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The comparison of cognitive function disorder before and after early therapy for cerebral toxoplasmosis in HIV/AIDS patients

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Abstract

Introduction: Toxoplasmosis is a common opportunistic disease that also affects human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) patients, but there are currently no research studies about cognitive function in cerebral toxoplasmosis patients, especially in terms of the effect of early treatment for this disease. The aim of the study was to compare cognitive function disorder of cerebral toxoplasmosis patients before and after early treatment of cerebral toxoplasmosis.

Material and methods: The longitudinal study were conducted among neuroinfection patients who registered in the Neurology Department of Saiful Anwar Hospital, Malang, Indonesia during January-December 2016. The inclusion criteria were: cerebral toxoplasmosis patients, HIV-positive status, head computed tomography (CT) scan performed, IgG and IgM toxoplasmosis, and patients willing participate in the study. The exclusion criteria were: other masses in the brain besides toxoplasma-derived, depression, patients not cooperative, or loss of consciousness. Samples were taken by continuous random sampling with Mini-Mental State Examination and Clock Drawing Test. The duration for anti-toxoplasma early therapy was 2-4 weeks.

Results: From a total of 31 patients, 13 patients met the inclusion criteria, with an average age of 37 years old (range, 26-67 years). The average CD4+ was 45.75 dl (8-85 dl). The result of cognitive function examination for pre-therapy was 24.85 and after therapy 26.54 (p = 0.07). The clock-drawing test before treatment was 3.15 and increased to 3.39 after treatment (p = 0.41).

Conclusion: No significant difference in cognitive function disorder before and after cerebral toxoplasmosis early therapy was found.

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Key words: clock-drawing test, cognitive function, HIV/AIDS, mini-mental state examination, toxoplasmosis.

Introduction

Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) has become a global problem. More than 95% of AIDS cases are found in developing countries. The average seroprevalence in adults starts from less than 1% in India and Europe to more than 10-20% in some African countries [1]. In HIV/AIDS patients, *Toxoplasma gondii*

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infection can cause cerebral toxoplasmosis; the decreased immune system allows *T. gondii* to proliferate, reactivating from latent infection, and becoming a severe disease [1].

Latent infection of *T. gondii* is suspected as the cause of a decrease of cognitive function in HIV/AIDS patients, measured using the speed of thinking processes and short-term memory as parameters [2].

In HIV/AIDS patients, *T. gondii* infections can cause cerebrum toxoplasmosis. In the immune deficit condition, *T. gondii* reactivates from latent infection and become a disease. *T. gondii* can become reactivated when T-CD4+ cells are below a concentration of 100 cell/µl, or if T-CD4+ levels drop below 100 cell/µl due to an opportunistic infection or malignancy that accompanies the disease. If not handled properly, it can be life-threatening condition. Cerebrum toxoplasmosis is a common cause of cerebral abscesses in people with AIDS [3, 4].

In advanced countries that implement high active antiretroviral therapy (HAART) widely, AIDS patients can survive longer. By using HAART, HIV/AIDS can shift into a chronic disease that can be controlled [5].

HAART medicines can decrease the incidence of cognitive disorder related to HIV (from mild cognitive disorder to HIV-associated dementia/HIV-D condition), such as opportunistic infection of the central nerve system (CNS) and distal sensory polyneuropathy associated with HIV [6-9].

Toxoplasma therapy with several anti-toxoplasmic phases, from the acute phase to the maintenance phase, provides good results, decreasing patient mortality, and disability rate; however, no research has been published on evaluation of the effect of such therapy on cognitive function, particularly post-acute toxoplasma therapy.

Table 1. Toxoplasmosis patients' basic data gathered for 1 year

Parameter	Result
Age (year)	34 (26-39)
Gender, male : female, *n* (%)	12 : 19 (40 : 60)
HIV transmission, *n* (%)	
Free sexual, homosexual	15 (50)
Drugs, tattoo	7 (24)
Unknown	9 (26)
Occupation, *n* (%)	
Private business	7 (24)
Housewife	6 (18)
Jobless	20 (62)
Duration of HIV diagnosis given, *n* (%)	
< 1 month	21 (69)
1-12 months	10 (33)
> 12 months	7 (21)
Level CD4+ (*t* test)	
Before toxoplasmosis early therapy	39.86
After toxoplasmosis therapy	51.71
Sexual orientation, *n* (%)	
Heterosexual	25 (82)
Homosexual	6 (18)
Outcome, *n* (%)	
Alive	17 (56)
Deceased	14 (44)

Material and methods

This present research was conducted after obtaining ethical approval from the Saiful Anwar Hospital, Malang, Indonesia, No.400/12/K.3/302/20015.

This was a longitudinal study, and samples were chosen using continuous random sampling from patients registered in the Saiful Anwar Hospital, Malang, East Java Indonesia from January to December 2016. In total, 31 patients were participating in this study, comprised of 12 females and 19 males (Table 1).

Inclusion criteria were cerebrum toxoplasmosis HIV-positive patients, immunoassay examination, contrast head CT scan performed, an increase in IgG/IgM titers, high consciousness (GCS 456) patients, and the will to participate in the study by signing an informed consent.

Exclusion criteria involved meningoencephalitis, cerebral tuberculoma, or another brain mass other than toxoplasma (cerebral tumor or cerebral abscess).

