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High Levels of Monocyte Chemoattractant Protein-1 Plasma Are A Risk Factor for Neurocognitive Disorders in Human Immunodeficiency Virus Infection with Antiretroviral Therapy

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ABSTRACT

Background: HIV-associated neurocognitive disorder (HAND) is a neurocognitive dysfunction caused by HIV infection. The prevalence of neurocognitive disorders of HIV in Indonesia is about 51%. Despite receiving antiretroviral therapy, HAND is still a common complication that causes morbidity in people with HIV. One of the foundations of HAND pathogenesis is inflammation. Infection of macrophages/microglia and astrocytes leads to excessive production of viral gene products and chemokines, one of them is Monocyte chemoattractant protein 1 (MCP-1). The purpose of this study was to determine plasma MCP-1 levels that increase the risk of neurocognitive disorders in HIV infection with antiretroviral therapy. ***Methods:*** This matched case-control study involved 76 subjects with HIV, 38 subjects with neurocognitive disorders, and 38 subjects without neurocognitive disorders. Cognitive status was reviewed based on MoCA-Ina examination criteria. Plasma MCP-1 levels were measured by enzyme-linked immunosorbent assay (ELISA). ***Results:*** Of the 76 subjects, the mean age of the case group was 42.08 ± 9.44 years and the control group was 42.16± 8.90 years. The cut point value based on the ROC curve of the plasma MCP-1 level was 82.14 pg/mL. It had an 86.8% sensitivity and 52.6% specificity for the occurrence of neurocognitive disorders in HIV. The risk of neurocognitive disorders in HIV was found in MCP-1 plasma ≥ 82.14 pg/mL (OR 7.33, p < 0.001, CI 95% = 2.35-22.83). Based on multivariate analysis, MCP-1 levels were independently associated with the incidence of neurocognitive disorders in HIV (AOR 11.01, CI 95% = 2.75-44.01, p=0.001). ***Conclusion:*** This study showed that high plasma MCP-1 levels were an event risk factor for neurocognitive disorders in HIV with antiretroviral therapy.

Keywords: MCP-1; neurocognitive disorders; HIV

INTRODUCTION

HIV-associated neurocognitive disorder (HAND) is a neurocognitive dysfunction caused by HIV infection and can be classified as asymptomatic neurocognitive disorders, mild neurocognitive disorders, and HIV-associated dementia. The prevalence of HAND in the United States is 33%, 14% of whom have asymptomatic neurocognitive disorders, 14% mild neurocognitive disorders, and 5% of HIV-related dementia. The prevalence of HAND in Uganda is 31%, India 33%, and Nigeria 28.8%. Results Based on research conducted on HIV patients at Cipto Mangunkusumo Hospital, Jakarta report that 51% had HIV-associated neurocognitive disorder (HAND) in March 2013-March 2014. Cognitive disorders experienced were memory (63%), fluency (40%), and attention (38%).[1,2,3]

Risk factors for neurocognitive disorders in HIV patients are CD4 counts of less than 350 cells/mm3, age over 50 years, and low education levels. HAND patients have symptoms that vary widely such as decreased concentration, slow thinking, forgetfulness, and behavioral changes. Some patients have difficulty maintaining focus while communicating.[4,5,6]

One of the foundations of HAND pathogenesis is inflammation. HAND is characterized by the presence of large numbers of HIV-infected macrophages in the brain, the formation of many giant cells, activation of astrocytes and microglia accompanied by dysregulation of chemokines/cytokines, and degeneration of neurons. Central nervous system (CNS) injury is primarily caused by the release of neurotoxic factors by glial cells activated by immune cells. Infection of macrophages/microglia and astrocytes leads to excessive production of viral gene products and chemokines, one of which is Monocyte chemoattractant protein-1.[7]

