REVIEW ON HUMAN TOXOPLASMOSIS IN MALAYSIA: THE PAST, PRESENT AND PROSPECTIVE FUTURE

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Abstract. We reviewed various studies regarding human toxoplasmosis in Malaysia. They showed a varying prevalence of specific *Toxoplasma* antibodies among the Malaysian population. The Malays have shown the highest seroprevalence of toxoplasmosis, by most studies, when compared to other races. Demographic profiles have shown that *Toxoplasma* seropositivity is higher in males than females, lower in people with higher incomes, higher in the unemployed and tends to increase with age. In general, the route of transmission, such as contact with a cat, consumption of undercooked meat and blood transfusion were shown to have no significant association with *Toxoplasma* seropositivity ($p>0.05$). The immune status (CD4 cell count < 200 cell/mm^3) was strongly associated with toxoplasmic encephalitis ($p<0.05$).

INTRODUCTION

Toxoplasmosis, refers to the clinical and/or pathological evidence of disease (Wong and Remington, 1994) caused by the ubiquitous, obligate intracellular protozoan, *Toxoplasma gondii*. Infection is usually acquired orally or transplacentally, rarely by inoculation in a laboratory accident, by blood or leukocyte transfusion, or from a transplanted organ. *Toxoplasma* infection is capable of causing a wide spectrum of disease, the preponderance of which is asymptomatic (chronic/latent infection). The infection in chronic form is estimated to vary from 10-50% of the population in Malaysia (Tan and Zaman, 1973; Nissapatorn *et al*, 2003a).

The prevalence of toxoplasmosis was estimated mainly by the detection of specific antibodies (IgG and/or IgM) to *T. gondii*. Various serological methods have been used in Malaysia, such as the indirect hemagglutination (IHA) test, Sabin Feldman dye test, indirect fluorescent antibody test (Yahaya, 1991), and the enzyme-linked immunosorbent assay (ELISA) (Nissapatorn *et al*, 2002). The indirect immunoperoxidase (IIP) technique has also been useful for the diagnosis of toxoplasmosis (Yahaya, 1991). An alternative approach for detection of toxoplasmosis, polymerase chain reaction (PCR), a molecular method is considered a new, noninvasive, rapid, sensitive and specific technique which has been developed to detect *T. gondii* in blood (Sumati *et al*, 1999; Nissapatorn *et al*, 2003e).

This paper aims to review the epidemiological data of human toxoplasmosis in terms of the prevalence and risk factors as well as the management in an attempt to eliminate this disease from Malaysia.

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THE SEROPREVALENCE OF HUMAN TOXOPLASMOSIS

Acquired toxoplasmosis

Newborns (congenital toxoplasmosis). A literature review showed there was one study conducted on 1,061 congenitally defective Malaysian children of 0 to 4 month old revealing a 0.4% positivivity for toxoplasmosis. Toxoplasmosis in these children was confirmed by the detection of specific *Toxoplasma*- IgM antibody. However, children of the same age with non-congenital abnormalities showed a higher prevalence of toxoplasmosis. A total of 8.2 intrauterine toxoplasmic infections per 1,000 live births was detected, of which one-third (2.7 per 1,000 live births) was overt, manifesting symptoms more of liver damage than eye or brain damage (Tan and Mak, 1985). Since then, no new data of congenital toxoplasmosis has been docu-

Table 1
The seroprevalence of *Toxoplasma* infection among the Malaysian population for the periods of 1971-1980, 1981-1990, 1991-2000 and 2001up to present.

