International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2015): 6.391

Correlation between Cognitive Impairment and the Rey Auditory-Verbal Learning Test in HIV Patients in Sanglah Hospital Denpasar

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Abstract. ***Background: Neurocognitive complications in HIV patients are known as HIV-associated neurocognitive disorder (HAND) with incidence rates as much as 51% and the domain most affected is memory (63%). Verbal memory impairment is one of the deficits that still exists even in the era of antiretroviral use. Memory impairment in HIV patients has an impact on the inability to work, dependency in activities of daily living and poor adherence to ARV treatment. Objective: To determine the correlation between cognitive impairment and Rey Auditory-Verbal Learning Test (RAVLT) on HIV patients in Sanglah Hospital Denpasar. Methods: A cross-sectional study was conducted involving 30 patients with HIV in outpatient clinic VCT Sanglah Hospital in the period from June to August 2016. Cognitive impairment was assessed when the score of Montreal Cognitive Assessment Indonesian version (MoCA-Ina) <26. Further examination with RAVLT consists of A1-5 trial, distractor, A6 trial (immediate recall), trial 7 (delayed recall) and recognition. Results: Lambda correlation test between cognitive impairment and immediate recall RAVLT yielded r=0.571, p=0.045 and delayed recall RAVLT was r=0.615, p=0.011, thus indicating a strong positive, statistically significant correlation (p<0.05). Furthermore, the recognition RAVLT yielded r=0.429, p = 0.068 which showed a moderate, non-significant correlation (p> 0.05). Conclusions: HIV patients who experience cognitive impairment had a greater likelihood for impairment of immediate recall and delayed recall of verbal memory assessed using RAVLT.***

Keywords: Cognitive impairment, MoCA Ina, Rey Auditory-Verbal Learning Test

1. Introduction

Human Immunodeficiency Virus (HIV) infection has become a worldwide pandemic, including Indonesia. The cumulative number of national HIV cases is 57.799, in which Bali ranked fifth in the total number of cases, i.e. 9.637[1]. The cognitive complication in the form of HIV-associated neurocognitive disorder (HAND) is frequently found in HIV patients [2]. The prevalence of HAND in Indonesia is 51%, in which memory is the most affected domain (63%) [3].

Memory is the core of cognitive development because it is involved in every learnng process. Episodic memory is part of the long term memory which gives information about events and the correlations between those events in someone's life. The episodic memory (autobiography) is activated by various interlinking events, faces, and places, to form memory that is affected by the physical environment, emotion, and feeling experienced during that process. Based on the learning substance, memory is divided into verbal (information acquired through language) and non-verbal memory (information acquired through visual, melody, sense of touch and smell) [4].

The problem in verbal episodic memory in HIV patients is often linked to the hippocampus impairment either in encoding or retrieval process. This underlines the theory that HIV affects the functional integrity of medial temporal system that supports the verbal memory. Neuroimaging studies showed decrease of hippocampal activity in HIV patients during encoding, and increase of hippocampal activation during recognition. Both of these contradictory processes were related to the deterioration of verbal episodic memory [5].

The viral load of HIV was found highest in hippocampus. Postmortem examination had demonstrated the neuroinflammation induced by microglia/macrophage activation among HIV patients on ARV treatment, and even higher in those prior to treatment. The hippocampus and putamen neurodegeneration contributed to the antemortem neurocognitive decline. Functional MRI studies showed a decrease on signal intensity in the right posterior hippocampus, right inferior frontal gyrus, and left cingulate gyrus [5].

The memory disturbance in HIV patients heavily affects their working capability, daily activity dependency, and low compliance during ARV treatment [6]. The verbal memory disturbance in HIV patients is one of the persisting deficits even after ARV treatment. Approximately 30-50% HIV patients showed attention/working memory deficit, motor skill problem, episodic memory and executive function impairment as a result of the damage to the frontostriatal pathway [7].

The cognitive assessment in the form of neuropsycology test is a primary component in diagnosis, however it takes considerable amount of time, affected by the level of education and language, and is not widely available in developing countries [8]. The Montreal Cognitive Assessment (MoCA) has been used widely to screen the cognitive dysfunction by assessing 8 cognitive domains (attention and concentration, executive function, memory, language, visuocontruction ability, abstraction, calculation, and orientation) and requires 10 minutes to complete, with

range of score 0-30 [9]. The validity and realiability test for the Indonesian version of MoCA (MoCA-Ina) has shown to be valid according to the transcultural validation protocol [10]. A study reported that MoCA with cut-off of <26 in 119 HIV patients used to screen the neurocognitive impairment, had sensitivity 59% and specificity 81% and found prevalence of HAND about 75% in HIV patients who underwent ARV treatment [11].

Rey Auditory Verbal Learning Test (RAVLT) is used to assess memory, and has been adapted and validated in Indonesian language. This test evaluates 5 learning components through 15 words list (A1-A5), followed by distractor list (B1), immediate recall (IR), delayed recall (DR) and recognition (Rec), each of which shows aspect of verbal learning [12].

