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Original Article

Toxoplasmosis in HIV/AIDS Patients: A Current Situation

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SUMMARY: The seroprevalence of toxoplasmosis among 505 of human immunodeficiency virus (HIV)/AIDS patients was 226 (44.8%; 95% CI 42.64 - 51.76): 27 (47.4%) and 199 (44.4%) showed *Toxoplasma* seropositivity with and without toxoplasmic encephalitis (TE), respectively ($P < 0.05$). The majority of these patients were in the 25 - 34 age group (44 versus 39%), male (86 versus 76%), and Chinese (49 versus 53%), though no statistical significance was found between the two. Significant differences between these two groups were noted, however, in terms of marital status, occupation, and present address. The heterosexual exhibited the most frequent behavior at risk for HIV infection, and accounted for 51 and 59% of patients with and without TE, respectively. Only 17/260 (6.5%) and 1/137 (0.7%) of them later acquired TE after receiving primary chemoprophylaxis (cotrimoxazole) and antiretroviral therapy including HAART ($P < 0.05$). Fifty-seven (11.3%) out of those 505 patients were diagnosed with AIDS-related TE. The most common clinical manifestation was headache (56%). The computed tomography scan findings showed most lesions to be multiple (96.4%), hypodense (66.7%), and in the parietal region (39.3%). Twenty-seven (47.4%) patients had chronic (latent) *Toxoplasma* infection as evidenced by seropositivity for anti-*Toxoplasma* (IgG) antibody. At the time of diagnosis, the range of CD4 cell count was from 0 - 239 with a median of 25 cells/cumm. We also found that a CD4 count of less than 100 cells/cumm was significantly associated with development of TE ($P < 0.05$). Clinical outcomes showed that among those who survived, 21 (36.8%), 16 (28.1%), and 2 (3.5%) of patients had completed treatment, transferred out, and were lost to follow up, respectively. Unfortunately, 18 (31.6%) of the cases were officially pronounced dead. Overall, 7 (12.3%) patients were detected as recurrent TE in this study.

INTRODUCTION

Toxoplasma gondii is a ubiquitous, intracellular protozoan parasite, and causes cosmopolitan zoonotic infection. Human latent toxoplasmosis occurs in about half the world's population though most cases are asymptomatic. With the advent of the human immunodeficiency virus (HIV) pandemic, toxoplasmic encephalitis (TE) has become one of the more frequent opportunistic infections and the most common cause of focal brain lesions complicating the course of AIDS (1,2). If untreated, TE is uniformly fatal (3). Few studies, however, have been done on toxoplasmosis among HIV/AIDS patients in Malaysia or in the Southeast Asian subcontinent. We therefore conducted this study expressly to determine the seroprevalence of toxoplasmosis among HIV/AIDS patients, and to determine the frequency distribution and the course of TE in term of sociodemographic characteristics, clinical manifestations, laboratory data, and the outcome of TE in AIDS patients.

MATERIALS AND METHODS

Patients: This retrospective and descriptive study was carried out at the Out-Patient Department and In-Patient Ward for infectious diseases in Hospital Kuala Lumpur, which holds 2,502 beds and is the largest government tertiary referral hospital. Its main focus is on public services. Each month, about 30 new and 300 follow-up patients with HIV-infection come to this hospital for medical treatment. We were able to review the medical records of 505 HIV-infected patients admitted from January 2001 to December 2002; 499 patients were newly diagnosed HIV patients, the other 6 previously diagnosed patients who were recruited for this study because they were diagnosed with recurrent TE coincident with its conductance. They were examined and their records were screened via on the standardized data collection sheet for demographic characteristics such as age, sex, race, marital status, occupation and present address, risk factors for HIV transmission, clinical and laboratory data, and outcome relating to toxoplasmosis.

