

Toxoplasma encephalitis in HIV/AIDS patients in Prof. Dr. I.G.N.G. Ngoerah General Hospital, Bali, Indonesia

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<https://doi.org/10.22146/inajbcs.v56i4.16763>

ABSTRACT

Submitted: 2023-05-18
Accepted : 2024-07-18

Toxoplasma gondii, an opportunistic infection in HIV/AIDS patients, is an obligate intracellular parasite that causes toxoplasma encephalitis (TE). The symptoms of TE range from subacute focal or global neurologic impairments to neuropsychiatric disorder, and infectious mass lesions. In clinical practice, presumptive diagnosis, including clinical syndrome, finding single or multiple brain lesions on neuroimaging evaluation are preferred. This study aimed to identify neurologic and radiologic characteristics of HIV/AIDS patients with TE in Prof. Dr. I.G.N.G Ngoerah Hospital, Denpasar, Bali. It was a retrospective study using medical records of patients with TE from January 2018 to December 2021. Of 122 subjects, 66.4% were male and 33.6% were female, age ranged from 19-59 y.o. with a median of age 33 y.o., and the CD₄ count median was 29.5 cell/mm³. Decreased consciousness was the most prevalent clinical symptom in 40.2% of subjects followed by headache in 18.9% of subjects. A structural lesion in neuroimaging was primarily found in the basal ganglia area of the brain (44.3%). The fatality rate (30.3%) was significantly associated with decreased consciousness, higher leukocyte levels, and a higher neutrophil-to-lymphocyte ratio ($p < 0.05$). Diagnosis of TE should be considered in immunocompromised young adults with subacute onset of focal and/or global neurological deficit and neuroimaging results showing hypodense lesion, particularly with ring-like enhancement, in the basal ganglia and corticomedullary junction area of the brain. An altered state of consciousness and NLR can indicate poor outcomes in HIV/AIDS patients with TE.

ABSTRAK

Toxoplasma gondii, patogen oportunistik pada pasien HIV/AIDS, merupakan parasit intraseluler obligat penyebab encephalitis toxoplasma (ET). Gejala ET bervariasi dari defisit neurologis fokal atau global subakut, gangguan neuropsikiatri, dan gejala umum lainnya yang menyerupai lesi massa infeksi lainnya. Di klinik, diagnosis praduga termasuk sindrom klinis, penemuan lesi otak tunggal atau multipel pada evaluasi neuroimaging untuk pengobatan empiris lebih diutamakan. Penelitian ini bertujuan untuk mengidentifikasi karakteristik neurologis dan radiologis pasien HIV/AIDS dengan ET di Rumah Sakit Prof. Dr. I.G.N.G Ngoerah, Denpasar, Bali. Penelitian retrospektif dilakukan menggunakan data rekam medis pasien yang didiagnosis dengan ET dari Januari 2018 hingga Desember 2021. Dari 122 subjek didapatkan 66,4% laki-laki dan 33,6% perempuan, rentang usia 19-59 tahun dengan median usia 33 tahun, dan median jumlah CD₄ 29,5 sel/mm³. Penurunan kesadaran merupakan gejala klinis terbanyak (40,2%), diikuti nyeri kepala pada (18,9%). Lesi struktural pada neuroimaging paling banyak ditemukan di area basal ganglia otak (44,3%). Tingkat kematian (30,3%) berhubungan nya dengan kondisi penurunan kesadaran, kadar leukosit tinggi, dan *neutrophil to lymphocyte ratio* yang lebih tinggi. Diagnosis ET harus dipertimbangkan pada pasien dewasa muda yang mengalami gangguan kekebalan tubuh dengan onset subakut defisit neurologis fokal dan/atau global dan hasil pencitraan saraf menunjukkan lesi hipodense, khususnya dengan peningkatan seperti cincin, di ganglia basal dan area sambungan kortikomeduler otak. Keadaan kesadaran dan NLR yang berubah dapat menunjukkan hasil yang buruk pada pasien HIV/AIDS dengan ET.

