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Seroprevalence of *Toxoplasma gondii* in HIV-infected patients admitted to a university hospital

Bir üniversite hastanesine başvuran HIV ile enfekte hastalarda Toxoplasma gondii seroprevalansı

Pınar Ergen, Fatma Yılmaz Karadağ, Özlem Aydın

[1]Medeniyet Üniversitesi Göztepe Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji, İstanbul, Türkiye

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ABSTRACT

Objective: *Toxoplasma gondii* may lead to opportunistic infections that threaten life in patients infected with HIV as opposed to the case of healthy individuals. It was aimed to investigate the seroprevalence of *Toxoplasma gondii* in HIV-infected patients admitted to our clinic.

Material and Method: The files of HIV-infected patients who were admitted to our polyclinic in the period of January 1995-December 2019 were examined. From the files, information was recorded on demographic characteristics, first diagnosis date, CD4+ T lymphocyte counts at first admission, HIV RNA, *T. gondii* IgG/M values and whether or not they received antibiotic prophylaxis.

Findings: Although the files of 804 HIV-infected patients were examined, data on *T. gondii* antibodies could be accessed only in the files of 685 patients. The median values of the ages and disease durations of the patients were respectively 33 (range: 17-83) and 4 (range 0-27) years. Among the patients, 88.5% (n: 606) were male. While no patients showed *T. gondii* IgM antibody positivity, 41.6% (n:285) had *T. gondii* IgG positivity. The CD4+ T lymphocyte count was under 100 in 10.0% (n: 68/678) of the patients, and among 36.8% (n: 25/68) of these patients, *T. gondii* IgG was positive. While *T. gondii* IgG positivity was significant in the patients over the age of 40 and those who were diagnosed before 2010, no significant relationship was found between sex, being men who have sex with men or not, CD4+ T lymphocyte counts and HIV-RNA values.

Conclusion: In patients with *T. gondii* IgG positivity, the risk of toxoplasmosis reactivation increases especially when the CD4+ T lymphocyte counts fall below 200. For this reason, investigating the seroprevalence of *T. gondii* in patients of all ages is important to be able to assess the risks that may develop, and it should be kept in mind that seropositivity may increase by advanced age.

Keywords: Toxoplasmosis, HIV, seroprevalence

ÖZ

Amaç: *Toxoplasma gondii*, sağlıklı bireylerin aksine HIV ile enfekte hastalarda hayatı tehdit eden fırsatçı enfeksiyonlara neden olabilmektedir. Kliniğimize başvuran HIV ile enfekte hastalarda *Toxoplasma gondii* seroprevalans araştırılması amaçlandı.

Gereç ve Yöntem: Ocak 1995-Aralık 2019 tarihleri arasında polikliniğimize başvuran, HIV ile enfekte hastaların dosyaları incelendi. Dosyalardan demografik bilgiler, ilk tanı tarihi, ilk başvurduklarında ölçülen CD4+ T lenfosit sayısı, HIV RNA, *T. gondii* IgG/M değerleri ve antibiyotik profilaksisi alıp almadıkları kayıt edildi.

Bulgular: HIV ile enfekte 804 hasta dosyası incelenmesine rağmen, sadece 685 hasta dosyasında *T. gondii* antikor verilerine ulaşılabildi. Hastaların yaş ve hastalık sürelerinin ortanca değerleri sırasıyla 33 (yaş aralığı: 17-83) ve 4 (yıl aralığı 0-27) yıldı. Çalışmaya katılanların %88,5' i (n:606) erkek hasta idi. Hastaların hiçbirinde *T. gondii* IgM antikor pozitifliği saptanmazken %41,6 (n: 285) 'da *T. gondii* IgG pozitifliği saptandı. Hastaların %10,0'unda (n: 68/678) CD4+ T lenfosit sayısı 100 altındaydı ve bunların %36,8 'inde (n: 25/68) *T. gondii* IgG pozitifti. *T. gondii* IgG pozitifliği istatistiksel olarak 40 yaş üzeri ve 2010 yılından önce tanı alan hastalarda anlamlı bulunurken cinsiyet, erkeklerle seks yapan erkek olup olmama, CD4+ T lenfosit sayısı ve HIV RNA değerleri ile arasında istatistiksel olarak ilişki saptanmadı.

