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THE RELATIONSHIP BETWEEN CD4 LEVELS AND FEATURES TOXOPLASMOSIS ENCEPHALITIS FROM NON-CONTRAST HEAD CT-SCAN HIV PATIENTS.

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ABSTRACT

Background. HIV/AIDS is known to cause central nervous system disorders, including opportunistic infections such as toxoplasmosis, triggered by Toxoplasma gondii. The activation of T. gondii is particularly prevalent in immunocompromised individuals, especially those with CD4 counts below 50. CT scans are commonly used for diagnosing cerebral toxoplasmosis.
Methods. This analytical research employs a cross-sectional design starting from February 2023 at H. Adam Malik General Hospital, Medan. Descriptive data analysis includes variables like age, gender, and CD4 levels. Bivariate analysis was conducted using Chi-square and Fisher Exact tests.
Results. The majority of subjects were male (66.7%), with an average age of 36.43 years. Sixty percent of patients had CD4 levels < 200 cells/mm3, while 40% had CD4 levels > 200 cells/mm3.
Conclusion. HIV patients with toxoplasmosis encephalitis typically exhibit clinical symptoms such as headaches and altered consciousness. CD4 levels are associated with the localization of lesions in brain lobes (frontal, occipital, temporal, parietal) and perifocal edema.

Keyword: HIV, AIDS, Toxoplasmosis, CD-4, encephalitis.

ABSTRAK

***Latar belakang**. HIV/AIDS diketahui menyebabkan gangguan sistem saraf pusat, termasuk infeksi oportunistik seperti toksoplasmosis, yang dipicu oleh Toxoplasma gondii. Aktivasi T. gondii sangat lazim pada individu dengan gangguan kekebalan, terutama mereka yang memiliki jumlah CD4 di bawah 50. CT scan biasanya digunakan untuk mendiagnosis toksoplasmosis serebral.*
***Metode**. Penelitian analitik ini menggunakan desain cross-sectional mulai Februari 2023 di Rumah Sakit Umum H. Adam Malik, Medan. Analisis data deskriptif mencakup variabel seperti usia, jenis kelamin, dan tingkat CD4. Analisis bivariat dilakukan dengan menggunakan uji Chi-square dan Fisher Exact.*
***Hasil**. Mayoritas subjek adalah laki-laki (66,7%), dengan usia rata-rata 36,43 tahun. Enam puluh persen pasien memiliki kadar CD4 < 200 sel/mm3, sementara 40% memiliki kadar CD4 > 200 sel/mm3.*
***Kesimpulan.** Pasien HIV dengan ensefalitis toksoplasmosis biasanya menunjukkan gejala klinis seperti sakit kepala dan perubahan kesadaran. Kadar CD4 dikaitkan dengan lokalisasi lesi di lobus otak (frontal, oksipital, temporal, parietal) dan edema perifokal.*

***Keyword:** HIV, AIDS, Toksoplasmosis, CD-4, Ensefalitis.*

1. Introduction

HIV (human immunodeficiency virus) and AIDS (Acquired Immunodeficiency Syndrome) present significant global public health challenges. HIV can lead to central nervous system disorders categorized into

opportunistic infections, neoplasms, and blood vessel disorders [1],[2]. Among these, toxoplasmosis, caused by the intracellular protozoan Toxoplasma gondii, frequently affects HIV patients. HIV/AIDS can reactivate Toxoplasma gondii due to compromised immunity [3].

Toxoplasma gondii primarily infects humans through consumption of undercooked meat (especially lamb and pork) containing infected tissue cysts, or through ingesting sporulated oocysts found in contaminated vegetables, fruit, or water tainted with cat feces. The parasite initiates infection in the intestines, later migrating through immune cells to infiltrate the brain. Activation of Toxoplasma gondii is common in immunocompromised individuals, particularly when CD4 counts are < 100 cells/mm³, with the highest risk seen in those with CD4 counts < 50 [1].