Diagnoses of TE were made based on the presence of at least two of the following findings: a history of neurological symptoms, neurological signs at admission, or suggestive computed tomography (CT), all associated with the introduction of anti-TE (fansidar + clindamycin/dapsone) therapy. Using the same form, we also analyzed files from AIDS patients with other central nervous system (CNS) infections, such as cryptococcosis, primary CNS lymphoma, and tuberculosis, for correction of finally undefined bias. All of these patients presented with neurological manifestations; 30 (52.6%) patients were diagnosed based only CT scan findings, 26 (45.6%) based on both CT scan findings and positive serodiagnosis, and one (1.8%) based on positive serodiagnosis. A good therapeutic response was defined as improvement of clinical condition, regression of neurological signs and

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symptoms, and/or improvement on CT scan. Recurrent TE was defined as a second episode that occurred after resolution of the first acute episode of TE or during its maintenance. Toxoplasmosis was screened by standard ELISA commercial kit (AxSYM, Abbott Laboratories, Abbott Park, Ill., USA) in accordance with the manufacturer's instructions. A titer of anti-*Toxoplasma* (IgG) antibody ≥3 IU/ml was considered positive in this study. AIDS-defining illnesses were also based on the 1993 Centers for Disease and Control and Prevention, but the criteria of CD4 cell count was not used.

Statistical analysis: The data was analyzed by using the statistical software SPSS version 10 (SPSS Inc., Chicago, Ill., USA). The data on quantitative variables were indicated by mean and range, the qualitative variables by frequency and percentage. Statistical analysis was estimated using either chi-square test or Fisher's exact test where appropriate. A *P*-value of <0.05 was regarded as statistically significant.

RESULTS

We retrospectively reviewed 505 HIV/AIDS patients who attended the Hospital Kuala Lumpur between January 2001 and December 2002. The seroprevalence of toxoplasmosis among these 505 HIV/AIDS patients was 226 (44.8%; 95% CI 42.64 - 51.76): 27 (47.4%) and 199 (44.4%) showed *Toxoplasma* seropositivity with and without TE, respectively ($P < 0.05$). We found that the mean age of patients with TE was significantly higher than that of patients without TE ($P < 0.05$). The majority of them were in the 25 - 34 age group (44 versus 39%), male (86 versus 76%), and Chinese (49 versus 53%), though no statistical significance was found between the two groups. Significant differences were noted between these two groups in terms of marital status, occupation, and present address. A high percentage of patients in both groups were mainly unemployed (75 versus 51%). The majority of patients with TE were single (70%) and resided outside Kuala Lumpur (68%), and that of patients without TE were married (51%) and resided in Kuala Lumpur (57.6%). Heterosexuals demonstrated the most frequent high risk behavior for HIV infection, and accounted for 51% of patients with TE and 59% of patients without TE. Overall, the range of CD4 cell count was from 0 - 1312 with a median of 229 cells/cumm, while the range of CD4 cell count was 0 - 239 with a median of 25 cells/cumm at the time of diagnosis in patients with TE. We also found a significantly relationship between CD4 cell count of less than 100 cells/cumm and development of TE ($P < 0.05$). Our data showed that 260 (51.5%) and 137 (27%) of patients received primary chemoprophylaxis (cotrimoxazole) and antiretroviral therapy including HAART before the onset of TE, and only 17/260 (6.5%) and 1/137 (0.7%) of those patients later (at the time of this study) had TE ($P < 0.05$) as shown in Table 1.