Sonuç: *T. gondii* IgG pozitif olan hastalarda özellikle CD4+ T lenfosit sayısı 200'ün altına düştüğünde toksoplazmoz reaktivasyonu gelişme riski artmaktadır. Bu nedenle her yaştaki hastada *T. gondii* seroprevalansının araştırılması gelişebilecek riskleri değerlendirebilmek için önemli olup, ilerleyen yaşla birlikte seropozitifliğin artabileceği unutulmamalıdır.

Anahtar kelimeler: Toksoplazmoz, HIV, seroprevalans

Corresponding Author/Sorumlu Yazar: Pınar Ergen, Medeniyet Üniversitesi Göztepe Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji, İstanbul, Türkiye
E-mail/E-posta: pergen71@hotmail.com
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INTRODUCTION

Toxoplasmosis is a zoonotic infection caused by *Toxoplasma gondii*, which is an obligate intracellular parasite. While the disease may develop as a result of contact with cat excrements or raw or undercooked consumption of foods contaminated with excrements, it may also be transmitted through the vertical path from the mother to the fetus in pregnancy. It was also reported to develop in the form of organ transplantation and laboratory accidents (1-3).

It is estimated that a third of the world's population are infected with toxoplasma (4). Although the disease usually progresses asymptomatically in adults and healthy children, it may lead to life-threatening conditions in immunosuppressed individuals.

In patients whose immune system is suppressed by the human immunodeficiency virus (HIV), toxoplasmosis may appear as an opportunistic infection According to the 2018 data of the World Health Organization (WHO), 37.9 million HIV-infected individuals are living in the world, and 23.3 million individuals received antiretroviral treatment by the end of 2018 (5). While the risk of encountering opportunistic infections is reduced by highly active antiretroviral therapy (HAART), toxoplasmosis continues to be a significant problem for HIV/ AIDS (Acquired Immune Deficiency Syndrome) patients (4, 6). One of the risk factors for development of toxoplasmic encephalitis is a CD4+ T lymphocyte count of under 100/mm3 (7).

There are few studies in Turkey which investigated the seroprevalence of toxoplasmosis in HIV-infected patients. In this study, our purpose is to determine the toxoplasma seroprevalences of patients with a diagnosis of HIV/ AIDS who were admitted to our polyclinic at their first admission and to closely monitor patients in terms of latent infection reactivation and primary toxoplasmosis that may develop especially in patients with low CD4+ T lymphocyte counts.

MATERIAL AND METHOD

This study was approved by the university/local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of Medeniyet University Göztepe Education and Research Hospital Ethics Committee. (Permission granted 20.11.2019, Decision No. 2019/0466).

The files of patients who were admitted to our polyclinic for the first time in the period of January 1995-December 2019 whose HIV positivity was confirmed by Western Blot test were examined. From the patient files, information was retrospectively collected on demographic characteristics, date of first diagnosis, CD4+ T lymphocyte count measured at first admission to the polyclinic, HIV RNA viral load, *T. gondii* IgG and IgM values and whether or not they received trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis.

T. gondii IgG and M studied with the ELISA method, CD4+ T lymphocyte counts studied with the flow cytometric method and HIV RNA values measured by the PCR method were determined and recorded. The files of 804 HIV-infected patients could be accessed, but 119 patients whose *T. gondii* data could not be reached were removed from the study, and only 685 patients were included in the analysis. The relationship between patients age, sex, period when HIV was diagnosed, being men who have sex with men (MSM) or not, CD4+ T lymphocyte counts and HIV RNA values during first application, and *T. gondii* seroprevalence was evaluated statistically.

Statistical analyses were carried out using the SPSS IBM 22,0 (SPSS Inc, Chicago II) software. The descriptive results of the categorical variables are shown as frequency distributions and percentages. The data not conforming to normal distribution are expressed as median (minimum-maximum). While the categorical variables were analyzed, chi-squared or Fisher's exact test was used.

RESULTS

In the study, the data of 685 patients, including 606 (88.5%) male and 79 (11.5%) female patients, were analyzed. Among the male patients, 57.6% (n: 349) were MSM (men who have sex with men). The median values of the ages and disease durations of the patients were respectively 33 (range: 17-83) and 4 (range: 0-27) years. The demographic data and *T. gondii* IgG antibodies of the patients are shown in **Table 1**. 285 (41.6%) of the patients showed *T. gondii* IgG seropositivity. 68 (10.0%) patients had CD4+ T lymphocyte counts of lower than 100 cells/ mm^3, while 25 (36.8%) of these patients were positive for *T. gondii* IgG. Median value of CD4 + T lymphocyte counts was 371 (range: 0-1860), median value of HIV RNA was 205.387 IU/ml (range: 2 -198.700.180). **Table 2** shows the Toxoplasma antibody distribution by CD4 + T lymphocyte counts and HIV RNA levels.

