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Toxoplasmosis: A Silent Opportunistic Disease in HIV/AIDS Patients

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Abstract: A total of 693 HIV/AIDS patients were recruited in this retrospective and descriptive study during April 2003 to December 2004, Hospital Kuala Lumpur, Malaysia. It was found that both genders were shown to be within the same range of age (M = 18-79 vs F = 18-73), while a median age was slightly higher in male (36 years) than female (31 years). The majority of both genders were significantly shown in the age group of 25 to 34 years, but a higher rate was evident in females (42%) ($p = 0.001$). It was even observed that male patients were mainly Chinese (44.7%) and single (57.3%) ($p = 0.001$), while the females were Chinese (40.6) and married (83.3%) ($p = 0.000$). However, the highest numbers of both genders were manifested to be heterosexuals (M = 47.6% vs F = 86.2%), followed by intravenous drug users (M = 39.3% vs F = 6.5%) ($p = 0.000$). The range of CD4 cell count was 0 to 1799 with a median of 230 cells/mm^3. The level of CD4 cell count of < 200 cells/mm^3 was significantly found in males (48.5%) and between 200 to 499 and ≥ 500 cells/mm^3 were 36.2 and 26.8% in females, respectively ($p = 0.001$). Overall, the *Toxoplasma* seroprevalence was 43.85% where seropositive of anti-*Toxoplasma* antibody relatively higher in males (50%) than in females (37.7%) ($p = 0.015$). *Toxoplasma* seropositivity was thoroughly evident among Malays (168; 51.1%), Intravenous Drug Users (IDUs) and patients with toxoplasmic encephalitis (TE) ($p = 0.001$). Furthermore, anti-retroviral therapy including HAART was more significantly found in patients with 9 seropositive *Toxoplasma* when compared to 2 seronegative and unknown serostatus patients ($p = 0.025$). Seventeen AIDS-related toxoplasmic encephalitis patients were diagnosed at the time of this study, depicting hemiparesis as the most common neurological manifestation in 11 (64.7%) patients, followed by headache and seizure in 6 (35.3%) and 3 (17.7%) patients, respectively. Interestingly, CT scan finding showed mass like structure with multiple (58.8%), ring enhancing lesions (100%), in parietal region (58.8%) and edema (29.4%) in these patients. Overall, the treatment outcome showed that 13 (76.5%) patients had completed treatment with maintenance, whereas, 3 (17.6%) patients were lost to follow up and 1 (6%) patient was transferred to another hospital. No relapse or death case was reported during the time of this study.

Key words: Toxoplasmosis, toxoplasmic encephalitis, opportunistic disease, HIV/AIDS, Malaysia

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INTRODUCTION

By the end of the last century, infectious diseases represented an important cause of morbidity and behavioral changes (Almeida and Lautenschlager, 2005). On a similar stand point, *Toxoplasma gondii* represents the most prominent infectious parasitic organism found in humans (Stroehle *et al*., 2005). With the concurrence of HIV/AIDS, opportunistic infections are still a major cause of death in HIV-infected patients in the HAART era (Bonnet *et al*., 2005) and toxoplasmosis accounts for the majority of hospitalizations to study the threatening consequences of parasitic infections (Valiant *et al*., 2005). Only a handful of studies on toxoplasmosis, particularly in HIV/AIDS patients, have been conducted in Southeast Asia or Asian continent, however, more works need to be carried out in order to gain a genuine management of this so-called silent opportunistic parasitic infection. We therefore, conducted this study to determine the seroprevalence of toxoplasmosis, the relationship of *Toxoplasma* seropositivity with various factors and also to determine the incidence of toxoplasmic encephalitis and its sequences.

MATERIALS AND METHODS

This retrospective and descriptive study was carried out in the Out-Patients Department (OPD) and In-Patients Ward (IPW) for infectious diseases in Hospital Kuala Lumpur (HKL), with 2,502 beds and being the largest government tertiary referral hospital and mainly focus on public services. There are about 30 new and 300 follow-up patients with HIV-infection per month who come for medical treatment in this hospital. The medical records of 693 newly diagnosed HIV-infected patients were reviewed in the duration of 20 months from April 2003 to December 2004, where 369 and 324 of these patients were recruited from the earlier and later years, respectively. Their medical records were screened for demographic profiles 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, in the standardized data collection sheet. Diagnosis of toxoplasmic encephalitis (TE) was made in 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. Applying similar strategy, we also analyzed AIDS patients with other CNS infections such as cryptococcosis, primary CNS lymphoma and tuberculosis, for correction of finally undefined bias. A good therapeutic response was defined as improvement of clinical condition, regression of neurological signs and symptoms, or improvement of CT scan. Similarly, 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 Park, Illinois, USA) in accordance with the manufacturer's instruction. The titer of anti-*Toxoplasma* (IgG) antibody ≥ 3 IU/mL was considered positive in this study. AIDS defining illnesses were also based on the Centers for Disease Control and Prevention (CDC), Atlanta, 1993.

