REVIEW

TOXOPLASMOSIS IN HIV/AIDS: A LIVING LEGACY

Veeranoot Nissapatorn

Department of Parasitology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Abstract. Toxoplasmosis has historically been considered one of the most important opportunistic infections detected in HIV/AIDS patients. The prevalence rates of latent *Toxoplasma* infections in HIV-infected patients has been found to vary greatly from 3% to 97%. Prevalence has been found to be related to ethnicity, certain risk factors, and reactivation of toxoplasmosis. Prior to antiretroviral therapy, toxoplasmic encephalitis (TE) was the most common focal cerebral lesion detected in AIDS patients with *Toxoplasma* infection, occurring in approximately half of *Toxoplasma*-seropositive patients. Other forms of dissemination have also been reported in AIDS patients in sites such as the eyes, lungs, heart and spinal cord. Anti-*Toxoplasma* therapy and chemoprophylaxis have shown effectiveness in reducing the incidence of TE, while noncompliance has been identified as a cause of relapse in these settings. Toxoplasmosis is one of the most common neuropathological complications found at autopsy. Rapid progress in the development of highly active antiretroviral therapy (HAART) has changed the observed patterns with TE, for which there has been a marked decrease in overall incidence. Subsequently, TE has been found to be significantly associated with the so-called "neurological immune restoration inflammatory syndrome" (NIRIS). *Toxoplasma* screening programs are recommended for all newly diagnosed HIV-positive patients. Chemoprophylaxis should be considered in HIV-infected patients who have a CD4 < 200 cells/mm^3, particularly in settings where resources are limited and there is not access to HAART. TE remains a cause of morbidity and mortality among AIDS patients.

INTRODUCTION

The coccidian *Toxoplasma gondii* is a ubiquitous and intracellular protozoan parasite that causes toxoplasmosis, which is a cosmopolitan zoonotic disease. *Toxoplasma* infections are reported in approximately half the world's population but most are asymptomatic.

T. gondii may serve as a cofactor for enhancing immunodeficiency in HIV-1. Co-infection with other pathogens in humans infected with HIV-1 may enhance the progression of the disease to AIDS (Lin and Bowman, 1992). In concurrence with HIV infection, toxoplasmic encephalitis (TE) occurs primarily due to reactivation of latent

Correspondence: Dr Veeranoot Nissapatorn, Department of Parasitology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.
Tel: 6 03 79676618; Fax: 6 03 79674754
E-mail: nissapat@gmail.com; veeranoot@um.edu.my

Toxoplasma infection and is one of the most frequent opportunistic infections, particularly in patients with full-blown AIDS. TE is the most common clinical presentation of toxoplasmosis (Luft and Remington, 1992), and is one of the most frequent causes of focal intracerebral lesions complicating AIDS (Matthiessen *et al*, 1992; Lanjewar *et al*, 1998; Nissapatorn *et al*, 2004; Valenta *et al*, 2009). TE is undoubtedly a serious and life-threatening disease but is treatable when there is a timely diagnosis and prompt treatment, and there are no other concurrent co-infections. This parasitic disease poses many diagnostic and therapeutic challenges for clinicians treating HIV-infected patients (Israelski and Remington, 1992), particularly in developing countries where the number of patients infected with HIV is increasing. This review focuses on the clinico-epidemiological aspects of toxoplasmosis in HIV/AIDS patients at the time of transition to the introduction of highly active anti-retroviral therapy (HAART). The epidemiology of toxoplasmosis in HIV/AIDS patients should be able to provide us with a better understanding of the clinical scenario and future management of this so-called "enigmatic parasite" of the tropics.

TOXOPLASMOSIS: PREVALENCE, RISK FACTORS, AND VIRULENCE

Table 1 shows the epidemiological data of *T. gondii* in HIV-infected patients. A total of 38 studies have been reported from different parts of the world including Asia, Europe, North America, South America and South Africa. The seroprevalence of toxoplasmosis (latent/chronic infection) varies greatly: ≥ 50% (11 studies), ≥ 40% (4 studies), ≥ 30% (6 studies), ≥ 20% (10 studies), and < 20% (7 studies). High rates of latent *Toxoplasma* infection (41.9-72%) were reported in South America and in approximately half the studies (≥ 40%) from the Asian continent. In North America, the rate of *Toxoplasma* infection was low. Four of 38 studies were conducted on HIV-infected pregnant women, 2 reported a high seroprevalence, 53.7% in Thailand and 72% in Brazil. Latent toxoplasmosis is still prevalent in coexisting with HIV infection. The level of anti-*Toxoplasma* (IgG) antibodies does not appear to be affected by antiretroviral drugs or therapeutic regimes/prophylaxis used to treat toxoplasmosis in these patients (Machala *et al*, 2009). Given the results of these epidemiological studies, screening for primary *Toxoplasma* infection should be carried out even though it is not very common. It may also prevent secondary reactivation later, especially in HIV-infected patients in limited resource settings where the majority are unable to access primary chemoprophylaxis and/or antiretroviral therapy.