2. Method

This was a cross-sectional, analytic observational study using nominal categorical variables. Subjects included were HIV patients who visited the VCT polyclinic at Sanglah Hospital between June to August 2016. Samples were taken by consecutive sampling, in which all subjects who visited the polyclinic and filled the eligibility criteria were taken as samples until the minimal number of subjects were met.

The inclusion criteria were HIV positive patients, aged 17-50 years old, and signed the informed consent form. The exclusion criteria were HIV patients with history of one or more neurological problems (e.g. stroke, seizure, head injury, intracranial tumor, or Parkinson), and had one or more risk factors of cognitive impairment (e.g. hypertension, DM, heart disease, dyslipidemia), major psychiatry problem (e.g. schizophrenia), or undergoing anti-psychotic medications, and HIV patients with poor activity of daily living (dependent).

All subjects who met the inclusion and exclusion criteria were asked for a structured interview by questionnaire, followed by Montreal Cognitive Assessment-Indonesia (MoCA Ina) to assess the cognitive function. Subject was assessed with cognitive impairment if the MoCA-Ina <26 and no cognitive impairment if the MoCA-Ina $\geq$26. RAVLT measures the encoding, consolidation, storage and retrieval ability in verbally collected information. The standard format was begun with reading out loud the list of 15 words (list A) and repeat it 5 times (trial 1-5) without pausing between each trial. The examiner then read the distractor (list B) containing 15 different words from the previous list and subject was then given one chance to recall. Immediately after the distractor task, subject is asked to recall as many words as possible from list A. The delayed recall (trial 7) is done by asking subject to recall as many words as possible from the list A after 20 minutes. Recognition test (trial 8) is done by asking the subjects to confirm whether the word read by examiner is on the initial list after a 20 minute-period [13]. This study had received a recommendation from the Ethics Committee on human research, Faculty of Medicine, Udayana University. Written consent was obtained from each subject after they understood the purpose and agreed to join the study.

We used the Lambda correlation test for hypothesis testing and set the p value to <0.05 for significance correlation between the cognitive impairment and the verbal memory. Data analysis was done using the Statistical Package for Social Science (SPSS) 17.0 for Windows.

3. Result

As many as 30 HIV patients under outpatient treatment in VCT polyclinic Sanglah General Hospital Denpasar were recruited, from the period of June-August 2016, and divided into two groups: 12 subjects with cognitive impairment and 18 without. The RAVLT examination was done for both groups. The basic characteristics of the subjects were shown in table 1.

Table 1: Basic Characteristics of Study Subjects

Variable	Cognitive Impairment	
	Yes n(%)	No n(%)
Age (years)	33.83±7.40	34.56±6.68
Age group (years)		
17-34	8(66.7)	9(50)
35-50	4(33.3)	9(50)
Sex		
Male	4(33.3)	13(72.2)
Female	8(66.7)	5(27.8)
Years of education		
<=9 years	9(75.0)	13(72.2)
>9 years	3(25.0)	5(27.8)
Mean CD4 value (cell/µl)	64.75±61.73	361.28±167.26
CD4 count (cells/µl)		
<=200	12(100)	2(11.1)
>200	0(0)	16(88.9)
Duration of ARV treatment		
<1 year	10(83.3)	14(77.8)
>1 year	2(16.7)	4(22.2)

In this study, the mean age of subjects with cognitive impairment was 33.83±7.40, and mostly found in the age group of 17-34 years old (66.7%). Subjects with normal cognitive function had mean age of 34.56±6.68 and were found in the same proportion in the age group of 17-34 years old (50%) and 35-50 years old (50%). The cognitive impairment was found more in female group (66.7%), while the cognitively normal subjects were found more commonly in male group (72.2%). Most of the subjects in both groups had >9 years of education; 75% in group with cognitive impairment and 72.2% in group with normal cognitive function. All subjects with cognitive impairment had CD4 <=200 cells/µl (100%), with mean CD4 64.75±61.73 cells/µl. The contrary was found in the normal group, all of whom had the CD4 >200 cells/µl with mean value 361.28±167.26 cells/µl. The length of ARV therapy was mostly >1 year in both group with cognitive function and group with normal cognitive function (83.3% and 77.8% respectively).

Table 2: Correlation between cognitive impairment and RAVLT

Variable	Cognitive Impairment		r	p
	Yes n(%)	No n(%)		
RAVLT immediate recall Impaired Normal	11(91.7) 1(8.3)	5(27.8) 13(72.2)	0.570	0.045*
RAVLT delayed recall Impaired Normal	10(83.3) 2(16.7)	3(16.7) 15(83.3)	0.615	0.011*
RAVLT recognition Impaired Normal	9(75.0) 3(25.0)	5(27.8) 13(72.2)	0.429	0.068

*statistically significant

The RAVLT result for the group with cognitive impairment showed 91.7% had problem with immediate recall, 83.3% in delayed recall, and 75% in recognition. Correlation test which was done for the RAVLT included the immediate recall, delayed recall and recognition. The result of Lambda correlation analysis between cognitive impairment and each of the above variables were as followed: the RAVLT immediate and delayed recall showed strong positive correlation, t while the RAVLT recognition showed medium correlation albeit statistically insignificant ($p>0.05$) (table 2). We can draw conclusion that in HIV patients assessed with RAVLT, there is a strong correlation between cognitive impairment and both immediate recall and delayed recall; and only medium correlation with recognition.