Statistical Analysis

The data were analyzed employing the statistical software, SPSS version 10 (SPSS Inc, Chicago, Ill., USA). The data with quantitative variables were indicated as mean and range,

while qualitative variables were indicated as 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

Table 1 shows the distribution of demographic and baseline characteristics of 693 HIV/AIDS patients. We found that these two genders were shown to be within the same age range (M = 18-79 vs F = 18-73), while a median age was slightly higher in males (36 years) than in females (31 years). The sex ratio between M:F was 4:1. The majority of both genders were significantly shown in the age group of 25 to 34 years, but a relatively higher rate was found in females (42%) ($p = 0.001$). It was also observed that the majority of male patients were Chinese (44.7%) and single (57.3%) ($p = 0.001$), while the females were Chinese (40.6%) and married (83.3%) ($p = 0.001$). Furthermore, the higher percentages of both genders were unemployed (M = 52.1% vs F = 58%) and resided in the city (M = 51.5% vs F = 55%); however, there was no statistically significant difference found between these two groups. The highest numbers of both genders were manifested to be heterosexuals (M = 47.6% vs F = 86.2%) ($p = 0.001$) followed by intravenous drug users (M = 39.3% vs F = 6.5%) ($p = 0.001$). The range of CD4 cell count was 0 to 1799 with a median of 230 cells/mm^3. The level of CD4 cell count of <200 cells/mm^3 was significantly found in males (48.5%) and between 200 to 499 and ≥ 500 cells/mm^3 were found in females with a percentage of 36.2 and 26.8%, respectively ($p = 0.001$). The higher rate of primary chemoprophylaxis was significantly found in males (56.4%) than females (45%).

From this study, further analysis showed interesting results in 329 patients with seropositive *Toxoplasma* status. Overall, *Toxoplasma* seroprevalence was 43.85% where seropositivity for anti-*Toxoplasma* antibody was relatively higher in males (50%) than in females (37.7%) ($p = 0.015$). Indeed, we found that *Toxoplasma* seropositivity was more common among Malays (168; 51.1%) as compared to others ($p = 0.001$). Moreover, IDUs showed a considerable relationship of *Toxoplasma* seropositivity than seronegativity or unknown serostatus, signifying that TE occurred more significantly in *Toxoplasma* seropositive (10 patients) than seronegative (2) or unknown (5) patients ($p = 0.001$) as shown in Table 2. At the time of TE diagnosis, HAART was more likely given to patients with *Toxoplasma* seropositivity (9 patients) as compared to 2 seronegative and unknown serostatus patients ($p = 0.000$), while the other 6 TE patients were not subjected to HAART (data was not shown).

During the period of this study, 245/693 (35.4%) patients were classified to be presenting AIDS defining illnesses. 17/245 (7%) of AIDS patients were diagnosed as having TE, out of which 10 patients were admitted to the hospital in 2003 while the remaining 7 cases were identified in 2004. TE patients were categorized as being in the age group of 25-34 years (9 cases), males (17 cases), Malays (9 cases), heterosexuals (11 cases) and married (10 cases), however, there was no statistical significance found between these associations ($p>0.05$). All patients showed clinical manifestations; 12/17 (70.6%) patients presented with neurological deficits, with 11/12 (91.7%) patients having hemiparesis and 1/12 (8.3%) of them exhibiting alteration of consciousness. In addition, 6 patients developed headache while 3 patients had seizure with generalized clonic-tonic type prior to their admission. Interestingly, CT scan finding showed mass like structure with multiple (58.8%), ring enhancing lesions (100%), in parietal region (58.8%) and edema (29.4%)

Table 1: Demographic and baseline characteristics of 693 HIV/AIDS patients attended in the Hospital Kuala Lumpur (HKL) during April-December 2003 (369 patients) to January-December 2004 (324 patients)

