J Surg Med. 2019;3(3):239-241.
DOI: 10.28982/josam.523350

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Toxoplasma gondii seroprevalence in rheumatoid arthritis patients treated with biological agents

Biyolojik ajanlarla tedavi edilen romatoid artritli hastalarda Toxoplasma gondii seroprevalansı

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Ethics Committee Approval: The approval for the study is obtained from the local Institutional Ethics Committee.
Etik Kurul Onayı: Çalışmanın onayı yerel Kurumsal Etik Komitesi'nden alınmıştır.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 06.02.2019
Accepted / Kabul Tarihi: 10.03.2019
Published / Yayın Tarihi: 11.03.2019

Abstract

Aim: Toxoplasma gondii infection appears to be asymptomatic in most of the patients but its mortality rate is high in immunocompromised patients and in those taking immunosuppressive drugs, when reactivated and untreated. Severe infections are well-known to occur in rheumatoid arthritis (RA) patients treated with immunosuppressive drugs such as tumor necrosis factor alpha antagonist. TNF-alpha is essential for granuloma formations, which are important for the defense against intracellular pathogens and the process. It seems it is inevitable that anti-TNF agents being used in RA disease treatment are going to create an incline towards all kind of infections, especially tuberculosis and other granulomatous infections (toxoplasmosis, histoplasmosis, etc.). We investigated the T. gondii seroprevalence in RA patients treated with biologic agents and disease modifying anti-rheumatic drugs, systemic lupus erythematosus patients treated with immunosuppressive drug combinations and compared them with healthy controls.

Methods: In this study we investigated the T. gondii seroprevalence in 33 rheumatoid arthritis (RA) patients treated with biologic agents, 26 RA patients treated with disease modifying anti-rheumatic drugs (DMARD), 15 Systemic lupus erythematosus (SLE) patients treated with immunosuppressive drug combinations and in 19 healthy controls.

Results: Toxoplasma IgM enzyme linked immunosorbent (ELISA) assay was negative for all groups. Whereas 29 (87.9%) of rheumatoid arthritis patients treated by the biologic agents, 21(80.8%) of rheumatoid arthritis patients treated by disease modifying antirheumatic drugs, 15 (100%) of Systemic lupus erythematosus patients and 4 (21.1%) of the controls were seropositive for Toxoplasma Ig G.

Conclusion: During the immunosuppressive treatment the risk of toxoplasma infection should be taken into consideration.

Keywords: Toxoplasma gondii, Rheumatoid arthritis, Biological agents

Öz

Amaç: Toxoplasma gondii enfeksiyonu çoğu hastada asemptomatik seyreder; ancak immun yetmezliği olan ve immunsupresif ilaç alan hastalarda nüks durumunda veya tedavi edilmediğinde mortalite oranı yüksektir. Romatoid artritli (RA) hastaların tümor nekrozis faktör alfa (TNF-alfa) antagonisti gibi immunsupresif ilaçlarla tedavi edildiğinde ciddi enfeksiyonlar gelişebileceği bilinmektedir. TNF-alfa romatoid artrit patogenezindeki önemi ile birlikte diğer inflamatuvar cevaplar ve immün sistemin enfeksiyonlarla mücadelesinde etkin rol oynayan önemli bir sitokindir.TNF alfa özellikle hücre içi patojenlere karşı savunmada önemli olan granülamatöz oluşumlar ve idame sürecinde çok önemlidir.Bu nedenle RA tedavisinde yaygın olarak kullanılan anti-TNF ajanların başta tüberküloz ve benzeri (toksoplazmozis,histoplazmozis vb.) granülomatöz enfeksiyonlar olmak üzere her türlü enfeksiyona karşı yatkınlık oluşturması kaçınılmaz görünmektedir.