The independent variable in this study was initial toxoplasmosis therapy. The variable depends on patient cognitive function level that can be measured with neuropsychologist tests such as the Mini-Mental State Examination (MMSE) and Clock Drawing Test (CDT). MMSE is a simple standard assessments for screening of cognitive impairment, which is often carried out by both health care and research practices especially in dementia [10], while CDT is a simple neuropsychometric assessment to asses several cognitive functions [11].

The statistical analysis process used a comparative examination of Wilcoxon test, *t*-tail with SPSS 23 program to test treatment differences.

Results

After one year of gathering the data, 31 cerebrum toxoplasmosis patients were treated in Saiful Anwar Malang Hospital. An average age of patients was 34 years, and there were more female patients (19) compared to male patients (12). Mostly, HIV had been transmitted to these patients by unsafe sexual intercourse; the HIV diagnosis was generally at the patient's first hospitalization, with very low CD4+ level (39.86%).

MMSE test results before the therapy was 24.846 (± 3.891), which means that patients experienced almost mild cognitive disorder. And after the treatment, an average MMSE increased to 26.539 (± 3.256). However, this improvement was not statistically significant (Table 2).

The CDT parameters showed that the average or median CDT results before the therapy was lower compared to that after the treatment. However, based on the Wilcoxon test results, there was no significant difference in CDT findings before and after the therapy.

Discussion

Explanation

The epidemiology data showed that cerebrum toxoplasmosis patients are mostly young. This is in agreement with previous data from the same hospital from 2014-2015 that showed that the average age of toxoplasmosis patients was 33.5 years old (range, 27-35 years), with more male patients compared to female patients. The high percentage of young patients is caused by young trending distribution of HIV/AIDS [12].

The average CD4+ level in cerebrum toxoplasmosis patients was 39.8 corresponding with the previous data, where the average level of CD4+ was 31. The low CD4+ level indicates patients' weak immune level, and the lower the level, they more likely to contract cerebrum toxoplasmosis [12]. However, from the other study, there was a relationship between CD4+ level and HIV dementia.

Mortality rate was also very high at 44%. It was lower compared to another study conducted in the same hospital, with a rate of 66.4%. The high-rate is caused by the severity of HIV disease and other complications from correlated disorders [12].

The difference of cognitive function before and after the therapy

There was no significant difference for statistical test and unpaired *t*-test on MMSE average value before and after early therapy of cerebrum toxoplasmosis ($p > 0.05$) [12].

From 13 subjects that were examined, very few of them experienced a decreasing value in MMSE test. Subjects with almost the same MMSE value before and after the test consisted of about 46.15%. The reason for this results may be the nature of toxoplasmosis, which is a focal disorder with a mass of parasitic infections, and the effect of clinical manifestation is based on the injection location. Cognitive disorders generally tend to disseminate in the brain, and are caused by an inflammatory reactions, which triggers damage to neurons, particularly influencing the memory.

Based on the Wilcoxon test evaluations, there was no significant difference in CDT results before and after early therapy of cerebrum toxoplasmosis. This examination should be performed if there is a cognitive disorder, especially vision spatial disorders in some cases. In this study, the CDT levels were almost normal before starting the therapy and slightly improved after early toxoplasmosis treatment. In future, the examination of spatial vision disorders is needed if the disease is related to lesion location, as seen in radiology images of cerebrum toxoplasma patients.

Table 2. The result of before and after therapy

Parameter	Before	After
Average (standard intersection)	24.846 (± 3.891)	26.539 (± 3.256)
Median (percentile 25-75)	23 (22.0-29.0)	28 (22.5-29.5)
Paired *t*-test result	$p = 0.070$ Wilcoxon test	

Table 3. The comparison of clock-drawing test results before and after therapy

Parameter	Before	After
Mean (SD)	3.154 (± 1.068)	3.385 (± 1.325)
Median (percentile 25-75)	3 (3.0-4.0)	4 (2.0-4.0)
Significant Wilcoxon test	$p = 0.408$	

The limitation of this study was relatively short time of MMSE and CDT assessment for pre- and post-early therapy. The initial treatment of cerebrum toxoplasmosis is about six weeks and then continued with a maintenance dose. In this study, the cognitive examination was completed one day before patients were allowed to go home, with inpatient time ranging from 3 to 4 weeks in the hospital. This may cause the results of this study to be biased.

Further study is needed to understand the long-term effect of toxoplasmosis therapy. The therapy should be maintained for 6, 9, 12, and 24 months to evaluate the difference in patients' cognitive function after the treatment.

Another weakness of this therapy was that the antiretroviral (ARV) factor was not included, because when MMSE and CDT level is being measured, the ARV treatment cannot be started to ensure the recovery from opportunistic disease and to avoid complications of ARV therapy, especially the occurrence of immune reconstitution inflammatory syndrome. Some studies have shown that ARV therapy on HIV patients could decrease the possibility of dementia, although sometimes ARV therapy can trigger dementia.

The complexity of this study was that cognitive tests need a quiet environment, take a long time to administer, and should be carried out in a sitting position. However in this study, there were some difficulties such as measurements being performed in the same inpatients' room, which is not ideal for examining both MMSE and CDT. Additionally, cognitive tests should be administered by well-trained staff, but in this study, tests were conducted by a neurology resident who happened to be in the room.

Conclusions

As seen from MMSE and CDT outcomes, there was no significant improvement on the cognitive function before and after early therapy of cerebrum toxoplasmosis in HIV/AIDS patients.

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Conflict of interest

The authors declare no conflict of interest with respect to the research, authorship, and/or publication of this article.

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