	No. of patients (%)		
Characteristics	Male (555)	Female (138)	p-value
Age	Range = 18-79 years Median = 36 years	Range = 18-73 years Median = 31 years	
Age group			0.000
15-24	29 (5.2)	24 (17.4)	
25-34	208 (37.5)	58 (42)	
35-44	200 (36)	33 (24)	
≥ 45	118 (21.3)	23 (16.7)	
Race			0.000
Malay	222 (40)	46 (33.3)	
Chinese	248 (44.7)	56 (40.6)	
Indian	74 (13.3)	17 (12.3)	
Foreigner	11 (2)	19 (13.8)	
Marital status			0.000
Single	318 (57.3)	23 (16.7)	
Married	237 (42.7)	115 (83.3)	
Career			0.296
Unemployed	289 (52.1)	80 (58)	
Laborer	115 (20.7)	21 (15.2)	
Nonlabourer	151 (27.2)	37 (26.8)	
Address			0.574
Kuala Lumpur	286 (51.5)	76 (55)	
Outsider	269 (48.5)	62 (45)	
Mode of HIV transmission			
Heterosexual	264 (47.6)	119 (86.2)	0.000
Homosexual	47 (8.5)	1 (0.7)	0.001
Intravenous drug used (IDUs)	218 (39.3)	9 (6.5)	0.000
Blood transfusion	1 (0.2)	2 (1.5)	0.042
Combined risk behaviors	83 (15)	3 (2.2)	0.000
Toxoplasma serostatus			0.015
Positive	277 (50)	52 (37.7)	
Negative	273 (49.2)	86 (62.3)	
Unknown	5 (1)	0	
Secondary reactivative of TE case			0.037
Yes	17 (3.1)	0	
No	538 (96.9)	138 (0)	
CD4 cell count (cell/mm^3)			0.000
Range = 0-1799; median = 230			
< 200	269 (48.5)	48 (34.8)	
200-499	173 (31.2)	50 (36.2)	
≥ 500	96 (17.3)	37 (26.8)	
Primary chmoprophylaxis			0.016
Yes	313 (56.4)	62 (45)	
No	242 (43.6)	76 (55)	
Anti-retroviral (HAART) therapy			0.321
Yes	196 (35.3)	55 (40)	
No	359 (64.7)	83 (60)	

found in these patients. The stereotactic biopsy was also used to confirm the diagnosis in one patient. Overall, 5/17 (29.4%) patients were diagnosed by only CT scan findings and the other 12/17 (70.6%) patients were deduced through both CT scan findings and positive serodiagnosis for anti-*Toxoplasma* antibody. TE was significantly found in patients with CD4 of <200 (13 patients), <100 (12 patients) and <50 (10 patients) cells/mm^3. Unfortunately, all TE cases occurred before primary chemoprophylaxis (cotrimoxazole, dapsone, fansidar and atovaquone) and HAART introduction. The treatment outcome showed that 13/17 (76.5%) patients indicated 9/10 (90%) patients and 4/7 (57%)

Table 2: The association between *Toxoplasma* seroprevalence and various possible or confounding factors in 693 patients

	Toxoplasma serostatus (693)			
Characteristics	Negative 359 (%)	Positive 329 (%)	Not known 5 (%)	p-value
Age group				0.958
15-24	28 (7.8)	25 (7.6)	0	
25-34	144 (40.1)	120 (36.5)	2 (40)	
35-44	116 (32.3)	115 (35)	2 (40)	
≥ 45	71 (19.8)	69 (21)	1 (20)	
Sex				0.015
Male	273 (76)	277 (84.2)	5 (100)	
Female	86 (24)	52 (15.8)	0	
Race				0.000
Malay	97 (27)	168 (51.1)	3 (60)	
Chinese	199 (55.4)	104 (31.6)	1 (20)	
Indian	43 (12)	48 (14.6)	0	
Foreigner	20 (5.6)	9 (2.7)	1 (20)	
Marital status				0.892
Single	178 (49.6)	160 (48.6)	3 (60)	
Married	181 (50.4)	169 (51.4)	2 (40)	
Career				0.126
Unemployed	174 (48.5)	192 (58.4)	3 (60)	
Laborer	80 (22.3)	55 (16.6)	1 (20)	
Nonlabourer	105 (29.2)	82 (25)	1 (20)	
Address				0.312
Kuala Lumpur	197 (55)	160 (48.6)	3 (60)	
Outsider	162 (45)	169 (51.4)	2 (40)	
Mode of HIV transmission				
Heterosexual				0.000
Yes	224 (62.4)	156 (47)	3 (60)	
No	135 (37.6)	174 (53)	2 (40)	
Intravenous drug user (IDUs)				0.000
Yes	85 (23.7)	139 (42.2)	3 (60)	
No	274 (76.3)	190 (57.8)	2 (40)	
CD4 level of 50 cells/mm^3				0.032
< 50 cells/mm^3	99 (27.6)	63 (19.2)	1 (20)	
≥ 50 cells/mm^3	254 (70.7)	255 (77.5)	1 (20)	
CD4 level of 100 cells/mm^3				0.002
< 100 cells/mm^3	134 (37.3)	87 (26.4)	2 (40)	
≥ 100 cells/mm^3	219 (61)	231 (70.2)	0	
Toxoplasmic encephalitis (TE)				.000
Yes	2 (0.6)	10 (3)	5 (100)	
No	357 (99.4)	319 (97)	0	
Antiretroviral (HAART) drugs				0.036
Yes	146 (40.7)	104 (31.6)	1 (20)	
No	213 (59.3)	225 (68.4)	4 (80)	
Primary chemoprpphylaxis				0.895
Yes	200 (55.7)	172 (52.3)	3 (60)	
No	159 (44.3)	157 (47.7)	2 (40)	

