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Correlation between IgG Anti-*Toxoplasmosis Gondii* Antibodies and Cognitive Function in Human Immunodeficiency Virus-Acquired Immunodeficiency Syndrome (HIV-AIDS) Patients with Cerebral Toxoplasmosis

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ABSTRACT

Background: Patients with HIV-AIDS are at increased risk for both opportunistic infections, such as cerebral toxoplasmosis, and cognitive impairment. IgG anti-Toxoplasmosis gondii (*T.gondii*) is a marker for latent infection. However, its role in cognition in HIV patients remains unclear. The study aims to determine the correlation between Ig-G anti-T.gondii and each domain cognitive function in HIV patients with cerebral toxoplasmosis.

Method: This was a cross-sectional study involving 110 HIV patients with cerebral toxoplasmosis who met the inclusion and exclusion criteria. We assessed cognitive function using Montreal Cognitive Assessment Indonesian Version (MoCA-INA) and measured the IgG anti-T.Gondii using the ELISA method. The Spearman correlation test was used to determine the correlation between Ig-G anti-T.gondii with each cognitive domain.

Results: There was a significant correlation between IgG anti-T.gondii and cognitive function. ($p = 0.004$, $r = -0.275$). There was also significant relation between IgG anti-T.gondii with attention ($p = 0.046$, $r = -0.19$), abstraction ($p = 0.036$, $r = -0.2$), and delayed recall ($p = 0.047$, $r = -0.19$). But there was no significant relation between Ig-G anti-T.gondii with visuospatial ($p = 0.171$), naming ($p = 0.521$), language ($p = 0.810$), and orientation ($p = 0.11$)

Conclusion: Lower Level Of IgG Anti-Toxoplasmosis Gondii Antibodies Is Associated With Worse Cognitive Function In Human Immunodeficiency Virus-Acquired Immunodeficiency Syndrome (HIV-AIDS) Patients with Cerebral Toxoplasmosis

Keywords: Cerebral Toxoplasmosis, Cognitive function, Ig-G anti toxoplasma.

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ABSTRAK

Latar Belakang: *Pasien dengan HIV-AIDS berada pada peningkatan risiko untuk kedua infeksi oportunistik, seperti toksoplasmosis serebral, dan gangguan kognitif. IgG anti-Toxoplasmosis gondii (T.gondii) adalah penanda untuk infeksi laten. Namun, perannya dalam kognisi pada pasien HIV masih belum jelas. Tujuan penelitian untuk mengetahui korelasi antara Ig-G anti T.gondii dengan masing-masing fungsi kognitif domain pada pasien HIV dengan toksoplasmosis serebral.*

Metode: *Ini adalah studi cross sectional yang melibatkan 110 pasien HIV dengan toksoplasmosis serebral yang memenuhi kriteria inklusi dan eksklusi. Kami menilai fungsi kognitif menggunakan Montreal Cognitive Assessment Indonesian Version (MoCA-INA) dan mengukur IgG anti T.Gondii menggunakan metode ELISA. Uji korelasi Spearman digunakan untuk mengetahui korelasi antara Ig-G anti T.gondii dengan masing-masing domain kognitif.*

Hasil: *Ada korelasi yang signifikan antara IgG anti T.gondii dan fungsi kognitif. (p = 0,004, r = -0,275). Ada juga hubungan yang signifikan antara IgG anti T.gondii dengan perhatian (p = 0,046, r = -0,19), abstraksi (p = 0,036, r = -0,2), ingatan tertunda (p = 0,047, r = -0,19). Namun tidak ada hubungan yang signifikan antara Ig-G anti T.gondii dengan visuospatial (p=0,171), penamaan (p=0,521), bahasa (p=0,810) dan orientasi (p=0,11)*

Kesimpulan: *Tingkat antibodi IgG Anti-Toxoplasmosis Gondii yang lebih rendah dikaitkan dengan fungsi kognitif lebih buruk pada pasien Human Immunodeficiency Virus-Acquired Immunodeficiency Syndrome (HIV-AIDS) dengan toksoplasmosis serebral*

