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AN EVALUATION OF THE PREVALENCE AND INCIDENCE OF CEREBRAL TOXOPLASMOSIS INFECTIONAND EVALUATING THE RESPONSE TO TREATMENT IN HIV POSITIVE PATIENTS IN SHIRAZ, IRAN

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ABSTRACT

Toxoplasma gondii is an obligate intracellular pathogen spread worldwide which has infected approximately one third of the world's population. Toxoplasmosis is a dangerous opportunistic disease in HIV Positive patients. The most significant side effect caused by itisToxoplasmosisEncephalitis which has an important role in re-activation of the disease. The prevalence of the Toxoplasmosis and ToxoplasmosisEncephalitisvaries from country to country.381 HIV Positive patients were examined in this study, all of whom were tested for the IgG anti-Toxoplasmosis. Patients with hidden Toxoplasmosisweredetected**.** Based on their clinical manifestations, all the patients were under supervision for an entire year. In case of the clinical manifestations such as fever, headache, dizziness, convulsion, or others, brain MRI were run for the patientsand in case of Toxoplasmosis Encephalitis, Pyrimethamine, Sulfadiazine And Leucovorin were administered for them. The patients' response to the medications and the drugs' possible side effects were investigated. The obtained results were analyzed by the SPSS software. In this study, the prevalence of infection with Toxoplasma gondii and the incidence of encephalitis have been reported respectively as 29% and 2.9 percent.The prevalence of neurological symptoms in patients with Toxoplasma encephalitis include the following items: headache: 75%, fever: 75%, paralysis: 43/8 %, amnesia: 37/5 %,

confusion: 37/5 %, 25% seizures and convulsion, 25 percent , 18.8%aphasia and 18.8 percent coma. 62 % of patients responded to the initial treatment of Toxoplasma encephalitis and 3/56 percent showed early treatment-related complications. Toxoplasma gondii is a common infection among the HIV positive patients and Toxoplasma encephalitis is one of the most important signs of the reactivation of the disease in these patients. The prevalence of both these infections in this study is in accordance with other studies. The analysis of the Toxoplasmosis infection and prophylaxis treatment in patients with CD4< 100 is recommended.

Keywords: Toxoplasma gondii, Toxoplasma encephalitis, HIV

INTRODUCTION

Toxoplasma gondii is an intracellular Protozoan which has infected a large number of people worldwide. It is a distinguished cause of disease in Immuno compromised patients. Toxoplasmosis usually remains as latent and asymptomatic in all healthy people and people with impaired immune systems. However, HIV positive patients are at the risk for the reactivation of the disease and the appearance of its symptom due to their immune deficiency [1, 2]. The reactivation of the latentToxoplasmosis in particular leads to cerebral toxoplasmosis, which, in its own turn can brings about the death of the patients if it goes unnoticed.The most common site of involvement of Toxoplasma gondii infection in people with HIV is the central nervous system which leads to neurologic symptoms[3, 4]. The early treatment for Toxoplasmosis Encephalitisis a combination of Pyrimethamine and Sulfadiazine. Such patients receive daily dose of Leucovorin, as well, in order to prevent the inhibition of folic acid synthesis chain and show less hematologic complication. However, in this case, the disease is more likely to return [5]. Due to the lack of information regarding the prevalence and the appearance of Toxoplasmosis infection and ToxoplasmosisEncephalitis in Iran, the aim of this paper holds an investigation of the prevalence and the appearance of the disease and its neurologic symptoms, and also the patients' response to the early treatment in order to compare these results with other studies performed in other countries and finally evaluate the necessity of administrating the prophylaxis treatment in HIV positive patients.

MATERIALS AND METHODS

381 HIV positive patients who were referred to behavioral disease center, affiliated with the University of Medical Sciences, Shiraz, for periodic checkups,

were enrolled in the study. These patients were initially visited by an internist resident. In case they agreed to participate in the study, an informed consent form which included age, sex, occupation, place of residence, and transmission of HIV infection was signed and completed by them. In all patients, anti-Toxoplasma antibodies were measured through immune fluorescent IgG. CD4 level was also measured. The patients were visited by the doctor every three months during the project's time span (12 months). They were given certain information about Toxoplasmosis-related brain disorder so that in case of fever, headache and focal neurological symptoms, an MRI could be run for them and the cerebral toxoplasmosis infection be detected. After the diagnosis of cerebral toxoplasmosis infection, Pyrimethamine, Sulfadiazine, and Leucovorin were administered for them. Treatment response signs including improvement of neurological symptoms, the patient's general status and changes in MRI were controlled. If the patient did not respond to the common treatment, other differential diagnoses such as Brain lymphoma and brain biopsy were recommended. However, no case of brain biopsy was recorded in the present study. The following drug side effect indexes were also analyzed in patients: fever, stress, vomiting, and inhibition of bone marrow. The inclusion criterion was an HIV diagnosis by WESTERN BLOT test and the completion of informed contest form by the patient. The exclusion criterion was the patient's refusal to participate in the study.

