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Original Article

Clinical presentation and outcome of toxoplasmic encephalitis in patients with human immunodeficiency virus type 1 infection

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Background and Purpose: Clinical manifestations and outcome of toxoplasmic encephalitis (TE) in patients at late stage of human immunodeficiency virus (HIV) infection have not been previously reported in Taiwan. The aim of this study was to describe the clinical and radioimaging characteristics and treatment response in HIV-infected patients with TE in Taiwan.

Methods: Medical records of all HIV-infected patients who were diagnosed as having TE between June 1994 and December 2006 at the National Taiwan University Hospital, Taipei, Taiwan, were reviewed by use of a standardized case record form. Diagnosis of TE was based on clinical manifestations, serology, and radioimaging findings plus clinical and radiographic response to anti-toxoplasmosis therapy.

Results: During the 12-year study period, 18 patients (1.2%) with 19 episodes of TE were identified. The median CD4+ lymphocyte count was 15 cells/μL and plasma HIV RNA load was 179,000 copies/mL at the diagnosis of TE. TE was the initial presentation of HIV infection in around two-thirds of the patients. Fever, focal neurological deficit, cognitive dysfunction, and altered mental status were the most common presenting symptoms. The typical radioimaging findings, multiple enhanced lesions with mass effect, were most common in the cerebral cortex, followed by the basal ganglia, cerebellum and brain stem. Compared with those who survived TE, the 3 patients who died of TE were older (52 vs 37 years, p=0.016) and had a higher incidence of cognitive impairment (100.0% vs 37.5%, p=0.063) and altered mental status (100.0% vs 18.8%, p=0.025).

Conclusions: TE was a rare HIV-related infectious complication in our cohort. Advanced age and altered mental status were associated with an increased mortality in HIV-infected patients with TE.

Key words: Acquired immunodeficiency syndrome; Encephalitis; HIV; Mortality; Risk factors; Toxoplasmosis

Introduction

Toxoplasmic encephalitis (TE) is a common presentation of *Toxoplasma gondii* infection of the central nervous system (CNS) in patients in the late stage of human immunodeficiency virus (HIV) infection [1,2]. The risk of TE in HIV-infected patients varies with the seroprevalence of *T. gondii* infection. The seroprevalence of *T. gondii* in the general population in Taiwan was reported to be at 2% to 10% [3,4], although a higher prevalence (up to 26.7%) was observed in certain subgroups [5]. In other countries, *T. gondii* seroprevalence rates of up to 26% have been reported, with incidence rates in the range of 0.4 to 0.7 per 100 person-years [6,7]. In Taiwan, the seroprevalence of *T. gondii* infection was estimated at 10.2% in HIV-infected patients, and the incidence of TE in Taiwan was reported to be 0.59 per 100 person-years [8].

Despite the decrease of incidence with the advent of highly active antiretroviral therapy (HAART) [9-11], TE remained the most frequent neurological disorder in a recent study [12], occurring more often in those with severe immunodeficiency, absence of primary prophylaxis, and lack of antiretroviral therapy (ART) [11,12]. Up to 23% of patients with TE may progress to

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death in 1 year [12]. Cognitive impairment, low CD4+ lymphocyte count, and absence of ART were associated with adverse prognosis [12].

The diagnosis of TE remains challenging. Patients with TE often present with a combination of signs and symptoms [13]. A definite diagnosis, which requires a pathologic examination of a brain biopsy, was made in as few as 4.4% of patients with TE [12]. A presumptive diagnosis of TE is made based on progressive neurological deficits, contrast-enhancing mass lesion(s) on radioimaging, and a successful response to specific treatment within 2 weeks [14]. In this study, we aimed to describe the clinical presentation, radioimaging features, and treatment response in HIV-infected patients with TE in Taiwan.

Methods

Study population

The National Taiwan University Hospital has been a major referral medical center for HIV management [15]. Patients diagnosed as having HIV infection between June 1994 and December 2006 were included in this study. Using a standardized case record form, we performed a retrospective review of medical records of HIV-infected patients in this hospital to collect data on demographic features, route of HIV transmission, status of HIV infection, clinical and radiographic characteristics, and ART.