Kata kunci: *Toksoplasmosis serebral, Fungsi kognitif, Ig-G anti toksoplasma.*

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1 Introduction

Toxoplasmosis is a parasitic infection caused by the Toxoplasma gondii (*T.gondii*) parasite, which can affect the brain and cause neurological symptoms. In patients with Human Immunodeficiency Virus-Acquired Immunodeficiency Syndrome (HIV-AIDS), cerebral toxoplasmosis is a common opportunistic infection that can affect cognitive function.[1,2,3]

Several studies have found that cognitive impairment was more common and more severe in HIV patients with cerebral toxoplasmosis. About 45% of HIV (Human Immunodeficiency Virus) patients were infected with *T. gondii*. Neurocognitive complications potentially occur in 3-20% of all HIV-infected individuals.[4,5]

Several factors associated with cognitive function in HIV patients include age, level of education, HIV disease stage and viral load, CD4 cell count [4,5], and use of antiretroviral therapy.[6,7,8,9]

The association between IgG anti-toxoplasmosis antibodies and cognitive function in HIV patients with cerebral toxoplasmosis has been found in several studies.[10-15] It is shown that higher levels of IgG anti-toxoplasmosis antibodies were associated with poorer cognitive function, while others have found no significant association.[16,17]

The severity of cognitive impairment can vary depending on the extent and location of brain lesions caused by the infection. The predominant cyst of toxoplasma located in the brain including the olfactory bulbs, amygdala, nucleus accumbens, frontal cortex, somatosensory cortex,

subcortex area, cerebellum, medulla oblongata, basal ganglia, septohippocampal and parahippocampal regions.[14,19,20]

The exact mechanism by which cerebral toxoplasmosis contributes to cognitive impairment in HIV patients is not fully understood. Recent studies have shown that *T.gondii* has direct and indirect mechanisms that are responsible for the cognitive behavior of the host.[21] It is also believed that the infection may cause damage to the brain leading to inflammation and disruption of neural networks. Cerebral toxoplasmosis can also exacerbate the effects of HIV on the brain and both conditions can lead to neuroinflammation and neuronal damage.[14,19,20]

Cognitive impairment in HIV patients with cerebral toxoplasmosis can affect multiple domains, including attention, memory, processing speed, motor skills, and executive function.[10-13] However, the association between *T. gondii* IgG and each cognitive domain remains unclear.

This study aimed to determine to find the relationship between Ig-G anti-toxoplasma and each cognitive domain function in Cerebral Toxoplasmosis with HIV-positive patients.

2 Method

This was analytical research with a cross-sectional design. We recruited 110 patients with HIV from Voluntary Counseling (VCT) in Adam Malik General Hospital, Medan, Indonesia from November 2022 until March 2023. The inclusion criteria were HIV patients with cerebral toxoplasmosis, aged 18-60 years, had at least 12 years level of education, were able to speak Bahasa Indonesia fluently, and gave written consent to participate in this research. Exclusion criteria were patients with previous cognitive disorders such as dementia, central nervous system (CNS) diseases, patients with aphasia, visual impairment, and hearing loss.

We collected data from medical records which included clinical symptoms, and positive serological of anti-*T. gondii* Ig-G. and radiological findings from computed tomography (CT) scans. The level of Ig-G antibody was measured using the immunoassay analysis method.

Diagnosis of HIV-AIDS was made by using rapid anti-HIV tests. Diagnosis of cerebral toxoplasmosis was made by clinical manifestation, serology test anti-*T. gondii* Ig-G and radiological findings.

Cognitive function was assessed by the Indonesian version of the Montreal Cognitive Assessment (MoCA – Ina). The MoCA-INA has been developed and validated in Indonesia and is useful as a brief cognitive tool in various clinical settings, including HIV-AIDS. [22,23] The MoCA Assesses several cognitive domains including executive function, visuospatial, attention and concentration, memory, language, calculation, and orientation. A score of 26 or above was considered normal.