STATISTICAL ANALYSIS

The gathered information was analyzed by the SPSS software. Chi square and T test were also used in the analysis process.

RESULTS

Out of the 381 HIV positive patients enrolled in the study, 121 patients (31.8%) were female and 260 patients (68.2%) were male. The entire population was divided into the four following age groups:

a) 0 to 15 years old: including 16 patients (4.2%)
b) 16 to 30 years old: including 62 patients (16.3%)
c) 31 to 50 years old: including 276 patients (72.4 %)
d) Above 50 years old: including 27 patients (7.1%)

The patients' place of residence was also checked. 61.7 % of them lived in Shiraz and the remaining 38.3 % lived in the suburbs.

6 (1.6 %) of patients were employees, 127 (33.3 %) were self-employed, 200 (52.5 %), unemployed, and 48 (6/12 %) were housewives.

Transmission of HIV infection in all patients was investigated. 119 patients (31.2%) were infected through drug injection needles. 139 patients (36.5%) were infected through unprotected sexual intercourse. 78 patients (20.5%) were infected through both drug injection needles and unprotected sexual intercourse. 18 patients (4.7%) were infected through blood products. In 16 of them (4.2%), the transmission occurred through the infected mother to the child and ultimately, 11 patients (2.9%) were infected through various other means.

The patients were divided into four groups based on the analysis of their blood's CD4. The first group included 17 patients (4.5%) who had CD4≤50. The 26 patients (6.8%) in the second group had a CD4 level ranging from 51 to 100. The third group had 86 patients (22.6%) who had a CD4 level ranging from 101 to 200 and finally the fourth group included 252 patients (66.1%) who had CD4> 200.

Serum level of IgG for Toxoplasma infection was measured. 110 (29%) had a positive and 271 patients (71%) had a negative antibody test. The percentage of Toxoplasma infection in men and women based on the Toxoplasmosisantibody test was respectively 22 % and 32%. All the patients were examined for Toxoplasma encephalitis. 11 cases were diagnosed with Toxoplasma encephalitis during a year follow-up (2.9% manifestation).Five patients had already developed Toxoplasma encephalitis before the study began. (4.2% prevalence).12.7% of HIV positive patients with positive Toxoplasmosisserology developed cerebral toxoplasmosis during the one year period of the study.

The prevalence of the neurologic complications in Toxoplasma encephalitis patients is as follows:

Based on the age, Toxoplasma encephalitis was not observed in patients 15 years old and younger. However, 4 people in 16 to 30 years old age group, 11 people in 16 to 30 years old age group, and one person in 31 to 50 years old age group had developed Toxoplasma encephalitis. In the age group of 16 to 30 years old, one person (25%) suffered from convulsion, aphasia, and coma. Two people (50%) suffered from headache, paralysis and confusion. Three patients (75%) had fever. In the age group of 31 to 50 years old, 1 patient (9.1%) suffered from aphasia, two people (18.2%) went into a coma, three patients (27.3) had seizure, and 4 patients (36.4%) showed signs of paralysis, amnesia and confusion. Ninepatients (81.8%) had headache and fever. Finally, the only patient who was more than 50 years old showed the signs ofheadache, paralysis and aphasia.

The most common neurologic symptoms in Toxoplasma encephalitis patients are as follows: 75% headache and fever, 43.8% paralysis, 37.5% amnesia and confusion, 25% seizure and 18.8% aphasia and coma.

Their response to treatment was similarly reported as follows:

The overall response in the entire population of the study was estimated as 62.5%. With respect to sex, both women participating in the study responded well to the treatment; however, from among the 14 men taking part in this study, only eight men (57.1%) responded to the treatment of Toxoplasma encephalitis. Based on the level of CD4, the results were reported as such: in the group with CD4≤50, 4 out of 7 patients (57.1%) responded to the treatment. In the second group which had a range of CD4 between 51 to 100, 3 out of 5 patients (60%) responded to the treatment. In the third group whose CD4 was between 101 to 200, 2 out of 3 patients (66.6%) responded to the treatment and in the last group with CD4>200, there was only one patient who responded well to the Toxoplasma encephalitis treatment.