Monocyte chemoattractant protein-1 (MCP-1) is a member of chemokine C-C and chemotactic factor monocytes. MCP-1 consists of 76 amino acids and is 13 kDa in size. MCP-1 is derived from various cells, including endothelial, fibroblast, epithelial, smooth muscle, mesangial, astrocytic, monocyte, and microglial cells. These cells are necessary for antiviral immune response in peripheral circulation and tissues. MCP-1 regulates the migration and infiltration of monocytes, memory T lymphocytes, and natural killer cells.[8]

An increase in MCP-1 will recruit additional monocytes that contribute to nerve inflammation. There is also an increase in arachidonic acid and quinolinic acid. Such mediators can cause dysregulation of blood-brain barrier permeability and astrocytic glutamate uptake a combination of inflammatory, chemotaxis, and neurotoxic factors that cause inflammation in the CNS. This leads to nerve damage and cognitive impairment.[9]

Research related to plasma MCP-1 with neurocognitive disorders in people with HIV is still limited. Based on the description above, to prove the role of MCP-1 in the occurrence of neurocognitive disorders in people with HIV, research on high plasma MCP-1 levels is a risk factor for neurocognitive disorders in HIV infection with therapy by antiretroviral therapy (ARV).

METHODS

This study is an observational analytical study with a matched case-control design. The location of this study was carried out at the VCT polyclinic of Sanglah Hospital from February 2021 to May 2021. The case group was 18-year-old HIV-positive people with antiretroviral therapy for at least six months who had neurocognitive disorders (MoCA Ina value < 26).

The control group was HIV sufferers aged ≥ 18 years with ARV therapy for at least six months without neurocognitive disorders (MoCA Ina values ≥ 26). In the control group, the sample selected an age range of no more than five years from the case group. This has been completed to match it with the research design.

Control variables such as gender, education, HIV stage, CD4 cell count, duration of ARV, and type of ARV will be controlled by analysis. Exclusion criteria in this study were intracranial infection, stroke, epilepsy, head trauma, intracranial tumors, hypertension, diabetes mellitus, severe psychiatric disorders (such as schizophrenia, and depression), or receiving antipsychotic drugs.

The MoCA Ina (Montreal Cognitive Assessment) examination was used to check for cognitive impairment, which is declared abnormal when the score < 26. Study subjects examined plasma MCP-1 levels and grouped them into high plasma MCP-1 and low MCP-1 groups. The cutoff point of the high MCP-1 is determined using a characteristic curve operating receiver (ROC). Data analysis uses descriptive statistical analysis, bivariate analysis with Chi-Square test, and multivariate analysis with multiple logistic regression.
The inference process had to be a 95% confidence interval and p-value.

RESULTS

The study involved 76 study subjects. Subjects with neurocognitive disorders as a case of 38 people and subjects without neurocognitive disorders were grouped as controls as many as 38 people. The basic characteristics of the research subjects are presented in Table 1.

Table 1. Characteristics of the research subject.

Variable	Case (n=38)	Control (n=38)
Age (Year)	42.08 ± 9.44	42.16 ± 8.90
Gender		
Male	24 (63.2%)	24 (63.2%)
Female	14 (36.8%)	14 (36.8%)
Education		
≤ 9 years	13 (34.2%)	7 (18.4%)
> 9 years	25 (65.8%)	31 (81.6%)
HIV Stage		
I-II	7 (18.4%)	20 (52.6%)
III-IV	31 (81.6%)	18 (47.4%)
CD4 count		
≤ 350 cell/mm^3	29 (76.3%)	14 (36.8%)
> 350 cell/mm^3	9 (23.7%)	24 (63.2%)
Duration of ARV		
≤ 5 years	23 (60.5%)	19 (50%)
> 5 years	15 (39.5%)	19 (50%)
Type of ARV		
Score ≤ 7	27 (71.1%)	21 (55.3%)
Score > 7	11 (28.9%)	17 (44.7%)

The Area Under Curve (AUC) value of the ROC method is 0.72 with p-value = 0.001 (CI 95%: 0.61-0.83). Statistically, the value of the area under the curve (AUC) of 72.4% is relatively good. Then the optimal value of the cut-off point is determined based on the furthest coordinate of the diagonal line. MCP-1 plasma greater than or equal to 82.14 pg/mL has a sensitivity of 86.8% and specificity of 52.6% for neurocognitive disorders. The ROC MCP-1 plasma curve with a risk of neurocognitive disorders in HIV is presented in Figure 1.