In the United States, an estimated 22.5% of people aged 12 and older are infected with Toxoplasma gondii, and between 10% and 40% of HIV-infected individuals carry antibodies to the parasite. Seropositivity rates vary globally, including 6.7% in Korea, 12.3% in China, 23.9% in Nigeria, 46% in Tanzania, and 47% in rural France. In Brazil, up to 50% of elementary school children and 50% to 80% of women of childbearing age show antibodies to Toxoplasma gondii [3].

There are two forms of toxoplasmosis: acute and chronic. Proliferative forms (tachyzoite) are linked to acute infections, while tissue cyst forms are linked to persistent infections. All bodily cells are invaded by tachyzoites during the acute phase, except for host nucleated cells like red blood cells. Tachyzoite enters the host cell via active penetration into the host plasmalemma or by phagocytosis. Parasites adhere to the microneme can recognize and target cells, and produce enzymes to mature rhoptries parasitophorus vacuoles. The chyzoite penetrates the host cell either by phagocytosis or active penetration into the host plasmalemma. Parasites stick to micronema, recognize and target cells, and mature rhoptries parasitophorous vacuoles by producing enzymes. In vitro, replication of intracellular tachyzoite occurs every 6-9 hours. Once the parasite has gathered 64–128 parasites in each cell, it will go on to infect other cells. The host immune system can cause them to become a tachyzoite or bradyzoite subpopulation. These parasites will induce immunity in 4 types of T cells, namely cell-mediated immune response as T.gondii are intracellular parasites. IL - 12 produced by macrophages also strengthens the work of CD4 + cells producing IFN - γ in. CD8 + cells also induce the release of IFN - γ, interferon γ (IFN - γ) plays a role in cyst formation by inhibiting replication in macrophages tachyzoite mice and inducing antigen-specific for bradyzoite. Although it plays a little part in the fight against toxoplasmosis, the humoral immune system is crucial for diagnosing the disease in people. The humoral immune system produces antibodies that can kill extracellular T. gondii and prevent parasite replication through the actions of its complement.

Histopathological analysis of tachyzoites detected in brain tissue or brain biopsy is usually required for a conclusive diagnosis of cerebral toxoplasmosis. Diagnostic imaging methods include magnetic resonance imaging (MRI) and computed tomography (CT) scans, which display one or more hypointense lesions in the basal ganglia and white matter, frequently with multiple-ring enhancement. Oedema is frequently seen with lesions, and it can be fatal [3],[4].

A 2019 study by Wibawani et al. at Dr. Soetomo Hospital, Surabaya, examined head CT scans of HIV/AIDS patients suspected of cerebral toxoplasmosis. They found hypodense lesions with mild edges were most frequent (83.3%), with perifocal edema surrounding the lesions as the second most common finding in patients with CD4 levels < 200 [5].

The correlation between CD4 levels and brain infection images from head CT scans in HIV patients remains unclear. Therefore, this study aims to determine if a correlation exists between CD4 levels and the imaging manifestations of toxoplasmosis encephalitis observed in non-contrast head CT scans of HIV patients.

2. Methods

This was an analytical research utilizing a cross-sectional design, conducted from February 2023 until the desired sample size was reached. The research was carried out in the Radiology Room of H. Adam Malik General Hospital in Medan, following approval from the Health Research Ethics Committee of the Faculty of Medicine, University of Sumatera Utara, and H. Adam Malik General Hospital, Medan.

A total of 30 patients who met the inclusion and exclusion criteria were enrolled in the study. Inclusion criteria included patients with HIV and clinical and radiological diagnoses of toxoplasmosis encephalitis who

underwent non-contrast head CT scans and had their CD4 levels measured. Patients with a history of head trauma, head surgeries, malignant diseases, or other opportunistic infections were excluded. Additionally, patients with incomplete, lost, or inaccessible medical records were not included.

Data were obtained from secondary sources, specifically medical records that met the study's criteria. Variables such as age, gender, and CD4 levels were collected for univariate analysis, which were presented as counts (n) and percentages (%). The bivariate analysis explored the relationship between CD4 levels and toxoplasmosis encephalitis imaging from head CT scans in HIV patients using Chi-Square and Fisher Exact tests as alternative methods. Statistical significance was determined at $p < 0.05$ for all tests.