Based on the findings of this study, the degree of response to treatment is in direct relation with the level of CD4 in the early phases of cerebral Toxoplasma.

Patients with Toxoplasma encephalitis were examined for the incident of drugs' side effect. In 9 patients (56.3%) the signs of side effect appeared. Long term cerebral complications, including Unilateral or bilateral cerebral palsy, seizure, aphasia and focal neurological deficit continued to exist in 30% of patients who did respond to the treatment.

The incidenceof cerebral Toxoplasma was analyzed with respect to age. In the group belonging to 15 year old or less, there was no incident of Toxoplasma encephalitis. In the group of 16 to 30 years old, 31 to 50, and above 50 years old, the incident of Toxoplasma encephalitis was respectively 4.9%, 2.57%, and 3.7%.

Theincidenceof disease was analyzed with respect to the patients' sex. The data revealed that the incidenceof the disease is 1.6% in women and 3.5% in men.

The incidencewas also checked with respect to the level of CD4. The incidenceresults are as follows:

a) CD4≤50: 29.4%
b) CD4 range of 51 to 100: 11.5%
c) CD4 range of 101 to 200: 2.3%
d) CD4> 200: less than 0.05

Table 1: The incidence of Cerebral Toxoplasma Based on Age, Sex and CD

The incidenceof cerebral Toxoplasma based on		Percent
age	15 year old or less	0
	16 to 30	4.9
	31 to 50	2.57
	above 50above 50	3.7

sex	**Male**	**3.5**
	Female	**1.6**
CD4	**CD4≤ 50**	**29.4%**
	CD4 range of 51 to 100	**11.5%**
	CD4 range of 101 to 200	**2.3%**
	CD4> 200	**> 0.05**

The prevalence ofdisease was analyzed with respect to the age. In patients of 15 years old or less, there was no incident of prevalence observed. In patients between 16 to 30 years old, 6.4%; in patients between 31 to 50 years old, 4% and in patients above 50 years old 3.7% of prevalence was detected.

The prevalence of disease was analyzed with respect to the patients' sex. The data revealed that the prevalence of the disease is 1.6% in women and 5.4 % in men.

The prevalence of the disease was also checked with respect to the level of CD4. The prevalence results are as follows:

CD4≤ 50: 41. b) CD4 range of 51 to 100: 19, c) CD4 range of 101 to 200: 3.4, d) CD4> 200: less than 0.05.

Table 2: The Prevalence of Cerebral Toxoplasma Based on Age, Sex and CD4

The prevalence of cerebral Toxoplasma based on		**Percent**
Age	**15 year old or less**	**0**
	16 to 30	**6.4%**
	31 to 50	**4%**
	above 50above 50	**3.7%**
Sex	**Male**	**5.4**
	Female	**1.6**
CD4	**CD4≤ 50**	**41**
	CD4 range of 51 to 100	**19**
	CD4 range of 101 to 200	**3.4**
	CD4> 200	**> 0.05**

With regard to the fact that the highest risk of infection with Cerebral Toxoplasma happens in CD4<100, the initial prophylaxis begins with the reduction of CD4 to less than 100. The prevalence of Cerebral Toxoplasma infection in CD4<100 was estimated as 27 percent.

The prevalence of the disease was also analyzed based on the disease transmission.

Table 3: The prevalence of the disease based on the HIV transmission

Variable	**Percentage**
Injection	**6.7**
Sexual intercourse	**2.8**
Unprotected sex and injection	**5.1**
Blood products and Congenital transmission	**0**

The prevalence was also checked based on the occupation of the patients. None of the employee patients developed Cerebral Toxoplasma. The self-employed patients showed a prevalence of Cerebral Toxoplasma was6.2, while this rate in

housewives and the unemployed was respectively 4 and 3 percent. 5.1 % of inhabitants of Shiraz and 2.7 % of patients residing in the suburb developed the Cerebral Toxoplasma prevalence.