Yöntemler: Bu çalışmada biyolojik ajanla tedavi edilen 33 romatoid artritli (RA), hastalığı modifiye edici ajanla tedavi edilen 26 RA'li, immunsupresif ilaç kombinasyonları ile tedavi edilen 15 sistemik lupus eritematozuslu (SLE) hasta ve 19 sağlıklı kontrolde enzim linked immunosorbent assay yöntemi ile Toxoplasma gondii seroprevelansı incelenmiştir.

Bulgular: Toxoplasma IgM düzeyleri ELISA yöntemi ile tüm gruplarda negatifti. Ancak biyolojik ajanla tedavi edilen 29 (%87.9) RA'li, hastalığı modifiye edici ajanla tedavi edilen 21(%80.8) RA'li ve 15 (%100) SLE'li hastada ve kontrol grubunda 4 (%21.1) kişide Toxoplasma Ig G seropozitifti.

Sonuç: Immun supresif tedavi sırasında hastalarda toxoplasma enfeksiyonu riski göz önünde bulundurulmalıdır.

Anahtar kelimeler: Toxoplasma gondii, Romatoid artrit, Biyolojik ajanlar

How to cite / Atıf için: İnal A, Taş D. Toxoplasma gondii seroprevalence in rheumatoid arthritis patients treated with biological agents. J Surg Med. 2019;3(3):239-241.

Introduction

Toxoplasma gondii is a widespread zoonotic protozoon of birds and mammals [1]. Researches show that about 30-40% of people can be infected with the protozoon during their lives. This infection appears asymptomatic in most of the people but in immunocompromised patients, including those with organ transplants, AIDS, cancer and in those taking immunosuppressive drugs, reactivated and untreated toxoplasmosis has a high mortality rate. Toxoplasmosis can cause severe neurologic or ocular disease in the fetus and adults [2]. Rheumatoid arthritis (RA) is a common crippling disease characterized by destructive joint inflammation and the production of rheumatoid factor (RF) auto-antibodies. RF producing B cells can be activated by the mitogenic effects of infectious agents (bacterial lipopolysaccharides, EBV, etc.). Stimulation of normal human B cells by EBV in vitro releases low affinity IgM RFs from B-1 (CD5+) cells. Antibodies stimulated in this way are usually polyreactive with restricted V-gene usage, little somatic mutation and idiotypical crossreactive. This could be the result of classical cross reactivity between microbial epitopes and IgG Fc. An-other possibility is that RFs are cross reactive with other autoantigens, and some RFs react with nuclear antigens [3].

The treatment of Rheumatoid arthritis (RA) has changed dramatically in recent years following the introduction of biologic agent therapies. Interleukin-1 (IL-1) and Tumor necrosis factor alpha (TNF-α) orchestrate many of the pathophysiological abnormalities including the local and systemic effects of inflammation and the development of joint damage. Clinical trials have shown the efficiency of cytokine inhibitors in reducing inflammatory activity as well as inhibiting joint destruction in patients with active RA [4].

Although biologic inhibitors have been shown to be effective in the treatment of patients with RA, in the long –term surveillance of the patients treated with TNF-α inhibitors, serious adverse events, particularly intracellular microorganism infections such as Tuberculosis, and other granulomatous infections (histoplasmosis, toxoplasmosis, listeriosis etc.) were observed. In the recent years several RA cases have been published who developed toxoplasmic chorioretinitis and cerebral toxoplasmosis during the treatment with anti-TNF-alpha agents [5,6].

In this study we investigated the T. gondii seroprevalence in RA patients treated with biologic agents and, disease modifying anti-rheumatic drugs, Systemic Lupus Erythematosus (SLE) patients treated with immunosuppressive drug combinations and compared them with healthy controls.

Materials and methods

We designed a cross sectional study with control group. Local Ethical Committee approval was obtained. In our study, we planned four groups; Group 1: RA patients treated with biologic agents, Group 2: RA patients treated with disease modifying antirheumatic drugs (DMARDs), Group 3: SLE patients treated with immunosuppressive drug combinations (cyclophosphamide + corticosteroids + chloroquine) and Group 4 (control group): healthy controls.

