Cerebral Toxoplasmosis in AIDS Patients : Clinical Manifestations and Laboratory Diagnosis

Weerayut Nunrungroj, M.D.*
Sumittra Charoenhirunyingyos, M.D.**
Darawan Wanachiwanawin, M.D.*
Vanna Mahakittikun, M.Sc.*
Rungsan Chaisewikul, M.D.***

Abstract :

Background : Patients with acquired immunodeficiency syndrome (AIDS) are susceptible to a variety of infections. Cerebral toxoplasmosis is one of the most common. The presumptive diagnosis is based on clinical manifestations, a positive *Toxoplasma* antibody test, characteristic neuroradiological abnormalities, and improvement after specific therapy. We evaluated not only the clinical manifestations and laboratory diagnosis but also its prevalence and the CD_4 count in relationship to the development of cerebral toxoplasmosis in order to determine its place in the natural history of HIV infection.

Methods : A retrospective cohort study was performed in 104 AIDS patients who were stratified into three levels: 35 with a definite diagnosis of cerebral toxoplasmosis, 41 with a probable diagnosis, and 104 with a possible diagnosis. The criterion for diagnosing "definite" illness was a good response to specific treatment. *Toxoplasma* IgG and IgM were detected using solid-phase enzyme immunoassay and monoclonal captured ELISA methods respectively in all patients. 65 cases without a definitive diagnosis were further investigated with a CT scan of the brain. The patient data were followed up on day 7 and 14.

Results : *Toxoplasma* IgG was present in 37 out of all cases (35.6%) and *Toxoplasma* IgM was positive in only one case. The study showed that ELISA was a valuable method for diagnosis in addition to a CT scan of the brain. The ELISA detected antibodies in 24 out of 35 cases with a "definite" diagnosis (sensitivity 68.6%, 95%CI 50.7% - 83.2%) and no antibody in 56 out of 69 cases with other diagnoses (specificity 81.2%, 95%CI 69.9% - 89.6%). The CT scan showed positive features in 30 out of 33 cases with "definite" diagnosis (sensitivity 90.9%, 95%CI 75.7% - 98.1%) but there were 4 (out of 32 cases) with a positive CT scan who were negative for the diagnosis, i.e., false positive, giving a specificity of 87.5%, 95%CI 71.0% - 96.5%. The most common clinical presentations were headache and neurological deficit. Interestingly, neurological deficit was the only clinical manifestation that was associated with cerebral toxoplasmosis, when the group with a definite diagnosis was compared with the other diagnosis group (p-value 0.006). In HIV seropositive patients with previous *Toxoplasma* infection, cerebral toxoplasmosis was present in 24 out of 37 cases who were positive for *Toxoplasma* IgG (positive predictive value 64.9%), particularly in individuals with a CD_4 count less than 100 cells/mm^3.

**Department of Parasitology, **Department of Pharmacology, ***Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

Conclusions : **The two most common clinical manifestations were headache and neurological deficit. Detection of *Toxoplasma gondii* IgG and CT scan of the brain are valuable tools for the diagnosis of cerebral toxoplasmosis. Cerebral toxoplasmosis is mainly caused by reactivation, as *Toxoplasma* IgM antibodies were found in only one case.**

Key words: *Toxoplasma gondii*, HIV, cerebral toxoplasmosis, ELISA, CT scan.

เรื่องย่อ :

โรคท็อกโซพลาสมาที่สมองในผู้ป่วยเอดส์ : อาการแสดงทางคลินิกและการตรวจวินิจฉัยโรค

วีรยุทธ นันท์รุ่งโรจน์ พ.บ.*, สุมิตรา เจริญหิรัญยิ่งยศ พ.บ., ดาราวรรณ วนะชิวนาวิน พ.บ.*, วรรณะ มหากิตติคุณ วท.ม.*, รังสรรค์ ชัยเสวิกุล พ.บ.*****

**ภาควิชาปรสิตวิทยา, **ภาควิชาเภสัชวิทยา, ***ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพมหานคร 10700.*

สารศิริราช 2545; 54: 330-337.