The risk factors of *Toxoplasma* infection in HIV-infected patients include age, race/ethnicity and other demographic characteristics. A study in the United States demonstrated *Toxoplasma* prevalence rates in HIV-infected women aged ≥ 50 years old were significantly higher than those who were younger (Falusi *et al*, 2002). This is dissimilar to a study from Malaysia which found HIV-infected patients in the younger age group had higher *Toxoplasma* seroprevalence rates than the olders, although the difference was not statistically significant (Nissapatorn *et al*, 2001). Given these findings, *Toxoplasma* infection is acquired irrespective of age, and preventive measures are needed to curb prevalence rates, especially in areas where the parasite is highly endemic. A study by Falusi and colleagues in 2001 further pointed out those women born outside the US were more likely to have higher rates of latent toxoplasmosis although race did not affect *Toxoplasma* seroprevalence among black and white women in that country

(Falusi *et al*, 2002). In Malaysia, a higher rate of *Toxoplasma* infection was more likely to be found among Malays, the predominant ethic group in this region, compared to others including Chinese and Indians (Nissapatorn *et al*, 2007). Traditionally, Malays keep cats as pets, which could explain this association. Based on these studies, demographic characteristics certainly make significant contributions to the epidemiological surveillance of *Toxoplasma* infection in a given population, such as HIV/AIDS patients.

Not much has been studied about how the T-cell response could affect *Toxoplasma*-seropositive patients. It has been recognized T-helper (CD4) cells are involved in *Toxoplasma* infection by stimulating T-cytotoxic cells which are able to lyse tachyzoites directly and participate in the activation of B-cells which then go on to produce antibodies against *Toxoplasma* (Ho-Yen, 1992). An earlier study showed that there is a greater likelihood of problems with *Toxoplasma* infection in situations in which there is a reduction in T-cell function (Pendry *et al*, 1990). Supporting this literature, an US study demonstrated a significant association between CD4 counts of 200-499 cells/mm^3 and *Toxoplasma*-seropositivity in patients (Falusi *et al*, 2002). The authors were unable to give an explanation regarding this association except that patients with low CD4 counts were more likely to be foreign born. Similar findings have not been reported in other studies (Nissapatorn *et al*, 2001, 2002). Regarding other risk factors, such as a history of close contact with cats, consumption of contaminated meat, and receiving blood transfusions from *Toxoplasma*-seropositive patients, there have been no significant associations found from other studies (Mark, 1993; Nissapatorn *et al*, 2001, 2002). This may be because these patients were exposed to *Toxoplasma* prior to contracting HIV infection. The patients may have acquired *Toxoplasma* infection from other sources, such as eating raw vegetables or drinking contaminated water. Risk factors, such as these which were not included in these studies. However, behavioral modification, such as avoiding close contact with cats and consumption of clean and properly cooked foods is advisable for HIV-infected patients regardless of *Toxoplasma* serostatus. Patients with *Toxoplasma* seropositivity were more likely to develop TE and tended to be patients receiving HAART (Nissapatorn *et al*, 2007). From this observation, primary chemoprophylaxis or antiretroviral drugs, including HAART (if available), should be instituted in these patients after clinical evaluation.

Apart from the host immune status, the genotype of the infecting parasites may influence the course of disease (Lindström *et al*, 2006). Genetic analyses have shown the vast majority of *T. gondii*-strains typed to date fall into one of the three clonal lineages, types I, II, and III (Howe and Sibley, 1995), which differ in virulence but do not show clear host or geographic boundaries (Lindström *et al*, 2006). Studies from different parts of the world have shown similar findings in which genotyping of the SAG2-locus revealed the type II allele for most disease-causing strains (reactivation of chronic infections) found in immunocompromised individuals (Dardé *et al*, 1992; Howe and Sibley, 1995; Howe *et al*, 1997; Fuentes *et al*, 2001; Lindström *et al*, 2006; Ajzenberg *et al*, 2009). The high prevalence of type II strains in human toxoplasmosis may simply reflect the source of strains that lead to human infection (Howe *et al*, 1997). The low level of gamma interferon and other factors related to the immune system in these patients may increase the possibility of reactivation of the infective forms of the parasite by developing bradyzoites and increasing the formation of