Keywords:
characteristics;
HIV/AIDS;
neurology;
radiology;
toxoplasma encephalitis

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INTRODUCTION

A study in Western countries reported central nervous system (CNS) complications occur in 30-70% of human immunodeficiency virus (HIV) patients. Neurologic abnormalities were observed in 90% of post-mortem CNS specimens of HIV/AIDS patients.¹ Neurologic symptoms commonly become the first clinical manifestations of HIV/AIDS patients.² Opportunistic infections (OIs) of CNS commonly happen in patients with low cluster of differentiation-4 (CD₄) count in the advanced stage of the disease.³

One of the most prevalent CNS opportunistic infections in people with HIV/AIDS is toxoplasma encephalitis (TE). Nicolle and Manceaux first reported toxoplasmosis in North Africa, which was isolated from *Ctenodactylus gondii*, a species of rodents.⁴ *Toxoplasma gondii* is an obligate intracellular parasite from *Apicomplexa* family causing toxoplasmosis. It is an opportunistic pathogen in HIV/AIDS patients.⁵ It has become the most common cause of space-occupying lesions in the brain, with different prevalences worldwide. A definitive diagnosis of TE is established with evidence of tachyzoites in brain biopsy samples and isolation of *T. gondii*.⁶ However, since this procedure is invasive in daily clinical practice, a presumptive diagnosis is preferred according to guidelines from The Centers for Disease Control (CDC) about criteria for AIDS-related cerebral toxoplasmosis, which include clinical syndrome, radiological findings, serology, molecular, and evaluation of treatment response to empirical treatment.⁷

The wide use of highly active antiretroviral therapy (HAART) combined with toxoplasmosis prophylaxis significantly decreases the incidence of TE. Before the anti-retroviral era, the incidence of TE was 3.9 cases per 100 people per year and decrease to 1

per 100 people afterward. The estimated number of HIV/AIDS patients with TE was 10-20%.³ In Indonesia, toxoplasma seroprevalence in Jakarta was 70%, 61.5% in Yogyakarta, and 65.24% in the southern part of Central Java, while a study in Gianyar, Bali, in HIV-positive patients aged ≥ 15 y.o. underwent anti-Toxoplasma IgG tests showed 56.7% seropositivity.⁸ This study aimed to identify neurologic and radiologic characteristics of HIV/AIDS patients with TE in Prof. Dr. I.G.N.G Ngoerah Hospital, Denpasar, Bali.

MATERIAL AND METHODS

Design

It was an observational study with retrospective design using medical records data and other administrative data from Prof. Dr. I.G.N.G Ngoerah Hospital, Denpasar, Bali as a referral hospital for Bali and Nusa Tenggara region in Indonesia from January 2018 to December 2021. This study was approved by the Ethics Committee of the Faculty of Medicine Udayana University/the Prof. Dr. I.G.N.G Ngoerah Hospital with number 476/UN14.2.2VII.14/LT/2021.

Procedure

The inclusion criteria of this study were HIV/AIDS patients diagnosed with TE in Prof. Dr. I.G.N.G Ngoerah Hospital and having complete medical records data. The exclusion criteria were HIV/AIDS patients in Prof. Dr. I.G.N.G Ngoerah Hospital without TE diagnosis. Data collected include gender, age, neurologic symptoms, HAART treatment status, outcome of the patient, lesion prediction on neuroimaging study either by brain computed tomography (CT) or magnetic resonance imaging (MRI) scan, complete blood count, CD₄ count, and serology tests results (anti-Toxoplasma IgG) according to reference range from

Alinity test kit from Abbott GmbH & Co. KG, Wiesbaden, Germany.

Data analysis

Data were presented as frequency/percentage and analyzed using Statistical Package for Social Sciences (SPSS) version 25 for Windows. Chi-square test was used to analyze the categorical data. Independent t-test was used if the data were normally distributed and the Mann Whitney test was used if the data were not normally distributed. A p value < 0.05 was considered statistically significant.

RESULTS

A total of 122 subjects who met the inclusion and exclusion criteria were

involved in this study. The characteristics of subjects are presented in TABLE 1. The median age of subjects was 33 (19 – 59 y.o.) with predominantly male (81 or 66.4%). The median CD4 count was 29.5 (cell/mm³).

Ring-enhancement lesions were mostly found in basal ganglia and corticomedullary junction (TABLE 1). Brain CT-scan evaluation was conducted in some patients after empirical therapy. The results showed improvement of the brain lesions (FIGURE 1).

The mortality rate in this study was 30.3% (37 patients). This mortality was significantly associated with a decrease in consciousness, higher white blood cell count (WBC), and higher neutrophil to lymphocyte ratio (NLR) (TABLE 2).