Table 2 illustrates that 57/505 (11.3%) of patients were diagnosed with AIDS-related TE. Headache (56%) was the most common clinical manifestation, followed by fever (45.6%) and hemiparesis (44%). Twenty-seven (47.4%) patients had chronic (latent) *Toxoplasma* infection as evidenced by seropositivity for anti-*Toxoplasma* (IgG) antibody. The CT scan findings showed most lesions to be multiple (96.4%), hypodense (66.7%), and in the parietal region (39.3%). Clinical outcomes showed that among those who survived, 21 (36.8%), 16 (28.1%), and 2 (3.5%) of patients had completed treatment, transferred out, and were lost to follow up, respectively. Unfortunately, 18 (31.6%) of cases, 16 acute and 2 relapse TE cases, were officially pronounced dead during hospitalization. The range of survival time from the initiation of anti-*Toxoplasma* therapy to death was between 2 to 528 days with a median of 15.5 days. The causes of death were TE in 6/57 (10.5%) and from TE-related other diseases in 12/57 (21.1%). From our data, we found that two of the decreased patients had received HAART before (1 patient) and at/after (1 patient) the onset of TE, respectively. At the time these patients were declared dead, the diseases concurrent with TE were as follows: 3 patients with pulmonary tuberculosis; 2 patients with sepsis; 1 patient with MRSA, septicemia, and toxic epidermal necrolysis syndrome; 1 patient with pneumonia and sepsis; 1 patient with cryptococcal meningitis; 1 patient with pancreatitis; 1 patient with G6PD deficiency; 1 patient with aspirated pneumonia; and 1 case with pulmonary tuberculosis and upper GI bleeding. Further, we found that only 1 patient experienced side effects from anti-*Toxoplasma* drugs (particularly fansidar), 4 patients were shown to be non-compliant to anti-tubercular therapy, and another 7 patients had shown signs of a weakening immune system due to complications of other, coexisting diseases. Overall, 7/57 (12.3%) of them were detected to have recurrent TE, presumably due to discontinuation of their maintenance therapy, and 6 cases had a history of TE prior to this study.

DISCUSSION

Our data showed the seroprevalence of latent *Toxoplasma* infection to be 44.8%. In Malaysia, a few previous studies involving HIV-positive patients have reported seroprevalence in a range of 20 - 51% (4-7). However, geographical variation of prevalence of toxoplasmosis has been found: 50% in Mexico (8), 36.7% in Spain (9), 53.7% in Thailand (10), and 15% in USA (11). Toxoplasmosis is a silent disease, which poses many diagnostic and therapeutic challenges for clinicians treating HIV infected patients (12). Based on the findings of this study, we support a screening program of *Toxoplasma* infection, such as the one implemented in this hospital, where latent toxoplasmosis is still prevalent with concurrent of HIV infection, in the past few years. Nevertheless, HIV-infected persons who are *Toxoplasma* seropositive may also be advised about preventive behavioral practices such as eating only well-cooked meats, washing their hands after outdoor activities involving soil contact and after contact with cats (13). Along with the support of our significant findings, primary chemoprophylaxis should be routinely given to any HIV-positive patients with *Toxcoplasma* seropositive status, in order to prevent the risk of developing life-threatening secondary reactivation of cerebral toxoplasmosis in association with AIDS (14). Therefore, evaluations of immunocompromised patients need to be constantly enforced; this will ultimately contribute to eliminate this opportunistic pathogen.

TE accounts for 11.3%, which result is similar to that in a previously reported study in Malaysia (6). TE is a secondary brain disease and the third most common opportunistic infection of the CNS among AIDS patients in this hospital. With regard to demographic profiles, we observed that the peak incidence of TE was in patients less than 50 years old, and highest among those between of 25 and 34. This is due to the fact that the incidence of TE is directly proportional to the prevalence of latent *Toxoplasma* infection, which increases with increasing age (15) and declines when one becomes much older. Moreover, one study found that racial origins and

Table 1. Demographic and baseline characteristics among 505 HIV/AIDS patients who attended at the Hospital Kuala Lumpur during January 2001 to December 2002