ผู้ป่วยเอดส์มีความเสี่ยงต่อการติดเชื้อได้หลากหลาย โรคท็อกโซพลาสมาที่สมองเป็นโรคหนึ่งที่พบได้บ่อย การวินิจฉัยโรคอาศัยลักษณะทางคลินิก การตรวจพบภูมิคุ้มกันต่อเชื้อท็อกโซพลาสมาเป็นผลบวก ลักษณะความผิดปกติทางรังสีของระบบประสาท และอาการของผู้ป่วยที่ดีขึ้นหลังให้การรักษาแบบจำเพาะ วัตถุประสงค์ของการศึกษาประกอบด้วย การประเมินอาการทางคลินิก, การตรวจภูมิคุ้มกันต่อเชื้อท็อกโซพลาสมาโดยวิธี ELISA, การถ่ายภาพตัดขวางสมองโดยใช้คอมพิวเตอร์ (CT scan), ความชุกและความสัมพันธ์ของจำนวน CD_4 ในผู้ป่วยเอดส์ที่ได้รับการวินิจฉัยเป็นโรคท็อกโซพลาสมาที่สมอง

ในรายงานนี้ได้ศึกษาลักษณะทางคลินิกแบบโคฮอร์ทย้อนหลังในผู้ป่วยเอดส์จำนวน 104 ราย ที่มีอาการทางคลินิกเข้าได้กับโรคท็อกโซพลาสมาที่สมอง และได้รับการตรวจภูมิคุ้มกันต่อเชื้อท็อกโซพลาสมาโดยวิธี ELISA โดยแบ่งเป็น 3 ระดับ คือ ระดับที่ 1 ได้แก่ กลุ่มที่ได้รับการยืนยันแน่นอน จำนวน 35 คน ระดับที่ 2 ได้แก่ กลุ่มที่มีโอกาสเป็นสูง จำนวน 41 คน ระดับที่ 3 ได้แก่ กลุ่มที่น่าจะเป็น จำนวน 104 คน โดยใช้เกณฑ์การวินิจฉัย คือ การตอบสนองต่อการรักษาแบบจำเพาะในวันที่ 7 และ 14 หลังการรักษา การตรวจทางห้องปฏิบัติการเพื่อช่วยในการวินิจฉัยโรคดังกล่าว ได้แก่ การตรวจภูมิคุ้มกันต่อเชื้อท็อกโซพลาสมาชนิดไอจีจีและไอจีเอ็ม และการถ่ายภาพตัดขวางสมองโดยใช้คอมพิวเตอร์ ผลการศึกษาพบว่า ผู้ป่วยมีผลบวกของภูมิคุ้มกันชนิดไอจีจีจำนวน 37 ราย จากจำนวนผู้ป่วย 104 ราย (ร้อยละ 35.6) และภูมิคุ้มกันชนิดไอจีเอ็มเพียงหนึ่งรายเท่านั้น การตรวจภูมิคุ้มกันต่อเชื้อท็อกโซพลาสมาโดยวิธี ELISA ช่วยในการวินิจฉัยโรคจำนวน 24 ราย จากจำนวนผู้ป่วย 37 ราย (ร้อยละ 64.9) ความไวและความจำเพาะของวิธีดังกล่าวคือ ร้อยละ 68.6 และ 81.2 ตามลำดับ ส่วนผู้ป่วยจำนวน 65 ราย ที่ยังไม่สามารถให้การวินิจฉัยโรคได้ได้รับการถ่ายภาพตัดขวางสมองโดยใช้คอมพิวเตอร์เพื่อช่วยในการวินิจฉัยโรคต่อไป ซึ่งผู้ป่วยจำนวน 34 ราย จากจำนวน 65 ราย (ร้อยละ 52.3) มีผลเข้าได้กับโรคท็อกโซพลาสมาที่สมอง ความไวและความจำเพาะของวิธีนี้คือ ร้อยละ 90.9 และ 87.5 ตามลำดับ อาการแสดงทางคลินิกของโรคท็อกโซพลาสมาที่สมองที่พบบ่อย ได้แก่ ปวดศีรษะ และความผิดปกติทางระบบประสาท ส่วนอาการทางคลินิกที่มีความสัมพันธ์กับโรคท็อกโซพลาสมาที่สมอง คือ ความผิดปกติทางระบบประสาท (p-value 0.006) ในกลุ่มผู้ป่วยที่มีภูมิคุ้มกันต่อเชื้อไวรัสเอชไอวี และภูมิคุ้มกันต่อเชื้อ