Bivariate analysis was conducted to assess the correlation between Toxoplasma Ig-G antibody levels with each domain of cognitive function using the Pearson test or Spearman test based on the normality of data distribution. The level of statistically significant was set at <0.05.

3 Results

From the 110 HIV patients with cerebral toxoplasmosis, the mean age was 35.09 ± 8.04 years old. Most of the subjects were male, which was 93 subjects (84.5%). The mean level of Ig-G anti-toxoplasmosis was 471.55±234.80 IU/mL. The average MoCA-Ina score was 19.65 ± 3.68. We classified the patients based on the MoCA-Ina score. The characteristic of the subject is seen in Table 1.

Table 1 Characteristics of subjects

Variable	Frequency (n = 110)	Cerebral Toxoplasmosis with impaired cognitive function (n = 105)	Cerebral Toxoplasmosis without impaired cognitive function (n = 5)
Age (years), mean ± SD	**35.09 ± 8.04**	**35.24 ± 8.02**	**32 ± 8.86**
Gender			
Male	93 (84.5%)	88 (83.8%)	5 (100%)
Female	17 (15.5%)	17 (16.2%)	0
Occupation, n (%)			
Admin	1 (0.9%)	1 (100%)	0
Architect	1 (0.9%)	1 (100%)	0
Housewife	6 (5.5%)	6 (100%)	0
Student	2 (1.8%)	2 (100%)	0
Nurse	2 (1.8%)	2 (100%)	0
Farmer	11 (10%)	11 (100%)	0
Civil servant	8 (7.3%)	8 (100%)	0
Driver	2 (1.8%)	2 (100%)	0
Private employee	46 (41.8%)	43 (93.5%)	3 (6.5%)
Unemployment	9 (8.2%)	8 (88.9%)	1 (11.1%)
Military / police	1 (0.9%)	1 (100%)	0
Self - employed	21 (19.1%)	20 (95.2%)	1 (4.8%)
Education, n (%)			
High school	75 (68.2%)	74 (98.6%)	1 (1.4%)
Diploma 3	4 (3.6%)	3 (75%)	1 (25%)
Bachelor's degree	29 (26.4%)	26 (89.7%)	3 (10.3%)
Master's degree	2 (1.8%)	2 (100%)	0
Ethnicity, n (%)			
Aceh	3 (2.7%)	3 (100%)	0
Batak	53(48.2%)	49 (92.5%)	4 (7.5%)
Jawa	17 (15.5%)	17 (100%)	0
Karo	14 (12.7%)	14 (100%)	0
Melayu	16 (14.5%)	15 (93.8%)	1 (6.2%)
Nias	3 (2.7%)	3 (100%)	0
Padang	2 (1.8%)	2 (100%)	0
Simalungun	1 (0.9%)	1 (100%)	0
Tionghoa	1 (0.9%)	1 (100%)	0
Marital status, n (%)			
Married	75 (68.2%)	72 (96.0%)	3 (4.0%)
Not Married	35 (31.8%)	33 (94.3%)	2 (5.7%)
Laboratorium			
Ig-G anti toxoplasmosis (IU/mL), mean ± SD	471.55 ± 234.80	478.15 ± 230.47	333.03 ± 310.12
MoCA-Ina Score			
MoCa – Ina test, mean ± SD	19.65 ± 3.68	19.3 ± 3.38	27 ± 1.00
Visuospatial	2.64 ± 1.43	2.54 ± 1.39	4.60 ± 0.55
Naming	2.91 ± 0.32	2.90 ± 0.33	3.00 ± 0.00
Attention	4.16 ± 1.18	4.10 ± 1.16	5.60 ± 0.55
Language	2.65 ± 0.67	2.63 ± 0.68	3.00 ± 0.00
Abstraction	1.15 ± 0.56	1.11 ± 0.54	1.80 ± 0.45
Delayed recall	1.35 ± 1.11	1.26 ± 1.06	3.20 ± 0.45
Orientation	4.81 ± 0.94	4.76 ± 0.94	5.80 ± 0.45

The level of IgG anti-T.gondii was correlated with MoCA-INA score (p 0.004, r -0.275) as shown in Table 2 and Figure 1