3. Results

Among 30 HIV patients with toxoplasmosis encephalitis, the majority were male, comprising 20 individuals (66.7%), and their average age was 36.43 years. Of these patients, 18 (60%) had CD4 levels below 200 cells/mm³, while 12 (40%) had CD4 levels above 200 cells/mm³ (Table 1).

Table 1 Demographic Characteristics of HIV Patients with Toxoplasmosis Encephalitis

Characteristics	**n = 30 (%)**
Gender,	
Man	20 (66.7)
Woman	10 (33.3)
Age, years	36.43
CD4 levels	
< 200 cells/mm3	18 (60)
> 200 cells/mm3	12 (40)

Based on Table 2, the most commonly reported symptom among the subjects was headache, affecting 16 individuals (53.3%). Decreased consciousness was experienced by 11 patients (36.7%), while seizures and limb weakness were each reported by 7 subjects (23.3%).

Table 2 Frequency Distribution of Clinical Symptoms in HIV Patients with Toxoplasmosis Encephalitis

Clinical Symptoms	**n=30 (%)**
Headache	
Yes	16 (53.3)
No	14 (46.7)
Seizures	
Yes	7 (23.3)
No	23 (76.7)
Weakness of Limbs, n (%)	
Yes	7 (23.3)
No	23 (76.7)
Decreased Consciousness,	
Yes	11 (36.7)
No	19 (63.3)

Lesions were most commonly located in the lobes (frontal, occipital, temporal, and parietal), found in 26 patients (86.7%). Specifically, lesions were located in the frontal lobe in 17 patients (56.7%), the temporal lobe in 12 patients (40%), the parietal lobe in 21 patients (70%), and the occipital lobe in 7 patients (23.3%). The second most common location was the basal ganglia in 13 patients (43.3%), followed by the thalamus in 6 patients (20%) and the cerebellum in 3 patients (10%).

Table 3. Location of Lesions Based on Head CT Scan Examination in HIV Patients with Toxoplasmosis Encephalitis

Lesion Location	**n = 30 (%)**
Lobes,	
Yes	26 (86.7)
No	4 (13.3)
Frontal Lobe	
Yes	17 (56.7)
No	13 (43.3)
Temporal Lobe	
Yes	12 (40)
No	18 (60)
Parietal Lobe,	
Yes	21 (70)
No	9 (30)
Occipital Lobe	
Yes	7 (23.3)
No	23 (76.7)
Basal Ganglia	
Yes	13 (43.3)
No	17 (56.7)
Thalamus	
Yes	6 (20)
No	24 (80)
Cerebellum	
Yes	3 (10)
No	27 (90)

Types of Lesions Based on Head CT Scan Examination of HIV Patients with Toxoplasmosis Encephalitis (Figure 1).

