

## ORIGINAL ARTICLE

# Head Computed Tomography Images of HIV/AIDS Patients with Suspected Cerebral Toxoplasmosis in Dr. Soetomo General Hospital Surabaya

Ria Wibawani<sup>1</sup>, Bambang Soeprijanto<sup>2\*</sup>, Widiana Ferriastuti<sup>2</sup>, Erwin A. Triono<sup>3</sup>

<sup>1</sup>Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia

<sup>2</sup>Department of Radiology, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia - Dr. Soetomo General Hospital Surabaya, Indonesia

<sup>3</sup>Department of Internal Medicine, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia - Dr. Soetomo General Hospital Surabaya, Indonesia

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## ABSTRACT

**Introduction:** *Toxoplasma gondii* is an intracellular pathogenic parasite with the majority of co-infections occurring in HIV/AIDS patients. This study assesses the head computed tomography (CT) images of cerebral toxoplasmosis in patients with HIV/AIDS.

**Methods:** This study was a cross-sectional design using head CT images of 35 HIV/AIDS patients with suspected cerebral toxoplasmosis. Variables include lesion type, location, size, CD4 count, and therapeutic result with anti-cerebral toxoplasmosis. All data analysed descriptively.

**Results:** From total 110, 35 patients met the inclusion criteria. 24 patients (68.6%) were male and 11 (31.4%) female, average age, was 36.1. 8 patients (22.3%) had lesions in cortical, 31 patients (88.6%) had < 1 cm lesion. Single lesions mainly calcified and found in the right centrum semiovale while multiple lesions were subcortical. A hypodense lesion with rim or nodular contrast enhancement is found in 75% of patients with CD4 > 200 in contrast to slight rim contrast enhancement and perifocal edema in patients with CD4 < 200. 20 patients (57.4%) had improved condition after anti-toxoplasmosis therapy.

**Conclusion:** Cerebral toxoplasmosis lesions in HIV/AIDS patients have various types of imaging findings, mostly multiple, with most frequent location being cortical and diameter < 1 cm. Total recovery is achieved in the majority of patients with therapy.

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## Introduction

Toxoplasmosis is an infection caused by *Toxoplasma gondii*, an obligate intracellular protozoan parasite.<sup>1</sup> Thirty percent of the world population have positive antibodies against *T. gondii*.<sup>2</sup> Toxoplasmosis frequently occurs in patients with HIV. In recent years, the number of HIV patients in developing countries, including Indonesia, has sharply increased.

HIV is a neurotropic virus which crosses the blood-brain barrier. HIV-associated central nervous system (CNS) diseases are categorized into 3 types: opportunistic infections, neoplasms, and vascular diseases. A meta-analysis by Wang et al. (2017) which included 34 countries showed that patients with HIV have a high incidence of *T. gondii* infection.<sup>2</sup> HIV/AIDS can promote reactivation of *T. gondii* infection due to weak immune condition.<sup>3</sup>

HIV and *T. gondii* interact and worsen a patient's condition. Under the immunodeficient

condition, especially when CD4 count < 100 cells/mm<sup>3</sup>, *T. gondii* is activated. The highest risk of activation is in patients with CD4 < 50 cells/mm<sup>3</sup>.

Diagnosis of cerebral toxoplasmosis can be made by neuroradiologic modalities, brain biopsy, empirical trials, as well as microbiologic, serologic, and PCR examinations. The gold standard for definitive diagnosis is a histopathological examination of brain biopsy or tachyzoite found in brain tissue.<sup>4</sup>

Imaging modalities that can be used in the diagnosis of cerebral toxoplasmosis include Magnetic Resonance Imaging (MRI) and Computed Tomography (CT). Although MRI is more sensitive, its availability and usage in health centers in Indonesia are still limited due to its high cost. Therefore, CT is still the preferred choice.<sup>5</sup> CT images can show single, multiple hypodense, or hypointense lesions in white matter and basal ganglia. The most common lesion found is multiple ring enhancement.<sup>6</sup> The lesion is

\*Correspondence: bambangsoeprijanto@yahoo.com

usually accompanied by edema which can be fatal. Cerebral toxoplasmosis is the most common HIV coinfection. Diagnosis is made using both clinical and neuroradiologic approach.<sup>3</sup>

From the explanation above, there is still not much data on head CT findings of suspected cerebral toxoplasmosis in Indonesia, therefore we conducted head CT profile study of HIV/AIDS patients with suspected cerebral toxoplasmosis.