Characteristics	Without TE (%) $n = 448$	With TE (%) $n = 57$	*P*-value
Range of age = 17 - 71 y	19 - 71 y	17 - 48 y	
Mean (± SD) = 36.6 ± 9.4 y[1)]	34.4 ± 7.30 y	36.9 ± 9.56 y	0.050
Male:Female ratio = 3.3:1	3.1:1	6.1:1	
Age group			0.321
15-24 y	26 (5.8)	4 (7)	
25-34 y	178 (39.1)	25 (44)	
35-44 y	160 (35.7)	23 (40.4)	
≥ 45 y	84 (18.8)	5 (8.8)	
Sex			0.083
Male	339 (75.7)	49 (86)	
Female	109 (24.3)	8 (14)	
Race			0.670
Malay	143 (32)	18 (31.6)	
Chinese	237 (53)	28 (49.1)	
Indian	46 (10.3)	6 (10.5)	
Others[2)]	22 (5)	5 (8.8)	
Marital status[1)]			0.002
Single	218 (48.7)	40 (70.2)	
Married	230 (51.3)	17 (29.8)	
Occupation[1)]			0.002
Laborer	84 (18.8)	8 (14)	
Nonlaborer	134 (30)	6 (10.5)	
Unemployed	230 (51.3)	43 (75.4)	
Present address[1)]			0.001
Kuala Lumpur	258 (57.6)	18 (31.6)	
Outsider	190 (42.4)	39 (68.4)	
Mode of HIV transmission			0.223
Heterosexual	266 (59.3)	29 (51)	
Homosexual	13 (3)	–	
Intravenous drug user	99 (22)	24 (42.1)	
Blood transfusion	7 (1.6)	1 (1.8)	
Combined	59 (13.2)	3 (5.3)	
Tattoo	1 (0.2)	–	
Not known	3 (0.7)	–	
Seroprevalence of toxoplasmosis[1)]			0.001
Positive	199 (44.4)	27 (47.4)	
Negative	249 (55.6)	4 (7)	
Not known	–	26 (45.6)	
CD4 cell count[1)]			0.001
< 100	140 (31.3)	34 (59.7)	
≥ 100	296 (66.1)	5 (8.8)	
Not known	12 (2.7)	18 (31.6)	
History of primary prophylaxis used[1)]			0.001
No	205 (45.8)	29 (51)	
Yes: before the occurrence of TE	243 (54.2)	17 (29.8)	
: at/after the occurrence of TE	–	11 (19.3)	
History of antiretroviral or HAART therapy[1)]			0.001
No	312 (69.6)	41	
Yes: before the occurrence of TE	136 (30.4)	1	
: at/after the occurrence of TE	–	15	

TE: toxoplasmatic encephalitis.
[1)]: $P < 0.05$ for differences between patients with and without TE by 2 samples χ^2 test.
[2)]: Other included foreigners who were classified as persons with foreign nationality and persons with first and/or family names that were clearly not Malaysian.

modes of transmission particularly among heterosexuals and intravenous drug users contributed to the occurrence of TE (16). Other characteristics remain incompletely defined. However, a few studies have demonstrated that cellular immunity and strain-specific difference in the parasite play an essential role in the development of TE (17-19).

In terms of the clinical scenario, focal neurological defects such as fever, headache, seizure, and hemiparesis were the most common symptoms found in our patients and in those in previous studies (20-24). Although these symptoms may mimic those of other neurological diseases, it is nonetheless recommended that the possibility of cerebral toxoplasmosis

Table 2. Clinical manifestations, investigations, and treatment outcome of 57 toxoplasmic encephalitis patients

Characteristics	No. of patients (%)
Clinical manifestation	
Headache	32 (56)
Fever	26 (45.6)
Hemiparesis	25 (44)
Alteration of conciousness	14 (24.6)
Seizure	8 (14)
Facial palsy	8 (14)
Others	5 (8.8)
Investigation *Toxoplasma* IgG-serostatus	
Positive	27 (47.4)
Negative	4 (7)
Not known	26 (45.6)
Computed tomography (CT) scan findings	
No CT scan finding recorded	1 (1.7)
Yes	56 (98.3)
Enhancement	
Ring: one	2 (3.6)
multiple	54 (96.4)
Density	
Hypodensity	55 (98.2)
Hyperdensity/isodensity	1 (1.8)
Areas of involvement	
Parietal (left = 14; right = 8)	22 (39.3)
Basal ganglia	20 (35.7)
Frontal (left = 10; right = 9)	19 (34)
Cerebrum (left = 7; right = 7)	14 (25)
Cerebellum (left = 4; right = 6)	10 (18)
Temporal (left = 4; right = 5)	9 (16.1)
Thalamus (left =3; right = 4)	7 (12.5)
Occipital	3 (5.4)
Others[1)]	5 (9)
Combined[2)]	16 (28.6)
Outcome survival	
Completed treatment	21 (36.8)
Transfer to other hospitals	16 (28.1)
Loss to follow up	2 (3.5)
Death (range = 2 - 528 days; median = 15.5 days)	
Only TE-related	6 (10.5)
TE-related other diseases	12 (21.1)