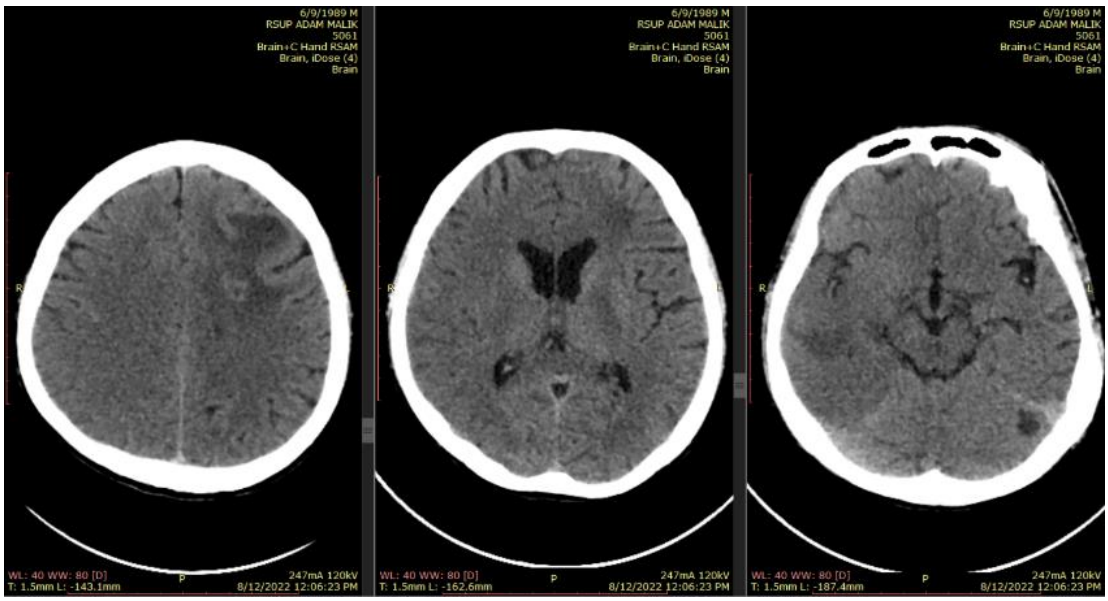


Figure 1 Sample example showing images of lesions in the left frontal and temporal lobes.

The study results showed that the most common type of lesion was hypodense, found in 29 people (96.7%). The second most common type of lesion was perifocal edema with 22 people (73.3%), and cerebral atrophy with 2 people (6.7%) (Table 4).

Table 4 Types of Lesions Based on Head CT Scan Examination of HIV Patients with Toxoplasmosis Encephalitis

Lesion Type	**n = 30 (%)**
Hypodense Lesions	
Yes	29 (96.7)
No	1 (3,3)
Perifocal Edema	
Yes	22 (73.3)
No	8 (26.7)

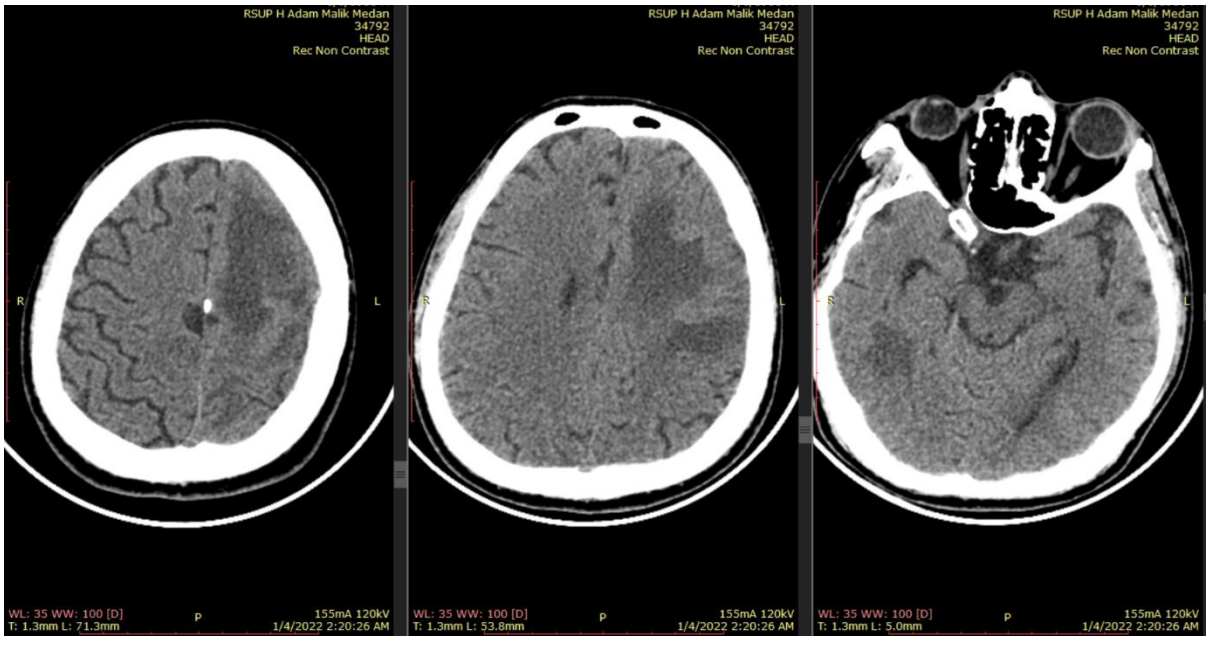


Figure 2 Sample sample showing a hypodense lesion with perifocal edema.