## Methods

### Subject determinations

This study is a cross-sectional study conducted at Dr. Soetomo General Hospital Surabaya from January 2018 – January 2019. Subjects of this study include all HIV/AIDS patients with suspected cerebral toxoplasmosis who had undergone CT examinations from January 2018 – January 2019. Inclusion criteria were a diagnosis of HIV, had undergone head CT as well as empirical anti-toxoplasmosis therapy. Patients whose medical record was missing or incomplete died, or discharged at own request was excluded. We collected data regarding sex, age, signs & symptoms, CD4 count, and therapeutic response.

### Imaging parameters

Patients were examined using a 128-slice CT Aquilion CX, TSX-101A (Toshiba Medical Systems Corp., Japan). All head CT images were reviewed by one neuroradiology consultants. Gathered data were analyzed based on lesion type, size, and location. Lesion type is defined as an abnormal change in brain parenchymal structure seen as a characteristic finding that is useful in diagnosing suspected cerebral toxoplasmosis. Lesion size is categorized into single or multiple and hypodense without contrast enhancement, hypodense with slight ring enhancement, ring enhancement, calcification, eccentric target sign, or perifocal edema. Location is defined as the distribution of area with abnormal changes in brain parenchyma due to *T. gondii* infection and is either cortical, cortical-subcortical, or corticomedullary junction, basal ganglia, thalamus, cerebellum, or periventricular. All descriptive data analyses were performed using SPSS for windows version 24.0 (IBM Corp.).

## Results

From total of 110 HIV/AIDS patients that were admitted with suspected cerebral toxoplasmosis, there were 35 who met the inclusion criteria. 24 patients (68.6%) were male with average age 36.1 years old. (Table 1)

CD4 count data are available in 16 patients. Twelve (75.0%) patients have CD4<200 with a mean of 54.26 cells/mm<sup>3</sup> while the remaining 4 (25.0%) have CD4>200 with a mean of 489.25 cells/mm<sup>3</sup>. Based on CD4 count data, most subjects in all categories (CD4<200, CD4>200, and no CD4 data) were male (83.3%, 75.0%, and 57.9% respectively).

Based on the location (Table 3), 4 patients (33.3%) with CD4 < 200 had lesions at corticomedullary junction and basal ganglia. On the other hand, 3 patients (75%) CD4 > 200 had in subcortical while in those without CD4 data, 12 (63.2%) are cortical-subcortical. 31 (88.6%) patients have small lesion (diameter< 1 cm), it was noticed in all patients with CD4 < 200. Large lesions are found in 1 (25.0%) patient with CD4 > 200 and 3 (15.8%) patients without CD4 data.

In terms of post-therapeutic results, 10 (58.3%) patients with CD4 < 200, 3 (75.0%) patients with CD4 > 200, and 10 (52.6%) patients without CD4 data achieved complete recovery. The remaining patients have either partial recovery or irreversible condition. Most patients (80%) with complete recovery have lesion diameter < 1 cm but the same applies to patients with partial recovery or irreversible condition (88.9%). None of the patients with lesion diameter > 1 cm achieved complete recovery. Lesions located at cortical, cerebellum, centrum semiovale, internal capsule, and periventricular mostly achieved complete recovery with anti-toxoplasmosis while those at the subcortical, corticomedullary junction, basal ganglia, thalamus, cortical-subcortical, corona radiata, external capsule, and insular lobe achieved either partial recovery or irreversible condition.

Problems in the head CT images are also identified. 7 (20.0%) have leptomeningeal enhancement and other 7 (20.0%) have gyral enhancement at right and left parieto-occipital lobes with dominance at Sylvian fissure and cerebellar tentorium, left fronto-parietal lobe, and both parieto-temporal lobes respectively. In patients with CD4 < 200, 3 (24.9%) have  $\pm 1.17$  cm midline shift to the right with  $\pm 0.7$  cm subfalcine herniation and 1 (8.3%) has  $\pm 0.58$  cm midline shift to the left. 4 (33.3%) patients with CD4 < 200 have communicating hydrocephalus and 2 (50.0%) with CD4 > 200 have non-communicating hydrocephalus. Other problems found in patients with CD4 < 200 include chronic cerebral infarction at left internal and external capsules as well as irregular left middle cerebral artery (MCA) which point towards vasculitis.

