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Toxoplasmosis: A Silent Threat in Southeast Asia

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Abstract: Toxoplasmosis represents the most prominent parasitic disease found in humans. The seroprevalence of toxoplasmosis was estimated to vary from <2% up to 70% in the Southeast Asian population. Contact with cat and consumption of uncooked meat were the most common risk factors in acquiring high rate Toxoplasma infection profusely. However, there were a very few reports of toxoplasmosis contracted through blood product or organ transplantation. In view of the clinical scenario, toxoplasmosis was an etiological factor in pregnant women related to factors such as abortion, stillbirth and bad obstetric history and required a consideration differential diagnosis of patients with unexplained lymphadenopathy. Moreover, toxoplasmosis was found to be a common cause in patients with infectious posterior uveitis. With the concurrent HIV/AIDS pandemic, toxoplasmosis was shown to be highly prevalent in HIV-infected patients, with substantial incidence of toxoplasmic encephalitis (TE) in AIDS patients being reported mainly from Malaysia, Singapore and Thailand. Majority of active TE patients presented with typical neurological manifestations with CD4 cell count of less than 100 cells/mm³. The laboratory investigations in the diagnosis to be taken into consideration included a positive Toxoplasma serodiagnosis and CT scan finding. Anti-Toxoplasma therapy was shown to be quite effective in treating TE, nonetheless, relapse of TE cases were still reported. Moreover, no outbreak in food and water borne toxoplasmosis has been documented in this subcontinent.

Key words: Toxoplasmosis, epidemiology, clinical perspective, health issue and Southeast Asia

INTRODUCTION

Toxoplasma gondii is a ubiquitous, intracellular protozoan parasite and zoonotic in nature. Toxoplasmosis is still prevalent in every part of the world even today and is a public health problem capable of causing a broad spectrum of diseases in different groups of population found in Southeast Asia (Iverarity et al., 2002; Suhardjo et al., 2003; Subsai et al., 2004; Nissapatorn et al., 2005). This literature review therefore aims to highlight epidemiological surveillances and clinical perspectives on toxoplasmosis in Southeast Asian people. Toxoplasmosis is definitely a subject of challenge in the field of infectious diseases that still need more efforts in its initial elimination and further steps should also be taken in eradicating this disease from this well known region.

MATERIALS AND METHODS

This literature review was carried out at the Department of Parasitology, University of Malaya Medical Centre from October to December, 2004. Since 1900, the first observation of *Toxoplasma* was found in a section of the spleen and bone marrow of Java sparrows and was given its definitive description by Nicolle and Manceaux in 1908. However, the first case of congenital toxoplasmosis in man was diagnosed in 1928. Later, *Sabin* and *Feldman* developed the first reliable serological assay

the Dye test to detect *Toxoplasma* serology in 1948. From these historical events, all related-data of this human pathogen were intentionally reviewed and obtained from the initial phases of its literature during the late 50s (1959), up to the new era (2005) from the prime and hi-tech search Medline, which is a systematic, informative and a very useful source in conducting this review. The abstracts of these previous works were collected from each country in Southeast Asia. Subsequently, all accessible original articles were carefully read and they highlighted the importance of its content. From this search, it is presumed that some works could not be traced due to the fact that they were either published by local journals that could not be accessed or were written in the native language, which might not be widely understood by others. Unfortunately, no study on toxoplasmosis has been reported in Brunei Darussalam, although it is a small but a rich country. Therefore, other 9 Southeast Asian countries were alphabetically included; Cambodia (2001-2003), Indonesia (1965-2003), Laos PDR (1992), Malaysia (1973-2005), Myanmar (1977), Philippines (1991-2000), Singapore (1967-2003), Thailand (1967-2004) and Viet Nam (1959-2003). Overall, a total number of 103 publications were successfully reported, which portrayed to the native people an awareness of this scientific documentation in the beginning of 21st century.