cysts in the brain (Gross *et al*, 1997). Few studies have reported regarding type I (Khan *et al*, 2005) and types I/III (Genot *et al*, 2007), and have reported a high rate of genetic polymorphism (Ferreira *et al*, 2008) in *T. gondii* strains isolated from immunocompromised patients. Despite differences, genotyping studies could improve the diagnosis and management of human toxoplasmosis and help in the development of novel drugs and vaccines. Surprisingly, genotyping of *T. gondii* strains has never been reported in HIV-infected patients from Asian continent even though there are a large number of these patients, endemic areas for latent *Toxoplasma* infection (Subsai *et al*, 2006; Nissapatorn *et al*, 2007), and cases of clinical toxoplasmosis detected in AIDS patients (Subsai *et al*, 2006; Lian *et al*, 2007; Ho *et al*, 2008). Future studies are recommended to elucidate genotyping distribution and the correlation between genotyping of *T. gondii* strains and human toxoplasmosis in Asian HIV patients.

It is unclear if there is an association between the genotype of *T. gondii* strain and human toxoplasmosis. One study suggests the type of infecting parasitic strain does not influence the pathogenesis of toxoplasmosis in immunocompromised patients, and recommends the need for specific prophylaxis in patients infected with *T. gondii*, regardless of the strain genotype (Honoré *et al*, 2000). Host factors are more important than parasite factors in patient resistance and susceptibility to toxoplasmosis in the immunocompromised (Ajzenberg *et al*, 2009).

TOXOPLASMOSIS: INCIDENCE AND CLINICAL IMPLICATIONS

Neurological complications of AIDS patients are often due to opportunistic infections (OIs) of the central nervous system. With the advent of the HIV pandemic, epidemiological studies have shown TE to be one of the most common OIs in AIDS patients and the most commonly reported CNS OI on 5 continents: Asia (India, Malaysia and Thailand), Europe (France, United Kingdom and Germany), North America (USA), South America (Brazil and Mexico), and recently from South Africa (Bhigjee, 2005; Amogne *et al*, 2006; Jowi *et al*, 2007). The occurrence of this parasitic disease is mainly due to the reactivation of latent *Toxoplasma* infection which has been shown to be significantly associated with a CD4 count < 100 cells/mm^3 (Renold *et al*, 1992; Nissapatorn *et al*, 2004).

The presumptive criteria for TE, including the clinical presentation, radio-imaging findings, molecular and sero-diagnosis for *Toxoplasma* infection, and a good response to anti-T*oxoplasma* therapy are helpful in the diagnosis. Based on various clinical studies, cerebral involvement is more common and more serious than extracerebral toxoplasmosis. TE typically causes neurological manifestations, such as headache, fever, seizures, hemiparesis, alteration of consciousness and coma. These symptoms mimic other brain diseases making it difficult to diagnose. A few studies in AIDS patients have shown extrapyramidal symptoms, such as hemichorea, choreoathetosis and Parkinsonism (Pestre *et al*, 1991; Hirose, 2000). Movement disorders in these patients, particularly in countries with a high prevalence of toxoplasmosis, should suggest TE (Noël *et al*, 1992). In AIDS patients, opportunistic infections may affect endocrine organs. Diabetes insipidus (DI) is uncommon but has been reported in relation to TE. Imaging studies may be pathological and assist in the diagnosis (Brändle *et al*, 1995; Sánchez *et al*, 2000). An unusual case of TE with massive intracerebral hemorrhage leading to a fatal vehicular crash was reported in a patient with AIDS (Gyori and Hyma, 1998). Only 2 cases with

Table 1
Summary of selected studies on seroprevalence of toxoplasmosis in HIV-infected patients from different continents in the world.