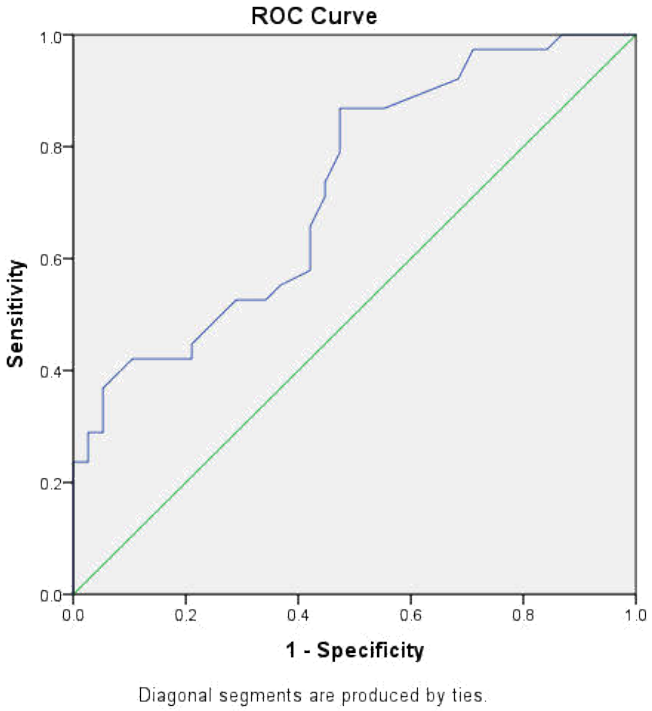

FIGURE 1: ROC Curves of Plasma MCP-1 Levels with Risk of Occurrence Neurocognitive disorders in HIV.

Association of Plasma MCP-1 Levels with Neurocognitive Disorders in HIV

After getting a cut-off of the plasma MCP-1 level, a statistical analysis was performed to calculate the Odds Ratio (OR) using the Chi-Square test method.

TABLE 2: Association of Plasma MCP-1 Levels with Neurocognitive Disorders in HIV.

	Neurocognitive Disorders	Without Neurocognitive Disorders	OR (CI 95%)	P Value
MCP-1 ≥ 82,14 pg/mL	33 (86,8%)	18 (47,4%)	7,33 (2,35-22,83)	<0,001
MCP-1 < 82,14 pg/mL	5 (13,2%)	20 (52,6%)		

Out of a total of 38 samples of patients with neurocognitive disorders, patients with MCP-1 Plasma ≥ 82.14 pg /mL were 33 patients (86.8%), while those with MCP-1 Plasma levels < 82.14 pg/mL as many as 5 patients (13.2%). In patients without neurocognitive disorders, patients with MCP-1 Plasma ≥ 82.14 pg/mL were 18 patients (47.4%), while those with MCP-1 Plasma < 82.14 pg/mL were 20 patients (52.6%). The Chi-square test showed p p-value of < 0.001 (p < 0.05), so Ho was rejected so that the level of MCP-1 Plasma ≥ 82.14 pg / mL is a risk factor for neurocognitive disorders.

The strength of the relationship parameter used the odds ratio (OR), where the plasma MCP-1 level has an OR value of 7.33 (CI 95%: 2.35 – 22.83), which means that HIV sufferers who have MCP-1 plasma levels ≥ 82.14 pg/mL have a 7.3 times chance of developing neurocognitive disorders compared to HIV patients with MCP-1 plasma levels < 82.14 pg / mL.