RESULTS

Table 1 shows that the seroprevalence of toxoplasmosis seems to increase with the time duration as particularly seen in Indonesia; 2 to 63% in 1964 to 1980 (De Roever-Bonnet et al., 1964; Yamamoto et al., 1970; Clarke et al., 1973a-b, 1975; Cross et al., 1975a-d, 1976; Partono and Cross, 1975; Durfee et al., 1976; Srisari, 1978; Srisari and Endardjo, 1980), 3.1 to 60% from 1981 to 1994 (Chomel et al., 1993) and 58 to 70% during 1995 till 2003 (Uga et al., 1996; Konishi et al., 2000; Terazawa et al., 2003). This largest country clearly showed the highest Toxoplasma prevalence in this region. Furthermore, only one study was reported in Laos PDR, where 15.3% of Toxoplasma seroprevalence was shown in a group of inhabitants with a prevalence increasing with age (Catar et al., 1992). However, in Malaysia, the seroprevalence of toxoplasmosis varied from 13.9 to 30.2% in healthy persons. The Malays showed the highest prevalence when compared to other ethnic groups, signifying that *Toxoplasma* seropositivity tends to increase with age. Moreover, a higher prevalence was found in males and unemployed individuals, whereas a lower rate was observed in people with higher incomes. The risk behaviors such as contact with cat and consumption of uncooked meat were found to be the main sources of Toxoplasma infection (Tan and Zaman, 1973; Dissanaike et al., 1977; Thomas et al., 1980; Sinniah et al., 1984; Zahedi et al., 1985; Hakim et al, 1994; Nissapatorn et al., 2002). Two cases of human acquired toxoplasmosis were reported in the early period (Leong et al., 1976) and thereby toxoplasmosis was also suggested to be given priority in the investigation of pyrexia of unknown origin (PUO) cases (Tan et al., 1978). Similarly, from 1975 to 2000, studies in the Philippines showed varying results of *Toxoplasma* seroprevalence from < 2 to 61.2% in different settings. The prevalence tended to increase with age and a significantly higher rate was found in rural than urban areas (Cross et al., 1997; Eduardo, 1991; Kawashima et al., 2000). Subsequently in Singapore, the first report on Toxoplasma seroprevalence was 41.3% in the sera of clinically suspected cases and 17.2% in healthy individuals (Singh et al., 1968). Taking into account the comparison between different regions, the highest Toxoplasma seropositivity was found among the Malays, with their living habits and sanitary conditions greatly attributing to this finding (Zaman and Goh. 1969).

During the period of 80s, *Toxoplasma* seroprevalence was 42.5% in clinically suspected cases (Lim *et al.*, 1982). From 1991 to date, 18.8% of *Toxoplasma* seroprevalence was shown in healthy individuals and the epidemiology and clinical profiles of patients presenting with acute toxoplasmosis were indicative of asymptomatic cervical lymphadenopathy (Mohan *et al.*, 1991a, b). The first

Table 1: The prevalence of *Toxoplasma* infection and clinical evidence of toxoplsmosis in different groups of the Southeast Asian population

		Toxoplasma sero	prevalence		
Country origin	Year	Healthy persons	Pregnant women	Children	Clinical toxoplasmosis (year)
Cambodia-	-	-	-	-	-
Indonesia	1964-1980	2-63%	-	-	Congenital toxoplasmosis (1976)
	1981-1994	3.1-60%	-	-	Congenital toxoplasmosis (1989)
	1995-2003	58-70%	-	-	-
Lao PDR	1992	5.3%	-	-	-
Malaysia	1973-2005	13.9-30.2%	23-49%	2-33.3%	Acquired toxolasmosis (1976)
					Congenital toxoplasmosis (2005)
Myanmar	1977	-	-	28.4-43.8%	-
Philippines	1977-2000	<2-61.2%	-	-	-
Singapore	1968-1990	17.2%	-	-	Congenital toxoplasmosis (1967, 1971, 1982 and 1989)
	1991-2003	18.8%	upto 17.2%	-	Acute toxoplasmosis
					(lymphadenopathy) (1991a and b)
Thailand	1967-2003	2.8-18.5%	1.4-21.7%	-	Fatal human toxoplasmosis (1978)
Viet Nam	1959-2003	7.7-24.3%	11.2%	-	-