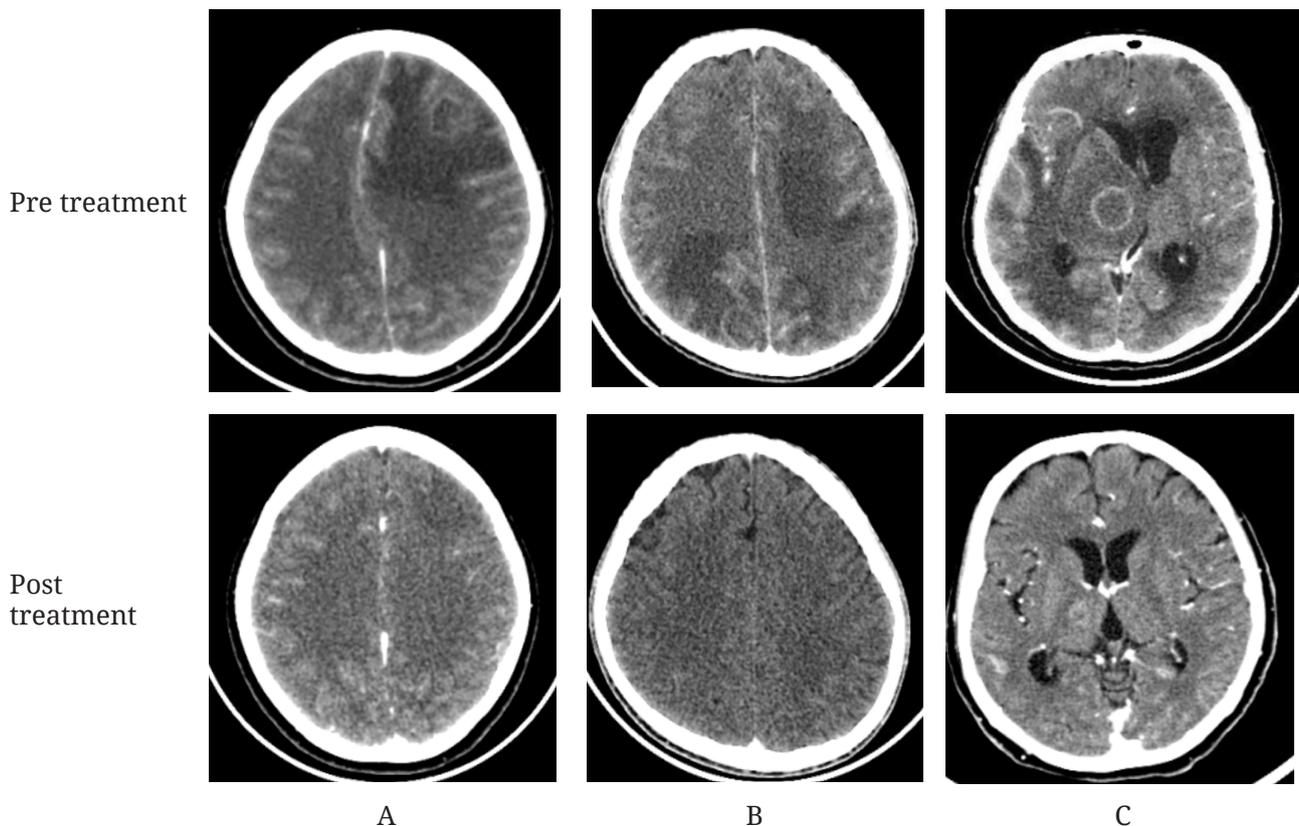


FIGURE 1. Pre- and post-treatment contrast head CT scans showing ring enhancing lesion surrounded by perifocal edema suggestive to toxoplasma encephalitis; A) cortical lesion; B) cortical and cortico-medullary junction lesions; C) basal ganglia lesion.