ท็อกโซพลาสมาชนิดไอจีจีเป็นผลบวก พบว่า ความเสี่ยงต่อการเกิดโรคท็อกโซพลาสมาที่สมองเป็นร้อยละ 64.9 โดยเฉพาะอย่างยิ่งในผู้ป่วยที่มีจำนวน CD_4 ต่ำกว่า 100 /มม^3 ผลสรุปพบว่า ลักษณะอาการทางคลินิกที่พบบ่อยของโรคท็อกโซพลาสมาที่สมองได้แก่ อาการปวดศีรษะ และลักษณะผิดปกติทางระบบประสาท การตรวจหาภูมิคุ้มกันต่อเชื้อท็อกโซพลาสมา กอนดิอิ ชนิดไอจีจี และการตรวจ CT scan ของสมองเป็นวิธีที่มีประโยชน์ในการวินิจฉัยโรคท็อกโซพลาสมาที่สมอง ส่วนการตรวจหาภูมิคุ้มกันต่อเชื้อท็อกโซพลาสมา กอนดิอิ ชนิดไอจีเอ็ม พบว่าไม่คุ้มค่าในการวินิจฉัยโรคท็อกโซพลาสมาที่สมอง เนื่องจากผู้ป่วยส่วนใหญ่เกิดโรคนี้จากการติดเชื้อครั้งก่อน

INTRODUCTION

Toxoplasmosis is distributed worldwide and is caused by the parasitic protozoan, *Toxoplasma gondii*. Man can acquire this infection by contamination with oocysts from cat feces, by ingestion of uncooked meat containing *T. gondii* cysts, or via the placental route[1,2]. Infected immunocompetent individuals are usually asymptomatic or have mild symptoms. In contrast, in immunocompromised individuals, especially those with human immunodeficiency virus (HIV) seropositive patients, toxoplasmosis causes a high rate of mortality and morbidity[3,4].

In HIV seropositive patients, toxoplasmosis is one of the most common opportunistic infection that influences the central nervous system (CNS). Most HIV seropositive patients, who have shown evidence of exposure to *T. gondii*, will develop cerebral toxoplasmosis in the end[5,6]. Symptoms and signs of cerebral toxoplasmosis include headache, fever, altered consciousness, tremor, sensory loss, seizures, and coma[7]. ELISA is one of the most popular diagnostic methods. A computerized tomography (CT) scan is also useful for diagnosing the disease[8-10].

The Thai Working Group on HIV/AIDS Projection (2000) have estimated that 984,000 Thai people (951,000 adults and 33,000 children) have been infected with HIV since the start of the epidemic and 695,000 Thais are currently living with HIV and AIDS[11]. The incidence of cerebral toxoplasmosis is found to be directly related to the prevalence of *Toxoplasma* antibodies in the population and the rate of HIV infection[12]. The prevalence of *T. gondii* infection in healthy and AIDS individuals is 5% and 16% respectively[13,14]. The greater the prevalence of *Toxoplasma* IgG in HIV seropositive patients, the greater the trend and risk for developing *Toxoplasma* encephalitis[8,9]. It has been suggested that HIV seropositive individuals who are seronegative for *Toxoplasma* IgG should be prevented from seroconverting[15].