Effect of Research Variables on Neurocognitive Disorders in HIV

Multivariate analysis is used to control the confounding variables that may influence the results of the study shown in Table 4.

TABLE 4: Results of Logistic Regression Analysis of Confounder Variable Models Neurocognitive Disorders in HIV.

Variable		*Adjusted OR*	CI 95%	P Value
Gender	Male Female	0.74	0.19-2.81	0.664
Education	≤ 9 Years > 9 Years	5.33	1.33-21.32	0.018
HIV Stage	III-IV I-II	8.34	2.19-31.72	0.002
CD4 Count	≤ 350 cell/mm^3 ≥ 350 cell/mm^3	2.01	0.59-6.78	0.258
Duration of ARV	≤ 5 years > 5 years	0.56	0.15-2.03	0.381
Type of ARV	Score ≤ 7 Score >7	3.45	0.72-16.58	0.121
MCP-1 Level	≥ 82.14 pg/mL < 82.14 pg/mL	11.01	2.75-44.01	0.001

Plasma MCP-1 levels, education, and HIV stage are statistically meaningful as independent risk factors for neurocognitive disorders in HIV. Plasma MCP-1 levels ≥ 82.14 pg/mL have odds of 11.01 times for neurocognitive disorders compared to people with HIV with MCP-1 plasma levels < 82.14 pg/mL. Education ≤ 9 years increases the risk of 5.33 times HIV neurocognitive disorder compared to education < 9 years. Stage III-IV HIV increases the risk by 8.34 times for neurocognitive disorders compared to stage I-II. Other factors such as gender, CD4 count, duration of ARV, and ARV type are not statistically meaningful as independent risk factors (p≥0.05).

DISCUSSION

Out of a total of 38 samples of patients with neurocognitive disorders, patients with MCP-1 Plasma ≥ 82.14 pg /mL were 33 patients (86.8%), while those with MCP-1 Plasma levels < 82.14 pg / mL as many as 5 patients (13.2%). In patients without neurocognitive disorders, patients with MCP-1 Plasma ≥ 82.14 pg/mL were 18 patients (47.4%), while those with MCP-1 Plasma < 82.14 pg/mL were 20 patients (52.6%). The Chi-square test showed a p < value of 0.001 (p < 0.05), proving that plasma MCP-1 levels ≥ 82.14 pg/mL were risk factors for neurocognitive disorders.

In this study, it was found that HIV patients with antiretroviral therapy who have high plasma MCP-1 levels significantly increased the risk factor for neurocognitive disorders by 7.33 times when compared to PEOPLE with HIV who had low plasma MCP-1 levels (OR 7.33; CI 95%: 2.35–22.83). Based on multivariate analysis, MCP-1 levels are independently associated with the incidence of neurocognitive disorders in HIV (AOR 11.01; CI 95%: 2.75-44.01; p=0,001).

These results are consistent with Ragin's study (2006) in which the study subjects were 11 HIV patients associated with dementia. All of the study subjects were HIV sufferers who had been on antiretrovirals. The study looked for the relationship between plasma MCP-1 and diffusion tensor imaging measurements of MRI centrum semiovale, caudate, and putamen. Results from this study found plasma MCP-1 levels correlated with subcortical injury.[10]

The association between high levels of MCP-1 and an increased risk of neurocognitive disorders in HIV is due to dysregulation of inflammatory, chemotaxis, and neurotoxic factors. HAND is characterized by the presence of large numbers of HIV-infected macrophages in the brain, the formation of many giant cells, activation of astrocytes and microglia accompanied by dysregulation of chemokines/cytokines, and degeneration of neurons. HIV enters the SSP through the Trojan Horse mechanism, crossing the blood-brain barrier formed by endothelial cells and astrocytes. In the CNS, infected monocytes can differentiate into macrophages and secrete some inflammatory mediators, especially chemokines such as MCP-1 further while increasing the migration of immune cells through the blood-brain barrier.[7,11]

HIV macrophage infection increases the number of tunneling nanotubes (TNT) connected to other macrophages. Infected cells also secrete viral proteins such as gp120 and tat that are harmful to neurons. The mechanism of neuronal cell apoptosis is mediated by the formation of complexes involving glutamate receptors such as N-methyl-D-aspartate receptor (NMDAR) and nitric oxide. This complex results in NMDAR activation and the entry of Ca^{2+}.