TABLE 1. Characteristics of subjects

Characteristics	n (%)
Gender	
Male	81 (66.4)
Female	41 (33.6)
Age (yr)	
≤ 35	74 (60.7)
> 35	48 (39.3)
Neurologic symptoms	
Decreased of consciousness	49 (40.2)
Headache	23 (18.9)
Hemiparesis	20 (16.4)
Seizure	20 (16.4)
Cranial nerve palsy	6 (4.9)
Behavioral change	4 (3.3)
HAART	
Pre- HAART	72 (59.0)
on HAART	50 (41.0)
CD4 count (cell/mm³)	
≤30	40 (32.8)
>30	38 (31.1)
N/A	44 (36.1)
IgG anti-toxoplasma	
Reactive	107 (87.7)
Non-reactive	7 (5.7)
N/A	8 (6.6)
Location of lesion*	
Basal ganglia	54 (44.3)
Corticomedullary-junction	39 (32.0)
Frontal lobe	37 (30.3)
Parietal lobe	32 (26.3)
Cerebellum	26 (21.3)
Temporal lobe	24 (19.7)
Thalamus	23 (18.9)
Occipital lobe	17 (13.9)
White matter	10 (8.2)
Pons	9 (7.4)
Midbrain	6 (4.9)

*based on neuroimaging

TABLE 2. Outcome and related factors

Variables	Outcome		p
	Died	Survive	
Gender [n (%)]			
Male	24 (18.0)	57 (46.7)	0.82
Female	13 (10.6)	28 (22.9)	
Age [n (%)]			
≤ 35	21 (17.2)	53 (43.4)	0.56
> 35	16 (13.1)	32 (26.2)	
Presentation [n (%)]			
DOC	25 (20.5)	24 (19.7)	0.00*
No DOC	12 (9.8)	61 (50)	
HAART [n (%)]			
On HAART	13 (10.6)	37	0.39
Pre- HAART	24 (18.0)	48	
WBC (median)	8.30	6.06	0.04*
NLR (median)	11.66	4.91	0.00*

DOC: decrease of consciousness; HAART: highly active anti-retroviral therapy; WBC: white blood cell; NLR: neutrophil to lymphocyte ratio

DISCUSSION

Of the 122 subjects involved in this study, 81 (66.4%) were male and 41 (33.6%) were female. It is consistent with some previous studies conducted in the United States where the risk of toxoplasmosis in males was 1.14 times higher compared to females.⁹ A study in Semarang, Central Java, Indonesia reported the incidence of cerebral toxoplasmosis among HIV/AIDS patients was 74.3%.¹⁰

Theoretically, there are no differences in toxoplasmosis risk between genders. A higher incidence rate in males is estimated to be related to a higher prevalence of HIV in the male population, as reported by the Indonesian Ministry of Health (2021). Males are more prone to HIV/AIDS due to deviations in sexual behavior such as a multi-sexual partner, anal sex, homosexuality, and intravenous drug/narcotics usage.¹¹ Moreover, awareness of HIV screening is better in males than

females related to the requirements of employees and the need for routine health checkups in some companies.¹²

The range of age of subjects in this study was 19 to 59 y.o, with a median of 33 y.o. This result was in line with the study by Hassana¹⁰ and the Indonesian Ministry of Health in 2014 which reported that range of age in AIDS patients in productive age (20-59 y.o.) was approximately 91%, mostly in the age group 20-39 y.o. (74%).⁸ This result reflected that exposure to HIV commonly occurs at a younger age when this age group begins sexually active, which is one of the HIV/AIDS risks. The latent period of HIV to induce constitutional symptoms is up to 8 yr. Opportunistic infections, including TE, tend to manifest in the advanced stage of the disease when the CD₄ count is decreased below 200 cells/mm³, which can happen within 2 to 10 yr without antiretroviral treatment¹³ and is mostly found in age group ≤35 y.o in our study.

The most common symptom among our patients was decreased consciousness (40.2%), followed by headache (18.3%), hemiparesis (16.4%), seizure (16.4%), cranial nerve palsy (4.9%), and behavioral changes (3.3%). The clinical manifestations of TE can vary due to the severity of the disease represented by the CD₄ count; patients can have altered mental status with or without focal neurologic deficits such as cranial nerve palsies, focal seizure, severe headache, and hemiplegia/hemiparesis. Non-focal neurologic deficits can be present as confusion, coma, or lethargy.¹⁴

Data of CD₄ counts were available in 78 of all subjects. All were <200 cells/mm³ with a average of 29.5 cells/mm³; similar to other publications reported that HIV patients with CD₄ count ≤200 cells/mm³ are at greater risk of CNS opportunistic infections, including TE, and this risk even higher in CD₄ count <100 cells/mm³.^{5,15,16} HIV is a fatal infection with CD₄ lymphocytes as the target. CD₄ lymphocytes circulate in blood vessels against viruses, bacteria, and other pathogens. CD₄ depletion causes the inability of the body to give adequate immune response to pathogens. Hence CD₄ count becomes the best indicator for clinicians in evaluating HIV/AIDS disease progressivity and effectivity of antiretroviral treatment.¹⁷