References	Prevalences	Donors	Percent positive by ethnic groups					Test used
			Malays	Chinese	Indians	Orang Asli[a]	Others[b]	
1971-1980								
Tan and Zaman, 1973	13.9 (728)	Healthy persons	**25.4**	5.0	19.6	-	-	IHA
Bisseru and Lim, 1974	4.6 (44)	Clinically suspected cases	-	-	-	4.6	-	Dye test
Cheah *et al*, 1975	27.4 (1,459)	Pregnant women	**38.8**	20.7	25.2	-	-	IFA
Leong *et al*, 1976		Clinically suspected cases (2)						IFA
Tan *et al*, 1976	23.0 (365)	Pregnant women	**33.0**	17.0	14.0	-	-	IFA
Dissanaike *et al*, 1977	16.0 (226)	Healthy persons	-	-	-	16.0	-	IFA
Tan *et al*, 1978	13.0 (161)	Clinically suspected cases	**50.0**	22.0	28.0	-	-	IHA
Thomas *et al*, 1980	20.9 (736)	Healthy persons	**33.9**	14.6	23.2	19.0	-	IFA
1981-1990								
Lim and Tan, 1983		Clinically suspected cases (31)[c]	**48.4**	25.8	25.8	-	-	IFA
Sinniah *et al*, 1984	30.2 (1,550)	Healthy persons	**37.7**	20.8	29.9	17.5	-	IFA
Tan and Mak, 1985	2.0 (405)	Children ≤ 4 months	-	2.0	-	-	-	IFA
Zahedi *et al*, 1985	25 (1,772)	Healthy persons	**30.4**	15.5	22.7	-	-	IFA
1991-2000								
Khairul Anuar *et al*, 1991a	27.9 (1,035)	Pregnant women	**29.8**	21.4	20.0	-	-	IFA
Zainul *et al*, 1992	45.8 (144)	Women with still births	47.5	**58.3**	42.0		35.7	ELISA / IFA
Lokman *et al*, 1994	10.6 (415)	Orang Asli patients	-	-	-	10.6	-	IFA
Haniffah *et al*, 1996		AIDS (TE), USM (case report)						ELISA
Ravichandran *et al*, 1998	31.6 (209)	Pregnant women	-	-	-	-	-	ELISA
Zurainee *et al*, 2000		Clinically suspected cases (134)[c]						ELISA/ISAGA
2001 up to present								
Shamilah *et a*l, 2001	31.3 /24.3	HIV positive/HIV negative	**42.1/27.0**	22.0/21.4	30.8/25.6	-	-	
Nissapatorn *et al*, 2002	21.0 /28.1	HIV-AIDS/HBD	**75.0/34.5**	22.2/44.8	16.7/31.3	-	50.0	ELISA
Nissapatorn *et al*, 2003b	51.2 (406)	AIDS, HKL	**47.5**	34.6	16.3	-	1.4	MEIA
Nissapatorn *et al*, 2003d	49.0 (200)	Pregnant women,UMMC	**55.3**	19.4	55.7	-	-	ELISA
Nissapatorn *et al*, 2003a	41.2 (301)	HIV/AIDS, HKL	**57.9**	38.7	29.6	-	25.0	ELISA

[a]Aborigines population; [b]Foreigners; [c]Ocular toxoplasmosis report

mented in Malaysia. The Department of Parasitology, Faculty of Medicine has recorded about a 2% positive rate for congenital toxoplasmosis (personal communication, 2002).

General healthy population

The first report of toxoplasmosis in Malaysia showed 13.9% of 728 sera collected from healthy persons of different age groups, races and occupations from various parts of West Malaysia, to be IHA positive (Tan and Zaman, 1973). The Sabin-Feldman dye test was used to detect *Toxoplasma*- specific IgG from 44 in-patients, who were admitted for various medical conditions, showing a rate of 4.6% (Bisseru and Lim, 1974). From 1975 to 1984, the main diagnostic test for *Toxoplasma* infection was the indirect fluorescent antibody (IFA) test. The seroprevalence of toxoplasmosis in the population has been increasing over the years (16% to 30%). From 1985 to present, the trend of toxoplasmosis prevalence has shown a similar figure (20% to 30%) (Zahedi *et al*, 1985; Shamilah *et al*, 2001; Nissapatorn *et al*, 2002).

Pregnant women

The earlier studies of the seroprevalence of toxoplasmosis in pregnant women was estimated to be 27.4% and 23.0% (Cheah *et al*, 1975; Tan *et al*, 1976). It is noted that from 1990 to now the percentage of *Toxoplasma* infection in this group of the population has significantly increased (Khairul Anuar *et al*, 1991; Ravichandran *et al*, 1998; Nissapatorn *et al*, 2003d).

Ocular toxoplasmosis

Ocular toxoplasmosis has been recorded in Malaysia (Lim and Tan, 1983). They reviewed 31 clinically suspected cases diagnosed as congenital ocular toxoplasmosis. Nineteen (63.3%) out of 31 patients presented with the cicartrical stage of the disease which is the most common presentation of ocular toxoplasmosis. Acute recurrences of chronic congenital ocular toxoplasmosis was seen in 12 patients. This usually occurs below the age of 40, as is the case in this series, and the number of recurrent attacks may vary from 1-13. In a recent study, a total of 134 patients suspected of having toxoplasmosis with clinical presentations ranging from blurred vision to severe retinal detachment. Of these patients, 72% were seropositive for *Toxoplasma* infection. Chorioretinitis and vitritis were found to be the most apparent symptoms, both having 100% correlation with serological positivity (Zurainee *et al*, 2000).