In Thailand, toxoplasmosis has been studied by a few researchers[13,14,16-21]. There are very limited data concerning cerebral toxoplasmosis. The aim of this cohort study is to study the clinical manifestations and diagnostic values of IgG, IgM, and CT scan brain for the diagnosis of cerebral toxoplasmosis in AIDS patients at Siriraj Hospital. It looked at the validity of the test in relationship to the clinical settings. We were also interested in its prevalence and CD_4 count related to the development of cerebral toxoplasmosis.

MATERIALS AND METHODS

A retrospective cohort study was performed in HIV seropositive patients, who had been investigated for *Toxoplasma* antibodies and had clinical manifestations that were compatible with a diagnosis of cerebral toxoplasmosis at Siriraj Hospital from May 1997 to November 2001. The sample size needed was calculated using a cluster sampling method ($Z\alpha = 1.96$, $p = 0.16$, $de = 2$, $d = 0.1$)[14,22]. The sample size was accepted at one hundred and three individuals.

104 AIDS patients were recruited to this study using the results of investigations for *Toxoplasma* antibodies and clinical manifestations as the criteria for entry. This group was identified as the "possible group". These "possible" patients were divided into two groups according to the results of the investigation used (*Toxoplasma* IgG and IgM, and/or CT scan of the brain). If laboratory results supported evidence of diagnosis of cerebral toxoplasmosis, we allocated them to the "probable group".

Although tissue biopsy is still the gold standard for diagnosis of cerebral toxoplasmosis, this procedure looks harmful and invasive to our patients. In this study, a definitive diagnosis depended on the individual's response to specific therapy (pyrimethamine plus sulfadiazine/ clindamycin/ dapsone) for cerebral toxoplasmosis within 14 days of initiating treatment. The assessment for clinical responsiveness was measured with observed clinical manifestation improvement. For each sign or symptom, normal outcome was assigned a value of 0, and abnormal one was assigned a value of 1. At day 7 and 14 for evaluating clinical outcomes, the sum of scores ranged between 0 and 2 was defined to be responsiveness to specific treatment or the sum of scores was lower than 50% of initial treatment score. 95% confidence intervals for sensitivity and specificity were calculated with n = 35.

Specimen methodology

Toxoplasma IgG antibodies were determined by a solid-phase enzyme immunoassay technique, Platelia® Toxo IgG (Sanofi Diagnostic Pasteur, France), in which the membrane protein p-30 was the major antigen. The cut-off value was taken as 6 IU/ml and a test was considered to be positive when its value was equal to or greater than this.

The Platelia® Toxo IgM (Sanofi Diagnostic Pasteur, France) is a monoclonal antibody capture IgM ELISA method. This test utilizes a monoclonal antibody to *T. gondii* conjugated with horseradish peroxidase for enzymatic assay signal development.

Statistical analysis

Descriptive frequency analysis, Cross tabulation, and Chi-square were used in the analysis, using the SPSS program.

RESULTS

104 AIDS patients, presenting with clinical manifestations compatible with a diagnosis of cerebral toxoplasmosis, and in whom *Toxoplasma* antibodies were investigated, presented between May 1997 and November 2001 were included. The male : female ratio was 5:1. The demographic data are shown in Table 1. The majority of patients (79.8%) were between 25 and 44 years old.

Table 1. Age range in 104 AIDS patients and 35 patients with definite cerebral toxoplasmosis.

Age (year)	No. of AIDS patients (%)	No. of patient with definite cerebral toxoplasmosis (%)
< 25	9 (8.7%)	2 (5.7%)
25 - 34	56 (53.8%)	21 (60.0%)
35 - 44	27 (26.0%)	8 (22.9%)
45 - 54	9 (8.7%)	3 (8.6%)
55 - 64	2 (1.9%)	1 (2.9%)
≥ 65	1 (1.0%)	0 (0.0%)

65 cases who had a neurological deficit or who did not yet have a definite diagnosis or had inconclusive results from other investigations, received further investigation with a CT scan of the brain except for 2 patients, one who was positive for both *Toxoplasma* IgG and IgM, and the other who rapidly responded to specific therapy for cerebral toxoplasmosis.