Ultimately, the Diagnostic methods of Cerebral Toxoplasma in the study's population were investigated. In most cases, diagnose was performed based on the positive serology, clinical features and MRI (87.5%). Two of the Cerebral Toxoplasmosis patients had the negative serology (12.5%), in whose case, diagnose was performed based on the clinical features and MRI. There was no case of brain biopsy. Similarly, PET, SPECT, and other differential diagnostic methods, which are generally used for Toxoplasma encephalitis and cerebrallymphoma, were not used in this study.

DISCUSSION

381 HIV positive patients were enrolled in this study. 72.4% of them were aged between 31 to 50. The patients were examined for the Anti-toxoplasmosis IgG test. The test result revealed that 29 of them had the positive Anti-toxoplasmosis IgG; a fact that underlies the prevalence of the toxoplasmosis infection in HIV patients. This finding is in accord with the study performed byAlvarado-Esquivel et al [6]in 2012. However, the study carried out by Uneke et al [7] in Nigeria or Okwuzu et al [8] in 2014 shows that the toxoplasmosis infection has a larger prevalence.

In this study, 22 percent of HIV positive women and 32 % of HIV positive men had positive serologic Toxoplasma. However, this was in contrast to the findings of Okwuzu et al [8] and Shimelis et al [9]. They found out that the percentage of Toxoplasma infection in women is higher than in men. This difference may be due to the difference in infection and transmission of HIV in Iranian society with that of other studies.

In this study the incident of Toxoplasma encephalitis has been reported as 2.9% which corresponds closely with a research carried out in France eight years ago[10].The majority of Toxoplasma encephalitis patients (68.7%) were in the age range of 31 to 50. A small number of them were under 30 years old and even lesser number of them was more than 50 years old. These results are synonymous with the study of Veeranoot et al. [11] in 2014. In their study, they stated that patients who are under 50 years old are exposed to the highest risk of Toxoplasma encephalitis; a result which has been confirmed by other studies as well[12, 13].

The patients have been divided into four groups based on the CD4. The ≤CD4 category had the largest number of patients. It was also concluded that the higher the

CD4, the fewer the number of the Toxoplasma encephalitis patients. Only one patient out of 16 diagnosed patients had CD4>200. The CD4≤50 category had the minimum level of the prevalence of HIV patient with a positive serologic Toxoplasma. The prevalence of Toxoplasma encephalitisis as follows:

1) CD4≤ 50: 41, **2**) CD4 range of 51 to 100: 19, **3**) CD4 range of 101 to 200: 3.4

This finding points to an increase in the prevalence in CD4<100.Veeranoot and colleagues [11] similarly found a close relation between CD4<100 and the incidence of Toxoplasma encephalitis. In a similar manner, Sellbrink et al. [14] confirmed that it is highly unlikely to find the incident of Toxoplasmosis infection at a CD4>200.

The prevalence of the neurologic symptoms was also investigated in this study. The most common symptom in patients of 16 to 30 years old was fever and least common symptoms included seizure, aphasia, and coma. However, headache and fever were reported in patients aged 31 to 50. Based on CD4, the most prevalent symptom in CD4≤50, and also in CD4 51 to 100 was fever. Nevertheless, in CD4>100, fever was the most prevalent symptom reported. By and large, in this study, the prevalence of neurologic symptoms included the following: headache, fever, paralysis, confusion, seizure, aphasia, and coma. Chaddha et al. similarly reported fever, seizure and headache as the most prevalent neurologic symptoms [15]. Ragnaud and colleagues [16] stated that fever, headache, seizure and paralysis are the most prevalent neurologic symptoms.

In this study, the diseasewasanalyzed based on the patients' occupation. The highest and lowest rate of prevalence of Toxoplasma encephalitis was detected respectively in self-employed individuals and in employees; a result which is in correspondence with the findings ofShimelis et al [9]. In their study, the highest rate of prevalence of Toxoplasma encephalitis was detected in self-employed individuals; however, the lowest rate of prevalence belongs to the student.

An increase in the level of CD4 caused a better response to treatment in patients. The minimum level of response belongs to the patients with CD4≤5. 56.3% of patients showed the signs of drugs' side effect throughout the treatment process.

The findings of this study correspond with the majority of other researches carried out prior to the present research. The prevalence of Toxoplasmosis infection in this research was less than the number reported in other researches; a fact than can probably be due to the lack of proper

cooperation on the side of the patients during the follow ups. Furthermore, the number of female patients with Toxoplasma encephalitis has been less than other studies, a fact which has been due to the lower rate of HIV prevalence in Iranian women. Similar to previous studies, the highest rate of Toxoplasma encephalitis prevalence in this study, too, has been reported in the age group of 30 to 50 years old. 37.5 % of Toxoplasma encephalitis patients did not respond to the early treatment with Pyrimethamine and Sulfadiazine. 56.3% of them manifested signs of drugs' side effect. Thus, a prophylaxis treatment with the CD4 level of <100 is recommended for the HIV patients.