Immunocompromised individuals (HIV/AIDS)

Toxoplasmosis has been implicated as one of the most common opportunistic infections and has posed many diagnostic and therapeutic challenges for clinicians treating HIV/AIDS patients. In spite of this, there are few reports of the seroprevalence of toxoplasmosis in immunocompromised individuals in Malaysia. Recent studies have shown 21%, 51.2%, and 41.2% rates of *Toxoplasma* prevalence in this group of the population (Nissapatorn *et al*, 2002; 2003a,b,c).

DEMOGRAPHIC PROFILE, RISK FACTORS, CD4 +T CELL COUNT AND ANTIBODY PREVALENCE

Ethnic group and antibody prevalence

Table 1 summarizes the major ethnic groups of Malaysia, namely Malay, Chinese, Indians and Aborigines. The data of various studies showed that the prevalence rate was highest among the Malays, followed by the Indians in the early studies (from 1973 to 1984) and the Chinese in later years (from 1991 to present).

Association of age, sex and antibody prevalence

The sera samples were collected from all age groups as well as from cord blood. The prevalence of *Toxoplasma* infection was considered to be acquired in early life and tended to increase with age (up to middle age) and then decline in later life (Tan and Zaman, 1973; Nissapatorn *et al*, 2003a). It is interesting to view the majority of studies showing that the prevalence of toxoplasmosis was higher in males than females (Tan and Zaman, 1973; Lim and Tan, 1983; Zurainee *et al*, 2000; Shamilah *et al*, 2001; Nissapatorn *et al*, 2002).

Socioeconomic status and antibody prevalence

A study showed the prevalence of toxoplasmosis was higher in lower income groups (71.8%) than higher (28.2%) income groups (Cheah *et al*,

1975). It also revealed that *Toxoplasma* seropositivity was higher among rural than in suburban dwellers (Thomas *et al*, 1980). One recent study showed a higher prevalence rate among individuals living in Kuala Lumpur than those outside Kuala Lumpur (Nissapatorn *et al*, 2003a).

Occupation and antibody prevalence

Studies on different occupations showed that the highest antibody prevalence rate (22.2%) in padi planters, followed by veterinarians (20.2%), workers in oil palm and rubber estates (13.5%), antimalarial laborers (10.1%) and underground tin miners (3.7%)(Tan and Zaman, 1973). In another study, it was found that zoo workers had the highest antibody prevalence rate (51.25%), followed by medical students (41.7%), vegetarian Hindu priests (29.4%) and housewives (25.0%) (Zahedi *et al*, 1985). In recent studies, investigations on three different occupational groups, found that unemployed persons had the highest prevalence rate (36.7% and 44.8%) followed by non-laborers (26.3% and 40.3%) and laborers (19.1% and 37.3%), respectively (Nissapatorn *et al*, 2002; 2003a).

Association between risk factors (contact with cat, consumption of undercooked meat and history of blood transfusion) and antibody prevalence

Very few studies have focused on the association between cat ownership and *Toxoplasma* seropositivity ($p < 0.02$) (Zahedi *et al*, 1985; Zainul *et al*, 1992). In contrary, a recent study found that there was no significant association between a single or combination of risk factors (contact with cat, consumption of undercooked meat and history of blood transfusion) and *Toxoplasma* seropositivity ($p > 0.05$) (Nissapatorn *et al*, 2002). The latest study also found no significant association between possible risk factors and disease transmission (Nissapatorn *et al*, 2003a).

Association between CD4 counts and antibody prevalence in HIV/AIDS

As we know, a CD4 count is a prognostic marker of AIDS-defining illness according to the communicable diseases control (CDC) in 1993 which is related to the progressiveness of HIV infection to full blown AIDS with opportunistic infections involved. A recent study showed no significant association between CD4 counts and *Toxoplasma* seropositivity ($p > 0.05$) (Nissapatorn *et al*, 2003a).

Association between CD4 count and toxoplasmic encephalitis (TE) in AIDS

The first reported case of toxoplasmic encephalitis occured in an AIDS patient with a CD4 count < 200 cell/mm^3 (Haniffah *et al*, 1996). Similar findings have also been noted by other investigators (Nissapatorn *et al*, 2003a,d).

Toxoplasmosis and its complication in AIDS

Some studies have documented 1 (4.8%) of 21 *Toxoplasma* seropositive immunocompromised patients developed TE as studied at the University Hospital (Nissapatorn *et al*, 2002). They also discovered that 14.9% of AIDS–related toxoplasmosis patients developed TE and relapsing TE was detected in 9.7% of previous TE patients at the Hospital Kuala Lumpur (Nissapatorn *et al*, 2003b). The latest study showed only 1 (0.8%) of 124 *Toxoplasma* seropositive patients had developed active TE (Nissapatorn *et al*, 2003a).

Toxoplasmosis in transplant recipients

At present, no data has been reported in Malaysia.