Definitions

Definite diagnosis of TE required a pathologic examination of a biopsy or autopsy. A presumptive diagnosis was made according to the criteria of the Centers for Disease Control and Prevention, USA, which included recent onset of a focal neurologic abnormality consistent with intracranial disease or a reduced level of consciousness; evidence by radioimaging (computed tomography or magnetic resonance imaging of the CNS) of a lesion having a mass effect or radiographic appearance that was enhanced by injection of contrast medium; and presence of serum antibody to *T. gondii* or successful response to therapy for toxoplasmosis [12,16]. Serum antibody to *T. gondii* was measured by Immulite 2000 solid-phase chemiluminescent enzyme immunoassay (Diagnostic Products Corporation, LA, USA). Non-survivors were defined as patients who died of TE. Patients who survived during the follow-up period or who died of causes unrelated to TE were categorized as survivors.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 13.0; SPSS, Chicago, IL, USA). Fisher's exact test and Mann-Whitney *U* test were employed for dichotomous variables and continuous variables, respectively. A p value <0.05 was considered to be statistically significant.

Results

Between June 1994 and December 2006, out of 1508 HIV-infected patients, 18 patients (1.2%) with a median age of 40 years (range, 25-57 years) developed 19 episodes of presumptive TE. In none of the cases was diagnosis made by biopsy or autopsy. The clinical characteristics of the 18 patients are shown in Table 1. Sexual contact was the most common route of HIV transmission. The patients were followed for a mean duration of 238 days (interquartile range [IQR], 41-811 days).

All patients presented at late stage of HIV infection, with a mean CD4+ lymphocyte count of 15 cells/μL (IQR, 9-33 cells/μL) and a mean plasma HIV RNA load of 179,000 copies/μL (IQR, 64,000-378,469 copies/μL). The mean time from the onset of symptoms to hospital visit was 14 days (IQR, 7-14 days). TE was the presenting acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection in the majority (13/19, 68.4%) of the patients. Among the 5 patients who had AIDS-defining illness prior to the diagnosis of TE, only one received primary prophylaxis against toxoplasmosis. The other 4 patients did not receive primary prophylaxis because of noncompliance (n = 2), a CD4+ lymphocyte count more than 100 cells/μL (n = 1), and an adverse drug reaction (n = 1).

Neurological symptoms and signs were observed in all of the patients, and included headache (15.8%), focal neurological deficit (60.0%), cognitive dysfunction (47.4%), altered mental status (31.6%), seizures (10.5%), and meningismus (5.3%). Fever was present in 73.7% of patients. The most common focal neurological deficits included hemiparesis (31.6%), aphasia (21.1%), ataxia (21.1%), and diplopia (15.8%).

All patients presented with elevated *Toxoplasma* immunoglobulin G titers and no positive immunoglobulin M result. Of 3 patients with available antibody titers of cerebrospinal fluid (CSF), only 1 patient had positive immunoglobulin G. The titer of immunoglobulin

Table 1. Clinical characteristics of 18 human immunodeficiency virus (HIV)-infected patients with 19 episodes of toxoplasmic encephalitis (TE)