More than half of our subjects (59%) were newly diagnosed as HIV positive at the time of admission or consultation to our department and had not started HAART, and some of those already on HAART were non-adherent to treatment. HAART treatment is known to lower TE incidence by as much as 1.9 % and decrease mortality by up to 3.5%. However, TE still correlates as the most common cause of neurological disorders in HIV, even after HAART administration.¹⁸ Factors associated with low CD₄ count in people on HAART treatment are low medication compliance, minimal consultation visits

to physicians, intolerance to HAART, and reluctance to medicine consumption due to the side effects of the drugs.¹⁸ TE incidence in people on HAART treatment ranges from 10 % to 30%. The TE rate decreased by 3.5% after six months of HAART initiation.¹⁹ In our study, the low adherence to HAART and pre-HAART conditions presumably related to low levels of CD₄ count and incidence of TE.

Toxoplasmosis is the most common OI, which causes encephalitis and focal lesions on brain imaging.²⁰ The predilection of TE, according to the result of the neuroimaging in this study, are basal ganglia (44.3%), the cortico-medullary junction (32%), and the frontal lobe (30.2%). Typical imaging of TE showed multiple lesions with ring-like or homogenous enhancement with perilesional vasogenic edema in 70-80% of cases. These lesions can be found in the superficial areas, corticomedullary junctions, and deeper locations such as basal ganglia and thalamus. Distribution in the cortical area and corticomedullary junction are consistent with the territory of medial cerebral artery vascularization and extravasation of parasites on the primary infection.^{21,22}

Not all of our subjects had serology results for IgG anti-Toxoplasma, but most were reactive (87.7%), and a small percentage were non-reactive (5.7%). Anti-toxoplasma IgG level raised within 1-2 of infection reached its peak in 6-8 wk and persists during a lifetime in some cases. A high level of IgG anti-toxoplasma accompanied by a high level of avidity represents reactivation of chronic or latent infection, which commonly happens in immunocompromised individuals such as HIV/AIDS patients with CD₄ level <100 cells/mm³ without adequate prophylaxis for toxoplasma. High levels of anti-toxoplasma IgM occur in the acute phase of toxoplasma primary infection. However, negative serology results for toxoplasma do not always rule out TE since there was a study reported

that 3-15% of TE cases were seronegative for *T. gondii* and 10-25% of cases had CD₄ count >100 cells/mm³.⁵

A mortality rate of 30.7% was reported in this study, similar to other studies (30-37.9%). The lethality in this study was significantly associated with DOC, as other studies also found that loss of consciousness associated with the lethality.^{23,24} Higher WBC and NLR were also found to be associated with death. Both parameters can indicate the presence of a more severe inflammatory response that lead to greater tissue damage and poorer outcomes.²⁵ These clinical and laboratory parameters should lead to more aggressive therapy to prevent fatality in TE patients.

Management of TE has been a challenge in our setting due to compliance with long-term treatment, complications or adverse events related to treatment, and availability of regimens. Standard regimens with pyrimethamine and sulfadiazine were not always continuously available, and conversion to alternative regimens such as cotrimoxazole and clindamycin were also effective in improving clinical and imaging of our toxoplasma encephalitis patients, similar to a study in India by Goswami *et al.*²⁶ Limitations of this study were incomplete retrospective data from the medical record and serology of toxoplasmosis was not routinely examined in HIV/AIDS patients in our setting. Data on HAART durations were also limited, so we could not conclude its relationship with lower CD₄ levels in the on-HAART group.

CONCLUSION

Diagnosis of TE should be considered in patients suspected or confirmed as immunocompromised young adults, with subacute onset of focal and/or global neurological deficit and neuroimaging results showing hypodense lesion, particularly with a ring-like enhancement, especially in

basal ganglia and corticomedullary junction area of the brain. An altered level of consciousness and NLR can be used to predict poor outcomes in HIV/AIDS patients with TE. Education and medication supervision should be strengthened for patients already on HAART treatment to achieve CD₄ count elevation and prevent life-threatening OIs, including TE.

ACKNOWLEDGEMENTS

Not applicable

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