Based on Table 5, in subjects with CD 4 levels < 200 cells/mm^3, 18 people had lesions in the lobes (frontal, occipital, temporal, and parietal), 4 people (22.2%) had lesions in the thalamus, and 2 people (11.1%) had lesions in the cerebellum. In subjects with CD4 levels > 200 cells/mm^3, there were 8 people (66.7%) with lesion locations in the lobes (frontal, occipital, temporal, parietal), 2 people (16.7%) had lesions in the thalamus, and 1 person (8.3%) with lesions in the cerebellum. Fischer's Exact test showed that there was a significant relationship between CD4 levels and the location of the lesion in the lobes (frontal, occipital, temporal, parietal) (p=0.018), but there was no significant relationship between CD4 levels and the location of the lesion in the thalamus (p=1.000) and lesions in the cerebellum (p=1.000).

Table 5. Relationship between CD4 levels and lesion location in the lobes, thalamus, and cerebellum

CD4	Lesion Location		P
	Yes (%)	No (%)	
Lobe Lesions (frontal, occipital, temporal, parietal)			
< 200 cells/mm3	18 (100)	0	0.018*
> 200 cells/mm3	8 (66.7)	4 (33.3)	
Thalamus			
< 200 cells/mm3	4 (22.2)	14 (77.8)	1.000*
> 200 cells/mm3	2 (16.7)	10 (83.3)	
Cerebellum			
< 200 cells/mm3	2 (11.1)	16 (88.9)	1.000*
> 200 cells/mm3	1 (8.3)	11 (91.7)	

*Fischer's Exact

Of the 18 people with CD 4 levels < 200 cells/mm^3, 9 people (50%) had lesions in the basal ganglia. Meanwhile, of the 12 subjects, 4 people (66.7%) had lesions located in the basal ganglia. The results of analysis using Fischer's Exact test showed that there was no significant relationship between CD4 levels and the location of the lesion in the basal ganglia (p=0.367) (Table 6).

Table 6. Relationship between CD4 levels and lesion location in the basal ganglia

CD4	Lesion Location in Basal Ganglia		P
	Yes (%)	No (%)	
< 200 cells/mm3	9 (50)	9 (50)	0.367*
> 200 cells/mm3	4 (33.3)	8 (66.7)	

*Chi-Square

Based on Table 7, in subjects with CD 4 levels < 200 cells/mm^3, 18 people (100%) had hypodense lesions, 16 people (88.9%) had perifocal edema lesions and 1 person (5.6%) had cerebral atrophy. Among the 12 subjects with higher CD4 levels, 11 (91.7%) had hypodense lesions, 6 (50%) had perifocal edema, and 1 (8.3%) had cerebral atrophy. Fischer's Exact test indicated a significant relationship between CD4 levels and perifocal edema (p=0.034), but not with hypodense lesions (p=0.400) or cerebral atrophy (p=1.000).

Table 7. Correlation of CD4 Levels with Lesion Type

CD4	Lesion Type		P
	Yes	No	
Hypodense			
< 200 cells/mm3	18 (100)	0	0.400*
> 200 cells/mm3	11 (91.7)	1 (8.3)	
Perifocal Edema			
< 200 cells/mm3	16 (88.9)	2 (11.1)	0.034*
> 200 cells/mm3	6 (50)	6 (50)	
Cerebral Atrophy			
< 200 cells/mm3	1 (5.6)	17 (94.4)	1.000*
> 200 cells/mm3	1 (8.3)	11 (91.7)	

*Fischer's Exact

4. Discussions

This study involved 30 HIV/AIDS patients with toxoplasmosis encephalitis who had undergone head CT scans. There were 20 male participants (66.7%) in the study, with an average age of 36.43 years, ranging from 18 to 76 years old. These findings align with research by Katia et al., which examined HIV patient characteristics in Canada, showing an average age of 35 years overall, 36 years for men, and 33 years for women [6].