The earliest diagnosis of the disease was made in 1992, and the toxoplasma antibody distribution in the infected patients based on years is shown in **Figure 1**.

Table 1. Distribution of patients according to demographic features

	T. gondii IgG positive n (%)	*T. gondii* IgG negative n (%)	Total n
Gender			
Woman	37 (46.8)	42 (53.2)	79
Male	248 (40.9)	358 (59.1)	606
Age			
18-40	179 (36.2)	315 (63.8)	494
41-60	85 (54.5)	71 (45.5)	156
61 and above	21 (61.8)	13 (38.2)	34
Education Level (n:351)			
University	85 (36.6)	147 (63.4)	232
Below university level	46 (38.7)	73 (61.3)	119
Contamination path			
Heterosexual relationship	126 (46.0)	148 (54.0)	274
Homosexual relationship	127 (36.4)	222 (63.6)	349
Unknown	32 (51.6)	30 (48.4)	62
Diagnostic History			
1992- 2000	10 (58.8)	7 (41.2)	17
2001-2009	42 (58.3)	30 (41.7)	72
2010-2019	233 (39.1)	363 (60.9)	596

Table 2. Toxoplasma antibody distribution by CD4 + T lymphocyte counts and HIV RNA levels

	T. gondii Ig G positive n (%)	*T. gondii* Ig G negative n (%)
CD4 + T Lymphocyte Counts (n:678)		
<100 (n: 68)	25 (36.8)	43 (63.2)
100-200 (n: 79)	29 (36.7)	50 (63.3)
201-500 (n: 334)	151 (45.2)	183 (54.8)
500 üzeri (n: 197)	76 (38.6)	121(61.4)
HIV RNA levels (n: 613)		
<10.000 (n:55)	25 (45.5)	30 (54.5)
10.000-100.000 (n:166)	58 (34.9)	108 (65.1)
100.001-1000000 (n:281)	119 (42.3)	162 (57.7)
>1.000.000 (n:111)	43 (38.7)	68 (61.3)

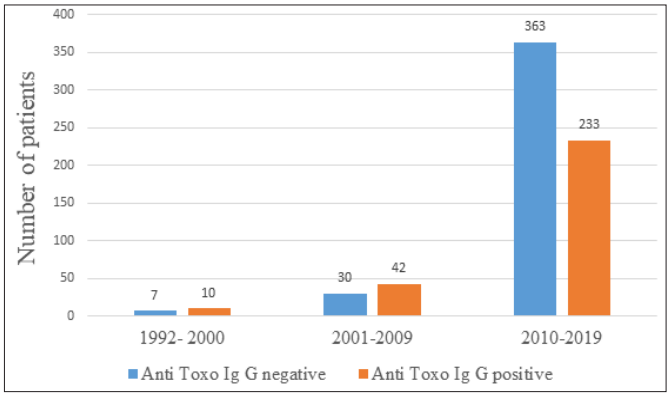

Figure 1. Toxoplasma antibody distribution in infected patients by years

T. gondii IgG positivity was significant in the patients over the age of 40 (p<0.001), while there was no significant relationship between sex (p=0.316) and CD4+ T lymphocyte counts (p=0.177), being MSM or not (p= 0.034) , HIV RNA values (p= 0.366). T.gondii IgG positivity within patients who diagnosed before 2010 and T.gondii IgG negativity within patients who diagnosed after 2010 were significantly higher. (p=0.003)

DISCUSSION

In the diagnosis of toxoplasmosis, investigation of IgG-type antibodies is a commonly used method. It is used in following immunosuppressive patients such as a HIV/AIDS and pregnant women (4). In two different studies investigating the seroprevalence of *T. gondii* IgG in HIV-infected patients in Turkey, respectively 614 and 164 patients were examined, and the rates were reported respectively as 43.5% and 52% (8, 9). In studies conducted in other countries, *T. gondii* IgG rates were determined as 21.1% in Iran, 9.7% in China, 13.6% in the USA, 57.6% in Ghana, 36.3% in Thailand and 80% in Brazil (10-15). In the meta-analysis conducted by Safarpour et al. (16) including 37 countries, 111 studies and 66,139 serum samples, the seroprevalence of *T. gondii* IgG was found as 44.22%. The *T. gondii* IgG positivity in our study was detected as 41.6%, which was similar to the results of previous studies in Turkey and the meta-analysis of Safarpour et al. (16). Seroprevalence rates may vary from country to country and based on ethnic and cultural structure, nutritional habits, education levels and socioeconomic levels.