According to the investigations performed above, the possible cases were stratified into two groups, 41 with a probable diagnosis of cerebral toxoplasmosis and 63 with CNS abnormality that mimicked cerebral toxoplasmosis. In the probable group, patients were divided into 4 subgroups, 20 patients positive for CT scan brain and *Toxoplasma* IgG, 14 patients positive for CT scan brain and negative for

Toxoplasma IgG, 3 patients negative for CT scan brain and positive for *Toxoplasma* IgG, and 4 patients positive for *Toxoplasma* IgG and no data available from a CT scan brain. 35 out of 41 patients with a probable diagnosis of cerebral toxoplasmosis had a good response to specific treatment and were classified as having definite diagnosis of cerebral toxoplasmosis.

The remaining 6 cases were as follows: 2 cases were lost to follow-up (positive for *Toxoplasma* IgG with no data for CT scan brain), 1 case was finally diagnosed as having a tuberculoma (positive for *Toxoplasma* IgG and CT scan brain, but did not improve after specific treatment), 3 cases had a different outcome or diagnosis; one had a cryptococcoma, one had a lymphoma and one died before day 7 after starting therapy. The first had a positive CT scan brain, the second was negative for *Toxoplasma* IgG and the third did not respond to specific treatment (Figure 1).

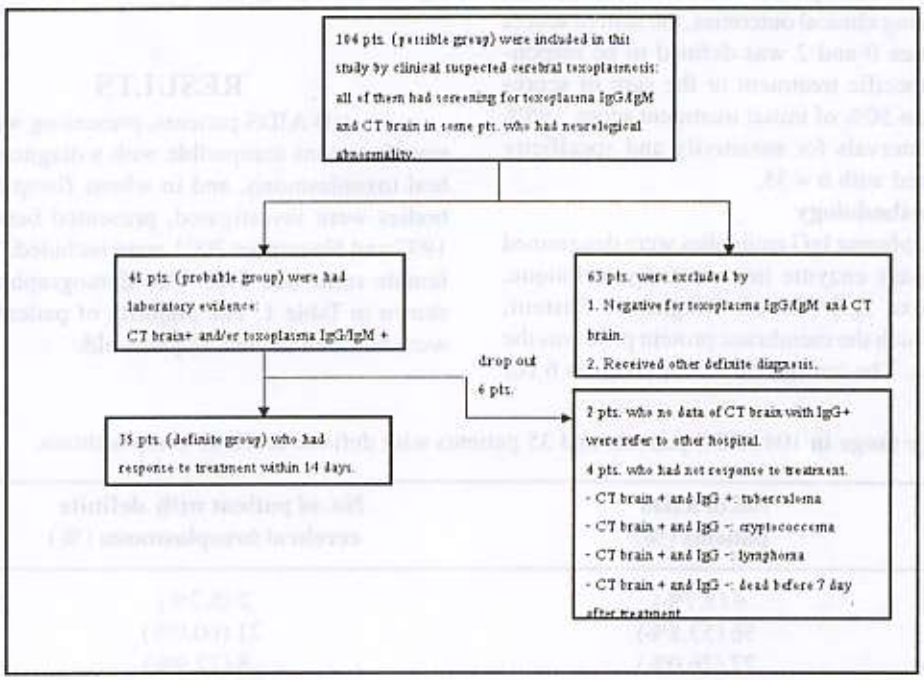

Figure 1. Flow chart illustrate level of groups in this study : possible, probable and definite respectively.

Table 2. Common clinical manifestations in the 35 cases with definite cerebral toxoplasmosis.

Clinical manifestations	No. of patients	Percent
Headache	30	85.7
Neurological deficit	30	85.7
Fever	18	51.4
Seizures	14	40.0
Meningeal irritation	11	31.4
Alteration of consciousness	11	31.4

Table 3. Clinical features of 35 cases definitively diagnosed with cerebral toxoplasmosis and 69 cases with suspected toxoplasmosis compared using the Chi-square test.