Table 2: The prevalence of *Toxoplasma* infection and clinical evidence of toxoplsmosis in patients with ocular diseases and other immunosuppressed

		Toxoplasma (IgG		
Country origin	Year	Ocular	Immunosuppressed ¹	Clinically diagnosed of ocular toxoplasmosis
Cambodia	-	-	-	-
Indonesia	1976-2003	-	-	Present (1976, 1982, 1988, 1991 and 2003)
Lao PDR	-	-	-	-
Malaysia	1974-2005-	31.1%/19.3%	-	Present (1974, 1983, 2000 and 2005)
Myanmar	-	-	-	-
Philippines	-	-	-	-
Singapore	1991	-	-	Present (1991a and b)
Thailand	1995-2001	12.5%/3.1%	11%	-
Vietnam	-	-	-	-

¹Immunosuppressed includes patients with organ transplant

study in Thailand showed that 4 out of 265 slaughter workers were *Toxoplasma* seropositivities (Sungkasuwan, 1967), while, a report of three fatal cases on human toxoplasmosis was found in the late 70s (Bunyaratvej *et al.*, 1978). *Toxoplasma* seroprevalence was between 2.8 to 18.5% in healthy persons and consumption of raw meat and contact with cats were among the risk factors contributing to *Toxoplasma* infection (Tanphaichitra *et al.*, 1976; Nabnien, 1979; Morakote *et al.*, 1984; Bunnag *et al.*, 1988; Maleewong *et al.*, 1989; Wongkamchai *et al.*, 1995; Maruyama *et al.*, 2000; Tantivanich *et al.*, 2001; Sukthana *et al.*, 2003). Viet Nam, the first Southeast Asian country, was also actively involved with epidemiological study on toxoplasmosis, with an incidence of 2.9% using toxoplasmin skin test as shown in the earliest study (Sery *et al.*, 1959). 15.7 and 24.3% of *Toxoplasma* seroprevalence were found in two different groups of population (Sery *et al.*, 1988); while 7.7% in intravenous drug users in one recent study (Buchy *et al.*, 2003).

In pregnant women, 23 to 49% of *Toxoplasma* prevalence was found in Malaysia (Cheah *et al.*, 1975; Tan *et al.*, 1976; Khairul Anuar *et al.*, 1991; Ravichandran *et al.*, 1998; Nissapatorn *et al.*, 2003a),

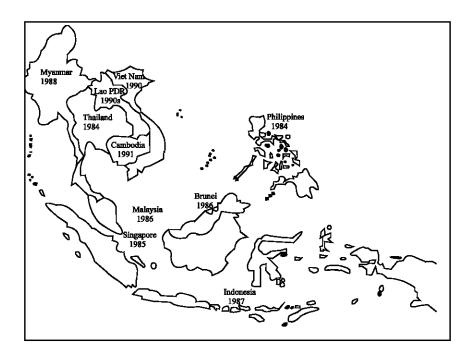


Fig. 1: The first case reported of HIV/AIDS in Southeast Asia

Table 3: The Prevalence of Toxoplasma infection and clinical evidence of toxoplasmosis in HIV/AIDS patients

Country origin	No. of HIV/AIDS ¹	Toxoplasma (+) ²	TE^3
Cambodia	170,000	No report	Rare
Indonesia	110,000	No report	No report
Lao PDR	1,700	No report	No report
Malaysia	51,000	21-44.8%	Yes/relapse
Myanmar	320,000	No report	No report
Philippines	8,900	No report	No report
Singapore	4,100	No report	Yes
Thailand	560,000	22.4-53.6%	Yes/relapse
Viet Nam	200,000	No report	No report