were, respectively notified in 2003 and 2004, had completed treatment with continuing its maintenance. 3/17 (17.6%) patients were lost to follow-up and 1/17 (6%) patient was transferred to another hospital. However, no relapse or death case was reported during the time of this study.

DISCUSSION

Seroprevalence of toxoplasmosis is still markedly high as evident from previous studies in Malaysia (Nissapatorn *et al*., 2003a, b; 2004; 2005) and elsewhere. Interestingly, *Toxoplasma*

seropositivity was significantly found in males, Malays and IDUs. This could be due to the fact that IDUs is the most common route of HIV transmission in this group of patients where both HIV and *Toxoplasma* infections share the same route of transmission, as both pathogens are blood-borne diseases. The other conducived reason could be the inclination of Malays to keep cats as pets as compared to other races. From this finding, we conclude that sex, race origin and behavioral practices contributed to the risk factors in acquiring *Toxoplasma* infection in this country. Moreover, one study showed interesting results that *Toxoplasma*-infected men were apparently to be taller and both men and women had lower fluctuating asymmetry, with a 2D: 4D ratio previously reported to be associated with higher pre-natal testosterone levels (Flegr *et al*., 2005). Our additional analysis showed that seropositive patients were more likely to develop TE and seropositivity was significantly seen in patients who were receiving HAART. This suggests that once the *Toxoplasma* serostatus is confirmed, it is necessary to take one step ahead by administering primary or secondary chemoprophylaxis to these patients or alternatively resorting to HAART. This practice should be exercised for all newly diagnosed HIV-positive patients regardless of *Toxoplasma* serostatus, in order to reduce the incidence of latent *Toxoplasma* infection and preventing the reactivation of TE or relapse.

Toxoplasmic encephalitis (TE) was one of the most common opportunistic infections found in this hospital and in other regions where HIV/AIDS was reported. TE is the most common cerebral focal lesion in AIDS and still accounts for high morbidity and mortality (Colombo *et al*., 2005; Bhigjee, 2005; Imam, 2005). One study suggested that TE should be considered in the differential diagnosis of meningoencephalitis in sexually active individuals, including cases without prior history or suspicion of HIV infection and those without any abnormalities in CT scan (Vidal *et al*., 2004). The usual clinical presentations of TE such as headache, seizure or hemiparesis were apparent in these patients. Nevertheless, an unusual feature of schizophrenia, which suggests that dopamine concentration in brain could play a role in behavioral changes of infected hosts, had been reported in one earlier study (Novotna *et al*., 2005). It was also observed that serum has always been the prime non-invasive and expensive specimen used to detect anti- *Toxoplasma* antibodies. However, saliva could also be provided as an alternative option for the detection of its antibodies (Stroehle *et al*., 2005; Singh *et al*., 2005). PCR has shown to be a clinical value with high titers of anti-*Toxoplasma gondii* IgG antibodies for the diagnosis of TE (Colombo *et al*., 2005). Moreover, CT scan is the most useful technique in identifying intracerebral lesions which showed typical ring lesion(s) in most studies including ours. Recent investigations revealed that ventriculitis and hydrocephalus could also be seen in adult AIDS patients (de Silva *et al*., 2005; Sell *et al*., 2005), which necessitated the importance to recognize such unusual phenomenon in order to perform specific therapy. One study suggested that Fluorine 18 fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) scan could be applied as an alternative imaging technique in localizing foci of infection, differentiating CNS lymphoma from toxoplasmosis, defining the extent of disease and monitoring response to treatment (Love *et al*., 2005). Thallium-201 brain SPECT imaging should be the initial diagnostic tool to determine the accuracy of lesions $\geq$2 cm (Young *et al*., 2005). We therefore support the need to improve our technical capacities in diagnostic laboratories for the management of cerebromeningeal diseases (Soumare *et al*., 2005).