Study (Ref)	City, Country	No. of patients and population group	Diagnostic sample/method	Seroprevalence
Asia				
Wongkamchai *et al*, 1995	Bangkok, Thailand	40 HIV-infected patients	Serum, ELISA[a]	42.5%
Meisheri *et al*, 1997	Bombay, India	89 HIV-infected patients (21-70 yrs)	Serum, ELISA	67.8%
Yoong and Cheong, 1997	Kuala Lumpur, Malaysia	49 HIV-infected patients	Serum, IFT[b]	59.0%
Chintana *et al*, 1998	Bangkok, Thailand	253 HIV seropositive pregnant women	Serum, DT[c]	21.1%
Sukthana *et al*, 2000	Bangkok, Thailand	190 HIV-infected patients (<20->40 yrs)	Serum, DT	23.2%
Oh *et al*, 1999	Seoul, South Korea	173 HIV-infected patients	Serum, ELISA	4.0%
Nissapatorn *et al*, 2001	Bangkok, Thailand	183 HIV/AIDS patients (18-60 yrs)	Serum, DT	22.4%
Shivaprakash *et al*, 2001	Pondicherry, India	216 HIV-infected patients (1.5-76 yrs)	Serum, ELISA	11.5% (IgM)
Wanachiwanawin *et al*, 2001	Bangkok, Thailand	838 HIV seropositive pregnant women	Serum, ELISA	53.7%
Shamilah *et al*, 2001	Kuala Lumpur, Malaysia	729 HIV-infected patients	Serum, IFT	31.3%
Nissapatorn *et al*, 2002	Kuala Lumpur, Malaysia	100 HIV/AIDS patients (20-73 yrs)	Serum, ELISA	21.0%
Nissapatorn *et al*, 2003	Kuala Lumpur, Malaysia	406 HIV/AIDS patients (17-74 yrs)	Serum, ELISA	51.2%
Nissapatorn *et al*, 2004	Kuala Lumpur, Malaysia	505 HIV/AIDS patients (17-71 yrs)	Serum, ELISA	44.8%
Hung *et al*, 2005	Taipei, Taiwan	844 non-hemophiliac HIV-infected patients	Serum, ELISA	10.2%
Nissapatorn *et al*, 2005	Kuala Lumpur, Malaysia	162 HIV/AIDS patients	Serum, ELISA	35.8% and 14.8% (IgM)
Naito *et al*, 2007	Tokyo, Japan	56 Non-hemophiliac HIV-infected patients (21-68 yrs)	Serum, ELISA	5.4%
Nissapatorn *et al*, 2007	Kuala Lumpur, Malaysia	693 HIV/AIDS patients (18-79 yrs)	Serum, ELISA	43.85%
Europe				
Holliman *et al*, 1990	London, UK	500 HIV-infected patients	Serum, AT[d] and DT	26.6% and 1.4% (IgM)
Sykora *et al*, 1992	Prague, Czechoslovakia	67 HIV-infected patients	Serum, CFT[e]	29.8%
Zufferey *et al*, 1993	Lausanne, Switzerland	715 HIV-infected patients	Serum, IFT and AT	50.0%
Letillois *et al*, 1998	Grenoble, France	37 HIV-infected patients	Serum, ELISA	64.9%
Millogo *et al*, 2000	Burkina Faso, France	1,828 HIV-positive patients	Serum, ELISA	25.4%
Machala *et al*, 2009	Prague, Czech Republic	626 HIV-infected patients	Serum, CFT	33.2%

North America				
Grant *et al*, 1990	New York, USA	411 AIDS patients	Serum, DT	32%
Israelski *et al*, 1993	California, USA	1,073 HIV-infected patients	Serum, AT and DT	9.5%
Minkoff *et al*, 1997	Brooklyn, USA	138 HIV-infected women	Serum, DT	20.2%
Ruiz *et al*, 1997	Rhode Island, USA	169 HIV seropositive pregnant women	Serum, DT	22.0%
Falusi *et al*, 2002	Chicago, USA	1,975 HIV-infected women	Serum, DT	15.1%
South America				
Wainstein *et al*, 1993	RS, Brazil	516 AIDS-related CNS toxoplasmosis (presumptive)	Serum and CSF	65% and 49%
Ganván Ramirez *et al*, 1997	Universidad de Guadalajara, Mexico	92 HIV/AIDS patients	Serum, ELISA	50% and 1% (IgM)
Cantos *et al*, 2000	SC, Brazil	2,994 HIV-infected patients	Serum, IFT and ELISA	41.9% and 0.87% (IgM)
Lago *et al*, 2009	Rio Grande do Sul, Brazil	168 HIV-infected pregnant women	Serum, ELISA	72.0%
South Africa				
Brindle *et al*, 1991	Kenya, Nairobi	94 HIV-infected patients	Blood (serum), ELISA and DT	22%
Zumla *et al*, 1991	Zambia and Uganda	373 (186-Uganda and 187-Zambia) HIV-infected patients	Blood (serum), DT and AT	34% and 4%
Woldemichael *et al*, 1998	Addis Ababa, Ethiopia	127 HIV-infected patients (18-45 yrs)	Blood (serum), DT and AT	74.2%
Uneke *et al*, 2005	Jos, Nigeria	219 HIV-infected patients	Blood (serum), ELISA	38.8%
Lindström *et al*, 2006	Kampala, Uganda	130 HIV-infected patients	Blood (serum), AT and PCR	54%
Hari *et al*, 2007	Johannesburg, South Africa	307 HIV-infected patients	Blood (serum), ELISA	8%

[a]ELISA, Enzyme-Linked Immunosorbent Assay; [b]IFT, Immunofluorescence Test; [c]DT, Sabin and Feldman Dye Test; [d]AT, Agglutination Test; and [e]CFT, Complement Fixation Test

AIDS presenting with atypical parkinsonism have been reported from Japan (Nakagawa *et al*, 1997; Murakami *et al*, 2000). These unusual neurological presentations of TE are rarely reported in Asia (Chaddha *et al*, 1999; Nissapatorn *et al*, 2004, 2007; Subsai *et al*, 2006).