 $^{1}4^{\text{th}}$ report on the global AIDS epidemic, UNAIDS, 2004. $^{2}Toxoplasma$ (IgG) seroprevalence. ^{3}TE : Toxoplasmic Encephalitis

and it was shown to be the highest *Toxoplasma* rate found in this region as compared to 1.4 to 21.7% in Thailand (Nabnien, 1979; Tantivanich *et al.*, 1980, 2001; Maleewong *et al.*, 1989; Chintana *et al.*, 1991, 1998; Daenseekaew *et al.*, 1992; Taechowisan *et al.*, 1997; Sukthana, 1999; Wanachiwanawin *et al.*, 2001), up to 17.2% in Singapore (Mohan *et al.*, 1991a; Wong *et al.*, 2000) and 11.2% in Viet Nam (Buchy *et al.*, 2003). Surprisingly, few studies have been reported on *Toxoplasma* seroprevalence in children, newborn or still births in this region. In Malaysia, 33.3% (Bisseru and Chong, 1974) and 2% (Tan and Mak, 1985) of *Toxoplasma* prevalence in children and 45.8% in women with still births (Zainul Rashid *et al.*, 1992) were reported. 43.8 and 28.4% *Toxoplasma* prevalence were found in 2 different groups of school children in Myanmar (Tin, 1977). In addition, 7.18 to 13.14% were found in the cord blood (Chintana, 1991; Taechowisan *et al.*, 1997) and up to 21.05% in the new born (Tantivanich *et al.*, 2001) were shown in Thailand. Interestingly, the clinically evident cases of congenital toxoplasmosis have been reported in two neighboring countries; Malaysia and Singapore (Lim, 1967; Paul, 1967, 1971, 1982; Nissapatorn *et al.*, 2005) and have focused their attention on its importance and associated problems (Singh *et al.*, 1972; Singh, 1987; Wong, 1987).

In patient with ocular diseases, few studies showed that 12.5 to 31.1% (IgG) and 3.1 to 19.3% (IgM) of *Toxoplasma* prevalence were found in Malaysia and Thailand (Wongkamchai *et al.*, 1995; Nissapatorn *et al.*, 2005). Interestingly, the evident cases of congenitally acquired ocular toxoplasmosis, which is a common vision-threatening disease and the most common of primary retinochoroiditis were mainly reported from Indonesia (Partono and Cross, 1976; Srisari, 1982; Kadarisman *et al.*, 1991; Suhardjo *et al.*, 2003). The critical stage of the disease was also found to be the most common occurrence in these patients (Lim and Tan, 1983). Patients with ocular manifestations of congenital toxoplasmosis where the incidence of congenital infection was high, belonged to the number of cases presenting with fetal wastage and the prevalence of ocular toxoplasmosis (Mohan *et al.*, 1991a, b). In addition, ocular manifestations and *Toxoplasma* serodiagnosis were the main useful tools of investigation (Chee *et al.*, 1992; Zurainee *et al.*, 2000; Nissapatom *et al.*, 2005). Among the immuosuppressed, 11% of *Toxoplasma* seroprevalence was found in patients with kidney transplants (Sukthana *et al.*, 2001) as shown in Table 2.

The first case of HIV/AIDS was reported in 1984. Since then, the epidemiological and clinical relevance of toxoplasmosis has been studied in a few dominant countries, although no study regarding this has been conducted in Indonesia, Laos PDR, Myanmar, Philippines and Viet Nam. The first report on seroprevalence of toxoplasmosis was conducted in Thailand (Wongkamchai et al., 1995). Since then, the varying Toxoplasma prevalence from 21 to 53.7% has been consistently reported from different settings in Malaysia (Shamilah et al., 2001; Nissapatorn et al., 2001, 2002, 2003b-d, 2004, 2005) and Thailand (Wongkamchai et al., 1995, 1999; Sukthana et al., 2000; Wanachiwanawin et al., 2001). In Viet Nam, a screening of toxoplasmosis was subjected for recommendation in HIV/AIDS patients (Buchy, 2003). After HIV/AIDS epidemict, toxoplasmic encephalitis (TE) was first reported in clinical practice found in Thailand (Thongchareon, 1992). The incidence of this opportunistic infection varied from place to place and mostly occurred at a time when the patient had a very low CD4 cell count (<100 cells/mm³). Reactivation of latent Toxoplasma infection and relapse of TE cases have been subsequently reported in AIDS patients (Swasdisevi, 1994; Haniffah et al., 1996; Ruxrungtham et al., 1996; Chariyalertsak et al., 2001; Pichit et al., 2001; Iverarity et al., 2002; Senya et al., 2003; Nissapatorn et al., 2003b-d, 2004, 2005; Subsai et al., 2004; Anekthananon et al., 2004) as shown in Fig. 1 and Table 3, respectively.

