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Submission date: 18-Aug-2020 04:52PM (UTC+0800)
Submission ID: 1370944304
File name: Low_CD4_Level.pdf (421.89K)
Word count: 2346
Character count: 12636

DOI Number: 10.37506/v11/i1/2020/ijphrd/194156

Low CD4 Level Increased the Risk of Cognitive Impairment in the HIV Patient

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Abstract

Background: HIV infection leads to neurological damage that results in cognitive and behavioural impairment called HIV-associated neurocognitive disorder (HAND). There are several factors associated with HAND which include the CD4 count. Patients who present with the CD4 level lower than 200 cells/ mm^3 are considered very vulnerable of experiencing neurological complications such as HAND.

Objective: To investigate the association between CD4 level and cognitive impairment evaluated using MoCA-INA among HIV patients.

Materials and Method: This cross-sectional study involves 72 consecutive patients with HIV (Human Immunodeficiency Virus) infection from the Infecion Ward of Soetomo General Hospital Indonesia. All participating patients was measured its cognitive impairment through MoCA-INA score. Blood samples were collected for CD4 evaluation. Statistics were evaluated with SPSS 25.0.

Results: The research participant consisted of 43 (59.7%) male and 29 (40.3%) female with mean age of 38.22 ± 9.159, CD4 level of 447.4 ± 247.48 and MoCA-INA score of 26.36 ± 2.770. Chi-Square analysis showed a significant difference (p-value of 0.023) in the cognitive function in the HIV patient with low CD4 (CD4<200cell/mm^3) compared tonormal CD4 (CD4≥200 cell/mm^3) with Odd Ratio of 4.900 (95% CI, 1.278–18.793).

Conclusions: Low CD4 level increase the risk of cognitive impairment assessed using MoCA-INA scoring system. These suggested that HIV patient with low CD4 should have initial screening of cognitive impairment.

Keywords: *Cognitive, Immunodeficiency, Mental Health, MoCA-INA.*

Introduction

UNAIDS (*Joint United Nations Programme on HIV/AIDS*) reported that the incidence of HIV infections across the globe reached 36.7 cases at the end of 2015. It has also been reported that there are approximately 5 million HIV cases around Asia.[1] Department of Health of the Republic of Indonesia reported the cumulative number of HIV and *Acquired Immunodeficiency Syndrome* (AIDS) cases from all 34 provinces and 407 districts/cities across the nation since the first time it was discovered in 1987 up to March 2016 were 198,219 and 78,292 cases, respectively.[2]

HIV could lead to neurological damage that results in cognitive and behavioral impairment called AIDS Dementia Complex (ADC) or HIV-associated neurocognitive disorder (HAND).[3] HAND is one of the most important HIV-related complications in this era of antiretroviral (ARV) therapy. ARV combination therapy

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using highly active antiretroviral therapy (HAART) is found to substantially improve the neurocognitive function and is attributed to a significant decline in the incidence of HAND. The prevalence of neurocognitive disorders, however, is still beyond the expected number that reaches over 50%. This is attributed to the fact that in this era of HAART, there has been a shift on HAND's clinical presentation towards milder disease that results in delayed diagnosis should the formal neurocognitive and neuropsychological assessment not performed due to subtle manifestation. The prevalence, incidence and severity of HAND is increased along with the increased population of HIV patients.[4] Several factors are thought to correlate with the occurrence of HAND and one of which is the CD4 counts. The patients who present with the CD4 level lower than 200 cells/mm^3 are at a substantial risk of developing neurological complications.[4] The low CD4 level can lead to decreased systemic immunity and increased proliferation of HIV within the central nervous system (CNS).[6] Furthermore, a series of processes will take place and lead to neural cell death and eventually the cognitive impairment/HAND; however, the studies investigating the association between CD4 counts and HAND are still limited.