Table 2 Correlation between Ig-G and MoCa – Ina Score

	MoCa-Ina		n
	R	***p***	
Ig-G levels	-0.275	0.004	110

*****Spearman test,

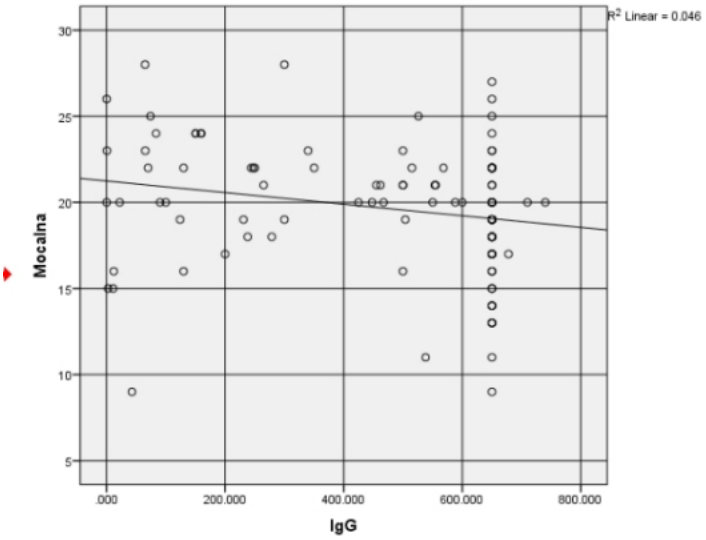

Figure 1 Correlation between Ig-G and MoCa – Ina

The correlation between Ig-G levels in each cognitive domain is shown in Table 3. There was a significant correlation between Ig-G anti-T.gondii with attention (p = 0.04, r =-0.19), abstraction (p = 0.036, r = -0.2), delayed recall (p = 0.047, r =-0.19), but there was no significant correlation between Ig-G anti-T.gondii with visuospatial (p = 0.17), naming (p = 0.521), language (p = 0.810, r=-0.02), orientation (p = 0.11, r =-0.15)

Table 3 Correlation between Ig-G and cognitive domain

	IgG	
	r	***p***
Visuospatial	0.132	0.17
Naming	-0.06	0.52
Attention	-0.19	0.04
Language	-0.02	0.81
Abstraction	-0.2	0.036
Delayed Recall	-0.19	0.047
Orientation	-0.15	0.110

*****Spearman test

4 Discussion

Cognitive impairment in HIV patients with cerebral toxoplasmosis is affected by several factors. This study found a significant correlation between Ig-G anti-T.gondii and MoCA-Ina score using

the Spearman test (r -0,275, p=0.004). This is supported by research conducted by Wiener et al (2020), showing evidence of correlation in seropositive Ig-G T. gondii with the working memory domain, while the verbal and memory function were not significantly correlated.[10,16,21] On the other hand, a study conducted by Gale et al (2020) showed a significant correlation between numeric memory and several executive functions. This is different from other previous studies which showed no significant correlation between seropositivity and cognitive function.[17] From the meta-analysis study conducted by de Haan (2021), it was found that there was a statistically significant correlation between T. gondii seropositivity and decreased processing speed, working memory impairment, short-term verbal memory, and executive function. Studies of rodents showed inhibition of neuronal functioning which may cause behavioral and cognitive changes like impaired reaction time, motor performance, memory, and learning.[10,13]

Encephalitis toxoplasmosis is one of the most common central nervous system infections in immunocompromised patients due to the secondary parasite reactivation of primary infection in the brain on HIV positive, especially if the CD4 count is below 200 sel/mm3.[24] Reactivation in primary infection is marked by the increased Ig-G titer, then followed by its stabilization. IgG antibody survives its lifetime.[26] Other factors affecting impaired cognitive function in HIV: HIV virulence, and low CD4 count.[4-8] High virulence will decline CD4 count. Patients with CD4 count less than 200 cells/mm^3 are riskier to have neurological complications[4,5,6] Chronic inflammation plays a major role in HIV–associated brain injury.[6,28]