Inclusion criteria for the cases were as follows: a) Having one of the diagnoses of RA, SLE and healthy person b) patients suffering from RA and SLE attending in the Rheumatology at least for a year. c) 18 years and older c) any gender d) who voluntarily participate in the study.

We used the enzyme linked immunosorbent assay (ELISA) sandwich technique (Virion-Serion Sandwich ELISA T. gondii IgM and IgG kits) for the detection of anti-T.gondii IgG and IgM anti-Bodies (lot number: Anti-T.gondii IgG; SHX.CB/08.09, Anti-T.gondii IgM; SFX.AQ/08.11).

Statistical analysis

The statistical analysis was performed by NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). One-way analysis of variance was used in the comparison of descriptive statistical methods (mean, standard deviation) as well as normal distribution variables, while Tukey multiple comparison test was used for subgroup comparisons and chi-square test was used for comparison of qualitative data. The difference in groups and controls were analyzed using Mann-Whitney U Test. A p value less than 0.05 was considered as statistically significant.

Results

Of Group 1, 23 were female and 10 were male. Their mean age was 38.9±9 years and the average disease duration was 7.9±3.1 years. Of Group 2, 20 of them were female and 6 were male. Their mean age was 33±5.4 years and the average of disease duration was 7.6±2.1 years Of Group 3, 10 of them were female and 5 were male with a mean age of 39±6.9 years and the average disease duration was 8.4±2.8 years. 14 of Group 4 were female and 5 of them were male with a mean age of 39.1±6.2 years. No statistically significant difference was observed between the gender distributions of group1, Group 2, Group3 and Group 4 (p=0.887). A statistically significant difference was observed between the mean age of group1, Group 2, Group3 and Group 4 (p=0.007). The mean age of Group 2 was significantly lower than the men age of Group 1, Group 3 and Group 4 (p=0.024, p=0.017 and p=0.011, respectively), but no statistically significant difference was found between the mean age of the other groups (p>0.05). Demographic differences can be seen in Table 1.

Sixteen of Group 1 were on infliximab therapy with the mean duration of 21.3±2.8 months, 8 of them were on etanercept therapy with a mean duration of 19.4±4.1 months and 9 of them were on adalimumab with a mean duration of 24.8±3.1 months. Treatment period and drugs can be seen in Table 2.

Table 1: Demographic differences

Patient groups	Male	Female	p	Mean age±SD	p	Treatments	Disease period (years)
Group 1	10	23		38.9±9		Biologic agents	7.9±3.1
Group 2	6	20		33±5.,4		DMARDs	7.6±2.1
Group 3	5	10	0.887	39±6.9	0.007	Immunosuppressive drug combination	8.4±2.8
Group 4	5	14		39.1±6.2		-	-

Table 2: Treatment period and drugs

Groups	Number	Drugs	Period
Group 1	16	Infliximab	21.3±2.8 months
Group 1	8	Etanercept	19.4 ±4.1 months
Group 1	9	Adalimumab	24.8±3.1 months
Group 2	26	DMARDs	7.6±2.1 years
Group 3	15	(Immunosuppressive drug combination: cyclophosphomide + corticosteroids + chloroquine)	8.4±2.8 years

Toxoplasma Ig M ELISA was negative for all groups. Whereas 29 (87.9%) of RA patients treated by the biologic agents, 21 (80.8%) of RA patients treated by DMARDs, 15 (100%) of SLE patients and 4 (21.1%) of the controls were seropositive for Toxoplasma Ig G. The seropositivity ratio was statistically significant and higher ($p<0.001$) in all patient groups regardless of the treatment type according to control group, although there were no statistically significant difference in seropositivity ratio between the patient groups ($p=0.08$).

Discussion

Toxoplasmosis is one of the most important zoonotic diseases worldwide and is caused by the protozoan T. gondii. Members of innate immunity; T cells, NK cells and cytokines are the main response cells for T.gondii. İnterferon gamma (IFN-gamma), TNF-α, IL-2, IL-6, IL-10, IL-12 and IL-15 are the most important cytokines in response to the infection [7].