Clinical features	Definite case (N = 35)	Suspected case (N = 69)	p-value
Headache	30 (85.7%)	50 (72.5%)	0.130
Neurological deficit	30 (85.7%)	41 (59.4%)	0.006*
Fever	18 (51.4%)	47 (68.1%)	0.097
Seizures	14 (40.0%)	21 (30.4%)	0.329
Meningeal irritation	11 (31.4%)	27 (39.1%)	0.441
Alteration consciousness	11 (31.4%)	20 (29.0%)	0.797

*Significance at 0.05 level

Out of 104 *Toxoplasma* IgG results, we found 35 patients with a definite diagnosis of cerebral toxoplasmosis. IgG antibody to *Toxoplasma* was present in 35.6%, of samples; 35 out of 99 specimens of serum and 2 out of 5 specimens of CSF. 24 out of 37 cases who were positive for *Toxoplasma* IgG (64.9%) were finally diagnosed with cerebral toxoplasmosis. 24 out of 35 cases with a definite diagnosis were positive for *Toxoplasma* IgG. The sensitivity and specificity of this test for the diagnosis were 68.6% (95%CI 50.7% - 83.2%) and 81.2% (95%CI 69.9% - 89.6%) respectively. *Toxoplasma* IgM was positive in one patient only.

In order to support the diagnosis of cerebral toxoplasmosis, a CT scan of the brain was performed in 65 cases that had neurological deficits or who did not yet have a definite diagnosis or had inconclusive results from other investigations. Out of 65 CT scan brain results, there were 33 patients with a definite diagnosis of this illness. The brain CT scans showed single or multiple mass lesions, usually with ring enhancement with contrast media, in 34 out of 65 cases examined. 30 out of 34 patients with a positive CT scan brain (88.2%) were finally diagnosed with cerebral toxoplasmosis. 30 out of 33 patients with a definite diagnosis of cerebral toxoplasmosis had a positive CT brain scan. The sensitivity and specificity of CT scan for diagnosis were 90.9% (95%CI 75.7% - 98.1%) and 87.5% (95%CI 71.0% - 96.5%) respectively.

The clinical manifestations of the 35 patients with a definite diagnosis included neurological deficits and headache as the most common clinical findings (Table 2). When we compared the clinical manifestations between the definite group and the rest, we found that neurological deficit discriminated between the two groups with statistical significance (Table 3). All patients who were finally diagnosed with cerebral toxoplasmosis had a CD_4 count less than 100 cells/mm^3 (range 0-96, 27.0 ± 29.6). Interestingly, 12 out of 14 cases with definite diagnosis had a CD_4 count less than 50 cells/mm^3.

DISCUSSION

We studied the presence of *Toxoplasma* IgG in AIDS patients who were suspected of having cerebral toxoplasmosis and found it was positive in 35.6%. This is similar to the two previous studies: 30% and 42.5% in the study by Holliman[23] and by Wongkanchai et al[20], respectively. Luft et al. concluded that in areas where the prevalence of *T. gondii* antibody was high, the incidence of cerebral toxoplasmosis might rise to 25-50% of HIV positive patients[9].

In the late phase of AIDS, Kasper mentioned that more than 50% of patients with clinical manifestations of toxoplasmosis had intracerebral involvement. Clinical findings at the time of presentation ranged from non-focal to focal dysfunction. These findings included encephalopathy, meningoencephalitis, and mass lesions. Patients might present with an altered mental state (75%), fever (10-72%), focal neurological findings (60%), headaches (56%),

and seizures (33%)[15]. These findings were found commonly in the present study (Table 2). Our study showed that the presence of neurological deficit was highly correlated with a definite diagnosis of cerebral toxoplasmosis with a p-value of 0.006 (Table 3).