In general, patients with associated problems of midline shift, leptomeningeal and gyral enhancement, hydrocephalus, vasculitis, intracerebral hemorrhage, and infarction only achieved partial recovery.

Comorbidities found in this study are in patients with CD4 < 200 which include right and left maxillary sinusitis as well as left maxillary, ethmoidal, and sphenoid sinusitis.

Table 1. Characteristics of HIV/AIDS patients with suspected cerebral toxoplasmosis in Dr. Soetomo General Hospital Surabaya.

Patient Characteristics	CD4 count (f,%)		
	CD4 count available (n=16)		CD4 count unavailable (n=19)
	<200 (n=12)	>200 (n=4)	
Sex			
Male	10(83.3%)	3 (75.0%)	11 (57.9%)
Female	2 (16.7%)	1 (25.0%)	8 (42.1%)
Age			
Oldest	25	33	23
Youngest	60	39	59
Average	36	37	36

Table 2. Lesion types of HIV/AIDS patients with suspected cerebral toxoplasmosis in Dr. Soetomo General Hospital Surabaya.

	Multiple				Single			
	CD4 count available (n=16)		CD4 count unavailable (n=19)	Total (n=35)	CD4 count available (n=16)		CD4 count unavailable (n=19)	Total (n=35)
	<200 (n=12)	>200 (n=4)			<200 (n=12)	>200 (n=4)		
Hypodense with slight rim contrast enhancement	10 (83.3%)	2 (50%)	16 (84.2%)	28 (80%)	-	-	-	-
Perifocal edema surrounding lesion	10 (83.3%)	2 (50%)	15 (78.9%)	27 (77.14%)	1 (8.3%)	-	-	-
Hypodense with rim contrast enhancement	6 (50%)	3 (75%)	9 (47.4%)	18 (51.43%)	-	-	-	-
Hypodense with nodular contrast enhancement	3 (25%)	3 (75%)	3 (15.8%)	9 (25.71%)	-	-	-	-
Eccentric target sign	3 (25%)	2 (50%)	6 (31.6%)	11 (31.43%)	-	-	-	-
Hypodense with slight nodular contrast enhancement	3 (25%)	-	4 (21.1%)	7 (20%)	-	-	-	-
Calcification	2 (16.7%)	1 (25%)	0 (0%)	3 (8.57%)	1 (8.3%)	-	-	-
Brain edema	2 (16.7%)	1 (25%)	2 (10.5%)	5 (14.29%)	-	-	-	-
Perifocal edema without contrast enhancement	2 (16.7%)	1 (25%)	3 (15.8%)	3 (15.8%)	-	-	-	-
Hypodense without contrast enhancement	2 (16.7%)	-	2 (10.5%)	4 (11.43%)	-	-	-	-

Table 4. Therapeutic response of HIV/AIDS patients with suspected cerebral toxoplasmosis in Dr. Soetomo General Hospital Surabaya.

Therapeutic response		CD4 Count (f,%)		Total (n = 35)	
		CD4 count available (n=16)			CD4 count un- available (n=19)
		<200 (n=12)	>200 (n=4)		
Recovery	Complete	7 (58.3%)	3 (75.0%)	10 (52.6%)	20 (57.4%)
	Partial	3 (25.0%)	-	1 (5.3%)	4 (11.4%)
No recovery	Death	1 (8.3%)	1 (25.0%)	7 (36.8%)	9 (25.7%)
	Irreversible condition	1 (8.3%)	-	1 (5.3%)	2 (5.7%)

Table 3. Lesion location of HIV/AIDS patients with suspected cerebral toxoplasmosis in Dr. Soetomo General Hospital Surabaya