In our country many researchers have been made about toxoplasmosis. In these studies the prevalence of toxoplasmosis was found about 12-60 % [7]. Hazardous infections are well-known to occur in RA patients treated with TNF-α antagonists [8]. At the Arthritis Advisory Committee Meeting that was held in March 2003, 2782 cases of opportunistic infections during the treatment with etanercept and 1100 cases of opportunistic infections during the treatment with infliximab were reported through August 2000 [8]. The most common organism was Mycobacterium tuberculosis. Other organisms that cause opportunistic infections include fungi such as Histoplasma capsulatum and Coccidioides immitis, Pneumocystis jirovecii, yeasts such as Cryptococcus neoformans and candida species, molds such as Aspergillus, bacteria such as Listeria monocytogenes and Nocardia, the protozoan Toxoplasma, and the Cytomegalovirus [9,10].

Immunosuppressive treatment for SLE and anti-TNF-α treatment for RA, affects the patient's quality of life [11]. Although the most clinical expressions of acquired toxoplasmosis cases are asymptomatic, 10 % of the infections may cause serious morbidity and mortality in immunocompromised patients and congenitally infected infants [12]. Toxoplasmosis persists as a latent infection for the lifetime of the host. Toxoplasmosis can reactivate when the host becomes immunocompromised. Recently a few infections like cerebral toxoplasmosis and toxoplasmic chorioretinitis were reported due to these treatments [5,6].

T. gondii can infect and replicate in all nucleated cells. Different studies have showed that some proteins of T.gondii antigen can induce T cell proliferation and cytokine production. The production of IFN-gamma has been particularly shown in Toxoplasmosis, but there are limited data about IL-5 in clinical studies. These studies showed that the changes in IFN-gamma and IL-5 production are related to antibody responses in patients with different stages of toxoplasmosis [12]. On the other hands, it shouldn't be forgotten that polyclonal activation in RA can show cross-reactivity against specific antibodies in toxoplasmosis. This reactivation, which to be developed against RF, can affect the clinical process of RA patients.

There are a number of methods for the diagnosis of toxoplasmosis; however, serologic tests are the usual means of establishing the diagnosis. ELISA is used commonly due to its overall performance and cost. There is no single serologic test that can be used to support the diagnosis of acute or chronic infection [13].

In acute infection, IgM antibodies appear within the first week of infection, which expresses the acute phase of the infection. In the next phase, T.gondii IgM antibody titers decrease and IgG type antibody titer increase in serum within the two weeks of primary infection. These IgG type antibodies remain in serum lifelong at certain levels. IgM antibody disappears but the decline rate is variable from individual to individual, it takes months, sometimes years. For the understanding of approximate contagion date of toxoplasma infections 'IgG' avidity ELISA tests are being used. IgG antibodies appearing early in toxoplasma infection bind to antigen less avidly than antibodies appearing later, which bind with high avidity. Although the change of avidity from low to high varies from individual to individual, the presence of high avidity indicates that the infection occurred at least 3 to 5 months earlier [14]. In this study, patient and controls were evaluated by non-avidity ELISA tests. In our cases, there were no IgM type antibodies that express the acute toxoplasmosis infection. When the IgG antibody positivity frequency was obtained, no significant differences were found between controls and patients.

A limitation of the present study was a small sample size of patients suffering from RA and SLE. Further studies should have a larger sample size of patients.

In conclusion, during the immunosuppressive treatment the risk of toxoplasma infection should be considered as a result of increased seropositivity ratio. Awareness of the associated adverse events is necessary when using biological therapies in the treatment of RA. Patients should be advised for the risk of infections and must be closely monitored for early signs of infection. When opportunistic infections occur, withdrawal of biological therapies may be considered earlier until the infection has been identified and controlled.

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