As cerebral toxoplasmosis is mostly caused by reactivation, the pattern of immunological response is mainly a positive *Toxoplasma* IgG with a negative *Toxoplasma* IgM[6,8]. This study showed positive IgG in 24 out of 35 "definite" cases (68.6%), whereas we found positive IgM in only 1 out of 35 "definite" cases (2.9%). This agrees with the results of Roddriguez et al. who studied a group of 16 patients with cerebral toxoplasmosis and found positive IgG with no IgM in all cases[6]. A study by Zuffery et al. in 47 HIV seropositive patients with toxoplasmic reactivation also found that IgM was positive in only 6%[24]. In addition, a previous study found that 74% were positive for *Toxoplasma* IgG in HIV seropositive patients who were suspected of having toxoplasmosis[20]. Nevertheless, the number of patients in previous studies was smaller than in our study.

From the neuroimaging point of view, we found that the sensitivity of a CT scan brain was 90.9% which was different from that of Luft et al. who found that the sensitivity of brain CT scan for the diagnosis of toxoplasmosis was about 69%[9]. Interestingly, 11 out of 33 "definite" patients (33.3%) with a positive brain CT scan were negative for *Toxoplasma* IgG. The false negative outcome of ELISA might be reduced by using a test with higher sensitivity[19]. While other procedures such as Western blot and polymerase chain reaction (PCR) might increase the specificity and act as confirmation test[6,21]. Nevertheless, we found 3 cases with a positive brain CT scan who were negative for *Toxoplasma* IgG and were finally diagnosed with other conditions. It has been suggested that a CT scan is not always reliable in distinguishing cerebral toxoplasmosis from lymphoma, kaposi's sarcoma, cytomegalovirus (CMV) infection, progressive multifocal leukoencephalopathy (PML) or herpes infection, however it may be useful when it is assessed in conjunction with a positive *Toxoplasma* IgG[8-10].

In this study, the ELISA technique and CT scan brain were both useful in diagnosing cerebral toxoplasmosis. Their sensitivity and specificity were high enough for clinical decision making. Although brain biopsy is the most certain method of diagnosis, the procedure is invasive and harmful to the patient. The combination of ELISA and CT scan might be feasible and practical. Cohn et al. analyzed the findings of brain CT scan together with a positive serologic test for *Toxoplasma*, and estimated "its" positive predictive value to be 80%[25].

Neither the Centers for Disease Control (CDC) nor the United State Public Health Service (USPHS) has recommended routine primary prophylaxis against toxoplasmosis. However, there is increasing evidence supporting the use of primary prophylaxis in all patients with *Toxoplasma* IgG and a CD_4 count less than 100 to 200 cells/mm^3, with trimethoprim-sulfamethoxazole[26,27]. In this cohort, all patients had also a CD_4 count less than 100 cells/mm^3. Moreover, almost all of our patients with a CD_4 count less than 50 cells/mm^3 could develop cerebral toxoplasmosis in the late phase of AIDS.

Ultimately, prevention of seroconversion in those negative for *Toxoplasma* IgG is also necessary. Advice should be given about not eating undercooked meat and to avoid materials contaminated by oocysts in cat feces. Meat should be heated to 60°C or frozen to kill cysts. Hands should be washed thoroughly after work in the garden, and all fruits and vegetables should be washed[15].

CONCLUSION

The two most common clinical manifestations of cerebral toxoplasmosis are headache and focal neurological deficit. The neurological deficit may be a helpful clue for differentiating this disease from other CNS abnormalities that mimic cerebral toxoplasmosis. Although the sensitivitiy, specificity, and positive predictive value of CT scan brain and *Toxoplasma* IgG are sufficient for clinical decision making, we still recommend that the combination of clinical manifestations and investigations are useful for diagnosing cerebral toxoplasmosis. Moreover, almost all patients were negative for *Toxoplasma* IgM; we concluded that these patients had reactivated previous infestation. In near future, screening for *Toxoplasma* IgG in HIV infected patients with a CD_4 count of less than 100-200 cells/mm^3 could be helpful in

deciding to give primary or secondary prophylaxis with trimethoprim-sulfamethoxazole in those who are positive for Toxoplasma IgG and to help prevent seroconversion in those who are negative for *Toxoplasma* IgG.

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