Lesson Location	Multiple			Single				
	CD4 count available (n=16)		CD4 count unavailable (n=19)	Total (n=35)	CD4 count available (n=16)		CD4 count un- avail- able (n=19)	Total (n=35)
	<200 (n=12)	>200 (n=4)			>200 (n=4)	>200 (n=4)		
Cortical-subcortical	2 (16.7%)	2 (50%)	12 (63.17%)	14 (40%)	-	-	-	-
Subcortical	3 (25%)	3 (75%)	7 (36.84%)	12 (34.29%)	-	-	-	-
Basal ganglia	4 (33.3%)	1 (25%)	7 (36.84%)	12 (34.29%)	-	-	-	-
Cortical	3 (25%)	2 (50%)	3 (15.79%)	8 (22.29%)	-	-	-	-
Thalamus	3 (25%)	2 (50%)	2 (10.52%)	7 (20%)	-	-	-	-
Internal capsule	-	1 (25%)	6 (31.59%)	7 (20%)	-	-	-	-
Cerebellum	3 (25%)	1 (25%)	2 (10.5%)	6 (17.14%)	-	-	-	-
Centrum Semiovale	3 (25%)	-	3 (15.79%)	6 (17.14%)	1 (8.3%)	-	-	-
Cortico-medullary junction	4 (33.3%)	1 (25%)	0 (0%)	5 (14.29%)	-	-	-	-
Periventricular	1 (8.3%)	-	0 (0%)	1 (2.86%)	-	-	-	-
Corona Radiata	-	-	1 (5.3%)	1 (2.86%)	-	-	-	-
External capsule	-	-	3 (15.8%)	3 (8.57%)	-	-	-	-
Insular Lobe	-	-	1 (5.3%)	1 (2.86%)	-	-	-	-

Table 5. Comorbidities of HIV/AIDS patients with suspected cerebral toxoplasmosis in Dr. Soetomo General Hospital Surabaya.

Comorbidities	CD4 count (f,%)			Total (n = 35)
	CD4 count available (n=16)		CD4 count unavailable (n=19)	
	<200 (n=12)	>200 (n=4)		
Right and left maxillary sinusitis	1 (8.3%)	-	-	1 (2.9%)
Left maxillary sinusitis	1 (8.3%)	-	-	1 (2.9%)
Left maxillary, left ethmoidal, left sphenoidal sinusitis	1 (8.3%)	-	-	1 (2.9%)
Right and left maxillary, ethmoidal, and sphenoidal sinusitis	1 (8.3%)	-	-	1 (2.9%)
Bilateral maxillary, ethmoidal, and sphenoidal sinusitis	-	1 (25.0%)	-	1 (2.9%)
Left sphenoidal sinusitis	-	1 (25.0%)	-	1 (2.9%)
Left sphenoidal and bilateral ethmoidal sinusitis	-	1 (25.0%)	-	1 (2.9%)
Right and left maxillary, right sphenoidal sinusitis	-	-	1 (5.3%)	1 (2.9%)
Left frontal and left ethmoidal sinusitis	-	-	1 (5.3%)	1 (2.9%)
Left maxillary sinus retention cyst and pansinusitis	-	-	1 (5.3%)	1 (2.9%)
Left maxillary sinusitis	-	-	2 (10.5%)	2 (5.7%)
Left maxillary, left ethmoidal sinusitis	-	-	1 (5.3%)	1 (2.9%)
Right and left frontal and maxillary sinusitis, left ethmoidal, left sphenoidal sinusitis	-	-	1 (5.3%)	1 (2.9%)

## Discussion

This study showed that CD4 levels may differentiate the characteristics of cerebral toxoplasmosis lesions found in head CT images. In CD4 > 200, lesions are mostly hypodense with rim or nodular contrast enhancement found at subcortical. In CD4 < 200, all lesions found were multiple, the majority are hypodense with slight rim contrast enhancement and perifocal edema surrounding the lesion at corticomedullary junction and basal ganglia.

Head CT is required as the initial neuroimaging modality in patients presenting with suspected cerebral infection. In cerebral toxoplasmosis, additional head MRI is performed to illustrate the lesion most clearly. However, MRI is expensive, time-consuming, and require significant patient cooperation, hence in cases where MRI is limited, diagnosis of cerebral toxoplasmosis with CT images is sufficient.<sup>7</sup>

In the CNS, tachyzoite infects astrocytes, neurons, microglia with varying affinity. Parasitic infiltration is then followed by an influx of CD4+ and CD8+ to control the extent of *T. gondii* infection and releases inflammatory cytokines. This can result in direct and/or indirect effects in the CNS illustrated in brain imaging findings characteristic for cerebral toxoplasmosis. Direct effects are caused by direct interaction between the parasite and effector proteins or remaining in host neuron, inducing changes in the

physiology of neurotransmitter. Indirect effects arise from CNS immune response which decreases in controlling the infection.<sup>8,9</sup>