REFERENCES

[1] Porter SB, Sande MA. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. N Engl J Med 1992; 327:1643–8.

[2] Renold C, Sugar A, Chave JP, et al. Toxoplasma encephalitis in patients with the acquired immunodeficiency syndrome. Medicine (Baltimore) 1992; 71: 224–39.

[3] Jones JL, Hanson DL, Dworkin MS, et al. Surveillance for AIDS-defining opportunistic illnesses, 1992–1997. MMWR CDC Surveill Summ 1999; 48: 1–22.

[4] Porter SB, Sande MA. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. N Engl J Med 1992; 327:1642.

[5] Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV infected adults and adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/contentfiles/lvguideline s/adult_oi.pdf (Accessed on January 17, 2014).

[6] Alvarado-Esquivel C, Estrada-Martínez S, García-López CR, Rojas-Rivera A, Sifuentes-Álvarez A, Liesenfeld O: Seroepidemiology of Toxoplasma gondii Infection in Tepehuanos in Durango, Mexico. Vector Borne Zoonotic Dis 2012;12:138–142.

[7] Uneke C.J, Duhlinska D.D, Njoku M.O, Ngwu B.A. Seroprevalence of acquired toxoplasmosis in HIV-infected and apparently healthy individuals in Jos, Nigeria. Parassitologia 2005; 47(2): 233-236.

[8] OkwuzuJ,Odunukwe N, Ezechi O, Gbajabiamila T, Musa A, Ezeobi P, Oke B, Somefun, Okoye R, Onyeitu C,

Adetunji M, Otubanjo A. Toxoplasma gondii infection in HIV/AIDS: prevalence and risk factors. Afr. J Cln. Expermicrobiol. 15(2): 97-102.

[9] Techalew Shimelis, Mekashaw Tebeje, Endale Tadesse, Belete Tegbaru and Ashenafi Terefe. Sero-prevalence of latent Toxoplasma gondii infection among HIV-infected and HIV-uninfected people in Addis Ababa, Ethiopia: A comparative cross-sectional study. BMC Research Notes 2009; 2: 213.

[10] Belanger F, Derouin F, Grangeot-Keros L, Meyer L. Incidence and risk factors of toxoplasmosis in a cohort of human immunodeficiency virus-infected patients: 1988-1995. HEMOCO and SEROCO Study Groups. Clin Infect Dis., 1999; 28:575.

[11] Veeranoot Nissapatorn, Christopher Lee, Kia FattQuek, Chee Loon Leong, Rohela Mahmud and Khairul Anuar Abdullah. Toxoplasmosis in HIV/AIDS Patients: A Current Situation. Jpn. J. Infect. Dis. 2004; 57:160-165.

[12] Falusi O, French AL, Seaberg EC, Tien PC, Watts DH, Minkoff H, Piessens E, Kovacs A, Anastos K, Cohen MH: Prevalence and Predictors of Toxoplasma Seropositivity in Women with and at Risk for Human Immunodeficiency Virus Infection. Clin Infect Dis 2002; 35:1414-1417.

[13] Jones JL, Kruszon-Moran D, Wilson M, McQuillan G, Navin T, McAuley JB: Toxoplasma gondii Infection in the United States: Seroprevalence and Risk Factors. Am J Epidemiol 2001; 154(4):351-364.

[14] Sellbrink H.I, Fuhrer-Burrow R, Raedler A, Albrecht H, Fenske S. Risk factors for severe Disease due to Toxoplasma gondii in HIV- positive patients.European Journal of Epidemiology, 1993;9(6): 633-637.

[15] Chaddha DS, Kalra SP, Singh AP, Gupta RM, Sanchetee PC. Toxoplasmic encephalitis in acquired immunodeficiency syndrome. J Assoc Physicians India. 1999 Jul; 47(7):680-4.

[16] Ragnaud JM, Morlat P, Dupon M, Lacoste D, Pellegrin JL, Chene G. Cerebral toxoplasmosis in AIDS.73 cases.Clinical Epidemiology Group on AIDS in Aquitania. Presse Med. 1993 May 29; 22(19):903-8.