The cognitive function consists of 5 major domains: attention, memory, visuospatial, verbal, and executive function, which are interconnected. Areas of the brain that control the attention are posterior parietal lobe, superior colliculus and lateral pulvinar nucleus, anterior cinguli gyri, and right frontal area.[27] Anatomically, the areas of the brain which are responsible for memory are the temporal media lobe (hippocampal, parahippocampal gyrus, and entorhinal cortex), diencephalon which surrounds the third ventricle (mamillary corpus, anterior nucleus, and dorsomedial thalamus), nucleus on the forebrain (septal nucleus, diagonal band and basal nucleus). All these structures together form a system called limbic system or papez circuit.[27]. Visuospatial function defines as the ability to recognize parts of the body and awareness of the body's position towards the room. The area of the brain responsible for this function is the primary visual cortex which is the anterior occipital lobe, medial of the calcarina fissure.[27] Language is another component that is controlled by both hemispheres which is dominantly controlled by the left hemisphere. The language center of the brain is located at the posterior-superior of the temporal lobe (Wernicke area) and motoric function while we speak is controlled by the infected prior frontal lobe (Broca area). Both these structure store is connected by arcuate fasciculus. Abstraction is the ability to think beyond what we observe. The frontal lobe is the dominant area that controls this function.[27] Executive function is a system that is regulated by the person itself to control the behavior of an individual. The executive function plays a role in maintaining

flexibility, emotional, sustained attention, task initiation, doing things, and goal-directed persistence. The area of the brain responsible for this function is the pre-frontal cortex[27]

The parasite *Toxoplasma gondii is* associated with cognitive disorders. Several mechanisms of T. gondii can affect cognitive function. First, the direct effect of the location of the cyst of *T. gondii* in the brain. The *T. gondii* life cycle, usually in the tachyzoid phase, will invade tissues and induce an immune response from inflammation which will be converted into bradyzoid. Bradyzoid will go back to intercellular tissue.[21] The cyst containing *T. gondii* will be distributed in a specific area of the brain that is responsible for the cognitive area. Other factors which can impair cognitive function such as metabolic, intoxication, post-operation, and systemic infection.[19,20] The predominant cyst of toxoplasma located in the brain including the olfactory bulbs, amygdala, nucleus accumbens, frontal cortex, somatosensory cortex, subcortex area, cerebellum, medulla oblongata, basal ganglia, septohippocampal and parahippocampal regions as shown in figure 2.[14,19,20]