Variable	Non-survival (n = 3) No. (%)	Survival (n = 16) No. (%)	Total (n = 19) No. (%)	*p*
Male	3 (100.0)	15 (93.8)	19	
Age (years; mean) [IQR]	52 (51-55)	37 (31-42)	40 (33-47)	0.016
Route of HIV transmission				
Homosexual	2 (67.7)	7 (43.7)	9 (47.3)	
Heterosexual	0 (0.0)	9 (56.3)	9 (47.3)	
Intravenous drug user	0 (0.0)	0 (0.0)	0 (0.0)	
Other	1 (33.3)	0 (0.0)	1 (5.2)	
Symptoms (days; mean) [IQR]	14 (9-14)	14 (7-18)	14 (7-14)	
Symptomatology				
Fever	2 (66.7)	12 (75.0)	14 (73.7)	
Headache	0 (0.0)	3 (18.8)	3 (15.8)	
Neurologic manifestation			19 (100.0)	
Focal sign	2 (66.7)	9 (56.3)	11 (60.0)	
Hemiparesis	0 (0.0)	6 (37.5)	6 (31.6)	
Aphasia	1 (33.3)	3 (18.8)	4 (21.1)	
Ataxia	2 (66.7)	2 (12.5)	4 (21.1)	
Diplopia	0 (0.0)	3 (18.8)	3 (15.8)	
Cognitive dysfunction	3 (100.0)	6 (37.5)	9 (47.4)	0.063
Altered mental status	3 (100.0)	3 (18.8)	6 (31.6)	0.025
Seizure	0 (0.0)	2 (12.5)	2 (10.5)	
Meningismus	0 (0.0)	1 (6.3)	1 (5.3)	
Laboratory data (mean [IQR] or percent positive)				
White cell count (/mm^3)	4390	4225	4290	
Serum *Toxoplasma* IgG (IU/mL)	103 (85-177)	250 (87-250)	>250 (76->250)	
Serum *Toxoplasma* IgM	0	0	0	
CSF *Toxoplasma* IgG (IU/mL)	50.6, 0	0		
CSF *Toxoplasma* IgM	0, 0	0		
CD4+ on diagnosis (cells/μL)	47 (27.5-66.5)	15 (9.5-31)	15 (9-33)	
Viral load (copies/μL)	179,000 (142,500-187,500)	256,000 (64,000-470,500)	179,000 (64,000-378,469)	
Image findings				
No. of lesions				
Single	0 (0.0)	2 (12.5)	2 (10.5)	
Multiple	3 (100.0)	14 (87.5)	17 (89.5)	
Involved region of lesions				
Cerebrum	3 (100.0)	15 (93.8)	18 (94.7)	
Basal ganglion	1 (33.3)	10 (62.5)	11 (57.8)	
Cerebellum	2 (66.7)	5 (31.3)	7 (36.8)	
Brain stem	0 (0.0)	3 (18.8)	3 (15.8)	
No. of regions involved				
One	1 (33.3)	6 (37.5)	7 (36.8)	
Two	1 (33.3)	4 (25.0)	5 (26.3)	
Three	1 (33.3)	5 (31.3)	6 (31.6)	
Four	0 (0.0)	1 (6.2)	1 (5.3)	
Features				
Contrast enhancement	2 (66.7)	15 (93.8)	17 (89.5)	
Perifocal edema	3 (100.0)	13 (81.3)	16 (84.2)	
Hydrocephalus	1 (33.3)	6 (37.5)	7 (36.8)	
Herniation	1 (33.3)	2 (12.5)	3 (15.8)	

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Status of HIV infection			
Presenting AIDS-defining opportunistic infection	3 (100.0)	10 (62.5)	13 (68.4)
Concomitant opportunistic infections			
Cryptococcus	1 (33.3)	2 (12.5)	3 (15.8)
Tuberculosis	1 (33.3)	3 (18.8)	4 (21.1)
Mycobacterium avian complex	0 (0.0)	1 (6.2)	1 (5.3)
Cytomegalovirus	0 (0.0)	1 (6.2)	1 (5.3)
Pneumocystis carinii	0 (0.0)	1 (6.2)	1 (5.3)
AIDS before diagnosis of TE	0 (0.0)	6 (37.5)	6 (31.6)
ART exposure	0 (0.0)	5 (31.3)	5 (26.3)
ART started on diagnosis of TE	0 (0.0)	3 (18.8)	3 (15.8)
Toxoplasma prophylaxis	0 (0.0)	2 (12.5)	2 (10.5)
Treatment			
Trimethoprim-sulfamethoxazole + clindamycin	2 (66.7)	11 (68.8)	13 (68.4)
Pyrimethamine + clindamycin	1 (33.3)	3 (18.8)	4 (21.1)
Trimethoprim-sulfamethoxazole + pyrimethamine + clindamycin	0 (0.0)	1 (6.2)	1 (5.3)
Trimethoprim-sulfamethoxazole + clindamycin + dapsone	0 (0.0)	1 (6.2)	1 (5.3)
Receipt of secondary TE prophylaxis	1 (100.0)[a]	9 (69.2)	10 (58.8)
Duration (days; mean) [IQR]	229 (229-229)	229 (205-412)	229 (207-378)
Follow-up (days; mean) [IQR]	38 (23-134)	257 (150-846)	238 (41-811)

Abbreviations: IQR = interquartile range; IgG = immunoglobulin G; IgM = immunoglobulin M; CSF = cerebrospinal fluid; AIDS = acquired immunodeficiency syndrome; ART = antiretroviral therapy

[a]Only 1 of 3 patients survived the initial episode.

M was negative in the 3 CSF samples. Among the 4 regions of the CNS evaluated, the cerebrum, basal ganglia, cerebellum and brain stem, the cerebrum was the most common location of TE (94.7%), followed by the basal ganglia (57.8%), cerebellum (36.8%) and brain stem (15.8%). Most of the lesions were multiple (89.5%) on presentation, involving one region in 36.8%, 2 regions in 26.3%, 3 regions in 31.6% and 4 regions in 5.3%. Typical contrast enhancement and perifocal edema were present in 89.5% and 84.2% of lesions, respectively. Hydrocephalus was observed in one-third of patients, while herniation was present in 3.