MoCA has been widely used in the assessment of cognitive function. We chose MoCA as the instrument for cognitive assessment in this study given the contents of the questionnaire that cover various cognitive domains, including executive function, visuospatial function, attention and concentration, memory, language, calculation and orientation.[7] Indonesian version of MoCA, also called MoCA-INA, has been developed and validated in Indonesia and thus can be used as an instrument for cognitive assessment in our population.

The objective of this study was to investigate the association between CD4 counts and the occurrence of cognitive impairment assessed using MoCA-INA scoring system among HIV patients.

Materials and Method

Research Design: This retrospective study consisted of patients with HIV infection from the Infection ward of Dr. Soetomo General Hospital, Surabaya. Eligible patients required to be ≥ 18 years old and diagnosed with HIV infection. Patient with depression, structural brain lession or illiterate are excluded.

Cognitive Impairment Measurement: Cognitive ability was measured by using Montreal Cognitive Assessment-Indonesian Version (MoCA-INA) score. All elligible patient requires to fill the questionaire.

CD4 measurement: CD4 measurement was done through blood sampling and analyzed using flowcytometry.

Statistical Analyses: Statistical analyses were performed using IBM SPSS Statistics 25.0. Data are considered significantly different if $p<0.05$. Non-parametric data were evaluated and compared using the chi-quare test.

Findings:

Demography of HIV patients: The demographic characteristics (age, gender, level of education, and ethnicity) and the clinical characteristics (body mass index, vascular risk factors, and CD4 counts) of the study participants are shown in table 1 and 2.

Table 1: Characteristic of the study participant

Variables (N = 72)	n (%)	Mean ± SD
Gender		
Male	43 (59.7)	
Female	29 (40.3)	
Age		**38.22 ± 9.159**
> 50 years	8 (11.1)	
≤ 50 years	64 (88.9)	
Years of education		**12.35 ± 2.738**
Level of education		
Elementary school	1 (1.4)	
Junior high school	15 (20.8)	
Senior high school (and equivalents)	37 (51.4)	
College/University degree	19 (26.4)	
Ethnicity		
Javanese	62 (86.1)	
Madurese	4 (5.6)	
Timor	2 (2.8)	
Malay	1 (1.4)	
Chinese	2 (2.8)	
Ambonese	1 (1.4)	

Table 2: Clinical Characteristics of Study Participants

Variables	n (%)	Mean ± SD
Body mass index		23.35 ± 4.854 (13.5-34.3)
Overweight - Obese	25 (34.7)	
Underweight- Normal	47 (65.3)	
Vascular risk factors		
Yes	13 (18.1)	
No	59 (81.9)	
CD4 counts		447.4 ± 247.48 (5-1427)
< 200	11 (15.3)	
≥ 200	61 (84.7)	
MoCA-INA score		26.36 ± 2.770 (16-30)
< 26	18 (25)	
≥ 26	54 (75)	

The statistical analyses from the patient demography showed no significant differences for all the confounding factor, hence a multivariate analysis was not necessary. The results for this analyses are presented in table 3.

Table 3: Clinical Characteristics of the Study Participants

	MoCA-INA		p	OR (95%CI)
	Impaired (%)	Normal (%)		
Age				
> 50 years	4 (22.2)	4 (7.4)	0.101	3.571 (0.791-16.123)
≤ 50 years	14 (77.8)	50 (92.6)		
Gender				
Female	7 (38.9)	22 (40.7)	1.000	0.926 (0.311-2.759)
Male	11 (61.1)	32 (59.3)		
Level of Education				
Elementary-high school	12 (66.7)	41 (75.9)	0.539	0.634 (0.198-2.026)
College/University degree	6 (33.3)	13 (24.1)		
Body Mass Index				
Overweight- obese	6 (33.3)	19 (35.2)	1.000	0.921 (0.298-2.845)
Underweight - Normal	12 (66.7)	35 (64.8)		
Vascular Risk Factors				
Yes	2 (11.1)	11 (20.4)	0.495	0.489 (0.097-2.450)
No	16 (88.9)	43 (79.6)		

Comparison between CD4 criteria on the HIV patient with cognitive impairment and normal function showed a significant differences (p = 0.023) with an odds ratio of 4.900 (95% CI, 1.278 – 18.793). Sugessting that low CD4 may increase the risk of cognitive impairment by 4.9 times. The result can be seen on the table 4.