[1)]: brain stem, pons, midbrain, and caudate nucleus.
[2)]: parieto-temporal, occipital, frontal, temporosubcortical, parasagital, and paraventricular.

be considered in every HIV-positive patient with neurological symptoms and that empirical therapy be instituted on wide indications (25). From our data, the CT scan findings of the majority of patients with TE showed a typical appearance of multiple, hypodense, ring-enhancing lesions in the cerebral hemisphere, particularly in the parietal area. In this study, CT scan was found to be the most useful approach by which to make TE diagnosis. Therefore, this rare but increasingly common infectious disease must be considered in the differential diagnosis of a patient with neuroimaging findings similar to those of metastatic tumor or brain abscess (26). Regarding serodiagnosis, 31 TE patients were shown be positive for anti-*Toxoplasma* antibodies, which indicates the importance of screening for this organism particularly in highly suspected patients. However, in HIV-infected patients the titers are often low, which makes disease phase definition and therapeutic decisions difficult (27). Twenty-six TE patients were diagnosed without anti-*Toxoplasma* antibodies status, which finding emphasizes, that the absence of this parameter does not exclude diagnosis (28). We also found a significant relationship between CD4 count of less than 100 cells/cumm and development of TE. This finding is in agreement with those reported in the literature (29-31). In clinical practice, CD4 cell count is considered to be a prognostic or risk factor to monitor the progression of HIV infection. Moreover, the association between very low levels of CD4 cell count in patients with TE has been consistently studied in different settings. We found that 29.8% of the patients in this study received primary chemoprophylaxis, and only 1.8% of patients received antiretroviral therapy including HAART before the occurrence of TE. This suggests that the costliness of HAART still plays a very crucial role in determining the survival of patients particularly in most of the developing countries where the majority of patients are unemployed (this was also the case among these patients). Overall, specific recommendations have been proposed, such as administration of primary chemoprophylaxis to all HIV-positive patients with a CD4 cell count of less than 200 cells/cumm. Nevertheless, one study showed that discontinuation of primary chemoprophylaxis in patients treated with antiretroviral combination treatment who experienced a sustained increase in their CD4 count within a certain period of follow up, no cases of TE were detected (32). Another recent experimental study revealed that melatonin and/or zinc supplementation might activate cellular immunity by stimulating CD4 and CD8+ production (33). However, immunotherapy is an evolving approach to restoring a competent immune system, and restoration may be the only cure for toxoplasmosis (34).

In the role of treatment, it was noted that the mortality rate was surprisingly high (31.6%), and death most frequently occurred in acute TE cases in which the patient died of TE-related other systemic diseases. This finding agrees well with those in one study showing that brain involvement remains a major cause of death in AIDS patients (35). TE is a treatable condition, particularly if no concurrent co-infections further the progression of immunodeficiency. Nonetheless, we should keep in mind that long-term of TE treatment is frequently limited by adverse drug reactions (28) and non-compliance to therapy. It is interesting to note that 12.3% of the patients in this study, like some percentage of those in other studies, had relapses of TE (21,36). All these patients discontinued their maintenance therapy, which poses as a major factor of relapse. However, one study showed that no relapse occurred in patients with a history of TE after discontinuation of secondary prophylaxis (37). In the era of HAART, this should be the only factor associated with a lower incidence of relapse (38).

We conclude that toxoplasmosis remains a highly prevalent infection particularly in HIV-positive patients in Malaysia. Low CD4 cell count is a significant factor contributing to the occurrence of TE in patients with AIDS. Therefore, among many approaches, an effective antiretroviral regimen including HAART therapy currently appears to be the most promising to lower the incidence of TE.

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