DISCUSSION

Toxoplasmosis is common and has a high prevalence among the Malaysian population. It is interesting to note that the highest seroprevalence of toxoplasmosis in most of the studies was in Malays, when compared with other races (Chinese and Indians). This finding is in agreement with other studies in this region (Partono and Cross, 1975, Gandahusada, 1978; Wong *et al*, 2000). This could be explained by the fact that Malays have a habit of keeping cats in their house which leads to close contact where they will be more likely exposed to contaminated cat feces, which was noted by other investigators (Tan and Zaman, 1973; Thomas *et al*, 1980).

As we know, predisposing factors (contact with cats, consumption of undercooked meat and blood transfusion) play a crucial role in *Toxoplasma* infection. In Malaysia, very few studies try to verify these associations either in healthy or immunocompromised, particularly HIV-posi-

tive, persons. One of the earliest studies showed a significant association between cat ownership and *Toxoplasma* seropositivity in healthy persons (Zahedi *et al*, 1985) which is contrary to other previous studies (Ganley and Comstock, 1980; DiGiacomo *et al*, 1990; Bobic *et al*, 1998). A recent study showed no significant association between contact with cats and *Toxoplasma* seropositivity in HIV-positive patients (Nissapatorn *et al*, 2002). This finding is in agreement with other investigators (Wallace *et al*, 1993; Glaser *et al*, 1994). This could be explained by the possibility that contact with cats may not pose a risk for *Toxoplasma* infection. Further study should be made in order to ascertain this association. So far, only two studies in Malaysia have shown that the role of consumption of undercooked meat had no impact on *Toxoplasma* seropositivity (Thomas *et al*, 1980; Nissapatorn *et al*, 2003a). This suggests that eating habits among Malaysians must continue to be wisely practiced in order to prevent the transmission of the *Toxoplasma* parasite and achieve a healthy life-style. Other studies showed a strongly significant association between the consumption of undercooked meat and *Toxoplasma* seropositivity (Knaus, 1991; Arias *et al*, 1996; Fan *et al*, 2001). Only one study in Malaysia has documented no significant association between history of a blood transfusion and *Toxoplasma* seropositivity (Nissapatorn *et al*, 2002). This observation is contrary to various earlier studies (Beauvais *et al*, 1976; Nelson *et al*, 1989; Evans, 1992). This indicates the importance of *Toxoplasma* screening among different population groups in order to prevent passive seroconversion, particularly in the post-transfusion period even though this risk factor has not so far posed a significant health problem.

Since the pandemic of HIV infection has spread throughout the world, toxoplasmosis has been implicated as one of the most important opportunistic infections in AIDS patients of which toxoplasmic encephalitis is the most common clinical disease, most frequently causing focal intracerebral lesions in these patients (Wong and Remington, 1994). The CD4 cell count is a prognostic marker which is related to the progression of HIV infection to full blown AIDS with the occurence of other opportunistic infections (AIDS-defining illness). Recent studies in Malaysia showed that CD4 cell count plays no role in association with *Toxoplasma* seropositivity (Nissapatorn *et al*, 2002). Whereas, patients have CD4 cell count of less than 200 cells/mm^3, show significantly developed toxoplasmic encephalitis (Nissapatorn *et al*, 2003b). This observation is supported by other recorded studies (Renold *et al*, 1992; Mariuz *et al*, 1997; Nascimento *et al*, 2001). Therefore, it is still recommended to monitor CD4 cell counts, *Toxoplasma* serodiagnostic status, as well as the implementation of life-long anti-*Toxoplasma* therapy in this treatable condition.

In view of the national prenatal screening program for toxoplasmosis and the controversy over its cost effectiveness, we need to find an appropriate strategy to combat this silent disease. Simple preventive measures, particularly in pregnant women, as part of a health education system in order to increase maternal awareness of the disease and to reduce risk of infection as outlined by investigators (Zainul *et al*, 1992) has been implemented and practiced in the nationwide medical care centers in Malaysia. There is a growing interest in toxoplasmosis among the scientific and the medical community in this country. The disease has been recognized as an important cause of morbidity among immunocompromised individuals and in congenital infection. Though there are many treatment modalities that are available the proper diagnosis of infection still poses a major problem in the management of patients. Current research is focused on the characterization of molecular markers and DNA amplification. More work needs to be done to ease patients of this treacherous infection that continues to inflict a major toll on the Malaysian population.

In conclusion, toxoplasmosis continues to be an important infection in Malaysia. Various factors contribute to the acquisition of *Toxoplasma* infection and worsen its condition. We should increase our awareness in terms of prevention and control measures in order to decrease the incidence of toxoplasmosis in this country.

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