Toxoplasmosis: From Source to Outbreaks

No ever-reported study of clinically evident of toxoplasmosis outbreak on food and water issue has been documented in the Southeast Asian subcontinent.

DISCUSSION

Toxoplasmosis is one of the most important infectious diseases, which causes epidemiological and clinical impacts in humans. This review confirms that these surveys have been successfully conducted over the past years and have greatly helped in the better understanding of this existing parasitic infection in this region. However, there were certain predisposing factors that play an important role in the acquisition of *Toxoplasma* infection. Indonesia and Philippines are good examples of countries sharing striking similarities in their geographical distributions based on over a thousand islands and Volcanic Mountains; moreover, both the countries show high *Toxoplasma* seroprevalence (upto 70%). In this context, geographical variations (mountainous or volcanic vs plain areas) could be one of the hypotheses to explain the contribution to the spreading of *Toxoplasma* infection. On a broader aspect, most countries have shown no difference in their life styles, particularly in the consumption of raw or half cooked meat, which is most probably and accidentally infected by *Toxoplasma* cyst; however, these studies are mainly conducted in the cities or the urban areas.

Therefore, it would be more interesting if future studies are carried out in the suburbs or rural places, including tribal areas and certain groups of inhabitants in the remote areas. Besides, health education particularly eating habits should be wisely practiced, since it is the most common route of *Toxoplasma* transmission. It was evident from the living conditions of different regions that certain groups were more exposed to *Toxoplasma* infection than others. Many studies found that Malays had the highest prevalent rate, which was due to the fact of their close contact with cats kept as pets particularly in these two neighboring countries of Malaysia and Singapore. Toxoplasmosis is considered as one of the blood borne diseases either via blood products or organ transplant, however, there were very few data on epidemiological aspects and none was documented on clinical evidence of toxoplasmosis. The importance of *Toxoplasma* screening is very much in need to promote the awareness among blood donation, which would further prevent passive seroconversion particularly during the post-transfusional period. So far, this factor has not posed a major public health problem in this region.

In pregnant women, the clinical implications of Toxoplasma infection during pregnancy are tremendously dangerous such as spontaneous abortion, still births or premature delivery with various fetal malformations. The studies in Malaysia showed the highest rate of Toxoplasma infection than other parts in this subcontinent, but the incidence of congenital toxoplasmosis was surprisingly scare or at very low rate. Overall, the evidence of congenital toxoplasmosis is not well documented in this region either due generally to the fact that no study has been properly conducted or it actually shows low incidence. Even though toxoplasmosis is relatively low in certain countries; however, a large proportion of antenatal women are still susceptible to this infection. This aspect strongly necessitates imparting health education, including general guidelines of primary prevention to childbearing seronegative women and pregnant women from preventing primary Toxoplasma infection during pregnancy. Mass or routine antenatal toxoplasmosis screening is cost effective and not appropriate to practice particularly in limited resource settings or low incidence of congenital toxoplasmosis, however, it could be justified in the area where high prevalence of Toxoplasma infection affects mothers, congenital toxoplasmosis and in countries where TORCHs screening is an applicable tool in that setting. In addition, women with bad obstetric history such as abortion (spontaneous or repeated), still birth or fetal malformations should be tested for Toxoplasma serological status, which can reduce the possibility of congenital toxoplasmosis.

