue many scientists even today and make for interesting research area in general. Special attention was paid to laboratory parameters (sedimentation of erythrocytes, CRP, RF, anti CCP test), necessary for detection, monitoring and diagnosis of the said diseases.
As a part of retrospective study, 74 patients’ medical histories were treated of which 46 cases of rheumatoid arthritis and 28 cases of reactive arthritis. Aforementioned study showed that even in our conditions women are more likely to contract rheumatoid arthritis. Considering the total number of treated patients (46), 67% are women (31 patients). The rest of 33% are male patients, in general aged over 50.

Analysis of rheumatoid arthritis patients’ structure revealed irrelevantly small percentage of patients aged under 30 (2%). Majority of patients of both sexes fall into age group of over 50 (59%). According to data found in professional literature, results reached concerning age groups and sex structures are in balance. Percentage of affected patients per age groups is thus relatively equated. Total number of patients falling under the age group under 30 amounts to 35%, equal to the percentage established for the group of over 50. Number of male and female patients is relatively equated as well (57%, to 43%).

This study focused on comparison of laboratory parameters values, i.e. of inflammation factors, which are necessary in order to detect and monitor inflammatory diseases, like arthritis itself. Following values were monitored and compared: C reactive protein (CRP), rheumatoid factor (RF), sedimentation of erythrocytes and antibodies for cyclic citrulated peptide (anti CCP). Values of CRP show significant increase in the case of acute inflammation, in fact they can increase up to hundred times within just 24 hours. For this reason, CRP is used during diagnostic process as replacement for erythrocytes sedimentation (SE) test that is used as diagnostic procedure for over 50 years. SE is extremely sensitive test for establishing acute inflammations, but it lacks in specific quality. In this study, it yielded positive values for 87% of patients suffering from rheumatoid arthritis, and for 79% of patients suffering from reactive arthritis.

For patients suffering from rheumatoid arthritis, value of SE is in generally higher (+ 10,2 mm/h). Largest average value of SE was established for age group over 50, for patients with rheumatoid arthritis. This value was 54,7 mm/h. CRP test is important as screening test for viral and bacterial infections. Namely, in the case of viral infections, which are accompanied by high sedimentation and white cell count, CRP remains in lower limit range when compared with the case of bacterial infection. For bacterial infections, its increase is considerably higher.
It is successfully applied in diagnostic of joints and muscle inflammations, for early detection of joint integument inflammations, as well as auxiliary method for diagnostic of symptoms and diseases of digestive tract. Chinese study (compiled by Qing C, Lei Y, Ma L, Xie P, Deng H), on sample of 66 patients suffering from rheumatoid arthritis, established positive values of CRP in 63,6% of cases. Egyptian study (compiled by Fathi NA, Ezz-Eldin AM, Mosad E, Bakry RM), also yielded similar results concerning values of CRP for patients suffering from rheumatoid arthritis. Positive values were established for 56, 7% of cases.

Our study shows positive values of CRP for 65% of patients suffering from rheumatoid arthritis. It is interesting that CRP is positive for 93% of cases for patients suffering from reactive arthritis. Average values are 40,5 mg/l (max 147 mg/l) for patients suffering from rheumatoid arthritis, and 41,2 mg/l (max 232 mg/l) for patients suffering from reactive arthritis. Apart for detection of acute inflammatory reactions, establishing CRP concentration is useful for monitoring of disease progress i.e. for establishing efficiency of the treatment. For example, by successful application of antibiotic treatment CRP concentration found in serum will decrease faster than erythrocyte sedimentation. So by monitoring CRP concentration, intake of lesser efficient or even inefficient antibiotics may be prevented i.e. they could be replaced by the more efficient one. In this sense, establishing of CRP values is of great importance for diagnostics and monitoring of infection treatments for premature or newly born children. But like Finish study already showed (compiled by Aho K, Palosuo T, Knekt P, Alha P, Aromaa A, Heliovaara M), this study as well showed that CRP cannot predict diagnosis not the course of disease for the patients suffering from rheumatoid arthritis. It is proven that RF test is more sensitive for diagnostic of rheumatoid arthritis. For as many as 93% of patients, it yielded positive values. However, we cannot claim that it has great specific quality because even patients suffering from reactive arthritis in 29% of cases show positive values of RF test. Aforementioned Egyptian study shows that the sensitivity of RF test for patients suffering from rheumatoid arthritis amounts to 71,7%, on sample of 60 patients with RA. Greek study conducted on 155 patients with RA simultaneously monitored sensitivity and specific qualities of RF test and anti CCP test. Average values thus reached for sensitivity are 63, 2% and 59,1% (redom), and for specific quality 95% and 91,2%. Turkish study (compiled by Keskin G, Inal A, Keskin D, Pekel A, Baysal O, Dizer U, Sengül A.) also showed higher sensitivity and specific quality of anti CCP test than RF test.