Overall, the prevalence of extracerebral toxoplasmosis (ECT) in patients with AIDS is estimated to be 1.5%-2% (Rabaud *et al*, 1994) which is far less common than CNS toxoplasmosis. Often associated with TE, ocular toxoplasmosis (OT) is the most common form of ECT, being detected in 50% of ECT in AIDS patients and having the best prognosis (Rabaud *et al*, 1994; Zajdenweber *et al*, 2005). OT, in contrast to intracranial disease, is uncommon in patients with AIDS (Heinemann *et al*, 1986). However, OT is a serious eye problem in HIV-infected patients, especially in developing countries (Chakraborty, 1999). OT is an important disorder and may be the first manifestation of life-threatening intracranial or disseminated *T. gondii* infections. Accurate diagnosis may allow early referral to a neurologist or infectious diseases specialist (Holland *et al*, 1988). Generally, OT tends to cause retinochoroidal scars with less retinal pigment and epithelial hyperplasia (Arevalo *et al*, 1997). It has no association between ocular findings and a positive titer for toxoplasmosis (Mansour *et al*, 1991). However, the presence of IgM antibodies may support this diagnosis, although antibody levels in AIDS patients may not reflect the magnitude of the disease (Gagliuso *et al*, 1990). OT was firstly reported in 2 of 34 AIDS patients with cotton wool spots as one of the most common retinal manifestations (Schuman and Friedman, 1983). It is also characterized by several features, including as single or multifocal retinal lesions in one or both eyes or massive areas of retinal necrosis. These lesions are not associated with a pre-existing retinochoroidal scar suggesting they are a manifestation of acquired rather than congenital disease (Gagliuso *et al*, 1990). A unique pattern of bilateral retinitis due to OT was observed in a patient in the late stages of AIDS in which the recognition of this pattern is important for appropriate treatment in immunosuppressed patients (Berger *et al*, 1993). Toxoplasmosis should therefore be considered in differential diagnosis in an AIDS patient with necrotizing retinitis (Moorthy *et al*, 1993).

Toxoplasmosis is known to cause widely disseminated extracerebral disease which is less common and more difficult to diagnose in AIDS patients. *Toxoplasma*-induced cystitis or pseudoneoplastic bullous cystitis are rarely detected in these patients. The diagnosis may be difficult because this condition is associated with misleading radiologic and endoscopic findings (Welker *et al*, 1994). With these studies, the diagnosis was confirmed by the presence of *Toxoplasma* cysts on histopathological examination of bladder biopsies (Hofman *et al*, 1993; Welker *et al*, 1994; Bron *et al*, 1995). Therefore, disseminated toxoplasmosis should be considered in the differential diagnosis of AIDS patients with culture-negative cystitis (Welker *et al*, 1994). For unclear reasons, gastrointestinal involvement is exceedingly rare and occurs in the context of severe immunosuppression and disseminated disease (Merzianu *et al*, 2005). Gastric toxoplasmosis has been reported in AIDS patients. It presents as diarrhea and other nonspecific GI symptom. Biopsy shows the presence of *Toxoplasma* trophozoites in the forms of tachyzoites, bradyzoites, and pseudocysts which are mandatory for a definite diagnosis. It responds well to anti-*Toxoplasma* therapy (Garcia *et al*, 1991; Alpert *et al*, 1996; Ganji *et al*, 2003; Merzianu *et al*, 2005). Interestingly, disseminated toxoplasmosis with

sepsis has also been found in AIDS patients and should be considered in patients with sepsis of unknown origin (Buhr *et al*, 1992; Artigas *et al*, 1993). ECT has also been diagnosed in the heart (Guerot *et al*, 1995), lung (Rabaud *et al*, 1996), liver (Mastroianni *et al*, 1996), and spinal cord (Overhage *et al*, 1990; Vyas and Ebright, 1996). ECT has a low incidence in AIDS patients. Many HIV-infected patients lack access to primary chemoprophylaxis and antiretroviral therapy, in limited resource setting hence, more cases are reported in this group.