HIV/AIDS patients have many differential diagnoses of co-infection with CNS involvement. Previous study in Bangkok, Thailand showed that frequently found are HIV encephalopathy (59.1%), cerebral toxoplasmosis (21.8%), tuberculous (TB) meningitis or tuberculoma (9.2%), cryptococcoma (8.8%), progressive multifocal leukoencephalopathy (3.1%), and lymphoma (2.1%). They found that cerebral toxoplasmosis lesion is most frequently multiple ring or nodular enhancement at corticomedullary junction and basal ganglia with surrounding edema and mass effect. This lesion type and location can serve as a reference in making the diagnosis and excluding the differential diagnoses of brain lesions in patients with HIV/AIDS. Cryptococcoma lesion is hypodense, multifocal, non-enhancing at basal ganglia and midbrain which represents the gelatinous pseudocyst and the presence of dilated perivascular space. Leptomeningeal enhancement can also be found. Progressive multifocal leukoencephalopathy also shows hypodense non-enhancing lesion without mass effect, commonly at the parietal and occipital lobes while lymphoma is more easily differentiated from toxoplasmosis because it commonly presents as hyperdense homogenous, heterogenous, or forming a ring-like pattern

at the periventricular white matter, basal ganglia, corpus callosum, and thalamus. CT image of HIV encephalopathy shows brain atrophy which is multifocal hypodense deep white matter and clinically proven with symptoms of dementia.<sup>10</sup>

TB meningitis or tuberculoma is the most difficult to differentiate with cerebral toxoplasmosis. Tuberculoma most commonly presents as ring/nodular enhancement with perilesion edema. Target sign can also be found in TB meningitis, seen as a rim-enhancing lesion with an area of central enhancement or calcification. However, if only ring-enhancement were found, it is difficult to differentiate between TB meningitis and cerebral toxoplasmosis and hence the patient's history of TB has to be considered. CNS TB is usually caused by hematogenous spread of bacteria and focal spread from intracranial or extracranial sources is rare. In TB meningitis, isodense or slight hyperdense enhancing exudates at basal cisterna is the most common finding and relatively specific in TB leptomeningeal enhancement. Meningeal enhancement is found in 90% cases and is the most sensitive finding of TB meningitis. Exudate is commonly found at the surface of the anteromedial temporal lobe, superior cerebellum, and the 3<sup>rd</sup> ventricle. In most cases, there may be some degree of meningeal involvement in the cerebral sulcus and ventricular fissure.<sup>11</sup> Other characteristic head CT lesions that can be found are leptomeningeal enhancement at basal cisterna and communicating hydrocephalus. Similar to the findings in this study, leptomeningeal enhancement is found in 3 patients with CD4 < 200, none in CD4 > 200, and 3 in patients without CD4 data. Overall, the majority of patients do not have the abnormality of leptomeningeal enhancement and gyral enhancement or hydrocephalus.

In total, post-therapeutic results of HIV/AIDS patients with suspected cerebral toxoplasmosis is the recovery in 68.9% of patients. This shows that the majority of patients have improved clinical conditions after treatment with empirical anti-toxoplasmosis. No recovery is found in 31.4% of patients in this study, similar to a study in Malaysia with a mortality rate of 31.6%, mostly in patients with acute cerebral toxoplasmosis which is also associated with their systemic illnesses.<sup>12</sup> In this study, 42.9% of patients have comorbidities such as maxillary, ethmoidal, sphenoidal, frontal sinusitis, and sinus retention cyst.

Limitation of this study is the number of samples obtained. Further studies with more samples and variables are required to achieve a more representative result. However, studies on head CT images of cerebral toxoplasmosis in HIV/AIDS patients are still rarely conducted. Findings from this study add more knowledge on CT characteristics of cerebral toxoplasmosis, especially associated with their therapeutic response.

## Conclusion

Characteristic head CT images of HIV/AIDS patients with suspected cerebral toxoplasmosis is multiple, hypodense with slight rim contrast enhancement, and located at cortical. Slight variations are found in patients with higher CD4 count. Patients with lesion diameter < 1 cm generally have a good success rate in empirical anti-toxoplasmosis. Additional problems found in the head CT images include leptomeningeal and gyral enhancement.

## Conflict of Interest

The author stated there is no conflict of interest

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