In our study, the IgG positivity within patients older than 40 and patients who diagnosed before 2010 was found significantly higher. The reason why IgG positivity is seen more in patients older than 40 is attributed to the increasing risk of exposure to infectious agents as age increases. It is thought that seronegativity is increased with increase in drinking safe water, increase in public awareness of the risks of eating raw meat and the infections that may develop with it and change in our feeding habits. The meaningful increase in seronegativity in patients who diagnosed after 2010 brings risk of development of acute infections in patients. It is important to prevent the reactivation of latent infection in seropositive patients, as well as to take the necessary precautions to prevent the disease in seronegative patients.

In our study, unlike the study made by Şenoğlu and their friends in 2018, we didn't find any meaningful difference in IgG positivity within patients who are MSM. (8) Also there wasn't any significant difference between men and women as well as between HIV RNA levels and CD4+ lymphocyte levels.

In HIV-infected individuals, *T. gondii* most typically and prevalently involves the central nervous system and causes toxoplasmic encephalitis, while it may also lead to chorioretinitis, pneumonia, myocarditis, hepatitis, pancreatitis and septic shock-like clinical pictures. Toxoplasmic encephalitis, which emerges as the reactivation of latent infection, may progress fatally in HIV-infected patients (4, 17, 18). None of these presentations have been encountered in patients who have been followed in our clinic since 1995.

In HIV/AIDS-diagnosed patients with a CD4+ T lymphocyte count of under 200 cells/mm³, accompanying history of cancer chemotherapy and those who have been using rituximab-like biological agents or long-term steroid treatments, it is recommended to provide prophylactic antibiotics therapy to prevent opportunistic infections (16,19).

Primary antibiotic prophylaxis is used to protect patients with both negative and positive *T. gondii* serology. In the application of prophylaxis, TMP-SMX is the firstly preferred agent (20). As an alternative treatment to TMP-SMX, dapsone or pyrimethamine in *T. gondii* IgG negative patients and atovaquone, dapsone + pyrimethamine + folinic acid or atovaquone + pyrimethamine + folinic acid in positive patients are recommended (19,20). Prophylactic antibiotics usage may be stopped in patients with CD4+ T lymphocyte counts of higher than 100 cells/mm³ for at least three months and undetectable HIV RNA levels (19). With the start of HAART usage, a reduction was observed in opportunistic infections like toxoplasmic encephalitis by the decrease in the HIV viral load and the increase in the CD4+ lymphocyte counts. A randomized controlled study showed that there was no increase in the risk of toxoplasmic encephalitis development despite stopping prophylaxis (21). In a study in Denmark including 6325 HIV-infected patients in the pre-HAART (1995-1996) and HAART (1997-2014) periods, it was reported that, despite the start of HAART usage, toxoplasmic encephalitis may still be a cause of mortality and morbidity, but neurological sequalae and mortality considerably decrease by treatment (22).

In this study, 160/800mg TMP-SMX per day treatment was started in all patients with CD4+ T lymphocyte counts lower than 200 cells/mm³. Latent toxoplasma reactivation or toxoplasmic encephalitis cases were not observed during the follow up of the patients.

CONCLUSION

HIV-infected patients with *T. gondii* IgG negativity should be provided information regarding protection from consumption of infected meats and contaminated foods and contact with infected animal excrements, prophylactic antibiotics should be applied on all patients with CD4+ T lymphocyte counts of lower than 200 cells/mm³, and antibody screening should be performed to assess the risk of toxoplasmosis that usually emerges as the reactivation of latent infection.

ETHICAL CONSIDERATIONS

Ethics Committee Approval: The study was carried out with the permission of Medeniyet University Göztepe Education and Research Hospital Ethics Committee. (Permission granted 20.11.2019, Decision No. 2019/0466).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Status of Peer-review: Externally peer-reviewed.

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