Table 4: Comparison between CD4 Group and Cognitive Impairment

	MoCA-INA		p	OR (95%CI)
	Impaired (%)	Normal(%)		
CD4 Counts			0.023	4.900 (1.278-18.793)
< 200	6 (33.3)	5 (9.3)		
≥ 200	12 (66.7)	49 (90.7)		
Total	18 (100)	54 (100)		

Discussion

This research showed that HIV patient with the CD4 counts of <200 cells/mm^3 are at 4.9 times higher risk of having impaired cognitive function based on MoCA-INA scoring system compared toHIV patient with CD4 counts of ≥ 200 cells/mm^3. Similarly, previous research also showed that CD4 level is a good predictor for HAND (HIV-associated Neurocognitive Disorder) which showed the p-value of 0.003 and odds ratio of 3.45 (95% CI, 1.51 – 7.91).[8] Another study also reported that the higher CD4 level is correlated with better cognitive function among HIV-AIDS patients evaluated using MoCA-INA (r = 0.347).[9] This suggested that HIV patient with low CD4 counts consistently showed increased risk of cognitive impairment, which should be screened properly.

The mechanism which responsible for the increased risk of cognitive impairment in the patient with low CD4 count is not fully explored in this research. However, we speculate that low CD4 level results in decreased systemic immunity among HIV patients and predisposes to the proliferation of the virus within the CNS.[5] A series of molecular processes will occur and result in both direct and indirect cellular death of the nervous system. The direct mechanism of cellular death involves neurotoxic effects exerted by the viral protein released from the infected monocytes and cause neural cell death via direct interaction between the viral protein and the neuron (gp120, Tat, and Vpr).[10]

On the other hand, the indirect cellular death mechanisms involve neurotoxic processes from the macrophages. The activated macrophages and microglial cells (in response to HIV infection or exposure to the viral particles) will secrete a number of mediators which consist of arachidonic acid and quinolinate, nitric oxide (NO), platelet activating factor, superoxide anions, matrix metalloprotease, chemokines, and pro-inflammatory cytokines including tumour necrosis factor (TNF). Subsequently, the cytokines and other substances released during this process, will interfere with neuro-protective function of the astrocytes (to maintain the blood brain barrier integrity and glutamate reuptake) as well ass increase the rates of apoptosis of the astrocytes.[10]

In addition, neurotoxic processes induced by the host factors, including secretion high amount of amino acids such as glutamate (an excitatory neurotoxic neurotransmitter at the very high level) and other N-methyl-D-Aspartate (NMDA) receptor agonists can create an excitotoxic environment that produces excessive NMDAR activation. Consequently, the intra-neuronal calcium concentration will reach the toxic level and lead to production of free radicals, including Reactive Oxygen Species (ROS) and NO as well as cellular death. These three processes subsequently lead to neural damage/cell death and eventually result in cognitive impairment/HAND.[10]

Clinical implication of this study is that patients with CD4 counts of <200 cells/mm^3 needs a baseline cognitive function assessment since their diagnosis of HIV infection. In order to implement these results, cohort studies are required to analyze the correlation and regression between CD4 counts and cognitive impairment among HIV patients.

Conclusion Patient with Low CD4 level of less than200 cells/mm^3 will have increased risk of cognitive impairment assessed byMoCA-INA scoring system. These suggested that the HIV patient with low CD4 should be screened for cognitive impairment to provide early prevention and treatment.

Conflict of Interest: The authors declare no conflict of interest

Source of Funding: This research received no external funding

Ethical Clearance: The research was conducted in accordance with the Helsinki declaration of 1975 as revised in 2000. All participating patient has signed written informed consent. The study protocol has been approved by the local ethics committee. Data which shows patient personal information was omitted.

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