The existence of clinically diagnosed toxoplasmosis in patients with ocular diseases has been periodically reported in different studies from Indonesia, Malaysia and Singapore. Whether ocular toxoplasmosis is either congenital or acquired, is still controversial, nonetheless, toxoplasmosis is not only the most common cause of posterior uveitis in majority of cases, but it should also be primarily considered in the differential diagnosis in any suspected patients with ocular diseases. Ocular presentations and *Toxoplasma* serodiagnosis are the primary sources of investigation; in addition, improvement of clinical and funduscopic conditions after the introduction of anti-*Toxoplasma* therapy should be the clue for the confirmation of toxoplasmosis.

HIV/AIDS is the subject of great interest and of utmost concern particularly in Southeast Asia, being a region of the fastest growing HIV epidemic in the world. Toxoplasmosis is still reported in clinical practices in co-existence with HIV/AIDS patients. *Toxoplasma* parasite is the most common cause of intracerebral lesions and one of the leading opportunistic pathogens and causes of death in AIDS patients. Due to its noteworthy significance, toxoplasmosis has been included in the centers for Disease Control and Prevention (CDC), Atlanta for AIDS defining illness till date. The incidence of toxoplasmic encephalitis (TE) is directly proportionate to the prevalence of *Toxoplasma* infection and the number of AIDS patients. The empirical diagnosis of TE is based on few criteria. The neurological presentations mimic other brain diseases and make the diagnosis difficult. Results from the brain involvement in either neuroimaging finding, which is widely used, or stereotactic brain biopsy (Yeo *et al.*, 2000), are useful in AIDS patients with cerebral lesions to confirm the etiology in majority

of cases. Serology (IgG and/or IgM antibodies), is shown as a sensitive investigation to determine whether TE is primary, which is less common, or secondary (reactivation), which occurs in more than 95% of these patients. However, other techniques are also used to detect the presence of organism, but the sensitivity and specificity are quite varied and depend on its availability or unavailability in the laboratory. Responding to anti-Toxoplasma therapy is the key to confirm the diagnosis of TE. Moreover, the occurrence of TE was significantly related to very low level of CD4 count and one study suggested that the correlation of imaging findings with CD4 counts is especially useful in obtaining a working diagnosis (Corr, 2003). Primary chemoprophylaxis should be compulsorily given to all new HIV infected patients particularly in poor resource settings, where they might not be able to access HAART. However, this is not an absolute hypothesis to explain the relationship between the occurrence of TE and its chemoprophylaxis in these patients. In due course, one study found that the mounting medical care cost for adult AIDS patients has become critical (Suwanagool et al., 1997) in certain countries where the number of HIV/AIDS patients is still increasing. In the era of HAART, it should be considered as the most effective approach in reducing the incidence of TE, however, it is still questionable whether it is the ideal option in case management regarding this parasite in times to come.

CONCLUSIONS

Toxoplasmosis is still shown to be highly prevalent in Southeast Asia. A few recognized, known and accepted risk behaviors to Toxoplasma infection have consistently been identified. Clinical toxoplasmosis in different groups of population has been periodically reported in this region. However, few recommendations could be conducive to the completeness of this literature review: firstly, more studies should be carried out in the area of Mae-Khong region (Cambodia, Lao PDR and Viet Nam) and with the epidemic of HIV/AIDS, toxoplasmosis should be more importantly given an attention due to the fact that suspected cases might be misdiagnosed and subsequently led to life-threatening or fatal condition. This is also an opportunity for researchers to focus on this pathogen in these patients and extend more works in other vulnerable groups; secondly, there are many other risk factors involved which are undiscovered and need to be investigated to further clarify the pathogenesis of this parasite; thirdly, the novel drugs including herbal medicine, should be given serious consideration in clinical trials, particularly in tackling the cystic stage of this parasite and reducing the treatment burden through new effective medicines of both private and government hospitals; and lastly, multi centers for studying toxoplasmosis should be established, which could serve as smart partnerships to strengthen the regional collaborations and also enhance the existing activities in terms of prevention and control measures, thereby logically conducting assessments according to their own feasibilities for the benefit of the affected individuals. It is therefore hoped that a new chapter of managing health issues regarding toxoplasmosis would be thoroughly successful in the future.

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