Most patients were treated with either a combination of trimethoprim-sulfamethoxazole and clindamycin (68.4%) or pyrimethamine and clindamycin (21.1%). The remaining 2 received a clindamycin and trimethoprim-sulfamethoxazole-based regimen containing either dapsone or pyrimethamine. Secondary prophylaxis was administered in 10 of the 14 patients who received follow-up at our hospital. Three patients continued ART pre-existing at the time of diagnosis of TE, while 10 patients started ART after the diagnosis. None of the patients who received secondary prophylaxis and HAART developed recurrence of TE. The sole patient who developed a second episode of TE was not compliant with HAART or secondary TE prophylaxis.

Three patients who died of TE were significantly older than the survivors (mean age, 52 vs 37 years; p=0.016 by two-tailed Mann-Whitney U test). Non-survivors died at a mean duration of 38 days (IQR, 8-229 days) while the survivors were followed up for 257 days (IQR, 150-846 days). All 3 fatal cases occurred in patients with an altered mental status, while only 18.8% of the survivors had consciousness abnormalities (p=0.025 by Fisher's exact test). A higher percentage of cognitive dysfunction was present in non-survivors (100.0% vs 37.5%; p=0.063 by Fisher's exact test). The duration of symptoms, presence of fever, radiographic features, CD4+ lymphocyte count, and anti-toxoplasmosis treatment did not affect patient survival.

Discussion

In this study, we found that TE was an uncommon opportunistic infection in our HIV-infected patients, accounting for only 1.2% of the cohort. The low prevalence or incidence of TE may be related to a lower background seroprevalence of *T. gondii* infection

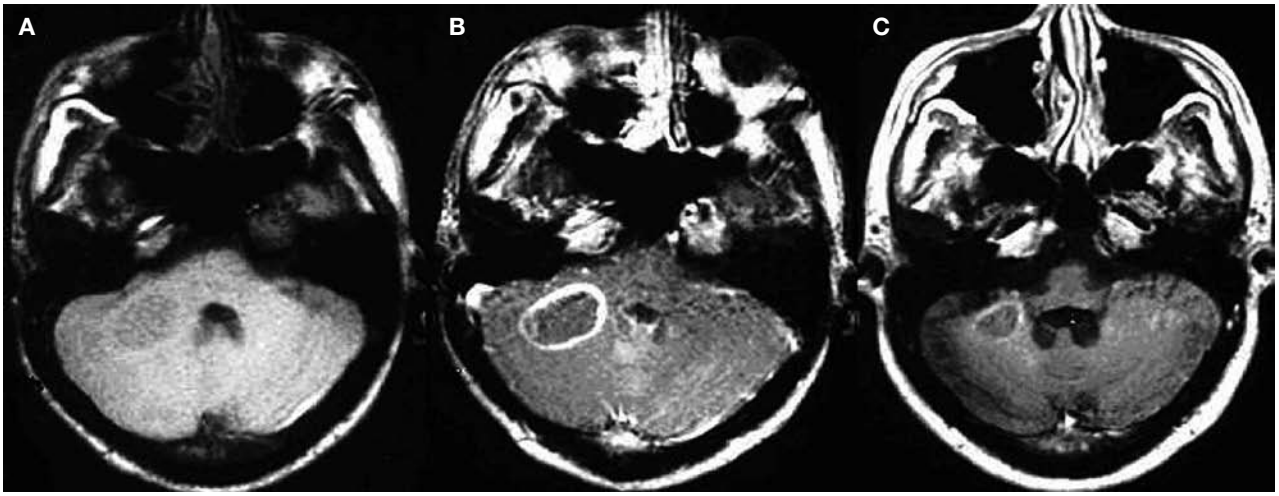

Fig. 1. T1-weighted magnetic resonance imaging studies. (A) A low-signal intensity cerebellar lesion. (B) A ring enhancement is seen after administration of gadolinium. (C) Follow-up enhanced T1-weighted scanning 2 months after anti-toxoplasmosis treatment shows improvement.

among our cohort [8,17] and the fact that ART was made available free of charge to HIV-infected patients, in particular HAART which was introduced in Taiwan in 1997.