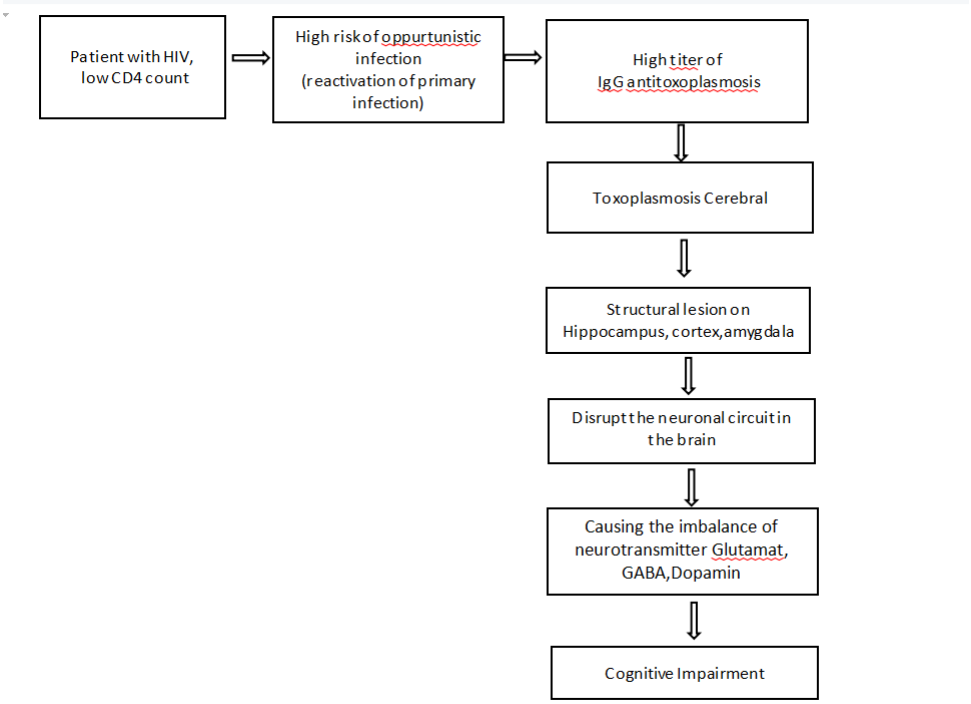

Figure 2 The parasite *Toxoplasma gondii is* associated with cognitive disorder

Second, the neurotransmitter modulation of the parasite *T. gondii* direct infection influences memory including the transduction of neurotransmitter signals by parasites which convert the dopamine concentration and its metabolism in the prefrontal cortex region and hippocampus which is important for short-term memory [10,11]. Dopamine dysregulation plays a role in neural plasticity in the hippocampus, which is important in memory and spatial orientation [14,20]. This is one of the factors assumed to cause behavioral and cognitive changes in toxoplasmosis patients [20]. This mechanism will be shown in Figure 3.

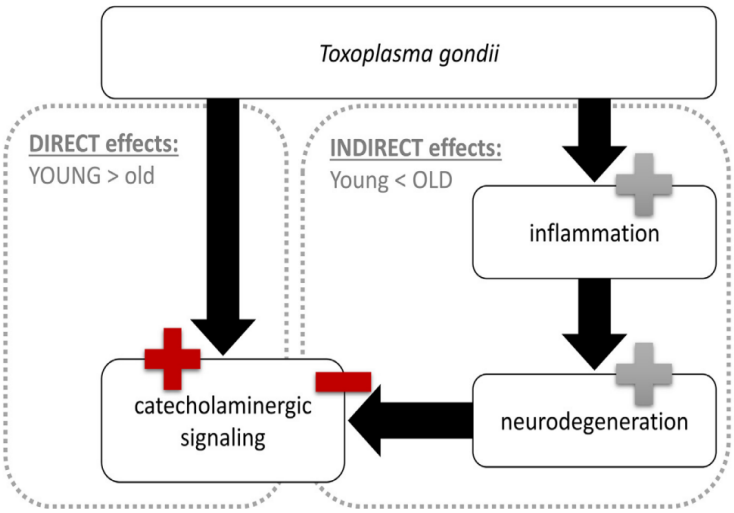

Figure 3 The mechanism of T.gondii affect cognitive function 17

The indirect effect is mediated by the immune response. Overactivation of the immune response results in neurodegenerative diseases due to the latent infection meaning the infection must be kept in a semi-dormant phase. Besides, *T. gondii* also triggers the production of TH1 by inducing INF-gamma to induce indoleamine-2,3-dioxygenase expressions. This will decrease tryptophan, a serotonin precursor. Decreased serotonin impairs only short-term memory but not long-term memory.[14,19,20,21]

High avidity of IgG anti-T.gondii is a marker for latent infection. *T.gondii* can impact cognition through ect and indirect effects mechanism resulting from the production of dopamine, meanwhile, the indirect effect is modulated by chronic neuroinflammation and thus results in reduced dopamine.

4.1 Superiority

The strength of this research is the large sample, with the total participant 110. The inclusion criteria include the age group of 18-60 years old and the minimum education of 12 years that can reduce the bias of cognitive impairment caused by degenerative and varying degrees of educational background

4.2 Limitation

This research does not include the onset of infection, other opportunistic infections, and the length of therapy that can give impact the cognitive function

5 Conclusion

In conclusion, there is a negative correlation between low levels of Ig-G anti-T.gondii and cognitive function in HIV patients with cerebral toxoplasmosis. There is a significant correlation between each cognitive domain which is attention, abstract, ion, and delayed recall.

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