In HIV-infected women, reactivation of latent toxoplasmosis may occur during pregnancy particularly in those who are severely immunocompromised, and results in maternal to fetal transmission of the parasite. Congenital transmission of toxoplasmosis has thus far been reported only in North and South America (Anonymous, 1996; Minkoff *et al*, 1997; Cruz *et al*, 2007; Lago *et al*, 2009) and has a low incidence. Congenital transmission of toxoplasmosis due to reactivation of latent infection during pregnancy occurs in mothers with very low CD4 cell counts (Minkoff *et al*, 1997) or in the presence of other immunological disorders (Montoya and Liesenfeld, 2004). One recent study reported congenital toxoplasmosis in an HIV-infected pregnant woman in whom there was a low titer of IgG to *T. gondii* and no IgM titer. It is important to keep this in mind in order not to miss an acute case of gestational toxoplasmosis (Lago *et al*, 2009). Another study reported a case of congenital toxoplasmosis in an infant born to an HIV-infected mother who had high anti-*Toxoplasma* IgG titers and negative IgM titers at nine weeks of gestation which underscores the need for special attention to maternal titers of anti-*Toxoplasma* antibody during HIV prenatal care (Cruz *et al*, 2007). Based on these studies, the seroprevalence of latent *Toxoplasma* infection is fairly common in HIV-infected pregnant women. This phenomenon is not significantly associated with an increased risk of congenitally acquired toxoplasmosis during pregnancy. There was a report of a case of TE in an immunocompromised HIV-infected pregnant woman who was at risk for transmitting HIV (low CD4 count and high viral load) and *Toxoplasma* infections to her fetus; she responded well to anti-*Toxoplasma* therapy and HAART (Nogueira *et al*, 2002). In this case, the combined *Toxoplasma* therapy (pyrimethamine and sulfadiazine) and HAART were beneficial to not only treat the mother but pervent trasmission to the fetus. Despite evidence of success, there have been reports of poor outcomes when an HIV-infected mother has TE during pregnancy, with vertical transmission of one or both infections to the fetus and increased morbidity and mortality in the mother (Mitchell *et al*, 1990; Vanhems *et al*, 1993; Marty *et al*, 1994; O'Riordan and Farkas, 1998). Due to the effectiveness of anti-*Toxoplasma* therapy and increasing availability of antiretroviral drugs, including HAART in pregnant women, the incidence of congenital toxoplasmosis should decline or even disappear.

NEUROPATHOLOGICAL FINDINGS OF TOXOPLASMOSIS BEFORE AND AFTER HAART

Toxoplasmosis is an the opportunistic infection, causing short-term and chronic morbidity and mortality (Seage *et al*, 2002, Bane *et al*, 2003; Kumarasamy *et al*, 2009). Autopsy findings confirm the presence of the parasite and demonstration of *Toxoplasma* cysts is diagnotic of disseminated toxoplasmosis in AIDS patients (Holch *et al*, 1993; Liu *et al*, 1994; Arnold *et al*, 1997).

The seroprevalence of toxoplasmosis is generally high in HIV-infected patients and approximately 10% of TE is reported in AIDS patients. There have been no reports of neuropathological findings related to toxoplasmosis found in AIDS patients in Malaysia and in neighboring countries in Southeast Asia, such as Thailand. This may be due to the fact it is not a common practice to conduct an autopsy on HIV/AIDS patients which could give the actual prevalence of AIDS-related TE being underestimated. TE is one of the most common opportunistic infections of the CNS (Wadia *et al*, 2001; Nobre *et al*, 2003) reported in an autopsy series conducted in India (Lanjewar *et al*, 1998) and in other clinical settings (Petito *et al*, 1986; Matthiessen *et al*, 1992; Wainstein *et al*, 1992; Mossakowski and Zeiman, 1997; Souza *et al*, 2008). The majority of AIDS-related diseases diagnosed at autopsy had not been clinically diagnosed or suspected antemortem (Eza *et al*, 2006). The importance of an autopsy in evaluating clinical management and diagnosis (Eza *et al*, 2006) should be periodically done; particularly in areas of high endemic OR high endemic areas for toxoplasmosis where antiretroviral drugs, such as HAART, cannot be fully accessed.

There is scanty data about AIDS-related neuropathological findings found during the era of HAART in Asia and Sub-Saharan Africa. This is mainly due to delayed introduction of these agents to these regions. It is expected more autopsy studies will be carried out in this part of the world in the near future. The incidence of toxoplasmosis in autopsy studies has declined since the introduction of HAART in various countries, such as USA (Langford *et al*, 2003) and France (Vallat-Decouvelaere *et al*, 2003). These studies show autopsy findings can be a valuable means of determining the range and relative frequency of infectious diseases in these patients (Lucas *et al*, 1993; Grant *et al*, 1997). In addition, this can potentially have an immediate impact on patient care by enabling appropriate interventions, based on the results, to be developed (Lucas *et al*, 1993).