An increase in intracellular Ca^{2+} leads to increased production and diffusion of nitric oxide which causes neuron apoptosis. Thus, the loss of astrocytes and dysfunction that occurs with HIV infection also result in metabolic dysregulation and neuron toxicity.[12,13]

Education of fewer than nine years is a risk factor for neurocognitive disorders in HIV (AOR 5.33; CI 95%: 1.33-21.32; p = 0.018). Research Gupta et al (2020) stated that low levels of education are a risk factor for meaningful cognitive impairment in people with HIV (OR 2.43, p<0.01). The same results were also obtained in the study of Pascal et al (2016), where low education more often experienced neurocognitive disorders in HIV (p = 0.018).[14,15]

Higher stages of HIV (III-IV) are a risk factor for neurocognitive disorders (AOR 8.34; CI 95%: 2.19-31.72; p=0,002). Based on research conducted by Njamnshi et al (2009), it was found that higher stages of HIV increase the risk of HAND (OR 7.43, p = 0.001). The same results were also obtained in the study by Animut et al (2019), where higher stages of HIV increased the risk of experiencing HAND (AOR 3.55, p < 0.05).[16,17]

Male sex was not associated with an increased risk of the incidence of neurocognitive disorders in people with HIV (AOR 0.74, CI 95%: 0.19-2.81, p=0.664). Research conducted in Yogyakarta reported that subjects who experienced cognitive impairment were more in men compared to women with a ratio of 2.3:1. There was no significant difference between men and women for neurocognitive disorders (p=0.404).[18]

CD4 less than 350 cells/mm^3 is not a risk factor for the incidence of neurocognitive disorders in people with HIV who get ARV therapy (AOR 2.01, CI 95%: 0.59-6.78, p = 0.258). The results of a study conducted by Mogambery et al (2017) stated there is no low CD4 relationship with HAND (p = 0.14). HIV-associated dementia is associated with low CD4. Asymptomatic neurocognitive disorders may occur independently of CD4 count.[19]

Prolonged use of ARVs less than five years is not associated with an increased risk of the incidence of neurocognitive disorders in people with HIV who get ARV therapy (AOR 0.56, CI 95%: 0.15-2.03, p = 0.381). Based on research conducted by Pascal et al (2016), the duration of antiretroviral therapy use is not associated with the occurrence of neurocognitive disorders (p = 0.63). In the event of a neurocognitive disorder in HIV, treatment is standard with a combination of antiretroviral therapy that aims to block viral replication in the peripheral and central nervous systems. Antiretroviral therapy can improve neurocognitive disorders that occur.[15]

An effectiveness score for ARV penetration to SSP of less than 7 is not a risk factor for the incidence of neurocognitive disorders in people with HIV (AOR 3.45, CI 95%: 0.72-16.58, p=0.121). The results of a study conducted by Cross et al (2013) stated no significant difference in neurocognitive disorders between the ARV effectiveness score group to the lower and higher SSPs (p=0.473). Different results were obtained from studies where high CNS penetration effectiveness scores were associated with a lower risk of cognitive impairment (OR 0.78, p=0.022). The effectiveness score of SSP penetration is still controversial in its use and requires further research.[20,21]

CONCLUSION

High plasma MCP-1 levels were an event risk factor for neurocognitive disorders in HIV with antiretroviral therapy.

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