Our study showcases that CCP test cannot be considered as the standard diagnostic method for RA yet, when we know that the said test was done for 50% of patients suffering from RA. From the entire number of tested patients (23 patients), positive test appeared for 21 patients, i.e. 91,3% of subjects. That it is the case of great specific quality was proven by the fact that anti CCP test was not positive for none of the patients suffering from reactive arthritis. When we speak of reactive arthritis, this study also monitored etiological causes, i.e. diseases that preceded arthritis development. Therefore, we can talk about few common causes of reactive arthritis. Infection of urinary tract was the cause in 32% of patients, Focalosis dentalis, i.e. inflammation of caries infected tooth in 18% of cases. Diseases of thyroid gland, as well as sarcoidosis are among common causes of reactive arthritis. Cause could not be determined in 25% of tested cases.

**Conclusions**

Based on the results reached through this study, as well as results of studies available and conducted by other authors, we can make following conclusions:

- From the entire number of treated patients suffering from rheumatoid arthritis (46 patients), 67% are female patients;
- Within the same tested patient group, patients over 50 constitute majority with 59%, while the percentage of patients under 30 is relatively insignificant with 2%;
- Within the group of patients suffering from reactive arthritis, proportion of male and female patients was relatively equated (57%, 43%);
- Value of erythrocytes sedimentation (SE) was positive for 87% of patients suffering from rheumatoid arthritis, and for 79% of patients suffering from reactive arthritis;
- Values of C-reactive protein (CRP) were positive for 65% of patients suffering from rheumatoid arthritis, and for 93% of patients suffering from reactive arthritis;
- Average values of CRP are 40,5 mg/l (max 147 mg/l) for patients suffering from rheumatoid arthritis, and 41,2 mg/l (max 232 mg/l) for patients suffering from reactive arthritis;
- Values of rheumatoid factors (RF) are positive for 93% of patients suffering from rheumatoid arthritis, but it is established that patients suffering from reactive arthritis in 29% of cases show positive values of RF test;
- Anti CCP test was done for 50% of patients with RA, and from the entire number of tested patients (23 patients), test was positive in 91,3% of cases;
- Anti CCP test was not positive for any patient suffering from reactive arthritis;
• Infection of urinary tract was the cause of reactive arthritis for 32% of patients; Focalositis dentalis in 18% of cases; thyroid gland disease for 14%, and sarcoidosis for 11% of patients cause could not be established for 25% of tested patients.

• Positive CRP and negative RF test in 71% of cases is direct indicator of infective or focal aetiology in the case of reactive arthritis.

**Literature**


KOMPARATIVNA KLINIČKA STUDIJA C-REAKTIVNOG PROTEINA I REAUMATIODNOG FAKTORA U REUMATOIDNOM I REAKTIVNOM ARTRITISU

Sažetak
Ovim radom pokušao se dati uvid u reumatoidni i reaktivni artritis, dvije bolesti koje i danas zainteresiraju mnoge naučnike, te čine zanimljivo područje za istraživanje. Retrospektivnom studijom su obrađene 74 historije bolesti pacijenata, 46 sa reumatoidnim, a 28 sa reaktivnim artritisom, lijenih na Klinici za bolesti srca i reumatizam, Kliničkog centra Univerziteta u Sarajevu, u periodu od 2 godine (2007. i 2008.). Od ukupnog broja obrađenih pacijenata sa reumatoidnim artritisom (46), čak 67% su činile žene. Većina pacijenata (59%) je u starosnoj grupi preko 50 godina. Udio pacijenata sa reaktivnim artritisom je prilike ravnomjerno podijeljen u starosne i polne grupe. Odnos muških i ženskih pacijenata je 57%, prema 43%. Ukupan broj pacijenata u grupi do 30 godina iznosi 35%, koliki je procenat i u grupi preko 50 godina. Studija pokazuje pozitivne vrijednosti CRP-a kod 65% pacijenata sa reumatoidnim artritisom. CRP je visok čak u 93% slučajeva pacijenata sa reaktivnim artritisom. Prosječne vrijednosti su 40,5 mg/l (max 147 mg/l) za pacijente sa reumatoidnim artritisom, a 41,2 mg/l (max 232 mg/l) za pacijente sa reaktivnim artritisom. Pokazalo se da je RF test puno osjetljивiji za dijagnostiku reumatoidnog artritisa. Čak 93% pacijenata je imalo pozitivne vrijednosti. Ovo govori o specifičnosti, dok pacijenti sa reaktivnim artritisom, u 29% slučajeva pokazuju pozitivne vrijednosti RF testa. Postoji signifikantna razlika u pozitivnosti testa između RA i reaktivnog artritisa. Anti CCP test je standardna metoda dijagnostike RA u svijetu, a također i u našim uslovima. Pozitivan test je bio kod 91,3% ispitanika sa RA. O velikoj specifičnosti govori činjenica da anti CCP test nije bio pozitivan ni kod jednog pacijenta sa reaktivnim artritisom.

Ključne riječi: artritis, reumatoidni, reaktivni, klinički, CR protein