THERAPEUTIC APPROACHES TOTOXOPLASMOSIS: CHEMOPROPHYLAXIS, ANTI-*TOXOPLASMA* REGIMENS AND HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY (HAART)

Primary chemoprophylaxis (with Cotrimoxazole) played an important role in preventing reactivation of toxoplasmosis in HIV-positive patients before the era of HAART (Behbahani *et al*, 1995; Duval *et al*, 2004; van Oosterhout *et al*, 2005). TE is still reported in HIV-infected patients with or without prophylaxis (Nissapatorn *et al*, 2004, 2007). Most patients with TE respond well to anti-*Toxoplasma* agents as demonstrated by findings from studies in various settings. The standard combination of pyrimethamine and sulfadiazine has been successfully used in treating this opportunistic disease but has been associated with high toxicity, such as Lyell's Syndrome or Steven-Johnson Syndrome (Haverkos, 1987; Behbahani *et al*, 1995; Caumes *et al*, 1995; Katlama *et al*, 1996; Torre *et al*, 1998). Several alternative therapies, principally used in patients intolerant to this combination, have been reported to be effective, including clindamycin and pyrimethamine or sulfadiazine (Dannemann *et al*, 1992; Tsai *et al*, 2002), clarithromycin and pyrimethamine (Fernandez-Martin *et al*, 1991, Dalston *et al*, 1995), clindamycin and 5-fluorouracil (Dhiver *et al*, 1993), azithromycin and pyrimethamine (Saba *et al*, 1993; Chang, 1996; Trotta *et al*, 1997; Jacobson *et al*, 2001), clindamycin and fansidar (Nissapatorn *et al*,

2004), Co-trimoxazole (Torre *et al*, 1998; Arens *et al*, 2007; Béraud *et al*, 2009), and atovaquone (Torres *et al*, 1997).

There is one case report of toxoplasmosis resistant to standard combination therapy (pyrimethamine and sulfadiazine) which improved with clindamycin and pyrimethamine (Huber *et al*, 1995). Another study suggested atovaquone is effective in AIDS cases with resistant toxoplasmosis (Lafeuillade *et al*, 1993). This helps to identify drugs which are effective and may act synergistically (McFadden *et al*, 2001). Relapses of TE are frequently observed in AIDS patients non-compliant to therapy or prophylaxis, and in those who develop adverse drug effects (Wong *et al*, 1984; Luft and Remington, 1992; Mariuz and Luft, 1992; Porter and Sande, 1992; Luft *et al*, 1993; Walckenaer *et al*, 1994; Caramello *et al*, 1995; Duran *et al*, 1995; Nissapatorn *et al*, 2004; Vidal *et al*, 2005; Béraud *et al*, 2009). There is no evidence of treatment–induced resistance so far reported contributing to a relapse of TE (Caramello *et al*, 1995). Few studies have come up with a solution to prevent relapses. Pyrimethamine and sulfadoxine twice a week appears to give promising results for the prevention of TE. Allergic reactions are usually mild and disappear on discontinuation, but may limit the value of this regimen (Ruf *et al*, 1993). Daily doses of pyrimethamine and sulfadiazine are more effective as maintenance therapy for preventing relapses of CNS toxoplasmosis (4.4 compared to 19.5 per 100 patient-years; incidence rate ratio, 4.36; p=0.024) than twice weekly administration (Podzamczer *et al*, 1995). Pyrimethamine and clinidamycin have been shown to be a valuable alternative for treatment but is less effective, particularly for long term prevention of relapses (Katlama *et al*, 1996). Azithromycin and pyrimethamine have been used as alternative therapy, but maintenance with this combination or oral azithromycin alone is associated with relapses (Wiselka *et al*, 1996; Jacobson *et al*, 2001).

Atovaquone is a unique naphthoquinone with broad-spectrum antiprotozoal activity. It has been found to be effective against *Toxoplasma* tachyzoites *in vitro* and may kill bradyzoites within cysts at higher concentrations. Atovaquone is frequently used in combination with other agents in treating TE. Experimental studies have shown the efficacy of atovaquone was enhanced when other agents were added, such as pyrimethamine, sulfadiazine, clindamycin or clarithromycin (Guelar *et al*, 1994). The intravenous preparation is highly effective in murine models with reactivated toxoplasmosis (Schöler *et al*, 2001; Dunay *et al*, 2004). In AIDS patients, the only study which reported failure with atovaquone in treating TE found a high temperature may induce inactivation of the product as well as the absence of food intake (Duran *et al*, 1995). Atovaquone has consistently been found to be a promising alternative for salvage therapy in TE patients who were intolerant of or who failed standard regimens (Kovacs, 1992; Guelar *et al*, 1994; Katlama *et al*, 1996; Torres *et al*, 1997; Chirgwin *et al*, 2002). However, the role of atovaquone in the treatment and prophylaxis of TE in AIDS patients is not well defined and more studies are required before a firm recommendation can be made (Baggish and Hill, 2002). An important question is whether the incidence of secondary reactivation or relapse cases of TE may begin to rise in the future. This depends on how the efficacy of the current treatment regimens and new novel drugs, particularly those which destroy the cyst/bradyzoite forms of *Toxoplasma* parasites. Another important factor is increasing resistance to antiretroviral drugs in HIV-positive patients and the subsequent decline in CD4 cell counts