The most common symptom among HIV patients with toxoplasmosis encephalitis was headache, reported by 16 individuals (53.3%). Decreased consciousness was noted in 11 patients (36.7%), while seizures and limb weakness were each reported by 7 individuals (23.3%). Another study by Nissapatorn et al. identified headache (67.7%), fever (51.6%), seizures (6.5%), hemiparesis (12.9%), hemiplegia (6.5%), aphasia (3.2%), and loss of consciousness (3.2%) as clinical symptoms in toxoplasmosis encephalitis patients. Clinical symptoms of toxoplasmic encephalitis can include mental status changes, intermittent or continuous fever, headaches, focal neurological deficits, restlessness, decreased consciousness, seizures, visual disturbances, and signs of meningeal irritation [7].

CT scans of the head in HIV patients with toxoplasmosis encephalitis revealed that lesions were most commonly located in the lobes (frontal, occipital, temporal, and parietal), found in 26 patients (86.7%). Neuroimaging with non-contrast and contrast-enhanced head CT scans typically shows hypodense, single, or multiple nodular lesions with ring enhancement, varying nodule sizes, and a predilection for the basal ganglia [8].

In this study, non-contrast head CT scans most frequently showed hypodense lesions in 29 patients (96.7%). Research by Kheerati et al., analyzing CT scan features in HIV patients, also found that encephalopathy and toxoplasmosis infections most commonly result in hypodense lesions.[9] Toxoplasmic encephalitis is the leading cause of CNS infections presenting as mass lesions in HIV patients [10].

Toxoplasmosis encephalitis is the most common cause of cerebral abscess in HIV patients with a CD4 count below 100 cells/mm³. Patients with CD4 counts below 50 cells/mm³ are at the highest risk. This infection often complicates advanced HIV stages and typically occurs when CD4 levels are below 100 cells/mm³, though it can also occur at 200 cells/mm³ [11]. A study at Imam Khomeini Hospital in Iran found that 10% of HIV/AIDS patients with positive toxoplasma serology had clinical toxoplasma encephalitis, with an average CD4 count of 66.4 ± 5.5 cells/µl, and a significant relationship between CD4 count and toxoplasmic encephalitis incidence ($P<0.001$) [12].

The average CD4 count in patients with neurological manifestations was 191.71 ± 117.7, with 64.7% having a CD4 count below 200. Lower CD4 counts are associated with increased neurological disorders in HIV patients.[13] Approximately 90% of TE cases have CD4 T lymphocyte counts below 200 cells/mm³, and 75% below 100 cells/mm³. Toxoplasmosis lesions often predominate in the basal ganglia, more so than other brain areas, leading to movement disorders such as parkinsonism, ataxia, chorea, ballismus, and rigidity [14],[16].
Brain CT scans in toxoplasmosis may show single or multiple nodular lesions, with contrast-enhanced imaging revealing thin-walled cavitary lesions with ring enhancement and surrounding white matter edema. Toxoplasmosis tends to involve the basal ganglia [17]. A study at Sanglah General Hospital, Denpasar, found lesions primarily in the thalamus, often multiple and accompanied by edema [18]. The distribution of lesion locations aids in diagnosing neurological impacts, reducing neurological disability and patient mortality.[19]
Non-contrast head CT scans typically show isodense or hypodense areas, especially in the basal ganglia or at the corticomedullary junction, with mass effect edema. Lesion sizes vary from 1 cm to over 3 cm [20]. Toxoplasmosis is the most common CNS infection causing focal cerebral lesions in HIV-positive patients. A review of 115 HIV-positive patients with confirmed toxoplasmosis found that 55% experienced headaches. In this study, 95% had CD4 counts below 200 cells/mm³, and 66% had counts below 100 cells/mm³, with a median CD4 count of 50 cells/mm³, supporting the need for brain imaging in advanced HIV patients with CD4 counts below 200 cells/mm³ [17].
This study had several limitations, including the use of only non-contrast head CT scans, which have lower sensitivity compared to contrast-enhanced CT or MRI. The small sample size was due to a limited database for retrospective study. Additionally, a malfunctioning CD4 counter during the research period prevented prospective data addition.

5. Conclusions

Most HIV sufferers with Toxoplasmosis Encephalitis have clinical symptoms such as headaches (53.3%) and decreased consciousness (36.7%). There is a correlation between CD4 levels and lesion locations in the lobes (frontal, occipital, temporal, parietal) as well as perifocal edema.

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