Symptoms of TE range from lethargy to coma, ataxia to hemiparesis, loss of memory to severe dementia, and focal to major motor seizures [1]. In a recent Italian study including 205 patients with TE [12], the most common neurological deficit was focal neurologic deficits (72.7%), followed by cognitive symptoms (45.9%) and abnormal mental status (33.6%). Hemiparesis and speech abnormality were the typical focal signs [18]. The clinical manifestations of TE in our patients were similar to those described in the literature [10,12]. Furthermore, we found that a higher proportion of patients presenting with cognitive impairment and abnormal mental status died of TE, which was similar to previous findings [12].

In this study, the most commonly affected CNS region in TE was the cerebral hemisphere, followed by the basal ganglia, cerebellum and brain stem. In an autopsy study of 23 patients with TE, the rostral basal ganglion was the most frequently affected region [19]. Since all these cases met the criteria of presumptive diagnosis of TE, multiple cerebral lesions with or without basal ganglial involvement was a clue to a clinical suspicion of TE. The radiological signs, including the presence of herniation, multiple foci and the location of the affected region(s), were not associated with mortality.

Magnetic resonance imaging is the preferred radioimaging study for focal brain lesions in HIV-infected patients because of its greater sensitivity in diseases involving the white matter or the posterior fossa [20]. Although the presence of multiple ring-enhancing lesions with surrounding edema and a positive serology is highly suggestive of TE, radiologic findings may vary [21]. A low-signal intensity area on T1-weighted magnetic resonance imaging (Fig. 1A) with a ring enhancement (Fig. 1B) is characteristic of TE. Improvement (Fig. 1C) may be seen in 86% after a 7-day treatment and in 96% at day 14 of treatment [18,21,22]. Other common focal brain lesions in HIV-infected patients may include progressive multifocal leukoencephalopathy, primary CNS lymphoma and tuberculosis, although *Nocardia*, varicella-zoster virus, *Aspergillus*, *Listeria*, *Treponema pallidum*, *Histoplasma* and *Cryptococcus* infections have been occasionally reported [21]. Lesions of progressive multifocal leukoencephalopathy differ from those of TE by their non-enhancing character, and differentiation of TE from primary CNS lymphoma and tuberculosis is difficult [23]. A typical homogenous enhancement may be present in primary CNS lymphoma, but ring enhancement also occurs [21]. Either single or multiple lesions with or without enhancement may be present in these cases [21]. A positive *Toxoplasma* serology titer with a clinical response is suggestive of TE, but the achievement of a definite diagnosis requires a brain biopsy [21], since a clinical diagnosis may be correct in only 34% to 48% of cases [21,24,25].

Severe immunodeficiency, absence of TE prophylaxis, and lack of ART were associated with increased risk of TE [12]. In our study, 68.4% of patients

presented with TE as the first clinical clue to the diagnosis of AIDS. These patients had depleted CD4+ lymphocyte counts and high plasma HIV RNA load and did not receive prophylaxis and ART, suggesting that diagnosis of HIV infection and access to appropriate HIV care in these patients was delayed because of lack of awareness of patients or treating physicians.

Pyrimethamine plus sulfadiazine or clindamycin has been a standard regimen for TE [26]. Since sulfadiazine and pyrimethamine were not always readily available in Taiwan, a combination of clindamycin and trimethoprim-sulfamethoxazole was prescribed in a majority of patients [26]. Although clinical improvement was observed in these patients, the efficacy of this combination remains to be determined. Secondary prophylaxis, with either trimethoprim-sulfamethoxazole or clindamycin, was administered in 58.8% of patients until the recovery of CD4+ lymphocyte after HAART. The median duration of treatment was 229 days, consistent with the recommended 6-month treatment [27]. Non-compliance and adverse drug reactions were the major reasons why the remaining one-third of patients did not receive secondary prophylaxis. Although discontinuation of maintenance therapy was proposed to be safe, failure was possible in a minority of patients [28]. The only patient who developed a second episode of TE did not comply with secondary prophylaxis and HAART.

Although clinical manifestations, radioimaging findings and response to anti-toxoplasmosis therapy were similar to previous reports in the literature [12], our findings that cognitive dysfunction and altered mental status were associated with a poor prognosis should be interpreted with caution because of the small number of cases of TE studied. Our study is also limited by the lack of definite diagnosis of TE. However, craniotomy to obtain a definite diagnosis is often considered in those HIV-infected patients with brain abscesses that fail to respond to anti-toxoplasmosis therapy [21].

In conclusion, TE was a rare HIV-related infectious complication in our cohort. Advanced age and altered mental status were associated with an increased mortality in HIV-infected patients with TE.

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