Since TE occurred before chemoprophylactic initiation, therefore its efficacy toward the incidence of TE could not be accurately assessed. However, primary chemoprophylaxis is still widely used to prevent secondary reactivation of latent *Toxoplasma* infection as was practiced in this study. The combination of recombinant interleukin (IL-12) and clindamycin (Tawfeek *et al*., 2001), or protein

Hsp90 (Echeverria *et al*., 2005) could help in preventing secondary reactivation of chronic *Toxoplasma* infection or relapse of TE. Twice-weekly pyrimethamine-sulfadoxine as primary prophylactic regimen might provide a convenient alternative for patients failing or intolerant to approved regimens (Schurmann *et al*., 2002). One experimental study showed that atovaquone appears to be superior to the standard maintenance therapy regimens in a murine model of reactivated TE and should be further investigated in clinical trials (Dunay *et al*., 2004). However, cotrimoxazole could be useful for patients awaiting immune reconstitution, which allows the interruption of TE maintenance therapy (Duval *et al*., 2004). Nevertheless, the discontinuation of secondary prophylaxis in patients with HAART who have stably reached a certain immune reconstitution is possible (Collazos, 2003). TE also developed in these patients before HAART introduction and it clearly showed that majority of patients with or without *Toxoplasma* seropositive status still have difficulty in benefiting from HAART where economic constraint is the main factor. Even though, international collaborations or networks are actively involved in HAART distribution particularly in developing countries, TE remains a highly prevalent disorder of the central nervous system, even in the late HAART era, particularly among severely immuosuppressed patients and in the absence of prophylaxis (Antinori *et al*., 2004). Interestingly, no seropositive pregnant women developed TE during this study, even though they received only 1 antiretroviral drug (AZT) as a standard regimen throughout pregnancy. One study suggested that the combination of HAART (AZT, 3TC and nelfinavir) with anti-*Toxoplasma* therapy had shown promising outcome in their efficacy and proved to be an important strategy to protect the unborn child from acquiring these co-infections (Nogueira *et al*., 2002). The role of HAART should therefore be highlighted and necessarily provided to all HIV-positive individuals with low level of CD4 cell count to prevent secondary reactivation of latent *Toxoplasma* infection.

From our observation, no new chemotherapy procedure was employed in treating TE patients or in clinical trials conducted in this hospital. Recent studies showed that Interferon (IFN)-gamma (Suzuki, 2002), de novo pyrimidine biosynthesis pathway (Fox and Bzik, 2002), HAART-Protease inhibitors (PIs) (Pozio, 2004), microneme protein MIC2 (Brossier and David Sibley, 2005), triazines (Mui *et al*., 2005) and iron-sulfur cluster biosynthesis pathways (Seeber *et al*., 2005) could serve as an alternative way toward the development of new drugs that might prove effective against or in controlling toxoplasmosis in the near future. At the same time, vaccine has become the target and seems to be another promising option in combating toxoplasmosis. *T. gondii* antigen-pulsed SRDCs, which synthesize large amounts of IL-12, induced protective immune responses against this intracellular pathogen (Ruiz *et al*., 2005). The associating antigens (SAG1 and GRA 4) and cytokine (GM-CSF) have been used for further development of a multiantigenic vaccine (Mevelec *et al*., 2005). In addition, oligodeoxynucleotides (ODN), which contain immunostimulatory CG motifs (CpG ODN), could provide a stable and effective adjuvant for this purpose (El-Malky *et al*., 2005). Prophylaxis and maintenance therapy against opportunistic infections are a mainstay of management of HIV-infected patients and have led to a significant improvement in quality of life and survival (Furrer and Cohort Study, 2002), which is an urgent need to focus attention particularly in the developing countries.

We conclude that toxoplasmosis has a significantly high prevalence in HIV-positive patients and certain characteristics play important risk factors in *Toxoplasma* acquisition. With strong evidences of HIV pandemic, toxoplasmic encephalitis remains as one of the AIDS defining illnesses in this era. Primary chemoprophylaxis and HAART are still required in the standard guideline for preventing reactivation of chronic *Toxoplasma* infection in HIV positive patients in our region.

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