4. Discussion

This study showed that cognitive impairment was more frequent in 17-34 years old age group (66.7%). The cognitive impairment in AIDS patient was found more frequently in younger age group with mean age of 43.4 in a study done in Brazil [14]. The study by Widyastuti et al. (2012) also showed that the cognitive impairment found the most in HIV patients between 30 to 40 years old (64.7%) [15]. The profile of cognitive impairment in young HIV patients matched the clinical picture of subcortical cognitive impairment. This strengthens the theory that the cognitive impairment in HIV patient is perpetrated by the HIV itself and that the impairment in verbal memory progresses faster with the age [16].

Approximately 75% HIV patients with low level of education suffers from cognitive impairment. Low level of education is an independent risk factor for the cognitive impairment in HIV patients [15, 17]. (Ronchi, 2002; Widyastuti; 2012). The low level of education is commonly associated with low social and economic status , as well as other factors such as infectious disease and malnutrition, all of which affect the cognitive function. On the contrary, high level of education may inhibit the cognitive impairment based on the cerebral reserve hypothesis which postulated that by continuous learning process, there will be more sprouting of the dendrite and myelin branches which would act as a kind of “extra reservoir” that helps with cognitive dysfunction long before a clinical symptom become apparent [17].

Cognitive impairment was found more frequent in the HIV patients with ARV treatment <1 year (83.3%). In fact, the ARV exerts beneficial effect for the cognitive function (Ronchi, 2002). The effect of ARV to the cognitive function in a study in Uganda showed that dementia in HIV improved, from 61% at the start of study to 4% after 6 months ARV therapy. The cognitive improvement was apparent on the neuropsychological examination in the verbal memory, psychomotor ability, and executive function domains. There was also improvement in functional capability [18, 19]. The ARV therapy was said to increase the cognitive impairment but this effect was not seen in every patient taking the ARV medications [20].

All patients diagnosed with cognitive impairment had CD4 <200 cells/µl, with mean value 64.75±61.73 cells/µl. The low CD4 level is a statistically significant risk factor for cognitive impairment in HIV patients (OR 6,4, CI 2.19-18.93) [15]. The immunocompromised state facilitates the entry of virus and, subsequently, brain damage. The CD4 is the proinflammatory marker in the case of brain damage in relation with the lymphocyte dysfunction [21].

RAVLT is related to the encoding and storage process in learning new information (learning A1-A4), and other process related to search and retrieval of information called free recall (IR, DR) and recognition (Rec) [12]. The HIV patients with cognitive impairment in this study were found with problem in verbal memory in various stages of memory: learning, immediate recall, delayed recall and recognition. The verbal memory impairment was found to be persistent in spite of elevated CD4 under HAART. The problem in attention/working memory, motor function, episodic memory, and executive function occur as a consequence of damage in frontostriatal pathway [7]. However in the post-HAART era, the clinical picture of cognitive problem in HIV patients involved more cortical domains [22].

In this study, we found a significantly strong positive correlation ($p<0.05$) between the cognitive impairment in HIV patients with the RAVLT immediate recall (r=0,571) and RAVLT delayed recall (r=0,615), and medium correlation between cognitive impairment and RAVLT recognition (r=0,429). The profile of cognitive impairment in HAND was similar to the subcortical cognitive impairment in which the neuropsychological test showed problem in the memory domain, specifically in learning and delayed recall, with good recognition [22]. A study by Paula et al. also showed similar pattern in the memory problem in patients with HIV [12]. The verbal episodic memory disturbance in the HIV patients was associated with hippocampal dysfunction, both in encoding and retrieval process. This emphasized that HIV affected the integrity of the medial temporal system function essential to the verbal memory. Neuroimaging studies in HIV patients showed decrease of hippocampal activation during the encoding process and increase of hippocampal activation during the recognition process [5].

5. Conclusion

HIV patients with cognitive impairment have greater chance to have impaired immediate recall and delayed recall in the verbal memory assessed with RAVLT. An early detection and assessment of cognitive problem in these patients can yield to prompt intervention if needed, so a better outcome may be expected.

6. Competing interests

The Authors declare that they have no competing interests.

7. Acknowledgments

Authors of the current article take this opportunity to thank all of the patients who warmly co-operated in this research program and I Nyoman Bagus Surya Antara for technical assistance and also Pristanova Larasanti and Andreas Soejitno for English translation and correction.

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