(Kuritzkes *et al*, 2000; van Vaerenbergh *et al*, 2001; Sacktor *et al*, 2002) which has been reported in the recent years. Medication choice is often directed by available therapy (Dedicoat and Livesley, 2006), particularly in resource-poor settings.

TOXOPLASMOSIS AND IMMUNE RESTORATION DISEASE (IRD)

The incidence of opportunistic infections, including TE and ECT has decreased, particularly in areas where antiretroviral therapy, including HAART, is accessible (Kaplan *et al*, 2000; Sacktor *et al*, 2002; Arruda *et al*, 2004; Vidal *et al*, 2005; Subsai *et al*, 2006; Lian *et al*, 2007). HAART has reduced relapse cases of toxoplasmosis and has improved survival in these HIV-positive patients (Vidal *et al*, 2005; Silva and Araújo, 2005). This may be due to successful suppression of virus replication followed by an increase in CD4+ lymphocytes, a partial recovery of T-cell specific immune responses and decreased susceptibility to both local and systemic opportunistic pathogens. However, some patients experience clinical deterioration following initiation of HAART, which is a consequence of the restored ability to mount an inflammatory response (Huruy *et al*, 2008). HIV-associated immune reconstitution disease (IRD) is the clinical worsening of opportunistic infections that results from enhancement of pathogen-specific immune responses among patients responding to antiretroviral treatment (ART) (Lawn and Wilkinson, 2006). So far, few cases of IRD associated with TE have been reported in the literature. The first reported case was an AIDS patient with a CD4 cell count of 83 cells/mm^3 who presented with a focal seizure after 3 weeks of ART (Tsambiras *et al*, 2001). The diagnosis was based on positive serology, multiple ring-enhancing intracerebral lesions on MRI and a positive response to anti-*Toxoplasma* therapy. Two other patients who received GPO-vir [Stavudine (D4T) + Lamivudine (3tc) + Nevirapine (NVP)] were reported in northern Thailand who developed hemiparesis (both patients) and confusion (one patient) along with typical ring enhancing lesions of the brain. They both were treated with pyrimethamine and sulfadiazine and subsequently showed clinical improvement and the radiological lesions resolved (Subsai *et al*, 2006). No clinical details of TE from other studies have been reported (Gonzalez-Castillo *et al*, 2001; de Boer *et al*, 2003; Jevtovic *et al*, 2005; Huruy *et al*, 2008; Klotz *et al*, 2009). No cases of IRD-related toxoplasmosis have been reported among AIDS patients in Malaysia to date even though TE is a common systemic opportunistic infections in AIDS patients (Nissapatorn *et al*, 2004; Lian *et al*, 2007). Toxoplasmosis is a common neurological opportunistic infection in industrialized countries for which ART is often initiated fairly early compared to developing or resource-limited settings. The overall incidence of IRD-related toxoplasmosis is less common than other opportunistic parasitic infections. This casts some doubt on whether this infection may be associated with IRD (Lawn and Wilkinson, 2006). As the use of HAART increases worldwide, the care for patients receiving HAART will need to incorporate monitoring for and treating of complications of IRD (Agmon-Levin *et al*, 2008), including impaired CD4-cell immune reconstitution in HIV therapy in patients with TE (Kastenbauer *et al*, 2009).

CONCLUSION

Despite a decline in both morbidity and mortality in HIV-infected patients in developed countries including the United States and Europe, toxoplasmosis remains an important disease and is unlikely to be eradicated. Toxoplasmosis still occurs in those not

diagnosed with HIV and not receiving medical care, those not receiving prophylaxis, and those not taking or not responding to HAART. There are few reports regarding drug resistance in toxoplasmosis. Resistance in HIV and the action of anti-retroviral therapy may contribute to an increasing incidence of TE. In developing countries where antiretroviral therapy (ART) is still lacking, HIV-infected patients are at high risk for TE, these regions include China, India, South America, Southeast Asia and most importantly sub-Saharan Africa. A better understanding of the clinico-epidemiology of toxoplasmosis, and improved efforts in prevention, diagnosis and treatment, are needed. The role of infection with this parasite requires further study, including as to whether infections, such as TE have an impact on HIV/AIDS patients.

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